Efficacy and Safety of Jin-Shui Huan-Xian Granule for Idiopathic Pulmonary Fibrosis: Study Protocol for a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background

Idiopathic pulmonary fibrosis is a critical disease with poor prognosis. Although different studies have been conducted for the treatment of idiopathic pulmonary fibrosis, limited treatments are available. Jin-shui Huan-xian granule, which is a Chinese medicine herbal compound, has shown a promising efficacy in reducing frequencies of acute exacerbations, improving exercise capacity the quality of life of patients for idiopathic pulmonary fibrosis.

Subjects and Methods:

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial. A total of 312 idiopathic pulmonary fibrosis patients will be enrolled and randomly allocated to one of the two groups with 1:1. After a 2-week washout period, 52-week treatment will also be performed for all the patients. Patients in experimental group will be given Jin-shui Huan-xian granule with Jin-shui Huan-xian placebo for control group. Outcome measures including acute exacerbations, pulmonary function, dyspnea, exercise capacity, quality of life will be evaluated in this study.

Discussion

Based on our previous study, it is hypothesized that JHG will reduce the acute exacerbations, improve exercise capacity, pulmonary function, quality of life, delay the disease progression-free. High-level evidence-based support for TCM in IPF will also be obtained in this study.

Trial registration:

http:www.clinicaltrials.gov : NCT04187690. Register data: December 11, 2019.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with poor prognosis and short median survival [1]. The etiology remains not completely clear[2]. With a low prevalence rate, some scholars consider it as a rare disease[3]. In China, it has also been included into the list of rare diseases in 2018. However, different studies show that it has been more common in recent years[4, 5]. After diagnosis, IPF patients will follow a median survival of 2–5 years[5]. Data also shows that, IPF patients in Sweden will spend an annual average of $ 13, 975 for hospitalization[6]. In America, a total of 2 billion dollars has been spend in the prevention and treatment of IPF every year[7]. IPF has caused a heavy socio-economic burden.

Although different studies have been performed recent years, the available treatments remain limited. As reported in the latest international guidelines for IPF, only pirfenidone and nintedanib are recommended in clinical application[8]. They could improve pulmonary function, quality of life, exercise capacity, and delay the disease progression for IPF patients[9–11]. However, the related side effects have also been reported. One study showed that a total of more than 10% of IPF patients taking pirfenidone or nintedanib have discontinued medication permanently due to side effects[12]. And their long-term effects are still under debate. Up to now, evidences for other drugs are still insufficient[13–20]. Limited researches have also been performed in non-drug treatment for IPF[21]. However, the levels of the available evidences are also low. It is urgent to conduct further researches for the treatments of IPF[22].

Traditional Chinese medicine (TCM) has different treatments and certain efficacy for respiratory disease. Chinese herbal medicine(CHM) is the most used measures. According to TCM theory and our previous studies, IPF should be treated according to *feiwei* or *feibi*, and the core TCM pathogenesis includes vital *qi* deficiency, lung collaterals obstruction, phlegm and blood stasis, and accumulation of damage. We have also developed a TCM therapeutic scheme for IPF based on the above studies. Then, the CHM formulation has been optimized to Jin-shui Huan-xian granule (JHG) by clinical application and basic experiments.

JHG is a Chinese medicine compound. Our previous study shows it has a potential treatment effect by inhibiting the differentiation of fibroblasts into myofibroblasts in pulmonary fibrosis mouse model[23]. We have also performed an exploratory trial to assess the efficacy and safety for IPF patients. The results show that, JHG could reduce the frequencies of acute exacerbation, improve lung function and exercise capacity with a reliable safety for IPF patients (to be published). To obtain the high-level evidence-based supports, we will conduct a randomized controlled trial to confirm the efficacy and safety of Jin-shui Huan granule for IPF.

Methods/design

Study design

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial. The efficacy and safety of JHG for IPF will be assessed in this study. We will recruit 312 stable IPF patients and randomly them into experimental or control group with a ratio of 1:1 after a wash-out period of 2 weeks. Then, all the enrolled patients will be given a 52-week treatment of JHG or placebo. Outcomes assessed in this study include frequencies of acute exacerbations, exercise capacity, proportion of progression-free patients, lung function, all-cause mortality, clinical symptoms and signs, dyspnea, health-related quality of life (HRQoL) and adverse events. The protocol follows Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018) [24]. The study will also be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The whole study flow-chart could be found Fig. 1.

Participants, eligibility criteria

Diagnosis criteria of IPF

The diagnosis of IPF will be performed referring to the classification and diagnosis standard of idiopathic interstitial pneumonia published by American Thoracic Society and European Respiratory Society in 2018[25]: (1) Patients with any other known causes of interstitial lung disease (ILD), such as occupational environment exposure, connective tissue disease or drugs, should be excluded; (2) for the patients without surgical lung biopsy, high-resolution CT (HRCT) should show a representation of usual interstitial pneumonia (UIP); (3) A specific combination of HRCT and lung biopsy histopathological results should be met for the patients with surgical lung biopsy. (4) If necessary, multi-disciplinary discussion would also be adopted for the difficult cases.

Diagnostic criteria of TCM syndromes

Because of that there is a lack of diagnostic criteria of TCM syndromes for IPF now, the differentiation of TCM syndromes will be refer to *Diagnostic criteria of TCM syndromes for diffuse interstitial lung disease*[26]. Two independent TCM researchers will perform the syndrome differentiation blindly. If any disagreement appears, the third researcher will be consulted and a consensus will be reached. The core TCM Pathogenesis, which is accumulation and damage of collaterals due to deficiency of vital *qi*, will also be taken into account[27]. So, IPF patients with the TCM syndromes including lung qi deficiency, lung-kidney qi deficiency, and yin deficiency and inner heat will also be enrolled in this study.

Inclusion criteria

Any the participant should meet all of the following criteria: (1) meeting the diagnostic criteria of IPF; (2) with ages of between 40 and 85 years old; (3) meet the criteria of TCM syndrome differentiation: patterns of lung qi deficiency, lung-kidney qi deficiency, and yin deficiency and inner heat [16]; (4) not participating in any other interventional trial within the previous one month before enrollment; (5) signing the informed consent form.

Exclusion criteria

The patients meeting any of the following criteria will be excluded: (1)Pregnant, breastfeeding women or patients with a recent pregnancy plan; (2) Delirious, dementia, or with any mental disorder; (3) Complicated with severe cardiac insufficiency, liver and kidney diseases, bronchial asthma, chronic obstructive pulmonary disease, tumor or thoracic deformity; (4) With a condition of limb dysfunction or bedridden; (5) Known to be allergic to any component of the therapeutic drugs.

Withdraw criteria

The enrolled patients will also be eliminated for any of the following criteria: (1) poor adherence of medication with rates of less than 80% or more than 120%, or taking any drug prohibited in this program, or discontinued the given drugs themselves; (2)not willing to continue the trial with any reason and may induce the incompleteness of study data; (3) should not continue to participate the trial due to allergy or serious adverse events; (4)patients who are no longer taking the given medication and physical

examination and lost in the visit. According to our previous study, the withdrawing rate will be not higher than 20%. All the records for all the eliminated patients will also be preserved.

Sample size

The calculation formula($n=(u_\alpha+u_\beta)^2(1+1/k)\sigma^2/\delta^2$)based on comparison of means of two independent samples has been adopted to calculating the target sample size. N and k*n represent the target sample size of experimental and control group respectively. The total variance (σ^2) will be represented by the sample variance (s^2). The formula ($s^2=(s_e^2+ks_c^2)/(1+k)$ and $\delta=|\bar{x}e - xc|$) has also been adopted. $\bar{x}_e$ and $\bar{x}_c$ represent the means of experimental and control group, while s_e and s_c represent the standard deviation (SD) respectively. Two-tailed values of α and β are 0.05 and 0.01 respectively. The ratio of experimental and control group samples in this trial is 1:1, so the *k* value is 1.

Based on our previous clinical trial (to be published), the frequencies of AEs and 6 minutes walking distance (6MWD) have been set up as the primary outcomes in this trial. There was a significant difference between the two groups in our previous study for AE. So, the calculation of sample size in this study will refer to 6MWT.

For 6MWD, the mean was 374.38 m in experimental group, with 342.57 m in control group. And the SD was 87.67 m in experimental group, with 81.18 in control group. The target sample size in each group was 124. Taking a drop-out rate of 20%, the target sample size is 156 in each group. And the total target sample size is 312.

Ethics, oversight, recruitment and dissemination

The study has been approved by the Ethical Committees of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine with an identifier (Version 2019.07.18.1.0.1.0) of 2019HL064-01. Any other revisions of the study protocol will also be submitted to the ethical committee for approval. The whole process of the trial will also be supervised by Ethical Research Committees of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine. The ethics committee is composed of people with different professions, including non-medical people. The approved protocol will protect the interests of participants. The Informed consent will be obtained from all individual participants by the special screener in every research center. Any adverse event will also be submitted to the ethical committees as soon as possible. All the participants will provide written informed consent. Blood, urine samples and exhaled breath condensate will be collected with the participants' consents for further researches. The authors are accountable for the accuracy of all aspects of the study. Any question related to any part of the work will be investigated and resolved.

Open recruitment for IPF patients will be performed both in outpatient and inpatient. Publishing recruitment advertisements will also be adopted. And the enrolled patients will be observed in 11 research centers in China, which are the First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Shanghai Shuguang Hospital, Dongzhimen Hospital of Beijing University of Traditional Chinese

Medicine, the Second Affiliated Hospital of Tianjin University of traditional Chinese Medicine, Hebei Province Traditional Chinese Medicine Hospital, Qingdao Hici Hospital, Henan Provincial People's Hospital, Henan Province Hospital of Traditional Chinese Medicine, Third Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou Chinese Medicine Hospital, Zhengzhou First People's Hospital. All the sub-centers have the qualification and experience with performing TCM trial. Recruitment will last for 12 months from September 2020 or until the target sample are completed. The results of this study will be disseminated to the public in peer-reviewed journals without any patient's personal information. The raw data will also be available on request to authors.

Randomization and masking

A design of block randomization has been applied to performing the allocation. All the enrolled patients, who meet inclusion criteria and sign the informed consent, will be randomly assigned into experimental or control group in a ratio of 1:1 after a two-week wash-out period. The random numbers from 001 to 312 were generated by SAS 9.2 and saved by an independent researcher. The random numbers and corresponding drug codes are the unique identification code of participants. All the patients, recruiters, data collectors, outcome assessors and sponsor will be all blind to the treatment allocation in the whole process of trial. In case of emergency, the corresponding random number and treatment allocation will be identified for researchers and supervisors as soon as possible. The randomization design and random numbers are provided by the Jiangsu Famous Medical Technology Co., Ltd. in Nanjing, China.

Procedures and interventions

Patients in the experimental group will be treated with JHG for 52 weeks, while the control group are treated with JHG placebo. JHG is a Chinese herbal compound medicine. The compounds of one dosage for JHG could be found in Table 1. The placebo used in this study will contain 5% of the same components of JHG. All the JHG and placebo will be produced and packed by Jiang Yin Tian Jiang Pharmaceutical Co. Ltd., Jiangsu, PR China without any difference at appearance, color, smell and weight. The drug quality will be tested by organization with specific qualifications before application and consistent with the required quality standards. Each dosage of JHG granules or placebo have been produced and packed into 4 bags with 10.9g per bag(Batch number: 2006337). JHG or JHG placebo will be prescribed 2 bags each time, twice a day orally with 5 days on and 2 days off.

Table 1
Components of Jin-shui Huan-xian granules.

Chinese name	Latin name	Parts of the substances	Amount (g)
Ren Shen	*Radix Ginseng*	Root	9
Shu Di Huang	*Rehm,annia glutinosa Libosch*	Root tuber	15
Mai Dong	*Ophiopogon japonicus*	Root tuber	12
Gua Lou	*Trichosanthes kirilowii Maxim*	Mature fruit	15
Zhe Bei Mu	*Fritillaria thunbergii Miq*	Bulb	9
Mu Dan Pi	*Paeonia Suffruticosa Andrew*	Root bark	9
Zhi Yin Yang Huo	*Epimedium brevicornu Maxim*	Whole herb	6
Chao Bai Guo	*Ginkgo biloba L*	Mature seed	9
Chen Pi	*Citrus reticulata Blanco*	Peel of fruit	9
Zhi Gan Cao	*Glycyrrhiza uralensis Fisch*	Root and rhizome	9

At the same time, all the patients will also be treated with conventional Western medicine. Considering the side effects and costs, the application of pirfenidone and nintedanib will not be limited uniformly. Among the whole procedure, all the patients will be visited at every 13 weeks and receive given physical examinations. Blood, urine samples and exhaled breath condensate will be collected with the participants' consents for further researches. If patients under AE, the Chinese medicine granule or placebo will be suspended until the condition become stable. To improve patients' adhere, the remained drugs and empty bags will also be returned except for regular telephone follow-up. The whole procedures for each patient could be found in Fig. 2.

Outcome measures

Assessment will be performed by outcome measures at baseline, end of treatment and the given follow-up points. The primary outcomes include frequencies of AEIPF, 6-minute walking distance (6MWT), and the proportion of patients with disease-progression free. The secondary outcomes include pulmonary function, all-cause mortality, clinical symptom and signs, dyspnea, and health-related quality of life (HRQoL).

Primary outcomes

Exacerbations of IPF

The frequencies of acute exacerbations of IPF, which is assessed by AEIPF-related hospitalization, is the primary outcome measure. AEIPF is characterized by significant respiratory deterioration, with unknown

cause within the past one month[28]. If the interval between any two AEIPF-related hospitalizations is less than 7 days, they are considered as one AE. The AE will be recorded at every visit, and the total number in the whole process (1-year treatment period) will be calculated. A higher number in a given period indicates the deterioration of IPF and worse prognosis. A lower number in experimental group will indicate better efficacy.

6MWD

6MWD is adopted to assessing the exercise capacity of IPF patients. It is evaluated by the distance an IPF patient can walk as fast as he can in 6 minutes. A longer distance indicates better exercise capacity for IPF patients.

Proportion of disease-progression free survivals

The endpoints of free disease-progression in this study include any of the following events[29]: forced vital capacity (FVC)decreased by 10%, diffusing capacity percentage of the predicted value (DLCO%) by 15% compared to baseline, patient death, and lung transplantation. At the end of treatment, the proportion of the patients without any of the above endpoints will be calculated.

Secondary outcomes

Pulmonary function

FVC and DLCO% will be examined at baseline and the end of the treatment. A positive change will indicate the improvement of pulmonary function.

All-cause mortality

Any death for IPF patients in this study with any cause will be recorded and counted. All-cause mortality will be calculated at the end of treatment in each group. A lower number in experimental group indicate a better efficacy for the intervention in improving prognosis.

Clinical symptom and signs

Assessment will be performed by clinical symptom assessment questionnaire. The clinical symptoms to be evaluated in this study include cough, expectoration, chest tightness, shortness of breath, wheezing and cyanosis. A score of 0–3 will be given to every symptom or sign with a higher score indicating a worse condition.

Dyspnea

Dyspnea will be assessed by modified Medical Research Council (mMRC) scores set up by American Thoracic Society[30]. A score of 0–4 will be given according to the degree of immediate dyspnea. A higher score indicates a worse dyspnea.

Health-related quality of life

HRQoL will be assessed by the COPD assessment test (CAT), St. George's respiratory questionnaire (SGRQ), 36-item short-form health survey (SF-36), and A Tool to Assess Quality of life in IPF(ATAQ-IPF), with a higher value indicating a better HRQoL for SF-36 and a worse HRQoL for CAT, SGRQ and ATAQ-IPF. CAT[31], which includes 8 items with a value of 0 to 5 for each item, is a self-assessment questionnaire commonly used in COPD evaluation. Because of the similarity of assessment symptoms, it was adopted in this study. SF-36[32], which includes 36 items in 8 domains, is a universal scale for the assessment of health impairment in a wide range field. SGRQ[33], with 50 items in 3 domains, is widely adopted to assess health impairment for respiratory diseases. The total scores of SGRQ and SF-36 will be counted by weighting of each item. ATAQ-IPF is an IPF-specific questionnaire to assess the HRQoL for IPF patients. There are 13 domains and 74 items with a score of 1–5 for each item in ATAQ-IPF[34]. All the questionnaires will be completed by patients themselves. Patients should choose an option which is most consistent to their current condition for each item. If necessary, the researchers could provide help. Then, the researchers complete scoring.

Safety outcomes

We will also evaluate the safety of interventions in this study. Safety outcome measures, including routine blood, urine and stool tests, liver and kidney function tests, and electrocardiography, will be examined. Any adverse events will also be recorded and managed according to degrees of damage at any time they occur during the treatment period. Then, we will also report to ethics committee for further management. Based on our previous studies, the possible adverse events are transient gastrointestinal discomfort without need to intervene.

Pulmonary function, routine blood, urine and stool tests, liver and kidney function tests, and electrocardiography will be tested and recorded at baseline(week 0), 6 months after treatment(week 26), and the end of treatment (week 52). 6MWT, clinical symptom and signs, MMRC, CAT, SF-36, SGRQ, and ATAQ-IPF will be completed and recorded at week 0, week 13, week26, week 39 and week 52 in the process of trial.

Quality control

To help to improve the quality of research, different quality control measures will be adopted throughout the whole process. Before the study, a research team including clinicians, statistician, ethicist, pathologist, radiologist, has been set up to discuss and form the study protocol. And standard operating procedures (SOPs) for each step of the trial, such as registration, recruitment, and visit for all the enrolled patients, have also been formulated by the research team to ensure the accuracy and completeness of the obtained data in the trial. Every researcher in each center will be trained on the SOPs. The research procedures, completion and normalization of case report forms (CRFs) in each center will also be examined periodically by independent researchers, which is another important means to help improve research quality.

Data management and statistical analysis plan

Statistical analysis will be conducted both in the intent-to-treat (ITT) and pre-protocol (PP) data. ITT analysis will be applied to analyzing the safety data. All the data from any included patients will be analyzed regardless of their withdrawal from the trial. The PP analysis will be adopted to assess the efficacy of the interventions. If data permit, sub-group analysis will also be performed to help clarify the therapeutic effect of interventions.

All the *P* values will be set as two-tailed with a significant level of 0.05. Measurement data will be shown with mean ± SD, median, inter-quartile range. Count data will be presented by frequency or composition ratio. Analysis of variance (ANOVA) will be used to test for differences of continuous variables, with the chi-square test for categorical variables. If necessary, paired t-test will be applied to intra-group comparison data with normal distribution and homogeneous variance, and Wilcoxon signed-rank sum test will be used for non-normal distribution or uneven variance. Repeated-measures ANOVA will be used to test continuous response variables that are measured at more than two time points for the same patient, such as 6MWT, clinical symptoms and signs, mMRC and HRQoL. To improve the quality of data, all the data management and statistical analysis will be conducted by the Jiangsu Famous Medical Technology Co., Ltd. in Nanjing, China.

Anticipated Results

Based on our previous study, it is hypothesized that JHG will reduce the frequencies of acute exacerbations, improve exercise capacity, pulmonary function, quality of life, delay the disease progression-free. High-level evidence-based support for traditional Chinese medicine in idiopathic pulmonary fibrosis will also be obtained in this study.

Discussion

TCM has a long history and certain efficacy in the treatment of respiratory diseases. However, there was still no consensus for disease name and core pathogenesis of IPF in TCM, which also limits the clinical application. We have also conducted abundant researches in TCM for IPF. Based on the summary of literatures and clinical experience, we hold that IPF should be treated referring to *feiwei* or *feibi* in TCM[35].

We have also conducted an exploratory trail to evaluate the efficacy and safety of TCM treatment based on syndrome differentiation preliminarily. The results preliminarily clarified the efficacy and safety of TCM treatment based on syndrome differentiation and provide evidence-based support for TCM in IPF. However, the interventions were given according to the different patterns of syndrome differentiation. It may be difficulty for clinical application, especially for Non TCM doctors. For TCM, treatment based on syndrome differentiation has been the critical method for thousand years. In general, TCM doctors will discriminate different patterns of syndromes first according to clinical performance and characteristics. However, clinical performance and characteristics are atypical, which would limit TCM syndrome

, which will limit the level of evidence. Therefore, to obtain

high-level evidence-based support and apply conveniently, the further confirmatory study for core TCM pathogenesis and Chinese medicine is urgent. As we also know, this is the first multi-centers large-sample randomized controlled trial to clarify the efficacy and safety of Chinese herbal medicine.

In recent years, different studies have shown the efficacy and safety of TCM for IPF[36, 37]. Most of them were small-sample study with a deficiency of standard design and research procedures for high-level evidences. Evidence-based supports of TCM for IPF have not been well presented. The clinical application has also been limited. In view of these deficiencies, we adopted a design of standard RCT based on the discussion and conclusion of the previous studies. The international standard study procedure, such as trial registration, patient enrollment and follow-up have also been adopted. To further improve the quality of study, related SOPs have also been formulated. In the future study process, the implementation of SOPs will be examined and discussed periodically. If necessary, we will adjust the part of unsuitable contents according to the actual state. We believe that, this study will also provide some references for the TCM standard researches.

Our previous study has revealed the possible active components and potential targets for JHG in the treatment of IPF[38]. A total of 136 compounds from JHG and 265 potential targets have been found. The compounds could exert synergistic effect by regulating these similar targets probably. JHG could also ameliorate pathological changes and collagen deposition in bleomycin-induced pulmonary fibrosis rats[23]. And inhibited NADPH oxidase 4 (NOX4) levels and increased the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) in lung tissues could also be found. In vitro, transforming growth factor β1 (TGF-β1)-induced differentiation of fibroblasts could also be significantly inhibited by JHG. So, we concluded that, JHG may show long-term effects in bleomycin-induced pulmonary fibrosis rats. The clinical efficacy of JHG will also be confirmed by the results of this study.

However, there are still some limitations for this study. This study aims to the core TCM pathogenesis and Chinese medicine for IPF. TCM treatment based on syndrome differentiation is not taken into account. The actual advantages of TCM, such as individualized treatment, will be discounted. However, it is unavoidable under the current research conditions. Combined with studies with other design types, such as cohort study, the advantages of TCM may be presented better at different levels.

Based our previous research, this study will confirm the hypothesis that JHG could reduce acute exacerbation, improve exercise capacity, delay disease progression, improve pulmonary function and quality of life for IPF patients with sound safety. The results will provide high-level evidence-based supports for TCM in the treatment of IPF. The study design will also provide critical references for TCM studies on core pathogenesis.

Abbreviations

6MWD: 6-minute walking distance; AE: acute exacerbation; ANOVA: Analysis of variance; ATAQ-IPF: A Tool to Assess Quality of life in IPF; CAT: COPD assessment test; DLCO%: diffusing capacity percentage

acity; HRQoL: health-related quality of life; ILD: interstitial lung

disease; IPF: idiopathic pulmonary fibrosis; JHG: Jin-shui Huan-xian Granule; mMRC: modified Medical Research Council; RCT: randomized controlled trial; SF-36: 36-item short-form health survey; SGRQ: St. George's respiratory questionnaire; SOPs: standard operating procedures; TCM: traditional Chinese medicine;

Declarations

Ethic statement

The protocol has been reviewed and approved by Ethics Committee of the First Affiliated Hospital of Henan University of traditional Chinese Medicine with an ID of 2019HL064-01. All the included patients will provide written informed consent before enrollment.

Trial status

This study has been conducted according to final study protocol with ID of 2019.08.06.1.0.1.0 and data of Aug 6, 2019. The enrollment began at Sep 1, 2020. At the moment of manuscript submitting, 103 IPF patients have been enrolled into this study and recruitment is in progress. All the enrollment will be completed before Sep 30, 2022. The whole study will be completed before Dec 31, 2022.

Competing interests

The authors declare that they have no competing interests.

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Contributions: (a) Conception and design: Jian-sheng Li, Xue-qing Yu; (b) Administrative support: Xue-qing Yu; (c) Provision of study materials or patients: Xue-qing Yu, Wei Zhang, Chengjun Ban, Jihong Feng, Lei Wu, Xuechao Lu, Limin Zhao, Yong Meng, Yong He, Weixian Luo; (d) Collection and assembly of data: Shu-guang Yang and Yang Xie; (e) Data analysis and interpretation: Xue-qing Yu, Shu-guang Yang; (f) Manuscript writing: Xue-qing Yu, Shu-guang Yang, and Jian-sheng Li; (g) Final approval of manuscript: All authors.

Data Availability. Data Availability is not applicable for this article as no data sets have been generated or analyzed during the current stage.

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Figures

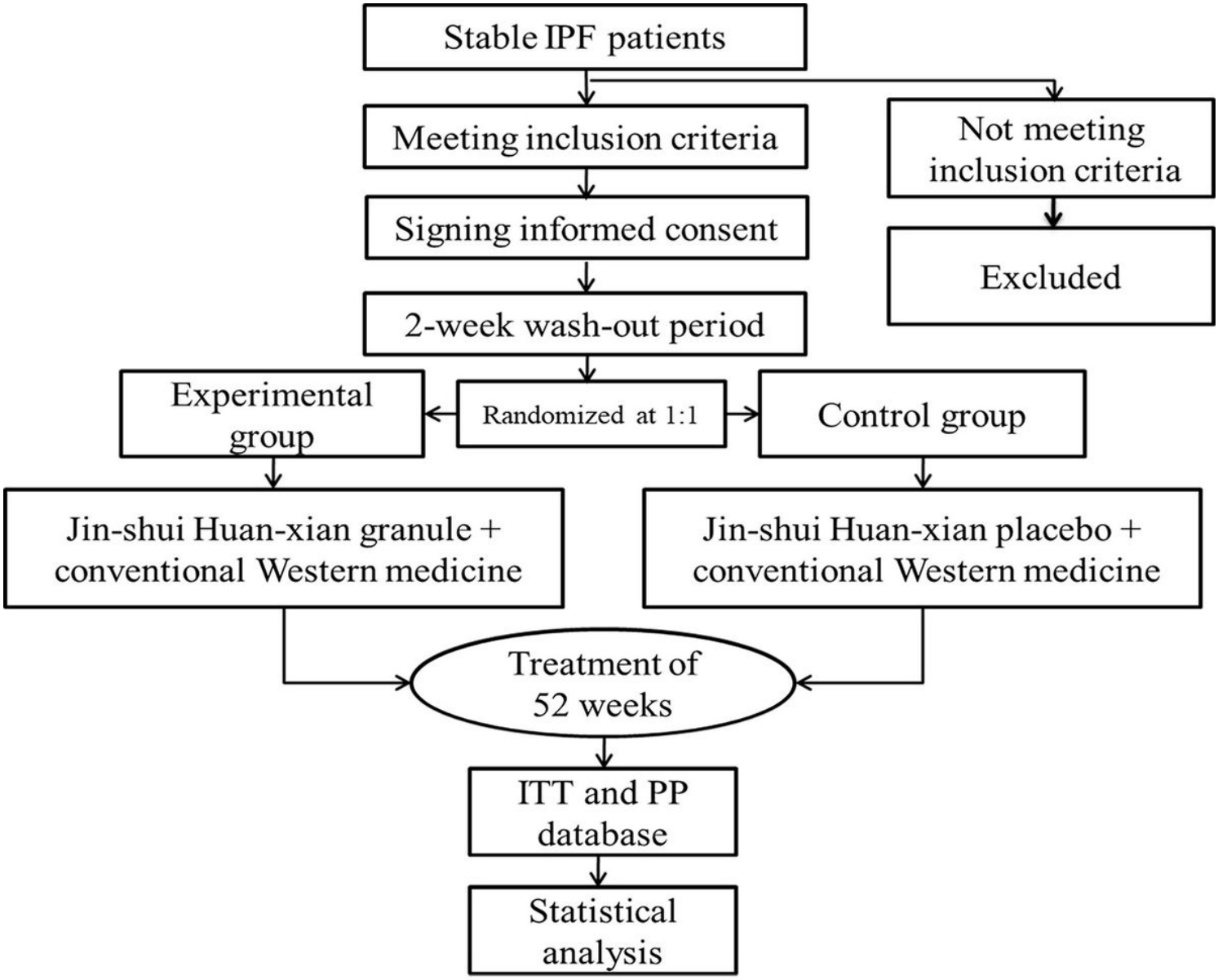

Figure 1

The whole study flow-chart could be found Figure 1.

	STUDY PERIOD					
	Enrollment	Allocation	Post-allocation			
TIMEPOINT*	-2 weeks	0	13 weeks	26 weeks	39 weeks	52 weeks
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
[Jin-shui Huan-xian granules for experimental group]		←	—	—	—	→
[Jin-shui Huan-xian placebo for control group]		←	—	—	—	→
ASSESSMENTS:						
[Acute exacerbations]		X	X	X	X	X
[FVC]		X		X		X
[DLCO%]		X		X		X
[FEV1]		X		X		X
[6MWT]		X	X	X	X	X
mMRC		X	X	X	X	X
Clinical symptoms and signs		X	X	X	X	X
CAT		X	X	X	X	X
SGRQ		X	X	X	X	X
SF-36		X	X	X	X	X

Figure 2

The whole procedures for each patient could be found in figure 2.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITTCMExtension2018checklist.docx