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Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol of A Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Abstract

Introduction: Psoriasis vulgaris (PV) is a common skin disease characterized by persistent localized erythematous scaly plaques. Yinxieling is a Chinese herbal formula for psoriasis, which has been used for more than 20 years in China. For facilitating application, PSORI-CM01 is developed from the optimization and simplification of Yinxieling tablet determined in the previous study and clinical practice. However, the scientific evidence for whether the PSORI-CM01 is more effective compared with original Yinxieling for psoriasis is still insufficient. Therefore, we designed a randomized clinical trial to investigate the effect, safety and cost-effectiveness of PSORI-CM01 granule compared with Yinxieling tablet on patients with psoriasis.

Methods and analysis: This on-going study is a two-arm parallel, randomized, double-blind, double-dummy clinical trial. 556 participants with psoriasis will be recruited and then randomly allocated into two groups in a 1:1 ratio. Participants in PSORI-CM01 group will receive PSORI-CM01 granule 5.5 g twice daily and five placebo tablets three times daily for 12 weeks. Participants in Yinxieling group will receive five Yinxieling tablets three times daily and placebo granule twice daily for 12 weeks. The primary outcome is reduction of Psoriasis Area and Severity Index (PASI) score. The secondary outcomes include relapse rate, visual analogue scale (VAS), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI). Cost effectiveness analysis will be carried out from a health and community care provider perspective.

Ethics and dissemination: This research protocol had been reviewed and approved by the institutional review boards of three trial centres (Guangdong Provicial Hospital of Chinese Medicine (B2014-026-01), Affiliated Hospital of Tianjin Chinese Medicine Academy (2014-KY-001) and Third Hospital of Hangzhou (B2014-026-01)). The findings will be disseminated to the public through conference presentations and open access journals.

Trial registration: Chinese Clinical Trial Registry: ChiCTR-TRC-14005185

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Strengths and limitations of this study

- We are carrying out a distinctive trial to provide evidence about the clinical effectiveness of Chinese medicine treatment for psoriasis before and after optimization and simplification.
- Participants will be randomised to either PSORI-CM01 granules with Yinxieling placebo tablet group or Yinxieling tablet with PSORI-CM01 placebo granules group.
- Primary outcome is reduction of PASI score during the treatment period and follow-up period.
- This trial is powered to show the effect of Chinese medicine on relieving symptoms of psoriasis

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Background:

Psoriasis is a chronic, immune-mediated, inflammatory disease skin disease characterized by erythema, scale and redness, thickening and scaling of the skin. Its main histopathologic change is accelerated cell proliferation of keratinocytes[1, 2]. However, its cause is still unknown. Though early concept of the pathogenesis of psoriasis focuses on the proliferation and differentiation of the keratinocytes, recent studies have recognized that dysregulation of immune system plays a critical role on the development of psoriasis. The interactions between dendritic cells, T cells, keratinocytes, neutrophils, and the cytokines released from immune cells are the core mechanism of how psoriasis developed[3]. Genetic, environmental and behavioral factors are thought to be triggers contribute to the onset of psoriasis[4]. The prevalence of psoriasis is estimated that the prevalence of the disease in adults ranges from 0.91% to 8.5% worldwide[5]. Clinically, psoriasis vulgaris is the most common subtype of psoriasis affecting approximately 90% of patients[6]. Psoriasis can also cost huge amount of economic loss. According to a systematic literature review conducted by the American academy of dermatology, the total burden of psoriasis was estimated as $35.2 billion in the U.S. per annum, directly and indirectly[7].

The most common treatments for psoriasis include topical medication, ultraviolet light, systematic drugs and biologics. Topical medications such as corticosteroids, retinoid and vitamin D analogues, are considered to be first line therapies for psoriasis vulgaris. Systematic drugs are for sever psoriasis, while ultraviolet lights and biologics are used when applicable and necessary[8].

A series of systematic reviews have shown that Chinese Medicine is an effective therapy for psoriasis[9-17]. Yinxieling tablet, a Chinese herbal medicine compound preparation with 10 ingredients (*angelica sinensis, radix paeoniae rubra, chloranthus spicatus, smoked plum, radix rehmanniae recen, ligusticum wallichii, radices lithospermi, curcuma zedoary, rhizome smilacis glabrae, liquorice*) for psoriasis, was developed by National Medical Master Guo-wei Xuan, a well-known Chinese medicine doctor. It was formulated according to traditional Chinese medicine theory, and was theoretically effective and safe. In resent 20 years clinical practice, Yinxieling tablets have been extensively used for treating psoriasis and shown a promising clinical efficacy on relieving symptoms of psoriasis and reducing relapsing rate. Molecular biological technologies were used to analyze the pharmacological mechanisms of multiple ingredients in Yinxieling tablet[18, 19]. These researches showed that Yinxieling tablets involved in the regulation of immune-mediated cells and interaction of cellular cytokines, which revealed the potential mechanism of Yinxieling tablets on psoriasis. When molecular and pharmacological mechanisms were explored, two clinical trials were carried out for confirming its clinical effectiveness. In Wang's study, 24 patients with psoriasis were equally randomized into two groups: treatment group received Yinxieling tablet for eight weeks and the

control group received Acitretin capsule for eight weeks. The therapeutic effect of Yinxieling tablet for the treatment of psoriasis was similar to that of Acitretin capsules, but there was less side effects appeared in Yinxieling tablet group[20]. In Dai's study, 90 patients in observation groups were treated with Yinxieling and 30 patients in control group were treated by placebo for 8 weeks. The result showed that Yinxieling decoction had therapeutical effect on psoriasis vulgaris[21]. However, there are limitations in the further development of Yinxieling because its complex compounds.

In order to expand the application of Yinxieling, an optimized formula PSORI-CM01 (former name YXBCM01) was developed, composed of only seven ingredients (radix paeoniae rubra, *smoked plum, chloranthus spicatus, radices lithospermi, curcuma zedoary, rhizome smilacis glabrae, liquorice*) of Yinxieling tablet which were found to have positive correlations with pharmacodynamic indicators by using computer systematic pharmacological method and orthogonal experiments[22, 23]. An observational study showed two months treatment of PSORI-CM01 for psoriasis vulgaris reduced PASI and DLQI scores with no adverse event[24]. Another 12-week observational study showed the PASI of patients with psoriasis reduced after PSORI-CM01 treatment and the metabolic variations visualized in patients with psoriasis before and after PSORI-CM01 treatment[25].

However, previous studies of PSORI-CM01 are all based on preliminary clinical observation. Whether clinical efficacy and safety of PSORI-CM01 granule are better than its prototype Yinxieling tablet or not is still uncertain. Therefore, a rigorously designed randomized controlled trial to determine PSORI-CM01 is more effective than Yinxieling tablet and to investigate the efficacy and safety of this new formula is warranted.

Method

Design

This is a double-dummy double-blind randomized controlled trial to investigate the efficacy and safety of the new formula PSORI-CM01 granule compared with its prototype Yinxieling tablet. This study will be performed in three centers in China: Guangdong Provicial Hospital of Chinese Medicine, Affiliated Hospital of Tianjin Chinese Medicine Academy and The Third Hospital of Hangzhou. Because Yinxieling tablet and PSORI-CM01 granules are in different preparation form, a double-dummy double-blind trial design was determined in order to guarantee rigorous blinding.

The study procedure consists of three components, initial screening, treatment period, and follow-up period, respectively. In the initial screening, patients with psoriasis will be recruited via dermatology clinic for physical examination and inclusion assessment. A two-week run-in period may be asked depending on the result of the assessment. If eligible, informed consent will be presented to the participant to sign on. All details in the informed consent will be clearly explained to the participant to assure their

understanding. Once informed consent is obtained, a participant will be given a random sequence number. All participants will be allocated into two groups with a ratio of 1:1. One group receives PSORI-CM01 granules with Yinxieling placebo tablet, while the other group Yinxieling tablet with PSORI-CM01 placebo granules (Fig. 1).

The trial protocol was approved by the Guangdong Provincial Hospital of Chinese Medicine ethics committee, and registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14005185).

Eligibility criteria

Inclusion criteria

Patients must meet all of the following criteria at the time of randomisation to be eligible for recruitment:

(1) In accordance with the diagnosis of psoriasis vulgaris referring to the "Clinical Guidelines of Psoriasis 2008" reported by the Chinese Medical Association[26];

(2) male or female patient between 18 to 65 years old;

(3) PASI more than 3 and less than 30, and BSA less than 30%;

(4) Informed consent.

Exclusion criteria

The trial exclusion criteria include any of the following:

(1) Psoriatic lesions can only be seen on face, scalp, nails, balanus, mucus and palmarplantar areas;

(2) Acute progressive psoriasis, and erythroderma tendency;

(3) Pregnant, lactating, or those who plan to become pregnant in a year; (4) SAS more than 50 or SDS more than 53, or with other psychiatric disorders;

(5) With history of primary cardiovascular, respiratory, digestive, urinary, endocrinologic and hematologic diseases, which cannot be controlled through ordinary treatments. Those who with malignant diseases, infections, electrolyte imbalance, acid-base disturbance. Patients with clinical test results listed below: AST or ALT 3 times more than normal upper limit; Creatinine 1.5 times more than normal upper limit; Hemoglobin elevates 20g/L more than normal upper limit; Platelet count less than $75.0*10^9$/L; White blood cell less than $3.0*10^9$/L; Or any other abnormal laboratory test results, assessed by investigators, that are not suitable for this clinical study;

(6) Allergic to any medicine or ingredients used in this study;

(7) Participating other clinical trials or participated within 1 month.

(8) Obtained corticosteroids or Retinoic acid acting on the skin over the previous 2 weeks; systemic therapy or phototherapy (UVB and PUVA) over the previous 4 weeks; biological therapy over the previous 12 weeks.

(9) Patients need systemic treatment with western medicine.

Interventions

PSORI-CM01 group

Participants in PSORI-CM01 group will receive PSORI-CM01 granules 5.5 g twice daily after meals and five placebo tablets three times daily after meals for 12 weeks.

Yinxieling group

Participants in Yinxieling group will receive five Yinxieling tablets three times daily after meals and placebo granules 5.5 g twice daily after meals for 12 weeks.

Outcome measures

Primary outcome

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.

Secondary outcomes

Secondary outcome measure include relapse rate, BSA, VAS and DLQI. The VAS and BSA will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period. The DLQI will be assessed by patients every 4 weeks during the treatment period. In follow-up period DLQI will only be assessed on the last week (the 24th week). Laboratory reports were also monitored until the last visit (Tab. 1).

Health economics

Economic evaluation will be carried out from Health Department of Guangdong Province perspective, which will be in form of cost-utility analysis and conducted using utility values obtained from the DLQI preference-based quality of life measure. DLQI is a dermatology-specific Quality of Life instrument for routine clinical use. It is a validated questionnaire with simple 10-question. At present the DLQI is the most frequently used instrument for evaluating the impact of skin disease and related treatment on patients' lives. DLQI will be measured at baseline and at 4 and 16 weeks for utility-based quality of life evaluation in this study. Resource use will include intervention costs, healthcare costs and community service costs, which will be calculated for each trial participant. We will analyze an incremental cost-effectiveness ratio (ICER) of cost per patient by calculating the incremental mean difference in costs between the two trial arms and incremental difference in patient outcome after

the follow-up.

Sample size

Since there is lacking of studies evaluating the effect of PSORI-CM01 granule or Yingxieling tablet on psoriasis for sample size calculation, we based on the previous study results and experts' opinions to assume the sample size using PASW Statistics software (version 18.0; IBM Inc., Chicago, IL, USA): Assumed that compare with Yingxieling tablet, the effective of PSORI-CM01 granule with an expected PASI improvement growth more than 1.5 is expected. Group sample sizes of 236 and 236 achieve 80% power to detect superiority using a one-sided, two-sample t-test. The margin of equivalence is . The true difference between the means is assumed to be 1.5. The significance level (alpha) of the test is 0.025. The data are drawn from populations with standard deviations of 1.1 and 2.5. Considering 15% loss to follow-up, 278 patients are needed in each arm, totaling 556 patients in all.

Randomisation and allocation

Eligible patients will be randomly assigned, in a 1:1 ratio, to one of the two treatment groups (PSORI-CM01 group or Yinxieling group) at the second visit through central randomization. Equal randomization will be conducted using a computer-generated random allocation sequence through the stratified block randomization method of the SAS software (version 9.12; SAS Institute, Inc., Cary, NC, USA) by the Key Unit of Methodology in Clinical Research (KUMCR) of Guangdong Provincial Hospital of Chinese Medicine. Allocation concealment will be ensured, as the randomization code will be released by the Interactive Web Response System for Chinese Medicine Trials (IWRS-CMT), which was a verified online randomization facility established by the KUMCR (http://www.gztcmgcp.net/sjxt /login.asp). After that, the participants will be randomly allocated to two different treating groups.

Test drugs and blinding

After the preliminary clinical observation, we changed the form of PSORI-CM01 formula to granules considering the preparation of oral granules is normally smooth, quick water absorption and swelling properties that allow easy swallowing.

The PSORI-CM01 granules and the matching placebo granules used in the trial were prepared by Tianjiang Pharmaceutical Co., Ltd. (Jiangyin, Jiangsu Province, China),

Yinxieling tablets and the matching placebo tablets were prepared by Kangyuan Pharmaceutical Co., Ltd. (Guangzhou, Guangdong Province, China). All drugs above met the requirements of the Good Manufacturing Practice (GMP). The main ingredients of placebo granules and placebo tablets are maltodextrin, lactose, and a natural edible pigment, will be similar to the PSORI-CM01 granules and Yinxieling tablets in appearance, weight, and taste.

The practitioners will be blind to the allocation arm according to the similar medical procedures. And the evaluation of participants and the analysis of the results will be performed by physician assessors and statisticians who are blinded to the group allocation.

Statistical analysis

All analyses will be performed with PASW Statistics and SAS 9.2 software by a statistician who is blinded to the random allocation of groups. Intent-to-treat (ITT) basis statistical analysis with a 95% confidence interval will be performed. The ITT analysis will include all patients who are randomized[27]. Safety analysis will be undertaken by analyzing the frequency of adverse events which are suspected as related to the treatment. The various parameters observed were compared using Chi-square test for non-continuous variables (i.e. the primary outcome relapse rate) and t-test and analysis of variance (ANOVA) for continuous variables. In order to distinguish the treatment effect and time effect, the repeated measures analysis of variance change from baseline will be performed for the different time point assessments. Statistical significance was established at $P< 0.05$.

Adverse events

Before the beginning and after the 12 weeks treatment, a medical history will be recorded for each patient, and standard laboratory examinations and specific laboratory investigations are also performed. The standard laboratory examinations including: hematologic parameter assessment (hemoglobin, red blood cell, platelet, and white blood cell counts); urinalysis (proteins, red blood cell, and white blood cell biochemical assessment (serum electrolytes); indices of renal function (creatinine, urea) and hepatic function (alkaline phosphatase, aspartate amino transferase, alanine amino transferase, and g-glutamil-trans-peptidase); and electrocardiogram. The specific laboratory investigations mainly include serum cytokine levels.

All adverse events will be collected and graded for severity and potential relation to

the treatments in the study by assessors at every visit. Safety evaluations included the incidence of treatment-induced or serious adverse events, dropout because of adverse events, and changes from baseline of PASI score and laboratory parameters. In case of severe adverse effects, all the drugs for this trial will be discontinued immediately.

Data management

All physicians, assessors and research assistants will attend training workshops before the conduction of trial. Investigators in different centers are all required to follow the standard operating procedures. The quality controllers from CRO (contract research organization) company will perform a regularly monitoring in each centre throughout the trial. All study data will be managed as detailed in the full trial protocol and in accordance with the data management plan which have been developed by Data Monitoring Committee of GPHCM (Guangdong Provincial Hospital of Chinese Medicine). The data collection included all information of case report forms. Data will be entered using the double entry method. To make sure data quality and data consistency between source data and data entered in the database，two research assistants will independently input the data from CRFs to data base by using a prespecified database software which have been developed by Data Monitoring Committee. The Data Monitoring Committee will assess the safety data and the critical efficacy outcomes after the trial is finished.

Discussion

Psoriasis is an immune-abnormal disease that progresses slowly over a long period with frequent symptoms recurrence. Psoriasis causes detrimental effects on the quality of life both in adults and children. Elevated rates of various psychopathologies, including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation have been reported in patients with psoriasis[28-32]. Psoriasis is not a disease affecting the skin only. Increasing evidence support the recognition of psoriasis as a chronic multisystem inflammation disorder with multiple associated comorbid conditions. Comorbidities linked to psoriasis include psoriatic arthritis, cardiovascular diseases, obesity, metabolic syndrome, malignancy, hypertension, inflammatory bowel disease[25].Psoriatic arthritis (PsA) is an erosive and deforming joint disease associated with psoriasis that affect 7% to 42% of the psoriasis population[33]. PsA-induced joint damaging complications not only lead to lower articular function and higher mortality but also affect patients' ability to work and affect their social

relationships[34].In patient with severely affected psoriasis, a 5-year shorter life expectancy tends to happen among them, mostly due to cardiovascular disease[34].What's more, psoriasis has strong connection with metabolic syndrome, making it a marker for increased risk for the morbidity and mortality associated with these diseases[35].

Treatments used for moderate-to-severe psoriasis (phototherapy, oral systemic, or biologic therapies) were received by 27.3% of the total psoriasis sample, of whom 37.2% used biologics[36]. Orally administered Chinese herbal medicine has been used for the clinical management of psoriasis for years. However, a number of high-quality clinical trials are needed before Chinese herbal medicine can be recommended for psoriasis. We conducted a series of systematic reviews to evaluated the effects of Chinese herbal medicine alone or in combination with pharmacotherapy for psoriasis [9-17]. The results showed that there is promising evidence of positive effects in a number of the studies of multi-herb formulations. And the most frequently used herbs for psoriasis in clinical trials were *angelica sinensis, rehmannia glutinosa, smilax glabra, paeonia veitchii, lithospermum erythrorhizon* and *salvia miltiorrhiza*. Most of them were compositions of the prescription in PSORI-CM01 formula.

We changed the form of PSORI-CM01 formula to granules in this study. Tablets containing micronized Chinese herbal medicine are not suitable for immediate release. Granules are solid when stored and that will swell and gel via water absorption. What's more, granules from simplified formulations offer great opportunities to improve continuous processes, present performances comparable to more complicated formulations and are able to correspond to requirements of the authorities. In this study, the micro-structure and tensile strength of the granules resembled that of tablets formed from the original ungranulated powder.

To our knowledge, this trial is the first study to compare the clinical effectiveness of Chinese medicine treatment for psoriasis before and after optimization and simplification. And we aim to provide supportive data for the effectiveness of PSORI-CM01 granule which is from the optimization of Yinxieling tablet determined in the previous study and clinical practice. This study is the third clinical trial which our research team has conducted on the effectiveness of PSORI-CM01 granule on patients with psoriasis. The first study was comparing oral PSORI-CM01 granule plus topical sequential therapy for moderate-to-severe psoriasis, which was a double-blind, randomized placebo controlled trial to evaluate the effectiveness of PSORI-CM01 combined with usual topical therapy compared to usual topical therapy in the clinical practice of Western medicine alone[37, 38]. The second study was evaluating oral

PSORI-CM01granule plus topical calcipotriol for psoriasis comparing with placebo plus topical calcipotriol for 12 weeks, which was a pilot randomized, placebo controlled, double-blinded trial[39]. These two trial aimed to evaluate the benefit of adding PSORI-CM01 granule to conventional treatments when treating psoriasis. Different from the above two trials, this clinical trial protocol acts as the foundation for evaluating Chinese medicine treatment on psoriasis.

For facilitating appropriate reference standards for scientific, ethical and safety issues before the trial begins, this protocol has been developed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 and Consolidated Standards of Reporting Trials (CONSORT) statement[40, 41].

Trial status

The recruitment phase began in November 2014. And so far 53 patients were recruited.

Abbreviations

ANOVA: Analysis of variance

BSA: Body Surface Area

CRO: contract research organization

DLQI: Dermatology Life Quality Index

ITT: Intent-to-treat

IWRS-CMT: Interactive Web Response System for Chinese Medicine Trials

KUMCR: Key Unit of Methodology in Clinical Research

PASI: Psoriasis Area and Severity Index score

SAS: Self-rating Anxiety Scale

SDS: Self-rating Depression Scale

VAS: Visual analogue scale

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Jingwen Deng, Danni Yao and Chuanjian Lu drafted the manuscript. Chuanjian Lu and Zehuai Wen participated in the design of the study, Danni Yao, Yuhong Yan, Ziyang He, Huimei Wu and Hao Deng coordinate the study. All authors participated in, read, and approved the final manuscript.

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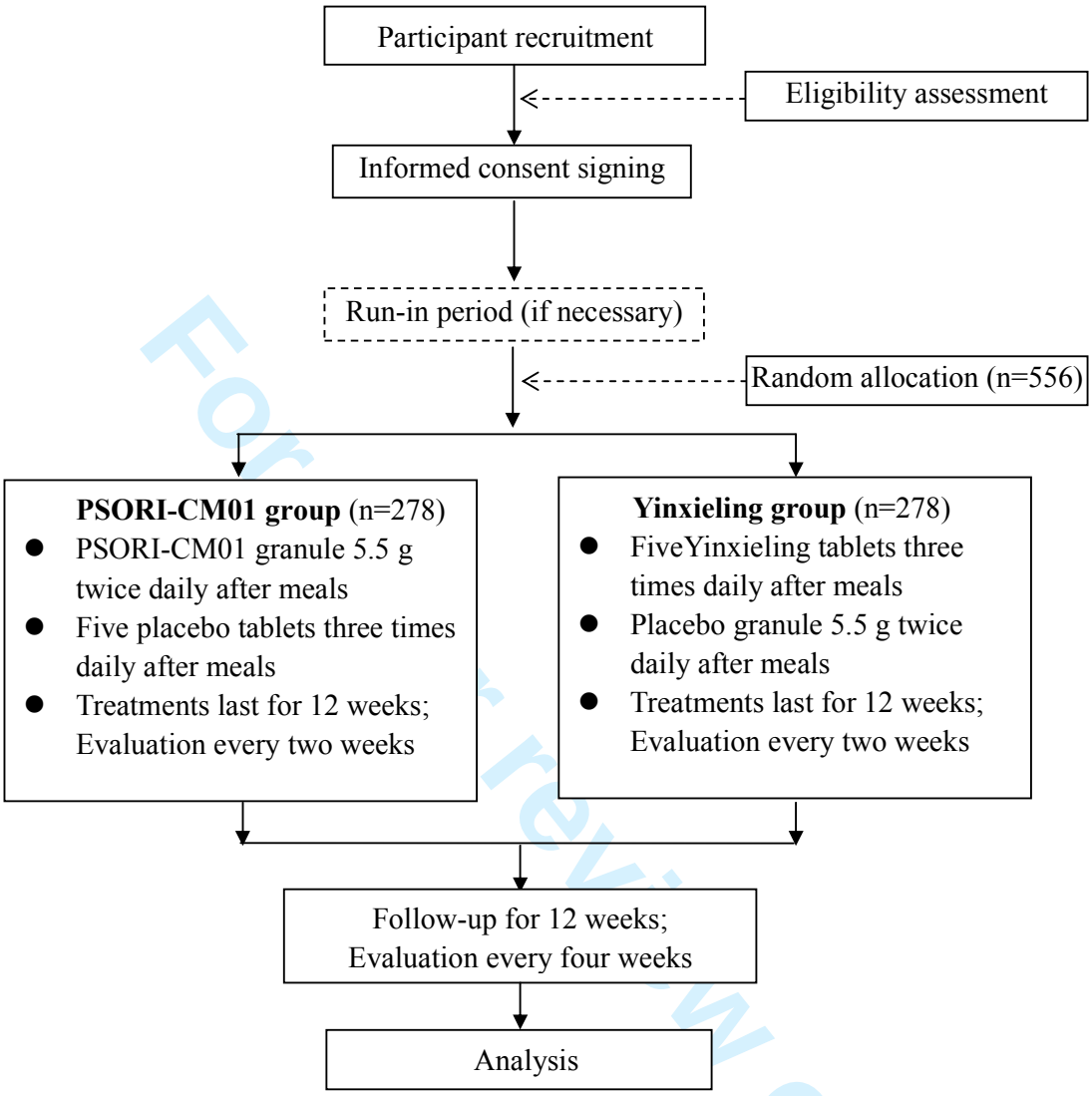

Figure 1. Flowchart of the study.

Table 1 Schedule for treatment and outcome measurements

	Period	Enrolment	Allocation	Treatment period						Follow-up period		
	Time points	-1w	0w	2w	4w	6w	8w	10w	12w	16w	20w	24w
Enrolment	Eligibility screening	●										
	Informed consent	●										
	Characteristic	●										
	Medical history	●										
	Laboratory examination		●						●			
	Biological specimens		●						●			
	Random allocation		●									
Intervention	PSORI-CM01 granules and placebo tablets		☆	☆	☆	☆	☆	☆	☆			
	Yinxieling tablets and placebo granules		★	★	★	★	★	★	★			
Assessment	CM syndrome		●						●			●
	PASI	●		●	●	●	●	●	●	●	●	●
	BSA	●		●	●	●	●	●	●	●	●	●
	VAS		●	●	●	●	●	●	●	●	●	●
	DLQI		●						●			●
	SAS	●										
	SDS	●										
	Safety assessment			●	●	●	●	●	●	●	●	●

☆: For PSORI-CM01 group

★: For Yinxieling group

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7, Table.1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8-9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Abstract

Introduction: Psoriasis vulgaris (PV) is a common skin disease that is characterized by persistent localized erythematous scaly plaques. Yinxieling is a Chinese herbal formula for psoriasis that has been used for more than 20 years in China. To facilitate application, PSORI-CM01 was developed based on the optimization and simplification of Yinxieling tablets performed in a previous study and in clinical practice. However, the scientific evidence regarding whether PSORI-CM01 is more effective for psoriasis than the original Yinxieling remains insufficient. Therefore, we designed a randomized clinical trial to investigate the effect, safety and cost-effectiveness of PSORI-CM01 granules compared with those of Yinxieling tablets for the treatment of patients with psoriasis.

Methods and analysis: This on-going study is a two-arm parallel, randomized, double-blind, double-dummy clinical trial. Five hundred fifty-six participants with psoriasis will be recruited and then randomly allocated into two groups in a 1:1 ratio. Participants in PSORI-CM01 group will receive a 5.5-g granule of PSORI-CM01 twice daily and five placebo tablets three times daily for 12 weeks. The participants in the Yinxieling group will receive five Yinxieling tablets three times daily and a placebo granule twice daily for 12 weeks. The primary outcome is the reduction of the Psoriasis Area and Severity Index (PASI). The secondary outcomes include relapse rate, visual analogue scale (VAS) scores, body surface area (BSA), and the Dermatology Life Quality Index (DLQI). Cost effectiveness analysis will be performed from a health and community care provider perspective.

Ethics and dissemination: This research protocol had been reviewed and approved by the institutional review boards of three trial centres (Guangdong Provicial Hospital of Chinese Medicine (B2014-026-01), Affiliated Hospital of Tianjin Chinese Medicine Academy (2014-KY-001) and Third Hospital of Hangzhou (B2014-026-01)). The findings will be disseminated to the public through conference presentations and open access journals.

Trial registration: Chinese Clinical Trial Registry: ChiCTR-TRC-14005185

[†]Jingwen Deng and Danni Yao contributed equally to this work.

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Strengths and limitations of this study

- We are performing a trial to provide evidence regarding the clinical effectiveness of a Chinese medicine treatment for psoriasis before and after optimization and simplification. There is no absolute placebo control, which means that this trial will be unable to assess the absolute efficacy and will assess only the relative efficacy.
- Participants will be randomized to either a PSORI-CM01 granule with Yinxieling placebo tablet group or a Yinxieling tablet with PSORI-CM01 placebo granule group. The primary outcome is the reduction of the PASI score at week 12.
- For broad use of the herbal formula, we designed PSORI-CM01 based on the rule "treated from the blood", which is related to the core pathogenesis of psoriasis in Traditional Chinese Medicine (TCM) theory. This formula can be applied to the blood heat, blood stasis, and blood dryness syndromes of psoriasis. Therefore, there is no stratification based on TCM syndromes in the design of the trial.

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Background:

Psoriasis is a chronic, immune-mediated, inflammatory skin disease characterized by erythema, scale and redness, and thickening and scaling of the skin. The main histopathologic change of psoriasis is accelerated keratinocyte cell proliferation[1, 2]. However, the cause of this disease remains unknown. Although an early concept of the pathogenesis of psoriasis focused on the proliferation and differentiation of keratinocytes, recent studies have recognized that dysregulation of the immune system plays a critical role in the development of psoriasis. The interactions between dendritic cells, T cells, keratinocytes, neutrophils, and the cytokines released from immune cells are the core mechanism of the development of psoriasis[3]. Genetic, environmental and behavioural factors are thought to be triggers that contribute to the onset of psoriasis[4]. The prevalence of psoriasis in adults is estimated to range from 0.91% to 8.5% worldwide[5]. Clinically, psoriasis vulgaris is the most common subtype of psoriasis and affects approximately 90% of patients[6].

The most common treatments for psoriasis include topical medication, ultraviolet light, systematic drugs and biologics. Topical medications, such as corticosteroids, retinoid and vitamin D analogues, are considered to be first-line therapies for psoriasis vulgaris. Systematic drugs are for severe psoriasis, while ultraviolet light and biologics are used when applicable and necessary[7].

A series of systematic reviews have demonstrated that Chinese Medicine contains an effective therapy for psoriasis[8-16]. Yinxieling tablets, which are a Chinese herbal medicine compound preparation with 10 ingredients (i.e., *angelica sinensis, radix paeoniae rubra, chloranthus spicatus, smoked plum, radix rehmanniae recen, ligusticum wallichii, radices lithospermi, curcuma zedoary, and rhizome smilacis glabrae, liquorice*) that is used for the treatment of psoriasis, was developed by the National Medical Master Guo-wei Xuan, who is a well-known Chinese medicine doctor. These tablets were formulated according to traditional Chinese medicine theory and are theoretically effective and safe. In TCM theory, three syndromes of psoriasis are generally acknowledged: blood stasis, blood heat, and blood dryness type. In the acute stage, the pathogenesis of psoriasis vulgaris is mostly blood heat that is obstructed on the surface of the skin. In the chronic stage, the pathogenesis of psoriasis vulgaris is blood deficiency that develops into dryness that prohibits the nourishing of the skin or blood stasis that obstructs blood flow in skin collaterals. Therefore, activating blood circulation and removing blood stasis should be the focus of curing of psoriasis. Yinxieling tablets play the role of activating blood circulation and removing blood stasis in the treatment of psoriasis[17].

In the recent 20 years of clinical practice, Yinxieling tablets have been extensively used for the treatment of psoriasis and have exhibited a promising clinical efficacy in terms of relieving the symptoms of psoriasis and reducing the relapsing rate. Molecular biological technologies have been used to analyse the pharmacological

mechanisms of multiple ingredients in Yinxieling tablets[18, 19]. These studies have demonstrated that Yinxieling tablets are involved in the regulation of immune-mediated cells and the interaction of cellular cytokines, which has revealed the potential mechanism of Yinxieling tablets in the treatment of psoriasis. In the exploration of the molecular and pharmacological mechanisms of Yinxieling tablets, two clinical trials have been performed to confirm their clinical effectiveness. In Wang's study, 24 patients with psoriasis were equally randomized into the following two groups: a treatment group that received Yinxieling tablets for eight weeks and a control group that received acitretin capsules for eight weeks. The therapeutic effect of the Yinxieling tablets in the treatment of psoriasis was similar to that of the acitretin capsules, but fewer side effects appeared in the Yinxieling tablet group[20]. In Dai's study, 90 patients in observation groups were treated with Yinxieling, and 30 patients in a control group were treated with placebo for 8 weeks. The result revealed that the Yinxieling decoction had a therapeutic effect on psoriasis vulgaris[21]. However, there are limitations to the further development of Yinxieling because of its complex compounds.

To expand the application of Yinxieling, an optimized formula, i.e., PSORI-CM01 (former name YXBCM01), was developed. This formula is composed of only seven ingredients (i.e., *radix paeoniae rubra, smoked plum, chloranthus spicatus, radices lithospermi, curcuma zedoary, rhizome smilacis glabrae, and liquorice*) of the Yinxieling tablet that were found to have positive correlations with pharmacodynamic indicators based on a computerized systematic pharmacological method and orthogonal experiments[22, 23]. An observational study revealed that two months of treatment with PSORI-CM01 for psoriasis vulgaris reduced the PASI and DLQI scores with no adverse events[24]. Another 12-week observational study revealed that the PASIs of patients with psoriasis were reduced after PSORI-CM01 treatment, and the metabolic variations were observed in patients with psoriasis before and after PSORI-CM01 treatment[25]. Our previous study demonstrated that PSORI-CM01 can reduce keratinocyte proliferation in vitro and inhibit epidermal hyperplasia in an imiquimod (IMQ)-induced psoriasis-form mouse model[26]. The PSORI-CM01 formula can also affect the IL-17/IL-23 axis and inhibit the expression of cytokines and chemokines and thus improve inflammatory conditions in the dermic microenvironment[27].

However, the previous studies of PSORI-CM01 are all based on preliminary clinical observations and animal experiments. Whether the clinical efficacy and safety of PSORI-CM01 granules are better than those of its prototype, i.e., the Yinxieling tablet, remains uncertain. Therefore, a rigorously designed randomized controlled trial to determine whether PSORI-CM01 is more effective than the Yinxieling tablet and to investigate the efficacy and safety of this new formula is warranted.

Method

Design

This is a double-dummy, double-blind, randomized, controlled trial to investigate the efficacy and safety of the new formula PSORI-CM01 granule compared with its prototype, the Yinxieling tablet. This study will be performed in three centres in China: the Guangdong Provincial Hospital of Chinese Medicine, the Affiliated Hospital of Tianjin Chinese Medicine Academy, and the Third Hospital of Hangzhou. Because Yinxieling tablets and PSORI-CM01 granules have different preparation forms, a double-dummy, double-blind trial design was selected to guarantee rigorous blinding.

The study procedure consists of three components, i.e., an initial screening, a treatment period, and a follow-up period. In the initial screening, patients with psoriasis will be recruited via a dermatology clinic for physical examination and inclusion assessment. A two-week run-in period may be requested depending on the results of the assessments. If eligible, written informed consent will be requested of the participants. Additional consent provisions for collection and use of participant data and biological specimens will be requested as well. All details of the informed consent will be clearly explained to the participant to assure their understanding. Once informed consent is obtained, a participant will be given a random sequence number. All participants will be allocated into two groups at a ratio of 1:1. One group will receive PSORI-CM01 granules with Yinxieling placebo tablets, and the other group will receive Yinxieling tablets with PSORI-CM01 placebo granules (Fig. 1). We will collect patients' information about TCM syndromes before and after the treatment. Target lesions will be recorded with digital photographs taken with SLR cameras at every visit.

The trial protocol was approved by the Guangdong Provincial Hospital of Chinese Medicine ethics committee, and registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14005185).

Eligibility criteria

Inclusion criteria

The patients must meet all of the following criteria at the time of randomization to be eligible for recruitment:

(1) The patients must meet the criteria for the diagnosis of psoriasis vulgaris referred to in the Clinical Guidelines of Psoriasis 2008 reported by the Chinese Medical Association[28].

(2) Male and female patients must be between 18 and 65 years old.

(3) A PASI of more than 3 and less than 30, and a BSA of less than 30% are required.

(4) Informed consent must be obtained.

Exclusion criteria

The trial exclusion criteria include any of the following:

(1) Psoriatic lesions can only be seen on the face, scalp, nails, anus, mucus and

palmar-plantar areas.

(2) Acute progressive psoriasis, an erythroderma tendency, and psoriatic arthritis are present.

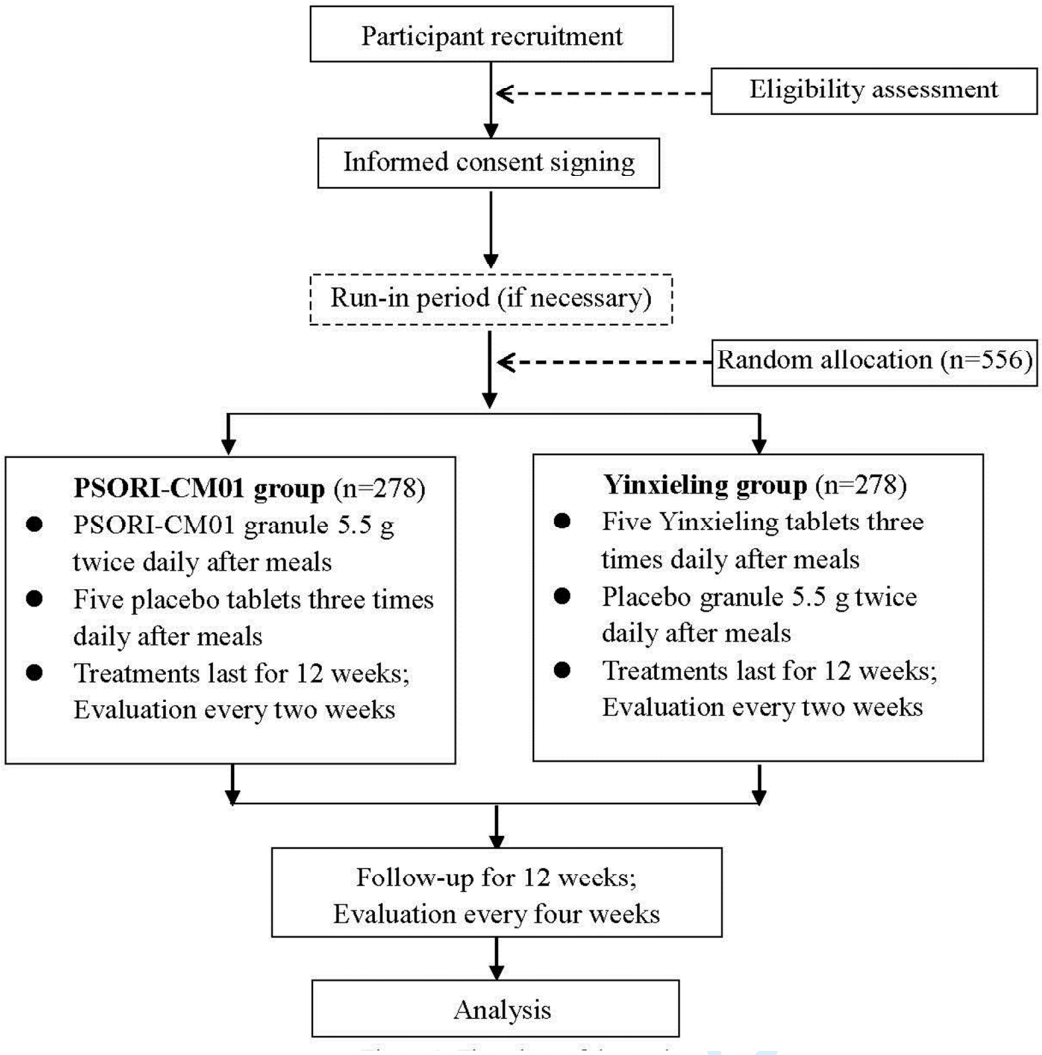

Figure 1. Flowchart of the study.

(3) Patients who are pregnant, lactating, and those who plan to become pregnant within a year will be excluded.

(4) Those with an SAS more than 50 or an SDS more than 53, and those with other psychiatric disorders will be excluded.

(5) Those with a history of primary cardiovascular, respiratory, digestive, urinary, endocrinologic and haematologic diseases that cannot be controlled with ordinary treatments will be excluded. Those with malignant diseases, infections, electrolyte imbalances, and acid-base disturbances will be excluded. Patients with the following clinical test results will be excluded: an AST or ALT 3 times greater than the normal upper limit, creatinine 1.5 times greater than the normal upper limit; haemoglobin elevated by 20 g/L above the normal upper limit; a platelet count less than $75.0*10^9$/L;

a white blood cell count less than $3.0*10^9$/L, and other abnormal laboratory test results, as assessed by the investigators, which are not suitable for this clinical study.
(6) Patients who are allergic to any medicine or ingredients used in this study will be excluded.
(7) Those participating other clinical trials and those who have participated in trials within 1 month will be excluded.
(8) Patients who have used corticosteroids or retinoic acid acting on the skin over the previous 2 weeks, those on systemic therapy or phototherapy (UVB and PUVA) with the previous 4 weeks, and those on biological therapy over the previous 12 weeks will be excluded.

Interventions

PSORI-CM01 group

Participants in PSORI-CM01 group will receive 5.5 PSORI-CM01 granules twice daily after meals and five placebo tablets three times daily after meals for 12 weeks.

Yinxieling group

Participants in Yinxieling group will receive five Yinxieling tablets three times daily after meals and placebo granules 5.5 g twice daily after meals for 12 weeks.

Outcome measures

Primary outcome

The primary outcome is the reduction in the PASI score, which will be calculated as follows：

Reduction of the PASI = PASI at baseline - PASI at week 12.

The PASI scores of the patients will be assessed every 2 weeks during the treatment period and every 4 weeks during the follow-up period. The PASI reduction calculated at week 12 will be considered the primary outcome.

Secondary outcomes

The secondary outcome measures include relapse rate, BSA, VAS and DLQI. The VAS and BSA will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period. The DLQI will be assessed by the patients every 4 weeks during the treatment period. In the follow-up period, the DLQI will only be assessed at the last week (the 24th week). Laboratory reports were also be monitored until the last visit (Table. 1).

Health economics

An economic evaluation will be performed from the perspective of the Health Department of Guangdong Province and will occur in the form of cost-utility analysis

and will be conducted using utility values obtained from the DLQI preference-based

Table 1 Schedule for treatment and outcome measurements

	Period	Enrolment	Allocation	Treatment period						Follow-up period		
	Time points	-1w	0w	2w	4w	6w	8w	10w	12w	16w	20w	24w
Enrolment	Eligibility screening	●										
	Informed consent	●										
	Characteristic	●										
	Medical history	●										
	Laboratory examination		●						●			
	Biological specimens		●						●			
	Random allocation		●									
Intervention	PSORI-CM01 granules and placebo tablets		☆	☆	☆	☆	☆	☆	☆			
	Yinxieling tablets and placebo granules		★	★	★	★	★	★	★			
Assessment	TCM syndrome		●						●			●
	PASI	●	●	●	●	●	●	●	●	●	●	●
	BSA	●	●	●	●	●	●	●	●	●	●	●
	VAS	●	●	●	●	●	●	●	●	●	●	●
	DLQI		●						●			●
	SAS	●										
	SDS	●										
	Safety assessment	●	●	●	●	●	●	●	●	●	●	●

☆: For PSORI-CM01 group

★: For Yinxieling group

quality of life measure. The DLQI is a dermatology-specific quality of life instrument for routine clinical use. This instrument is a validated questionnaire with a simple 10-question format. At present, the DLQI is the most frequently used instrument for evaluating the effects of skin disease and related treatments on patients' lives. The DLQI will be measured at baseline and at 4 and 16 weeks for utility-based quality of life evaluation in this study. Resource use will include intervention costs, healthcare costs and community service costs, which will be calculated for each trial participant. We will analyse an incremental cost-effectiveness ratio (ICER) of the cost per patient by calculating the incremental mean difference in costs between the two trial arms and the incremental difference in patient outcome after the follow-up.

Sample size

Due to the lack of studies evaluating the effects of PSORI-CM01 granule and Yinxieling tablets on psoriasis that are available for sample size calculation, we performed the sample calculation based on our previous study's results and experts' opinions[29]. The superiority-test for two means was used for the sample size calculation. We assumed that the superiority margin of the PASI was 1.5, and the standard deviations were 1.1 and 2.5 for the PSORI-CM01 granules and Yinxieling tablets, respectively. The significance level (alpha) of the test was 0.025, and statistical power was 80%. A sample size of 236 was deemed necessary for the each arm after the calculations. Considering a 15% loss to follow-up, 278 patients are needed in each arm for a total of 556 patients. The PASW Statistics software (version 18.0; IBM Inc., Chicago, IL, USA) was used for the calculations.

Randomisation and allocation

Eligible patients will be randomly assigned, in a 1:1 ratio, to one of the two treatment groups (PSORI-CM01 group or Yinxieling group) at the second visit through central randomization. Equal randomization will be conducted using a computer-generated random allocation sequence through the stratified block randomization method of the SAS software (version 9.12; SAS Institute, Inc., Cary, NC, USA) by the Key Unit of Methodology in Clinical Research (KUMCR) of Guangdong Provincial Hospital of Chinese Medicine. Allocation concealment will be ensured, as the randomization code will be released by the Interactive Web Response System for Chinese Medicine Trials (IWRS-CMT), which was a verified online randomization facility established by the KUMCR (http://www.gztcmgcp.net/sjxt /login.asp). After that, the participants will be

randomly allocated to two different treating groups.

Test drugs and blinding

After preliminary clinical observations, we changed the form of the PSORI-CM01 formula to granules because the preparation of oral granules normally involves smooth, quick water absorption and swelling properties that allow for easy swallowing.

The PSORI-CM01 granules and the matching placebo granules used in the trial were prepared by Tianjiang Pharmaceutical Co., Ltd. (Jiangyin, Jiangsu Province, China). The Yinxieling tablets and the matching placebo tablets were prepared by Kangyuan Pharmaceutical Co., Ltd. (Guangzhou, Guangdong Province, China). All of the above drugs met the requirements of Good Manufacturing Practice (GMP). The main ingredients of the placebo granules and the placebo tablets are maltodextrin, lactose, and a natural edible pigment, and these ingredients are similar to those of the PSORI-CM01 granules and Yinxieling tablets in appearance, weight, and taste.

The practitioners will be blind to the allocation arm, and the arms will have similar medical procedures. Moreover, the evaluations of the participants and the analysis of the results will be performed by physician assessors and statisticians who are blinded to the group allocation.

Statistical analysis

All analyses will be performed with PASW Statistics and SAS 9.2 software by a statistician who is blinded to the random allocation of groups. Intent-to-treat (ITT)-based statistical analyses with 95% confidence intervals will be performed. The ITT analyses will include all of the patients who are randomized[30]. Safety analysis will be undertaken by analysing the frequency of adverse events that are suspected to be related to the treatment. 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. To distinguish the treatment effect and the time effect, repeated measures analysis of variance of the change from baseline will be performed for the different time point assessments. A subgroup analyses will be performed based on the severity of the disease and the TCM syndromes. Statistical significance will be established at $P< 0.05$.

Adverse events

Before the beginning of, and after 12 weeks of treatment, medical histories will be recorded for each patient, and standard laboratory examinations and specific laboratory investigations will also be performed. The standard laboratory examinations will include the following: haematologic parameter assessment (haemoglobin, and red blood cell, platelet, and white blood cell counts); urinalysis (proteins, and red and white blood cell biochemical assessments (serum electrolytes), indices of renal function (creatinine and urea) and hepatic function (alkaline phosphatase, aspartate amino transferase, alanine amino transferase, and g-glutamyl-transpeptidase); and electrocardiograms. The specific laboratory investigations mainly include the serum cytokine levels.

All adverse events will be collected and graded for severity and potential relation to the treatments by assessors at every visit. The safety evaluations include the incidence of treatment-induced or serious adverse events, dropout due to adverse events, and laboratory parameter changes. In cases of severe adverse effects, all drugs in this trial will be immediately discontinued.

Data management

All physicians, assessors and research assistants will attend training workshops before the conduction of trial. Investigators in different centre will all be required to follow the standard operating procedures. The quality controllers from the contract research organization (CRO) Guangdong International Clinical Research Center of Chinese Medicine (Guangzhou, China) will perform regular monitoring in each centre throughout the trial. All study data will be managed as detailed in the full trial protocol and in accordance with the data management plan, which was developed by the Data Monitoring Committee of the Guangdong Provincial Hospital of Chinese Medicine (GPHCM). The data collection will include all information in the case report forms. The data will be entered using the double entry method. To ensure data quality and data consistency between the source data and the data entered into the database, two research assistants will independently input the data from the CRFs into database using a prespecified database software that was developed by the Data Monitoring Committee. The Data Monitoring Committee will assess the safety data and the critical efficacy outcomes after the trial is finished.

Discussion

Psoriasis is a disease of immune abnormality that progresses slowly over a long period with frequent symptom recurrences. Psoriasis causes detrimental effects on the quality of life of both adults and children. Elevated rates of various psychopathologies, including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation, have been reported in patients with psoriasis[31-35]. Psoriasis is not a disease that only affects the skin. Increasing evidence supports the recognition of psoriasis as a chronic multisystem inflammation disorder with multiple associated comorbid conditions. Comorbidities linked to psoriasis include psoriatic arthritis, cardiovascular diseases, obesity, metabolic syndrome, malignancy, hypertension, and inflammatory bowel disease[25]. Psoriatic arthritis (PsA) is an erosive and deforming joint disease that is associated with psoriasis and affects 7% to 42% of the psoriasis population[36]. PsA-induced joint damaging complications not only lead to lower articular function and higher mortality but also affect patients' abilities to work and their social relationships[37]. In patients with severe psoriasis, the life expectancy is reduced by 5 years primarily due to cardiovascular disease[37]. Additionally, psoriasis has a strong connection with metabolic syndrome, which makes it a marker for increased risks of the morbidities and mortalities associated with these diseases[38]. Psoriasis can also cause substantial economic loss. According to a systematic literature review conducted by the American Academy of Dermatology, the total direct and indirect burden of psoriasis is estimated to be $35.2 billion in the U.S. per annum[39].

The treatments used for moderate to severe psoriasis (i.e., phototherapy and oral systemic and biologic therapies) were received by 27.3% of the total psoriasis sample, of whom 37.2% used biologics[40]. Orally administered Chinese herbal medicine has been used for the clinical management of psoriasis for years. However, a number of high-quality clinical trials are needed before Chinese herbal medicine can be recommended for psoriasis. We conducted a series of systematic reviews to evaluate the effects of Chinese herbal medicine alone and in combination with pharmacotherapy for psoriasis [8-16]. The results revealed that there is promising evidence of positive effects from a number of studies of multi-herb formulations.

We changed the form of the PSORI-CM01 formula to granules in this study. 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. Tablets containing micronized Chinese herbal medicine are not suitable for immediate release. Granules are solid when stored and will swell and gel via water absorption. Additionally, granules from simplified formulations offer great opportunities to improve continuous processes, present performances comparable to more complicated formulations and are able to correspond to the requirements of the authorities. In this study, the micro-structure and tensile strength of the granules resembled those of the tablets formed from the original ungranulated powder.

To our knowledge, this trial is the first study to compare the clinical effectiveness of Chinese medicine treatment for psoriasis before and after optimization and simplification. Moreover, we aim to provide supporting data for the effectiveness of the PSORI-CM01 granule that resulted from the optimization of Yinxieling tablet as determined in a previous study and clinical practice. This study is the third clinical trial that our research team has conducted on the effectiveness of the PSORI-CM01 granule for patients with psoriasis. The first study compared oral the PSORI-CM01 granule plus topical sequential therapy for moderate to severe psoriasis and was a double-blind, randomized placebo-controlled trial that evaluated the effectiveness of PSORI-CM01 combined with usual topical therapy compared with the usual topical therapy that is used in the clinical practice of Western medicine alone[29, 41]. The second study evaluated oral PSORI-CM01 granule plus topical calcipotriol for psoriasis relative to placebo plus topical calcipotriol over 12 weeks; this study was a pilot randomized, placebo-controlled, double-blinded trial[42]. These two trials aimed to evaluate the benefits of the addition of PSORI-CM01 granules compared with conventional treatments of psoriasis. In contrast to the above two trials, the present clinical trial protocol acts as the foundation for evaluating the treatment of psoriasis with Chinese medicine.

For facilitating appropriate reference standards for scientific, ethical and safety issues before the trial begins, this protocol has been developed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 and Consolidated Standards of Reporting Trials (CONSORT) statement[43, 44].

Trial status

The recruitment phase began in November 2014. Thus far, 63 patients have been recruited. The estimated end date for this study is in October 2018.

Abbreviations

ANOVA: Analysis of variance

BSA: Body Surface Area

CRO: contract research organization

DLQI: Dermatology Life Quality Index
IMQ: imiquimod
ITT: Intent-to-treat
IWRS-CMT: Interactive Web Response System for Chinese Medicine Trials
KUMCR: Key Unit of Methodology in Clinical Research
PASI: Psoriasis Area and Severity Index
SAS: Self-rating Anxiety Scale
SDS: Self-rating Depression Scale
TCM: Traditional Chinese Medicine
VAS: Visual analogue scale

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Jingwen Deng, Danni Yao and Chuanjian Lu drafted the manuscript. Chuanjian Lu and Zehuai Wen participated in the design of the study, Danni Yao, Yuhong Yan, Ziyang He, Huimei Wu and Hao Deng coordinate the study. All authors participated in, read, and approved the final manuscript.

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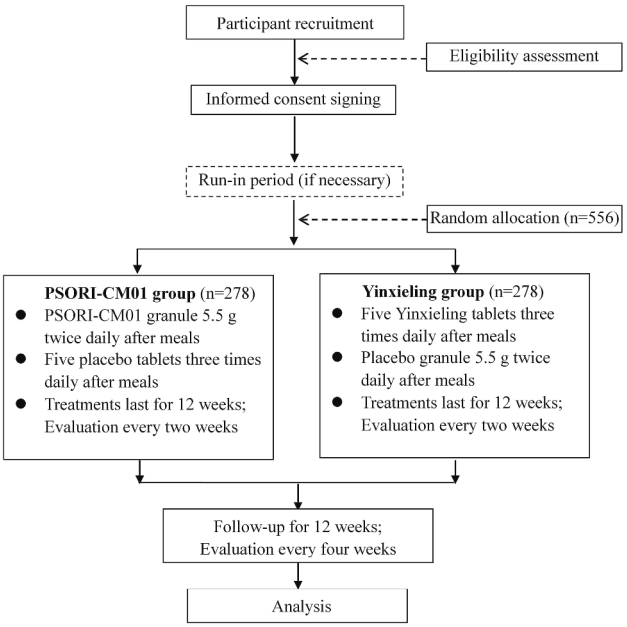

Figure 1. Flowchart of the study.

297x420mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7, Table.1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8-9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 6,15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6,7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10,11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10,11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10,11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11.12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1, 6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Abstract

Introduction: Psoriasis vulgaris (PV) is a common skin disease that is characterized by persistent localized erythematous scaly plaques. Yinxieling is a Chinese herbal formula for psoriasis that has been used for more than 20 years in China. To facilitate application, PSORI-CM01 was developed based on the optimization and simplification of Yinxieling tablets performed in a previous study and in clinical practice. However, the scientific evidence regarding whether PSORI-CM01 is more effective for psoriasis than the original Yinxieling remains insufficient. Therefore, we designed a randomized clinical trial to investigate the effect, safety and cost-effectiveness of PSORI-CM01 granules compared with those of Yinxieling tablets for the treatment of patients with psoriasis.

Methods and analysis: This on-going study is a two-arm parallel, randomized, double-blind, double-dummy clinical trial. Five hundred fifty-six participants with psoriasis will be recruited and then randomly allocated into two groups in a 1:1 ratio. Participants in PSORI-CM01 group will receive a 5.5-g granule of PSORI-CM01 twice daily and five placebo tablets three times daily for 12 weeks. The participants in the Yinxieling group will receive five Yinxieling tablets three times daily and a placebo granule twice daily for 12 weeks. The primary outcome is the reduction of the Psoriasis Area and Severity Index (PASI). The secondary outcomes include relapse rate, visual analogue scale (VAS) scores, body surface area (BSA), and the Dermatology Life Quality Index (DLQI). Cost effectiveness analysis will be performed from a health and community care provider perspective.

Ethics and dissemination: This research protocol had been reviewed and approved by the institutional review boards of three trial centres (Guangdong Provicial Hospital of Chinese Medicine (B2014-026-01), Affiliated Hospital of Tianjin Chinese Medicine Academy (2014-KY-001) and Third Hospital of Hangzhou (B2014-026-01)). The findings will be disseminated to the public through conference presentations and open access journals.

Trial registration: Chinese Clinical Trial Registry: ChiCTR-TRC-14005185

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Strengths and limitations of this study

- We are performing a trial to provide evidence regarding the clinical effectiveness of a Chinese medicine treatment for psoriasis before and after optimization and simplification. There is no absolute placebo control, which means that this trial will be unable to assess the absolute efficacy and will assess only the relative efficacy.
- Participants will be randomized to either a PSORI-CM01 granule with Yinxieling placebo tablet group or a Yinxieling tablet with PSORI-CM01 placebo granule group. The primary outcome is the reduction of the PASI score at week 12.
- For broad use of the herbal formula, we designed PSORI-CM01 based on the rule "treated from the blood", which is related to the core pathogenesis of psoriasis in Traditional Chinese Medicine (TCM) theory. This formula can be applied to the blood heat, blood stasis, and blood dryness syndromes of psoriasis. Therefore, there is no stratification based on TCM syndromes in the design of the trial.

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Background:

Psoriasis is a chronic, immune-mediated, inflammatory skin disease characterized by erythema, scale and redness, and thickening and scaling of the skin. The main histopathologic change of psoriasis is accelerated keratinocyte cell proliferation[1, 2]. However, the cause of this disease remains unknown. Although an early concept of the pathogenesis of psoriasis focused on the proliferation and differentiation of keratinocytes, recent studies have recognized that dysregulation of the immune system plays a critical role in the development of psoriasis. The interactions between dendritic cells, T cells, keratinocytes, neutrophils, and the cytokines released from immune cells are the core mechanism of the development of psoriasis[3]. Genetic, environmental and behavioural factors are thought to be triggers that contribute to the onset of psoriasis[4]. The prevalence of psoriasis in adults is estimated to range from 0.91% to 8.5% worldwide[5]. Clinically, psoriasis vulgaris is the most common subtype of psoriasis and affects approximately 90% of patients[6].

The most common treatments for psoriasis include topical medication, ultraviolet light, systematic drugs and biologics. Topical medications, such as corticosteroids, retinoid and vitamin D analogues, are considered to be first-line therapies for psoriasis vulgaris. Systematic drugs are for severe psoriasis, while ultraviolet light and biologics are used when applicable and necessary[7].

A series of systematic reviews have demonstrated that Chinese Medicine contains an effective therapy for psoriasis[8-16]. Yinxieling tablets, which are a Chinese herbal medicine compound preparation with 10 ingredients (i.e., *angelica sinensis, radix paeoniae rubra, chloranthus spicatus, smoked plum, radix rehmanniae recen, ligusticum wallichii, radices lithospermi, curcuma zedoary, and rhizome smilacis glabrae, liquorice*) that is used for the treatment of psoriasis, was developed by the National Medical Master Guo-wei Xuan, who is a well-known Chinese medicine doctor. These tablets were formulated according to traditional Chinese medicine theory and are theoretically effective and safe. In TCM theory, three syndromes of psoriasis are generally acknowledged: blood stasis, blood heat, and blood dryness type. In the acute stage, the pathogenesis of psoriasis vulgaris is mostly blood heat that is obstructed on the surface of the skin. In the chronic stage, the pathogenesis of psoriasis vulgaris is blood deficiency that develops into dryness that prohibits the nourishing of the skin or blood stasis that obstructs blood flow in skin collaterals. Therefore, activating blood circulation and removing blood stasis should be the focus of curing of psoriasis. Yinxieling tablets play the role of activating blood circulation and removing blood stasis in the treatment of psoriasis[17].

In the recent 20 years of clinical practice, Yinxieling tablets have been extensively used for the treatment of psoriasis and have exhibited a promising clinical efficacy in terms of relieving the symptoms of psoriasis and reducing the relapsing rate. Molecular biological technologies have been used to analyse the pharmacological

mechanisms of multiple ingredients in Yinxieling tablets[18, 19]. These studies have demonstrated that Yinxieling tablets are involved in the regulation of immune-mediated cells and the interaction of cellular cytokines, which has revealed the potential mechanism of Yinxieling tablets in the treatment of psoriasis. In the exploration of the molecular and pharmacological mechanisms of Yinxieling tablets, two clinical trials have been performed to confirm their clinical effectiveness. In Wang's study, 24 patients with psoriasis were equally randomized into the following two groups: a treatment group that received Yinxieling tablets for eight weeks and a control group that received acitretin capsules for eight weeks. The therapeutic effect of the Yinxieling tablets in the treatment of psoriasis was similar to that of the acitretin capsules, but fewer side effects appeared in the Yinxieling tablet group[20]. In Dai's study, 90 patients in observation groups were treated with Yinxieling, and 30 patients in a control group were treated with placebo for 8 weeks. The result revealed that the Yinxieling decoction had a therapeutic effect on psoriasis vulgaris[21]. However, there are limitations to the further development of Yinxieling because of its complex compounds.

To expand the application of Yinxieling, an optimized formula, i.e., PSORI-CM01 (former name YXBCM01), was developed. This formula is composed of only seven ingredients (i.e., *radix paeoniae rubra, smoked plum, chloranthus spicatus, radices lithospermi, curcuma zedoary, rhizome smilacis glabrae, and liquorice*) of the Yinxieling tablet that were found to have positive correlations with pharmacodynamic indicators based on a computerized systematic pharmacological method and orthogonal experiments[22, 23]. An observational study revealed that two months of treatment with PSORI-CM01 for psoriasis vulgaris reduced the PASI and DLQI scores with no adverse events[24]. Another 12-week observational study revealed that the PASIs of patients with psoriasis were reduced after PSORI-CM01 treatment, and the metabolic variations were observed in patients with psoriasis before and after PSORI-CM01 treatment[25]. Our previous study demonstrated that PSORI-CM01 can reduce keratinocyte proliferation in vitro and inhibit epidermal hyperplasia in an imiquimod (IMQ)-induced psoriasis-form mouse model[26]. The PSORI-CM01 formula can also affect the IL-17/IL-23 axis and inhibit the expression of cytokines and chemokines and thus improve inflammatory conditions in the dermic microenvironment[27].

However, the previous studies of PSORI-CM01 are all based on preliminary clinical observations and animal experiments. Whether the clinical efficacy and safety of PSORI-CM01 granules are better than those of its prototype, i.e., the Yinxieling tablet, remains uncertain. Therefore, a rigorously designed randomized controlled trial to determine whether PSORI-CM01 is more effective than the Yinxieling tablet and to investigate the efficacy and safety of this new formula is warranted.

Method

Design

This is a double-dummy, double-blind, randomized, controlled trial to investigate the efficacy and safety of the new formula PSORI-CM01 granule compared with its prototype, the Yinxieling tablet. This study will be performed in three centres in China: the Guangdong Provincial Hospital of Chinese Medicine, the Affiliated Hospital of Tianjin Chinese Medicine Academy, and the Third Hospital of Hangzhou. Because Yinxieling tablets and PSORI-CM01 granules have different preparation forms, a double-dummy, double-blind trial design was selected to guarantee rigorous blinding.

The study procedure consists of three components, i.e., an initial screening, a treatment period, and a follow-up period. In the initial screening, patients with psoriasis will be recruited via a dermatology clinic for physical examination and inclusion assessment. A two-week run-in period may be requested depending on the results of the assessments. If eligible, written informed consent will be requested of the participants. Additional consent provisions for collection and use of participant data and biological specimens will be requested as well. All details of the informed consent will be clearly explained to the participant to assure their understanding. Once informed consent is obtained, a participant will be given a random sequence number. All participants will be allocated into two groups at a ratio of 1:1. One group will receive PSORI-CM01 granules with Yinxieling placebo tablets, and the other group will receive Yinxieling tablets with PSORI-CM01 placebo granules (Fig. 1). We will collect patients' information about TCM syndromes before and after the treatment. Target lesions will be recorded with digital photographs taken with SLR cameras at every visit.

The trial protocol was approved by the Guangdong Provincial Hospital of Chinese Medicine ethics committee, and registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14005185).

Eligibility criteria

Inclusion criteria

The patients must meet all of the following criteria at the time of randomization to be eligible for recruitment:

(1) The patients must meet the criteria for the diagnosis of psoriasis vulgaris referred to in the Clinical Guidelines of Psoriasis 2008 reported by the Chinese Medical Association[28].

(2) Male and female patients must be between 18 and 65 years old.

(3) A PASI of more than 3 and less than 30, and a BSA of less than 30% are required.

(4) Informed consent must be obtained.

Exclusion criteria

The trial exclusion criteria include any of the following:

(1) Psoriatic lesions can only be seen on the face, scalp, nails, anus, mucus and

palmar-plantar areas.

(2) Acute progressive psoriasis, an erythroderma tendency, and psoriatic arthritis are present.

(3) Patients who are pregnant, lactating, and those who plan to become pregnant within a year will be excluded.

(4) Those with an SAS more than 50 or an SDS more than 53, and those with other psychiatric disorders will be excluded.

(5) Those with a history of primary cardiovascular, respiratory, digestive, urinary, endocrinologic and haematologic diseases that cannot be controlled with ordinary treatments will be excluded. Those with malignant diseases, infections, electrolyte imbalances, and acid-base disturbances will be excluded. Patients with the following clinical test results will be excluded: an AST or ALT 3 times greater than the normal upper limit, creatinine 1.5 times greater than the normal upper limit; haemoglobin elevated by 20 g/L above the normal upper limit; a platelet count less than $75.0*10^9$/L; a white blood cell count less than $3.0*10^9$/L, and other abnormal laboratory test results, as assessed by the investigators, which are not suitable for this clinical study.

(6) Patients who are allergic to any medicine or ingredients used in this study will be excluded.

(7) Those participating other clinical trials and those who have participated in trials within 1 month will be excluded.

(8) Patients who have used corticosteroids or retinoic acid acting on the skin over the previous 2 weeks, those on systemic therapy or phototherapy (UVB and PUVA) with the previous 4 weeks, and those on biological therapy over the previous 12 weeks will be excluded.

Interventions

PSORI-CM01 group

Participants in PSORI-CM01 group will receive 5.5 PSORI-CM01 granules twice daily after meals and five placebo tablets three times daily after meals for 12 weeks.

Yinxieling group

Participants in Yinxieling group will receive five Yinxieling tablets three times daily after meals and placebo granules 5.5 g twice daily after meals for 12 weeks.

Outcome measures

Primary outcome

The primary outcome is the reduction in the PASI score, which will be calculated as follows：

Reduction of the PASI = PASI at baseline - PASI at week 12.

The PASI scores of the patients will be assessed every 2 weeks during the treatment

period and every 4 weeks during the follow-up period. The PASI reduction calculated at week 12 will be considered the primary outcome.

Secondary outcomes

The secondary outcome measures include relapse rate, BSA, VAS and DLQI. The VAS and BSA will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period. The DLQI will be assessed by the patients every 4 weeks during the treatment period. In the follow-up period, the DLQI will only be assessed at the last week (the 24th week). Laboratory reports were also be monitored until the last visit (Table. 1).

Health economics

An economic evaluation will be performed from the perspective of the Health Department of Guangdong Province and will occur in the form of cost-utility analysis and will be conducted using utility values obtained from the DLQI preference-based quality of life measure. The DLQI is a dermatology-specific quality of life instrument for routine clinical use. This instrument is a validated questionnaire with a simple 10-question format. At present, the DLQI is the most frequently used instrument for evaluating the effects of skin disease and related treatments on patients' lives. The DLQI will be measured at baseline and at 4 and 16 weeks for utility-based quality of life evaluation in this study. Resource use will include intervention costs, healthcare costs and community service costs, which will be calculated for each trial participant. We will analyse an incremental cost-effectiveness ratio (ICER) of the cost per patient by calculating the incremental mean difference in costs between the two trial arms and the incremental difference in patient outcome after the follow-up.

Sample size

Due to the lack of studies evaluating the effects of PSORI-CM01 granule and Yinxieling tablets on psoriasis that are available for sample size calculation, we performed the sample calculation based on our previous study's results and experts' opinions[29]. The superiority-test for two means was used for the sample size calculation. We assumed that the superiority margin of the PASI was 1.5, and the standard deviations were 1.1 and 2.5 for the PSORI-CM01 granules and Yinxieling tablets, respectively. The significance level (alpha) of the test was 0.025, and statistical power was 80%. A sample size of 236 was deemed necessary for the each arm after the calculations. Considering a 15% loss to follow-up, 278 patients are needed in each arm for a total of 556 patients. The PASW Statistics software (version 18.0; IBM Inc., Chicago, IL, USA) was used for the calculations.

Table 1 Schedule for treatment and outcome measurements

	Period	Enrolment	Allocation	Treatment period						Follow-up period		
	Time points	-1w	0w	2w	4w	6w	8w	10w	12w	16w	20w	24w
Enrolment	Eligibility screening	●										
	Informed consent	●										
	Characteristic	●										
	Medical history	●										
	Laboratory examination		●						●			
	Biological specimens		●						●			
	Random allocation		●									
Intervention	PSORI-CM01 granules and placebo tablets		☆	☆	☆	☆	☆	☆	☆			
	Yinxieling tablets and placebo granules		★	★	★	★	★	★	★			
Assessment	TCM syndrome		●						●			●
	PASI	●	●	●	●	●	●	●	●	●	●	●
	BSA	●	●	●	●	●	●	●	●	●	●	●
	VAS	●	●	●	●	●	●	●	●	●	●	●
	DLQI		●						●			●
	SAS	●										
	SDS	●										
	Safety assessment	●	●	●	●	●	●	●	●	●	●	●

☆: For PSORI-CM01 group

★: For Yinxieling group

Randomisation and allocation

Eligible patients will be randomly assigned, in a 1:1 ratio, to one of the two treatment groups (PSORI-CM01 group or Yinxieling group) at the second visit through central randomization. Equal randomization will be conducted using a computer-generated random allocation sequence through the stratified block randomization method of the SAS software (version 9.12; SAS Institute, Inc., Cary, NC, USA) by the Key Unit of Methodology in Clinical Research (KUMCR) of Guangdong Provincial Hospital of Chinese Medicine. Allocation concealment will be ensured, as the randomization code will be released by the Interactive Web Response System for Chinese Medicine Trials (IWRS-CMT), which was a verified online randomization facility established by the KUMCR (http://www.gztcmgcp.net/sjxt /login.asp). After that, the participants will be randomly allocated to two different treating groups.

Test drugs and blinding

After preliminary clinical observations, we changed the form of the PSORI-CM01 formula to granules because the preparation of oral granules normally involves smooth, quick water absorption and swelling properties that allow for easy swallowing.

The PSORI-CM01 granules and the matching placebo granules used in the trial were prepared by Tianjiang Pharmaceutical Co., Ltd. (Jiangyin, Jiangsu Province, China). The Yinxieling tablets and the matching placebo tablets were prepared by Kangyuan Pharmaceutical Co., Ltd. (Guangzhou, Guangdong Province, China). All of the above drugs met the requirements of Good Manufacturing Practice (GMP). The main ingredients of the placebo granules and the placebo tablets are maltodextrin, lactose, and a natural edible pigment, and these ingredients are similar to those of the PSORI-CM01 granules and Yinxieling tablets in appearance, weight, and taste.

The practitioners will be blind to the allocation arm, and the arms will have similar medical procedures. Moreover, the evaluations of the participants and the analysis of the results will be performed by physician assessors and statisticians who are blinded to the group allocation.

Statistical analysis

All analyses will be performed with PASW Statistics and SAS 9.2 software by a statistician who is blinded to the random allocation of groups. Intent-to-treat (ITT)-based statistical analyses with 95% confidence intervals will be performed. The

ITT analyses will include all of the patients who are randomized[30]. Safety analysis will be undertaken by analysing the frequency of adverse events that are suspected to be related to the treatment. 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. Rank or skewed (not follow normality) data in these analyses will be examined using Wilcoxon signed-rank test. To distinguish the treatment effect and the time effect, repeated measures analysis of variance of the change from baseline will be performed for the different time point assessments. A subgroup analyses will be performed based on the severity of the disease and the TCM syndromes. Statistical significance will be established at $P< 0.05$.

Adverse events

Before the beginning of, and after 12 weeks of treatment, medical histories will be recorded for each patient, and standard laboratory examinations and specific laboratory investigations will also be performed. The standard laboratory examinations will include the following: haematologic parameter assessment (haemoglobin, and red blood cell, platelet, and white blood cell counts); urinalysis (proteins, and red and white blood cell biochemical assessments (serum electrolytes), indices of renal function (creatinine and urea) and hepatic function (alkaline phosphatase, aspartate amino transferase, alanine amino transferase, and g-glutamyl-transpeptidase); and electrocardiograms. The specific laboratory investigations mainly include the serum cytokine levels.

All adverse events will be collected and graded for severity and potential relation to the treatments by assessors at every visit. The safety evaluations include the incidence of treatment-induced or serious adverse events, dropout due to adverse events, and laboratory parameter changes. In cases of severe adverse effects, all drugs in this trial will be immediately discontinued.

Data management

All physicians, assessors and research assistants will attend training workshops before the conduction of trial. Investigators in different centre will all be required to follow the standard operating procedures. The quality controllers from the contract research organization (CRO) Guangdong International Clinical Research Center of Chinese Medicine (Guangzhou, China) will perform regular monitoring in each centre

throughout the trial. All study data will be managed as detailed in the full trial protocol and in accordance with the data management plan, which was developed by the Data Monitoring Committee of the Guangdong Provincial Hospital of Chinese Medicine (GPHCM). The data collection will include all information in the case report forms. The data will be entered using the double entry method. To ensure data quality and data consistency between the source data and the data entered into the database, two research assistants will independently input the data from the CRFs into database using a prespecified database software that was developed by the Data Monitoring Committee. The Data Monitoring Committee will assess the safety data and the critical efficacy outcomes after the trial is finished.

Discussion

Psoriasis is a disease of immune abnormality that progresses slowly over a long period with frequent symptom recurrences. Psoriasis causes detrimental effects on the quality of life of both adults and children. Elevated rates of various psychopathologies, including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation, have been reported in patients with psoriasis[31-35]. Psoriasis is not a disease that only affects the skin. Increasing evidence supports the recognition of psoriasis as a chronic multisystem inflammation disorder with multiple associated comorbid conditions. Comorbidities linked to psoriasis include psoriatic arthritis, cardiovascular diseases, obesity, metabolic syndrome, malignancy, hypertension, and inflammatory bowel disease[25]. Psoriatic arthritis (PsA) is an erosive and deforming joint disease that is associated with psoriasis and affects 7% to 42% of the psoriasis population[36]. PsA-induced joint damaging complications not only lead to lower articular function and higher mortality but also affect patients' abilities to work and their social relationships[37]. In patients with severe psoriasis, the life expectancy is reduced by 5 years primarily due to cardiovascular disease[37]. Additionally, psoriasis has a strong connection with metabolic syndrome, which makes it a marker for increased risks of the morbidities and mortalities associated with these diseases[38]. Psoriasis can also cause substantial economic loss. According to a systematic literature review conducted by the American Academy of Dermatology, the total direct and indirect burden of psoriasis is estimated to be $35.2 billion in the U.S. per annum[39].

The treatments used for moderate to severe psoriasis (i.e., phototherapy and oral systemic and biologic therapies) were received by 27.3% of the total psoriasis sample, of whom 37.2% used biologics[40]. Orally administered Chinese herbal medicine has been used for the clinical management of psoriasis for years. However, a number of high-quality clinical trials are needed before Chinese herbal medicine can be recommended for psoriasis. We conducted a series of systematic reviews to evaluate the effects of Chinese herbal medicine alone and in combination with pharmacotherapy for psoriasis [8-16]. The results revealed that there is promising evidence of positive effects from a number of studies of multi-herb formulations.

We changed the form of the PSORI-CM01 formula to granules in this study. 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. Tablets containing micronized Chinese herbal medicine are not suitable for immediate release. Granules are solid when stored and will swell and gel via water absorption. Additionally, granules from simplified formulations offer great opportunities to improve continuous processes, present performances comparable to more complicated formulations and are able to correspond to the requirements of the authorities. In this study, the micro-structure and tensile strength of the granules resembled those of the tablets formed from the original ungranulated powder.

To our knowledge, this trial is the first study to compare the clinical effectiveness of Chinese medicine treatment for psoriasis before and after optimization and simplification. Moreover, we aim to provide supporting data for the effectiveness of the PSORI-CM01 granule that resulted from the optimization of Yinxieling tablet as determined in a previous study and clinical practice. This study is the third clinical trial that our research team has conducted on the effectiveness of the PSORI-CM01 granule for patients with psoriasis. The first study compared oral the PSORI-CM01 granule plus topical sequential therapy for moderate to severe psoriasis and was a double-blind, randomized placebo-controlled trial that evaluated the effectiveness of PSORI-CM01 combined with usual topical therapy compared with the usual topical therapy that is used in the clinical practice of Western medicine alone[29, 41]. The second study evaluated oral PSORI-CM01 granule plus topical calcipotriol for psoriasis relative to placebo plus topical calcipotriol over 12 weeks; this study was a pilot randomized, placebo-controlled, double-blinded trial[42]. These two trials aimed to evaluate the benefits of the addition of PSORI-CM01 granules compared with conventional treatments of psoriasis. In contrast to the above two trials, the present clinical trial protocol acts as the foundation for evaluating the treatment of psoriasis

with Chinese medicine.

For facilitating appropriate reference standards for scientific, ethical and safety issues before the trial begins, this protocol has been developed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 and Consolidated Standards of Reporting Trials (CONSORT) statement[43, 44].

Trial status

The recruitment phase began in November 2014. Thus far, 63 patients have been recruited. The estimated end date for this study is in October 2018.

Abbreviations

ANOVA: Analysis of variance

BSA: Body Surface Area

CRO: contract research organization

DLQI: Dermatology Life Quality Index

IMQ: imiquimod

ITT: Intent-to-treat

IWRS-CMT: Interactive Web Response System for Chinese Medicine Trials

KUMCR: Key Unit of Methodology in Clinical Research

PASI: Psoriasis Area and Severity Index

SAS: Self-rating Anxiety Scale

SDS: Self-rating Depression Scale

TCM: Traditional Chinese Medicine

VAS: Visual analogue scale

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Jingwen Deng, Danni Yao and Chuanjian Lu drafted the manuscript. Chuanjian Lu and Zehuai Wen participated in the design of the study, Danni Yao, Yuhong Yan, Ziyang He, Huimei Wu and Hao Deng coordinate the study. All authors participated in, read, and approved the final manuscript.

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Figure captions:

Figure 1. Flowchart of the study

Table captions:

Table 1. Schedule for treatment and outcome measure

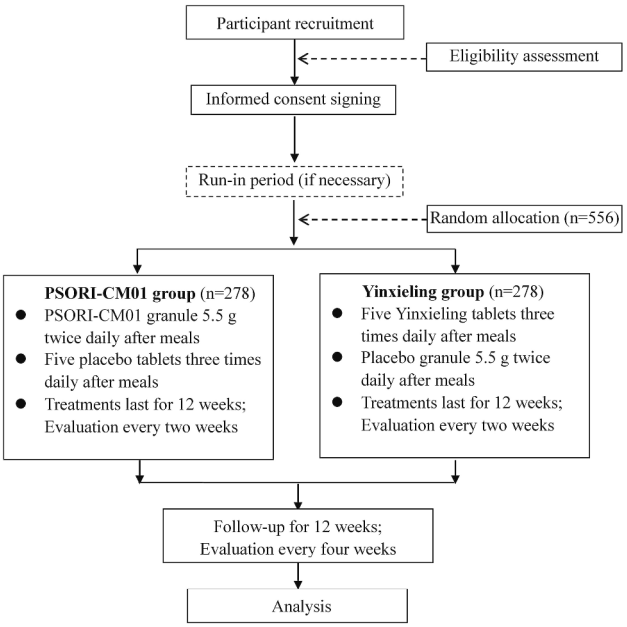

Figure 1. Flowchart of the study.

297x420mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7, Table.1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8-9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 6,15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6,7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10,11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10,11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10,11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11.12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1, 6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Oral Chinese Herbal Medicine for Psoriasis Vulgaris: Protocol for a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial

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Abstract

Introduction: Psoriasis vulgaris (PV) is a common skin disease that is characterized by persistent localized erythematous scaly plaques. Yinxieling is a Chinese herbal formula for psoriasis that has been used for more than 20 years in China. To facilitate application, PSORI-CM01 was developed based on the optimization and simplification of Yinxieling tablets performed in a previous study and in clinical practice. However, the scientific evidence regarding whether PSORI-CM01 is more effective for psoriasis than the original Yinxieling remains insufficient. Therefore, we designed a randomized clinical trial to investigate the effect, safety and cost-effectiveness of PSORI-CM01 granules compared with those of Yinxieling tablets for the treatment of patients with psoriasis.

Methods and analysis: This on-going study is a two-arm parallel, randomized, double-blind, double-dummy clinical trial. Five hundred fifty-six participants with psoriasis will be recruited and then randomly allocated into two groups in a 1:1 ratio. Participants in PSORI-CM01 group will receive a 5.5-g granule of PSORI-CM01 twice daily and five placebo tablets three times daily for 12 weeks. The participants in the Yinxieling group will receive five Yinxieling tablets three times daily and a placebo granule twice daily for 12 weeks. The primary outcome is the reduction of the Psoriasis Area and Severity Index (PASI). The secondary outcomes include relapse rate, visual analogue scale (VAS) scores, body surface area (BSA), and the Dermatology Life Quality Index (DLQI). Cost effectiveness analysis will be performed from a health and community care provider perspective.

Ethics and dissemination: This research protocol had been reviewed and approved by the institutional review boards of three trial centres (Guangdong Provicial Hospital of Chinese Medicine (B2014-026-01), Affiliated Hospital of Tianjin Chinese Medicine Academy (2014-KY-001) and Third Hospital of Hangzhou (B2014-026-01)). The findings will be disseminated to the public through conference presentations and open access journals.

Trial registration: Chinese Clinical Trial Registry: ChiCTR-TRC-14005185

[†]Jingwen Deng and Danni Yao contributed equally to this work.

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Strengths and limitations of this study

- We are performing a trial to provide evidence regarding the clinical effectiveness of a Chinese medicine treatment for psoriasis before and after optimization and simplification.
- There is no absolute placebo control, which means that this trial will be unable to assess the absolute efficacy and will assess only the relative efficacy.
- For broad use of the herbal formula, we designed PSORI-CM01 based on the rule "treated from the blood", which is related to the core pathogenesis of psoriasis in Traditional Chinese Medicine (TCM) theory.
- There is no stratification based on TCM syndromes in the design of the trial because PSORI-CM01 can be applied to the blood heat, blood stasis, and blood dryness syndromes of psoriasis.

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Background:

Psoriasis is a chronic, immune-mediated, inflammatory skin disease characterized by erythema, scale and redness, and thickening and scaling of the skin. The main histopathologic change of psoriasis is accelerated keratinocyte cell proliferation[1, 2]. However, the cause of this disease remains unknown. Although an early concept of the pathogenesis of psoriasis focused on the proliferation and differentiation of keratinocytes, recent studies have recognized that dysregulation of the immune system plays a critical role in the development of psoriasis. The interactions between dendritic cells, T cells, keratinocytes, neutrophils, and the cytokines released from immune cells are the core mechanism of the development of psoriasis[3]. Genetic, environmental and behavioural factors are thought to be triggers that contribute to the onset of psoriasis[4]. The prevalence of psoriasis in adults is estimated to range from 0.91% to 8.5% worldwide[5]. Clinically, psoriasis vulgaris is the most common subtype of psoriasis and affects approximately 90% of patients[6].

The most common treatments for psoriasis include topical medication, ultraviolet light, systematic drugs and biologics. Topical medications, such as corticosteroids, retinoid and vitamin D analogues, are considered to be first-line therapies for psoriasis vulgaris. Systematic drugs are for severe psoriasis, while ultraviolet light and biologics are used when applicable and necessary[7].

A series of systematic reviews have demonstrated that Chinese Medicine contains an effective therapy for psoriasis[8-16]. Yinxieling tablets, which are a Chinese herbal medicine compound preparation with 10 ingredients (i.e., *angelica sinensis, radix paeoniae rubra, chloranthus spicatus, smoked plum, radix rehmanniae recen, ligusticum wallichii, radices lithospermi, curcuma zedoary, and rhizome smilacis glabrae, liquorice*) that is used for the treatment of psoriasis, was developed by the National Medical Master Guo-wei Xuan, who is a well-known Chinese medicine doctor. These tablets were formulated according to traditional Chinese medicine theory and are theoretically effective and safe. In TCM theory, three syndromes of psoriasis are generally acknowledged: blood stasis, blood heat, and blood dryness type. In the acute stage, the pathogenesis of psoriasis vulgaris is mostly blood heat that is obstructed on the surface of the skin. In the chronic stage, the pathogenesis of psoriasis vulgaris is blood deficiency that develops into dryness that prohibits the nourishing of the skin or blood stasis that obstructs blood flow in skin collaterals. Therefore, activating blood circulation and removing blood stasis should be the focus of curing of psoriasis. Yinxieling tablets play the role of activating blood circulation and removing blood stasis in the treatment of psoriasis[17].

In the recent 20 years of clinical practice, Yinxieling tablets have been extensively used for the treatment of psoriasis and have exhibited a promising clinical efficacy in terms of relieving the symptoms of psoriasis and reducing the relapsing rate. Molecular biological technologies have been used to analyse the pharmacological

mechanisms of multiple ingredients in Yinxieling tablets[18, 19]. These studies have demonstrated that Yinxieling tablets are involved in the regulation of immune-mediated cells and the interaction of cellular cytokines, which has revealed the potential mechanism of Yinxieling tablets in the treatment of psoriasis. In the exploration of the molecular and pharmacological mechanisms of Yinxieling tablets, two clinical trials have been performed to confirm their clinical effectiveness. In Wang's study, 24 patients with psoriasis were equally randomized into the following two groups: a treatment group that received Yinxieling tablets for eight weeks and a control group that received acitretin capsules for eight weeks. The therapeutic effect of the Yinxieling tablets in the treatment of psoriasis was similar to that of the acitretin capsules, but fewer side effects appeared in the Yinxieling tablet group[20]. In Dai's study, 90 patients in observation groups were treated with Yinxieling, and 30 patients in a control group were treated with placebo for 8 weeks. The result revealed that the Yinxieling decoction had a therapeutic effect on psoriasis vulgaris[21]. However, there are limitations to the further development of Yinxieling because of its complex compounds.

To expand the application of Yinxieling, an optimized formula, i.e., PSORI-CM01 (former name YXBCM01), was developed. This formula is composed of only seven ingredients (i.e., *radix paeoniae rubra, smoked plum, chloranthus spicatus, radices lithospermi, curcuma zedoary, rhizome smilacis glabrae, and liquorice*) of the Yinxieling tablet that were found to have positive correlations with pharmacodynamic indicators based on a computerized systematic pharmacological method and orthogonal experiments[22, 23]. An observational study revealed that two months of treatment with PSORI-CM01 for psoriasis vulgaris reduced the PASI and DLQI scores with no adverse events[24]. Another 12-week observational study revealed that the PASIs of patients with psoriasis were reduced after PSORI-CM01 treatment, and the metabolic variations were observed in patients with psoriasis before and after PSORI-CM01 treatment[25]. Our previous study demonstrated that PSORI-CM01 can reduce keratinocyte proliferation in vitro and inhibit epidermal hyperplasia in an imiquimod (IMQ)-induced psoriasis-form mouse model[26]. The PSORI-CM01 formula can also affect the IL-17/IL-23 axis and inhibit the expression of cytokines and chemokines and thus improve inflammatory conditions in the dermic microenvironment[27].

However, the previous studies of PSORI-CM01 are all based on preliminary clinical observations and animal experiments. Whether the clinical efficacy and safety of PSORI-CM01 granules are better than those of its prototype, i.e., the Yinxieling tablet, remains uncertain. Therefore, a rigorously designed randomized controlled trial to determine whether PSORI-CM01 is more effective than the Yinxieling tablet and to investigate the efficacy and safety of this new formula is warranted.

Method

Design

This is a double-dummy, double-blind, randomized, controlled trial to investigate the efficacy and safety of the new formula PSORI-CM01 granule compared with its prototype, the Yinxieling tablet. This study will be performed in three centres in China: the Guangdong Provincial Hospital of Chinese Medicine, the Affiliated Hospital of Tianjin Chinese Medicine Academy, and the Third Hospital of Hangzhou. Because Yinxieling tablets and PSORI-CM01 granules have different preparation forms, a double-dummy, double-blind trial design was selected to guarantee rigorous blinding.

The study procedure consists of three components, i.e., an initial screening, a treatment period, and a follow-up period. In the initial screening, patients with psoriasis will be recruited via a dermatology clinic for physical examination and inclusion assessment. A two-week run-in period may be requested depending on the results of the assessments. If eligible, written informed consent will be requested of the participants. Additional consent provisions for collection and use of participant data and biological specimens will be requested as well. All details of the informed consent will be clearly explained to the participant to assure their understanding. Once informed consent is obtained, a participant will be given a random sequence number. All participants will be allocated into two groups at a ratio of 1:1. One group will receive PSORI-CM01 granules with Yinxieling placebo tablets, and the other group will receive Yinxieling tablets with PSORI-CM01 placebo granules (Fig. 1). We will collect patients' information about TCM syndromes before and after the treatment. Target lesions will be recorded with digital photographs taken with SLR cameras at every visit.

The trial protocol was approved by the Guangdong Provincial Hospital of Chinese Medicine ethics committee, and registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14005185).

Eligibility criteria

Inclusion criteria

The patients must meet all of the following criteria at the time of randomization to be eligible for recruitment:

(1) The patients must meet the criteria for the diagnosis of psoriasis vulgaris referred to in the Clinical Guidelines of Psoriasis 2008 reported by the Chinese Medical Association[28].

(2) Male and female patients must be between 18 and 65 years old.

(3) A PASI of more than 3 and less than 30, and a BSA of less than 30% are required.

(4) Informed consent must be obtained.

Exclusion criteria

The trial exclusion criteria include any of the following:

(1) Psoriatic lesions can only be seen on the face, scalp, nails, anus, mucus and

palmar-plantar areas.

(2) Acute progressive psoriasis, an erythroderma tendency, and psoriatic arthritis are present.

(3) Patients who are pregnant, lactating, and those who plan to become pregnant within a year will be excluded.

(4) Those with an SAS more than 50 or an SDS more than 53, and those with other psychiatric disorders will be excluded.

(5) Those with a history of primary cardiovascular, respiratory, digestive, urinary, endocrinologic and haematologic diseases that cannot be controlled with ordinary treatments will be excluded. Those with malignant diseases, infections, electrolyte imbalances, and acid-base disturbances will be excluded. Patients with the following clinical test results will be excluded: an AST or ALT 3 times greater than the normal upper limit, creatinine 1.5 times greater than the normal upper limit; haemoglobin elevated by 20 g/L above the normal upper limit; a platelet count less than $75.0*10^9$/L; a white blood cell count less than $3.0*10^9$/L, and other abnormal laboratory test results, as assessed by the investigators, which are not suitable for this clinical study.

(6) Patients who are allergic to any medicine or ingredients used in this study will be excluded.

(7) Those participating other clinical trials and those who have participated in trials within 1 month will be excluded.

(8) Patients who have used corticosteroids or retinoic acid acting on the skin over the previous 2 weeks, those on systemic therapy or phototherapy (UVB and PUVA) with the previous 4 weeks, and those on biological therapy over the previous 12 weeks will be excluded.

Interventions

PSORI-CM01 group

Participants in PSORI-CM01 group will receive 5.5 PSORI-CM01 granules twice daily after meals and five placebo tablets three times daily after meals for 12 weeks.

Yinxieling group

Participants in Yinxieling group will receive five Yinxieling tablets three times daily after meals and placebo granules 5.5 g twice daily after meals for 12 weeks.

Outcome measures

Primary outcome

The primary outcome is the reduction in the PASI score, which will be calculated as follows：

Reduction of the PASI = PASI at baseline - PASI at week 12.

The PASI scores of the patients will be assessed every 2 weeks during the treatment

period and every 4 weeks during the follow-up period. The PASI reduction calculated at week 12 will be considered the primary outcome.

Secondary outcomes

The secondary outcome measures include relapse rate, BSA, VAS and DLQI. The VAS and BSA will be assessed every 2 weeks during the treatment period and every 4 weeks in the follow-up period. The DLQI will be assessed by the patients every 4 weeks during the treatment period. In the follow-up period, the DLQI will only be assessed at the last week (the 24th week). Laboratory reports were also be monitored until the last visit (Table. 1).

Health economics

An economic evaluation will be performed from the perspective of the Health Department of Guangdong Province and will occur in the form of cost-utility analysis and will be conducted using utility values obtained from the DLQI preference-based quality of life measure. The DLQI is a dermatology-specific quality of life instrument for routine clinical use. This instrument is a validated questionnaire with a simple 10-question format. At present, the DLQI is the most frequently used instrument for evaluating the effects of skin disease and related treatments on patients' lives. The DLQI will be measured at baseline and at 4 and 16 weeks for utility-based quality of life evaluation in this study. Resource use will include intervention costs, healthcare costs and community service costs, which will be calculated for each trial participant. We will analyse an incremental cost-effectiveness ratio (ICER) of the cost per patient by calculating the incremental mean difference in costs between the two trial arms and the incremental difference in patient outcome after the follow-up.

Sample size

Due to the lack of studies evaluating the effects of PSORI-CM01 granule and Yinxieling tablets on psoriasis that are available for sample size calculation, we performed the sample calculation based on our previous study's results and experts' opinions[29]. The superiority-test for two means was used for the sample size calculation. We assumed that the superiority margin of the PASI was 1.5, and the standard deviations were 1.1 and 2.5 for the PSORI-CM01 granules and Yinxieling tablets, respectively. The significance level (alpha) of the test was 0.025, and statistical power was 80%. A sample size of 236 was deemed necessary for the each arm after the calculations. Considering a 15% loss to follow-up, 278 patients are needed in each arm for a total of 556 patients. The PASW Statistics software (version 18.0; IBM Inc., Chicago, IL, USA) was used for the calculations.

Table 1 Schedule for treatment and outcome measurements

	Period	Enrolment	Allocation	Treatment period						Follow-up period		
	Time points	-1w	0w	2w	4w	6w	8w	10w	12w	16w	20w	24w
Enrolment	Eligibility screening	●										
	Informed consent	●										
	Characteristic	●										
	Medical history	●										
	Laboratory examination		●						●			
	Biological specimens		●						●			
	Random allocation		●									
Intervention	PSORI-CM01 granules and placebo tablets		☆	☆	☆	☆	☆	☆	☆			
	Yinxieling tablets and placebo granules		★	★	★	★	★	★	★			
Assessment	TCM syndrome		●						●			●
	PASI	●	●	●	●	●	●	●	●	●	●	●
	BSA	●	●	●	●	●	●	●	●	●	●	●
	VAS	●	●	●	●	●	●	●	●	●	●	●
	DLQI		●						●			●
	SAS	●										
	SDS	●										
	Safety assessment	●	●	●	●	●	●	●	●	●	●	●

☆: For PSORI-CM01 group

★: For Yinxieling group

Randomisation and allocation

Eligible patients will be randomly assigned, in a 1:1 ratio, to one of the two treatment groups (PSORI-CM01 group or Yinxieling group) at the second visit through central randomization. Equal randomization will be conducted using a computer-generated random allocation sequence through the stratified block randomization method of the SAS software (version 9.12; SAS Institute, Inc., Cary, NC, USA) by the Key Unit of Methodology in Clinical Research (KUMCR) of Guangdong Provincial Hospital of Chinese Medicine. Allocation concealment will be ensured, as the randomization code will be released by the Interactive Web Response System for Chinese Medicine Trials (IWRS-CMT), which was a verified online randomization facility established by the KUMCR (http://www.gztcmgcp.net/sjxt /login.asp). After that, the participants will be randomly allocated to two different treating groups.

Test drugs and blinding

After preliminary clinical observations, we changed the form of the PSORI-CM01 formula to granules because the preparation of oral granules normally involves smooth, quick water absorption and swelling properties that allow for easy swallowing.

The PSORI-CM01 granules and the matching placebo granules used in the trial were prepared by Tianjiang Pharmaceutical Co., Ltd. (Jiangyin, Jiangsu Province, China). The Yinxieling tablets and the matching placebo tablets were prepared by Kangyuan Pharmaceutical Co., Ltd. (Guangzhou, Guangdong Province, China). All of the above drugs met the requirements of Good Manufacturing Practice (GMP). The main ingredients of the placebo granules and the placebo tablets are maltodextrin, lactose, and a natural edible pigment, and these ingredients are similar to those of the PSORI-CM01 granules and Yinxieling tablets in appearance, weight, and taste.

The practitioners will be blind to the allocation arm, and the arms will have similar medical procedures. Moreover, the evaluations of the participants and the analysis of the results will be performed by physician assessors and statisticians who are blinded to the group allocation.

Statistical analysis

All analyses will be performed with PASW Statistics and SAS 9.2 software by a statistician who is blinded to the random allocation of groups. Intent-to-treat (ITT)-based statistical analyses with 95% confidence intervals will be performed. The

ITT analyses will include all of the patients who are randomized[30]. Safety analysis will be undertaken by analysing the frequency of adverse events that are suspected to be related to the treatment. 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. Rank or skewed (not follow normality) data in these analyses will be examined using Wilcoxon signed-rank test. To distinguish the treatment effect and the time effect, repeated measures analysis of variance of the change from baseline will be performed for the different time point assessments. A subgroup analyses will be performed based on the severity of the disease and the TCM syndromes. Statistical significance will be established at $P< 0.05$.

Adverse events

Before the beginning of, and after 12 weeks of treatment, medical histories will be recorded for each patient, and standard laboratory examinations and specific laboratory investigations will also be performed. The standard laboratory examinations will include the following: haematologic parameter assessment (haemoglobin, and red blood cell, platelet, and white blood cell counts); urinalysis (proteins, and red and white blood cell biochemical assessments (serum electrolytes), indices of renal function (creatinine and urea) and hepatic function (alkaline phosphatase, aspartate amino transferase, alanine amino transferase, and g-glutamyl-transpeptidase); and electrocardiograms. The specific laboratory investigations mainly include the serum cytokine levels.

All adverse events will be collected and graded for severity and potential relation to the treatments by assessors at every visit. The safety evaluations include the incidence of treatment-induced or serious adverse events, dropout due to adverse events, and laboratory parameter changes. In cases of severe adverse effects, all drugs in this trial will be immediately discontinued.

Data management

All physicians, assessors and research assistants will attend training workshops before the conduction of trial. Investigators in different centre will all be required to follow the standard operating procedures. The quality controllers from the contract research organization (CRO) Guangdong International Clinical Research Center of Chinese Medicine (Guangzhou, China) will perform regular monitoring in each centre

throughout the trial. All study data will be managed as detailed in the full trial protocol and in accordance with the data management plan, which was developed by the Data Monitoring Committee of the Guangdong Provincial Hospital of Chinese Medicine (GPHCM). The data collection will include all information in the case report forms. The data will be entered using the double entry method. To ensure data quality and data consistency between the source data and the data entered into the database, two research assistants will independently input the data from the CRFs into database using a prespecified database software that was developed by the Data Monitoring Committee. The Data Monitoring Committee will assess the safety data and the critical efficacy outcomes after the trial is finished.

Discussion

Psoriasis is a disease of immune abnormality that progresses slowly over a long period with frequent symptom recurrences. Psoriasis causes detrimental effects on the quality of life of both adults and children. Elevated rates of various psychopathologies, including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation, have been reported in patients with psoriasis[31-35]. Psoriasis is not a disease that only affects the skin. Increasing evidence supports the recognition of psoriasis as a chronic multisystem inflammation disorder with multiple associated comorbid conditions. Comorbidities linked to psoriasis include psoriatic arthritis, cardiovascular diseases, obesity, metabolic syndrome, malignancy, hypertension, and inflammatory bowel disease[25]. Psoriatic arthritis (PsA) is an erosive and deforming joint disease that is associated with psoriasis and affects 7% to 42% of the psoriasis population[36]. PsA-induced joint damaging complications not only lead to lower articular function and higher mortality but also affect patients' abilities to work and their social relationships[37]. In patients with severe psoriasis, the life expectancy is reduced by 5 years primarily due to cardiovascular disease[37]. Additionally, psoriasis has a strong connection with metabolic syndrome, which makes it a marker for increased risks of the morbidities and mortalities associated with these diseases[38]. Psoriasis can also cause substantial economic loss. According to a systematic literature review conducted by the American Academy of Dermatology, the total direct and indirect burden of psoriasis is estimated to be $35.2 billion in the U.S. per annum[39].

The treatments used for moderate to severe psoriasis (i.e., phototherapy and oral systemic and biologic therapies) were received by 27.3% of the total psoriasis sample, of whom 37.2% used biologics[40]. Orally administered Chinese herbal medicine has been used for the clinical management of psoriasis for years. However, a number of high-quality clinical trials are needed before Chinese herbal medicine can be recommended for psoriasis. We conducted a series of systematic reviews to evaluate the effects of Chinese herbal medicine alone and in combination with pharmacotherapy for psoriasis [8-16]. The results revealed that there is promising evidence of positive effects from a number of studies of multi-herb formulations.

We changed the form of the PSORI-CM01 formula to granules in this study. 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. Tablets containing micronized Chinese herbal medicine are not suitable for immediate release. Granules are solid when stored and will swell and gel via water absorption. Additionally, granules from simplified formulations offer great opportunities to improve continuous processes, present performances comparable to more complicated formulations and are able to correspond to the requirements of the authorities. In this study, the micro-structure and tensile strength of the granules resembled those of the tablets formed from the original ungranulated powder.

To our knowledge, this trial is the first study to compare the clinical effectiveness of Chinese medicine treatment for psoriasis before and after optimization and simplification. Moreover, we aim to provide supporting data for the effectiveness of the PSORI-CM01 granule that resulted from the optimization of Yinxieling tablet as determined in a previous study and clinical practice. This study is the third clinical trial that our research team has conducted on the effectiveness of the PSORI-CM01 granule for patients with psoriasis. The first study compared oral the PSORI-CM01 granule plus topical sequential therapy for moderate to severe psoriasis and was a double-blind, randomized placebo-controlled trial that evaluated the effectiveness of PSORI-CM01 combined with usual topical therapy compared with the usual topical therapy that is used in the clinical practice of Western medicine alone[29, 41]. The second study evaluated oral PSORI-CM01 granule plus topical calcipotriol for psoriasis relative to placebo plus topical calcipotriol over 12 weeks; this study was a pilot randomized, placebo-controlled, double-blinded trial[42]. These two trials aimed to evaluate the benefits of the addition of PSORI-CM01 granules compared with conventional treatments of psoriasis. In contrast to the above two trials, the present clinical trial protocol acts as the foundation for evaluating the treatment of psoriasis

with Chinese medicine.

For facilitating appropriate reference standards for scientific, ethical and safety issues before the trial begins, this protocol has been developed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 and Consolidated Standards of Reporting Trials (CONSORT) statement[43, 44].

Ethics and dissemination

This research protocol had been reviewed and approved by the institutional review boards of three trial centers (Guangdong Provicial Hospital of Chinese Medicine (B2014-026-01), Affiliated Hospital of Tianjin Chinese Medicine Academy (2014-KY-001) and Third Hospital of Hangzhou (B2014-026-01)).

The Biological Resource Center of Guangdong Provincial Hospital of Chinese Medicine approved the biobank procedure. Written informed consent will be given by participants. The informed consent forms for participation in clinical trial and the biobanking part are separated. The results will be disseminated to the public through conference presentations and open access journals.

Trial status

The recruitment phase began in November 2014. Thus far, 63 patients have been recruited. The estimated end date for this study is in October 2018.

Abbreviations

ANOVA: Analysis of variance

BSA: Body Surface Area

CRO: contract research organization

DLQI: Dermatology Life Quality Index

IMQ: imiquimod

ITT: Intent-to-treat

IWRS-CMT: Interactive Web Response System for Chinese Medicine Trials

KUMCR: Key Unit of Methodology in Clinical Research

PASI: Psoriasis Area and Severity Index

SAS: Self-rating Anxiety Scale

SDS: Self-rating Depression Scale

TCM: Traditional Chinese Medicine

VAS: Visual analogue scale

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Jingwen Deng, Danni Yao and Chuanjian Lu drafted the manuscript. Chuanjian Lu and Zehuai Wen participated in the design of the study, Danni Yao, Yuhong Yan, Ziyang He, Huimei Wu and Hao Deng coordinate the study. All authors participated in, read, and approved the final manuscript.

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Figure captions:

Figure 1. Flowchart of the study

Table captions:

Table 1. Schedule for treatment and outcome measure

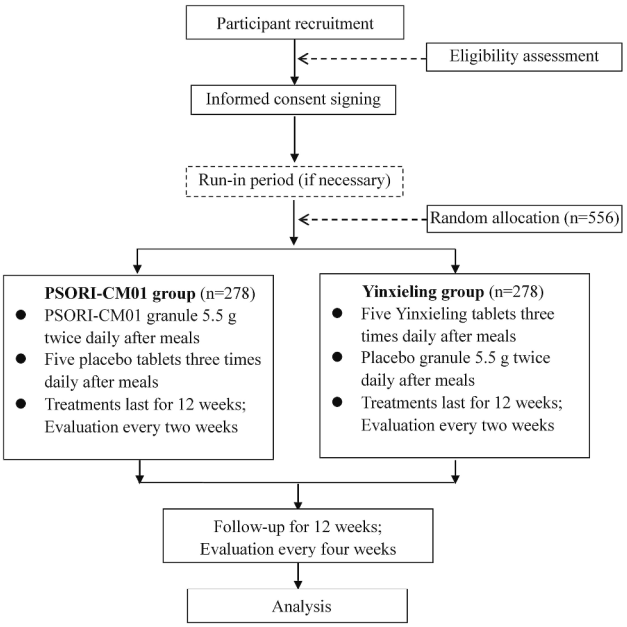

Figure 1. Flowchart of the study.

297x420mm (300 x 300 DPI)

广东省中医院伦理委员会

Institutional Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine

知情同意书·知情告知页（研究简介）

Information Leaflet for Informed Consent

亲爱的患者

您的医生已经确诊您患有寻常型银屑病疾病。

我们将邀请您参加一项“YXBCM01 颗粒治疗寻常型银屑病的双盲双模拟随机对照试验”，本研究将“YXBCM01 颗粒”与院内制剂“银屑灵片”进行比较，以观察他们对于银屑病的疗效和安全性。治疗途径是中药颗粒剂冲溶口服以及片剂口服。

在您决定是否参加这项研究之前，请尽可能仔细阅读以下内容，它可以帮助您了解该项研究以及为何要进行这项研究，研究的程序和期限，参加研究后可能给您带来的益处、风险和不适。如果您愿意，您可以请您的医生给予解释，或者可以和您的家属、朋友一起讨论，帮助您做出决定。

研究介绍

一、研究背景和研究目的

银屑病是临床常见的皮肤病之一，目前西医治疗有一定效果，但存在不良反应大、复发率高和价格昂贵等缺点。中医学在治疗银屑病方面占有重要的地位，积累了丰富的治疗经验，可有效缓解症状、减少复发率、控制病情发展，且价格适宜，尚未发现不良反应，适合长期使用。

本项研究目的是采用双盲双模拟随机对照试验设计，观察优化方 YXBCM01 颗粒相对于银屑灵片剂的疗效，评价优化方是否非劣于片剂。

本研究将在 3 个研究中心进行，预计有 64 余名受试者自愿参加。

本项研究已经得到广东省中医院伦理委员会批准。广东省中医院伦理委员会已经审议此项研究是遵从赫尔辛基宣言原则，符合医疗道德的。

二、哪些人不宜参加研究

①皮损单独见于颜面、头皮、指甲、皱折、龟头、粘膜、掌跖部位的患者。

②银屑病急性进展、有红皮病倾向的患者。

③妊娠、哺乳期或 1 年内计划妊娠者。

④心理测量量表 SAS 标准分＞50 分或 SDS 标准分＞53 分，或合并其他精神疾病的患者。

⑤合并有循环系统、呼吸系统、消化系统、泌尿系统、内分泌系统和造血系统等严重原发性疾病、常规用药无法控制的患者，合并肿瘤的患者，有严重感染、水、电解质及酸碱平衡紊乱的患者。或临床检测指标属于以下几种情况之一的患者：谷丙转氨酶或谷草转氨酶增高＞3 倍正常值上限；肌酐增高＞1.5 倍正常值上限；血红蛋白增高＞20g/L 正常值上限；血小板计数减少＜75.0×10e9/L；白细胞计数减少＜3.0×10e9/L；或其

他实验室检查异常研究者判断不适合参与此试验的患者。

⑥已知对本研究中所用药物过敏的患者。

⑦正在参加其它药物临床试验者或 1 个月内参加过其它临床试验者。

⑧2 周内曾用激素、维甲酸类等外用药物治疗者；4 周内曾接受系统治疗或紫外光治疗者；12 周内曾使用生物制剂治疗者。

⑨需进行西医系统治疗的患者。

三、如果参加研究将需要做什么

1．在您入选研究前，您将接受以下检查以确定您是否可以参加研究

医生将询问、记录您的病史，对您进行全面的体格检查。

您需要进行血常规、尿常规、肝功能、肾功能、心电图以及系统生物学指标（代谢组学、蛋白质组学、脂组学）检查。

2.若您以上检查合格，将按以下步骤进行研究

研究开始将根据计算机提供的随机数字，决定您接受 YXBCM01 颗粒+银屑灵片模拟剂治疗或银屑灵片+ YXBCM01 颗粒模拟剂治疗。参加这项研究的患者分别有 50%的可能性被分入这两个不同的治疗组。您和您的医生都无法事先知道和选择任何一种治疗方法。治疗观察将持续 24 周。

治疗期 12 周：治疗期间，您将每 2 周到医院就诊，并如实向医生反映病情变化，医生将记录您的病情变化情况。同时，医生会给您做皮损严重程度评分、拍照、填表，治疗前后均有一次体检，包括血常规、尿常规、肝肾功能及心电图检查等安全性检查。（研究期间共采血 2 次、心电图检查 2 次）。

随访期间 12 周：这时候研究结束了。随访期间不用药物维持，您还应该每 4 周到医院就诊，医生将询问记录您病情的变化，给您做皮损严重程度评分、拍照、填表。如果您出现皮肤瘙痒等情况，医生会给予处理。（研究和随访期间，若您的病情出现加重，随时到医院复诊）

3.需要您配合的其他事项

您需要按医生和您的约定的时间来医院就诊。您的随访非常重要，因为医生将判断您接受的治疗是否真正起作用。

您需要按医生指导用药，并请您在每次服药后及时、客观地在《患者日志》中记录。您在每次随访时都必须归还未用完的药物及其包装，并将正在服用的其他药物带来，包括您有其他合并疾病须继续服用的药物。

在研究期间您不能使用治疗银屑病的其他内服和外用药物。如您需要进行其他治疗，请事先与您的医生取得联系。

关于饮食、生活起居的规定：清淡饮食，避免感冒。

四、参加研究可能的受益

您和社会将可能从本项研究中受益。此种受益包括您的病情有可能获得改善，以及本项研究可能帮助开发出一种新治疗方法，以用于患有相似病情的其他病人。

您将在研究期间获得良好的医疗服务。

您将得到因参加临床试验的交通补贴。

五、参加研究可能的不良反应、风险和不适、不方便

所有治疗方法都有可能产生不良反应。尽管到目前为止没有发现该治疗方法有任何不良反应，如果在研究中您出现任何不适，或病情发生新的变化，或任何意外情况，不管是否与

治疗方法有关，均应及时通知您的医生，他/她将对此作出判断和医疗处理。

医生将尽全力预防和治疗由于本研究可能带来的伤害。如果在临床试验中出现不良事件，医学专家委员会将会鉴定其是否与试验有关。医院将对与试验相关的损害提供治疗的费用及法律法规规定相应的经济补偿。

您在研究期间需要按时到医院随访，做一些理化检查，这些都有可能给您造成麻烦或带来不便。

此外，任何治疗都有可能出现无效情况，以及因治疗无效或者因合并其他疾病等原因而导致病情继续发展。这是每个就医患者都将面临的治疗风险，即使不参加本项临床研究，治疗风险都将存在。在研究期间，如果医生发现本项研究所采取的治疗措施无效，将会终止研究，改用其他可能有效的治疗措施。

六、有关费用

课题组将支付您参加本项研究期间所做的与研究有关的检查（血常规、尿常规、肝功能、肾功能及心电图检查）费用，免挂号费，并免费提供研究用药，研究结束后您将得到因参加临床试验的交通补贴费 300 元。

如果发生与试验相关的损害，课题组将支付您的医疗费用。如果严重不良反应住院医疗，课题组将依照相关法律给予相应的补偿。

如果您同时合并其他疾病所需的治疗和检查，将不在免费的范围之内。

七、个人信息保密的吗？

您的医疗记录（研究病历/CRF、化验单等）将完整地保存在医院，医生会将化验检查结果记录在您的门诊病历上。研究者、申办者代表和伦理委员会将被允许查阅您的医疗记录。任何有关本项研究结果的公开报告将不会批露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私。除本研究外，有可能在今后的其他研究中会再次利用您的医疗记录和病理检查标本。

八、怎样获得更多的信息？

您可以在任何时间提出有关本项研究的任何问题。您的医生或研究者将给您留下他/她的电话号码以便能回答您的问题。

如果您对参加研究有任何抱怨，请联系伦理委员会办公室。

如果在研究过程中有任何重要的新信息，可能影响您继续参加研究的意愿时，您的医生会及时通知您。

九、可以自愿选择参加研究和中途退出研究

是否参加研究完全取决于您的自愿。您可以拒绝参加此项研究，或在研究过程中的任何时间退出本研究，这都不会影响您和医生间的关系，都不会影响对您的医疗有其他方面利益的损失。

您的医生或研究者出于对您的最大利益考虑，可能会随时终止您参加本项研究。

如果您不参加本项研究，或中途退出研究，还有很多其他可替代的治疗方法，如光疗法等。您不必为了治疗您的疾病而选择参加本项研究。

如果您因为任何原因从研究中退出，您可能被询问有关您使用试验方法的情况。如果医生认为需要，您可能被要求进行实验室检查和体格检查。这对保护您的健康十分有利。

十、研究结束后标本会如何处理？

研究结束后，我们将储存本研究剩余的血液/皮肤标本，储存时间为 10 年。这些标本未来可能用于与皮肤病相关的其他科学研究，并按实际需求在不同的研究实验机构(包括国外机构)进行检测。

如果您同意把您的标本储存用于未来的研究，我们会给予标本代码/编号，同时对您的个人隐私信息进行严格保密，在和其他研究者共同利用这些标本进行研究时，保证不会泄露您的个人信息使其他人能识别这是您的标本。除了我们，其他研究者不会知道那个标本是属于您的。其他研究者必须通过标本所在机构的医学伦理委员会审查后才有权使用您的标本进行科学研究。

十一、现在该做什么？

在您做出参加研究的决定前，请尽可能向您的医生询问有关问题，直至您对本项研究完全理解。

是否参加本项研究由您自己决定。您可以和您的家人或者朋友讨论后再做出决定。

感谢您阅读以上材料。如果您决定参加本项研究，请告诉您的医生或研究助理，他她会为您安排一切有关研究的事务。

请您保留这份资料。

知情同意书·同意签字页

Signature Leaflet for Informed Consent

临床研究项目名称：YXBCM01 颗粒治疗寻常型银屑病的双盲双模拟随机对照试验
有关课题资助单位的任务下达文件证明：
伦理审查批件号：

同意声明

我已经阅读了上述有关本研究的介绍，而且有机会就此项研究与医生讨论并提出问题。我提出的所有问题都得到了满意的答复。

我知道参加本研究可能产生的风险和受益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：

- 我随时可以向医生咨询更多的信息。
- 我可以随时退出本研究，而且不会受到歧视或报复，医疗待遇与权益不会受到影响。

我同样清楚，如果我中途退出本研究，特别是由于药物的原因使我退出研究时，我若将病情变化告诉医生，完成相应的体格检查和理化检查，这将对我本人和整个研究十分有利。

如果因患病我需要采取任何其他的药物治疗，我会在事先征求医生的意见，或在事后如实告诉医生。

我同意药品监督管理部门、伦理委员会或申办者代表查阅我的研究资料。

我同意□ 或拒绝□ 除本研究以外的其他研究利用我的医疗记录和病理检查标本。

我将获得一份经过签名并注明日期的知情同意书副本。

最后，我决定同意参加本项研究。

患者签名：_____ ----年--月--日

志愿者的联系电话：_____ 手机号：_____

我确认已向患者解释了本试验的详细情况，包括其权利以及可能的受益和风险，并给其一份签署过的知情同意书副本。

医生签名：_____ 日期：_____年_____月_____日

医生的工作电话：_____ 手机号：_____

研究者办公室联系电话：020-81887233-35934

Institutional Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine

Informed Consent Form

This Informed Consent Form has two parts:

- **Information Leaflet for Informed Consent (to share information about the study with you)**
- **Signature Leaflet for Informed Consent (for signatures if you agree that you may participate)**

PART I: Information Leaflet for Informed Consent

Dear Sir/Madam,
We are doing research on psoriasis, which is very common in this country.

I am going to give you information and invite you to participate in a research PSORI-CM01 compared with Yinxieling for Psoriasis Vulgaris: a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial. This research is to investigate the effect, safety and cost-effectiveness of PSORI-CM01 granules compared with those of Yinxieling tablets for the treatment of patients with psoriasis. You do not have to decide today whether or not you agree that you may participate in the research. Before you decide, you can talk to anyone you feel comfortable with.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Introduction

1. Background

Psoriasis is one of the most common diseases. The therapies that are currently being used is not as good as we would like it to be. Traditional Chinese medicine plays an important role in the treatment of psoriasis, has accumulated rich experience in the treatment, can effectively relieve symptoms and reduce the relapse rate, disease control, and the price is appropriate, has not found adverse reactions, suitable for long-term use. The purpose of this research to investigate the effect, safety and cost-effectiveness of PSORI-CM01 granules compared with those of Yinxieling tablets for the treatment of patients with psoriasis.

2. Participant selection

The participants must meet all of the following criteria at the time of randomization to be eligible for recruitment:
The participant must meet the criteria for the diagnosis of psoriasis vulgaris referred to in the Clinical Guidelines of Psoriasis 2008 reported by the Chinese Medical Association.
Male and female patients must be between 18 and 65 years old.
PASI of more than 3 and less than 30, and a BSA of less than 30% are required.
The trial exclusion criteria include any of the following:
Psoriatic lesions can only be seen on the face, scalp, nails, anus, mucus and palmar-plantar areas.
Acute progressive psoriasis, an erythroderma tendency, and psoriatic arthritis are present.
Participant who are pregnant, lactating, and those who plan to become pregnant within a year will be excluded.
Those with an SAS more than 50 or an SDS more than 53, and those with other psychiatric disorders will be excluded.
*Those with a history of primary cardiovascular, respiratory, digestive, urinary, endocrinologic and haematologic diseases that cannot be controlled with ordinary treatments will be excluded. Those with malignant diseases, infections, electrolyte imbalances, and acid-base disturbances will be excluded. Patients with the following clinical test results will be excluded: an AST or ALT 3 times greater than the normal upper limit, creatinine 1.5 times greater than the normal upper limit; haemoglobin elevated by 20 g/L above the normal upper limit; a platelet count less than 75.0*109/L; a white blood cell count less than 3.0*109/L, and other abnormal laboratory test results, as assessed by the investigators, which are not suitable for this clinical study.*
Participants who are allergic to any medicine or ingredients used in this study will be excluded.
Those participating other clinical trials and those who have participated in trials within 1 month will be excluded.
Participants who have used corticosteroids or retinoic acid acting on the skin over the previous 2 weeks, those on systemic therapy or phototherapy (UVB and PUVA) with the previous 4 weeks, and those on biological therapy over the previous 12 weeks will be excluded.

3. Procedures and Protocol

Before you are selected for the study, you will be subject to the following examinations to see if you can take part in the study.
The doctor will ask and record your medical history, and give you a thorough physical examination.
You will need routine blood tests, urinalysis, liver function, renal function, ECG, and systematic biological markers (metabolomics, proteomics, and lipid microscopy).
If you have passed the above inspection, you will follow the following steps:

Because we do not know if the PSORI-CM01 granule is better than Yinxieling tablets for treating this disease, we need to make comparisons. You taking part in this research will be put into groups which are selected by chance, as if by tossing a coin.

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the medicines or treatment is doing, we will find out which treatment you are getting and make changes.

You may come to clinic during each of the visits and during the procedures. In the first visit, a small amount of blood, equal to about a teaspoon will be taken from your arm. There may be slight bruising but this will disappear in a few days.

In the next visit, you will be given either the PSORI-CM01 granule and placebo tablet or the Yinxieling tablets and placebo granule that is used for psoriasis. Neither you nor we will know, until later in the study, which treatments you were given. The drugs will be given by a trained healthcare worker. After the treatment.

We will ask your physician to give us the details of your health and illness related information. If you do not wish us to do that, please let us know. However, because your health records are very important for the study, if we cannot look at the health records, we will not be able to include you in the study.

At the end of the study, we will contact you by clinic to tell you which of the two treatments you were given.

4. Benefits

If you participates in this research, you will have the following benefits: any treatment about this research will be no charge to you. In addition, you will receive travel allowance for clinical trials. There may not be any other benefit for you but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

5. Side Effects

These treatments can have some unwanted effects or some effects that we are not currently aware of. However, we will follow you closely and keep track of these unwanted effects or any problems. We will give you a telephone number to call if you notice anything out of the ordinary, or if you have concerns or questions. You can also come to clinic at anytime and ask to see us.

We may use some other medicines to decrease the symptoms of the side effects or reactions. Or we may stop the use of one or more drugs. If this is necessary we will discuss it together with you and you will always be consulted before we move to the next step.)

6. Charge

The charge for the examinations during the study (blood routine, urine routine, liver function, kidney function and ECG) and relevant drugs will be free. After the end of the study you will get 300 RMB for your lost time and travel expense. In case of side effects

associated with the study, we will pay your medical expenses. If you combine the treatment and examination required for other diseases, you will not be free of charge.

7. Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected from the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a code on it instead of your name. Only the researchers will know what your code is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except your clinician.

The knowledge that we get from this study will be shared with you before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. Afterwards, we will publish the results in order that other interested people may learn from our research.

8. Getting for More Information

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of your clinician.

This proposal has been reviewed and approved by Institutional Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine, which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the Institutional Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine, contact Xiaoyan Li, 020-81887233-35934.

9. Right to Refuse or Withdraw

You do not have to agree to take part in this research if you do not wish to do so and refusing to allow you to participate will not affect your treatment at this Centre in any way. You will still have all the benefits that you would otherwise have at this Centre. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this Centre will be affected in any way.

10. Biological Samples

The tissues/blood samples or any other human biological material will be stored for 10 years only for the research purpose. We will provide information about this and obtain consent specifically for such storage and use in addition to consent for participation in the study

***11.* Voluntary Participation**

Before you make your decision to participate in the study, please ask your doctor questions as much as possible until you fully understand the study.

Your decision to participate in this study is entirely voluntary. It is your choice whether to participate or not. You can discuss it with your family or friends before making a decision.

Thank you for reading this document. If you decide to participate in this study, please tell your doctor or research assistant, who will arrange all the research procedure for you. You will be given a copy of the full Informed Consent Form.

PART II: Signature Leaflet for Informed Consent

Trial: PSORI-CM01 compared with Yinxieling for Psoriasis Vulgaris: a Randomized, Double-Blind, Double-Dummy, Multicenter Clinical Trial.

Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.

I also understand that I can *stop participating in the research at any time*, especially because side effect of the drugs. If I need to take any other medication, I'll ask the doctor for advice or tell the doctor exactly after the event.

I agree with the drug administration, the ethics committee, or the bid representative to review my research materials.

I agree with □ or refuse □ medical records and pathological examinations in this study for other use.

I will receive a signed copy of this informed consent.

I consent voluntarily to participate as a participant in this study.

Signature of Participant_____ Date_____

Phone number of Participant_____

I confirm that I have explained the details of the trial to the participant, including his/her rights and possible benefits and risks, and I have kept a copy of the signed informed consent.

Signature of Researcher /person taking the consent _____

Date_____

Phone number of Researcher /person taking the consent _____

Phone number of the Institutional Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine：020-81887233-35934

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7, Table.1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	7-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8-9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	15
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 6,15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6,7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8, Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10,11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10,11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10,11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11.12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1, 6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.