

Traditional Chinese Medicine (Xiao Tan San Jie Granule) for Covid-19 Patients in Rehabilitation Stage: Study Protocol for a Randomized Controlled Trial

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Study protocol

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Abstract

Background: The Corona Virus Disease 2019 (Covid-19) caused pandemic all over the world. As more and more patients gradually are recovering from Covid-19, they still have some symptoms like short of breath, cough, and phlegm. how to improve their quality of life and shorten the rehabilitation time is still no widely recognized clinical program. In this study, we designed Xiao Tan San Jie (XTSJ) Granule based on traditional Chinese medicine (TCM) theory and assess its efficiency and safety during rehabilitation stage of Covid-19 patients.

Method/Design: This study is a 12-week, randomized, double-blinded, controlled, clinical trial that will include 132 Covid-19 patients. Eligible participants will be randomly assigned to XTSJ granule group or placebo group. Participants will receive 28 days treatment. The primary outcome assessment is scores of lung CT scan at week 2 and week 4. The secondary outcome assessment includes pulmonary function test, scores of Visual Analogue Scale (VAS) of Covid-19 symptoms, Scores of Qi Deficiency and Phlegm Stasis syndrome scale, Scores of St. George's Respiratory Questionnaire (SGRQ) at week 2 and week 4.

Discussion: In TCM theory XTSJ granule has a regulate effect on respiratory function, lung infection, cough and phlegm which has the potential treatment effect on COVID19 patients. This study will provide initial evidence regarding the efficacy and safety of XTSJ granule for Covid-19 patients in rehabilitation stage.

Trial registration: This study was prospectively registered on Chinese Clinical Trial Registry(number: ChiCTR2000031672). Registration date: April 6,2020.

Background

The Corona Virus Disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in Wuhan, Hubei province of China [1]. The general symptoms include fever, fatigue, dry cough, and gradually breathing difficulties. It presents pulmonary consolidation in pathology. The imaging shows multi-lateral or multi-lobe infiltration [2]. After the outbreak occurred, China quickly responded to the pandemic, established sheltered hospitals, implement strict quarantine, and issue a diagnosis and treatment plan. The number of confirmed cases was gradually decreasing and new cases of each day was less than 10 since 17, March. The current outbreak has been clearly controlled. And the recovery rate is getting higher and higher [3, 4]. However, patients discharged from hospital still have different degrees of lung dysfunction or interstitial lung disease, and therefore certain degrees of respiratory impairment [5, 6]. The prognosis and recovery of patients has profound impact on quality of life and economic burden of individuals, which is worthy of same attention. With a deeper understanding of the disease and rich experience in diagnosis and treatment, we focus not only on the treatment of the Covid-19 but also how to help patients recover from the sequela of the disease.

Since the outbreak of Covid-19, traditional Chinese medicine (TCM) has been playing an important role in the prevention and treatment. Some studies showed it could effectively reduce the disease progress rate

from mild to severe and alleviate even cure the typical symptoms [7, 8]. It has a long history to apply Chinese medicine in rehabilitation [9], which accumulated abundant experiences. Chinese medicine in rehabilitation includes a variety of treatments like Chinese Herbs, acupuncture, physical therapy et al [10, 11]. This study aims to evaluate the effectiveness and safety of XTSJ granule for patients ever infected by Covid-19 and currently are in the rehabilitation stage. This rigorous designed randomized controlled trial (RCT) will provide an evidence with high level certainty regarding the value of TCM for controlling the epidemic and managing sequelae from Covid-19.

Method/design

Design

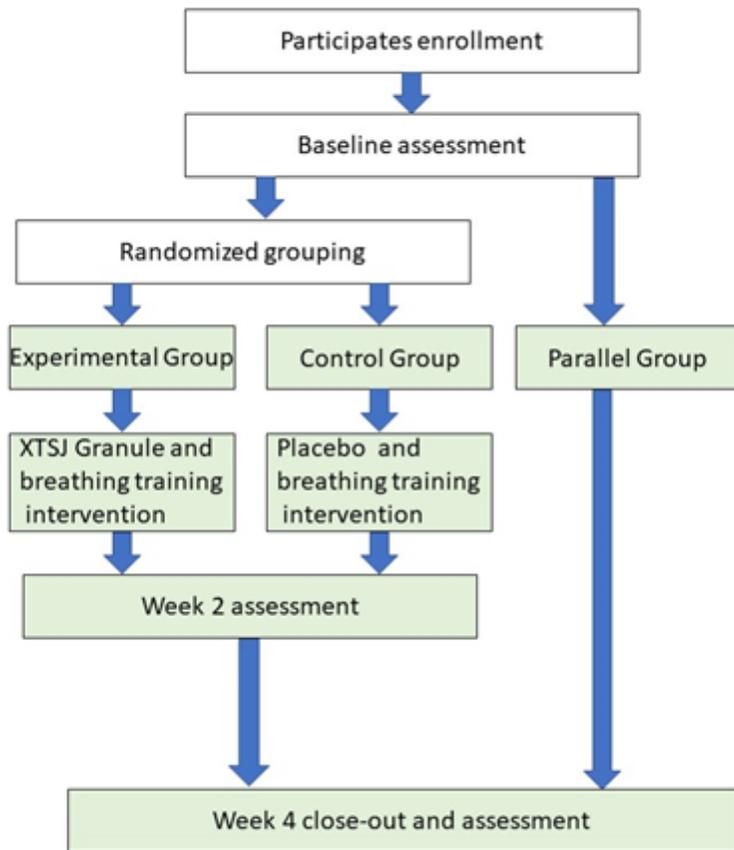
This study is designed as a randomized, double-blind, multi-center, placebo-controlled trial. All participants will be recruited and followed by three medical centers (ChiBi, DongHu, XiHu hospital) from HuangGang, China. Informed consent should be obtained from eligible participants before randomizing them into either XTSJ granule or placebo group. Both groups will receive the same respiratory training as the basic treatment. Besides, patients who don't consent to randomization but are strongly eager to receive treatment will be included in a nonrandomized XTSJ granule group.

The study's schedule and flow chart is shown below(Tables 1 and 2).

Table 1
Schedule of Recruitment, Intervention, and Assessment.

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	
TIMEPOINT	-1w	0	2w	4w
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTION:				
Control				
Experimental				
Pharrell Observation				
ASSESSMENTS:				
Participant battery	X			X
Informant battery	X			X
Lung CT scan		X		X
Pulmonary function		X		X
Scores of scales		X	X	X

Table 2. Study Flow Chart.



Ethics

This study has been approved by the Ethics Committee of Beijing University of Chinese Medicine (No: 2020BZHYLL0111) in accordance with the principles of the Declaration of Helsinki (2013 version). Each eligible patient must sign a written informed consent before they are enrolled in the study. Participants will be informed in details about the risks and benefits of participating in this trial.

Sample size calculation

This is a pilot study. The parameters for further sample size calculation in future expanded scale studies will be derived from the results of this trial. Feasibility including acceptability, efficiency and safety for XTSJ granule will be explored. Based on the principle of precision and efficiency, the sample size of 55 per group was planned in this study [12]. Assuming the possible loss to follow-up rate is 20%, the total sample size will be 132, i.e. 66 patients for each group. We prepared 75 packages (1 package for each person) of drugs for each group to guard against the possible wastage of drugs or packing.

Randomization

An independent clinical research institution—GCP ClinPlus Co., Ltd. (GCP for short) (Beijing) company will generate the random sequence using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). Block randomization will be used to maintain the balance between groups in each center. The random sequence will be preserved by GCP ClinPlus Co., Ltd. If an emergency event occurs during the trial, the blinding could be uncovered with the consent of principal investigator of this study. Formal unblinding will be performed by GCP company once the trial ended.

Non-randomization Group

For patients who don't consent to randomization but are strongly eager to receive treatment, as this situation could reflect the real clinical scenario in future, we recruit them into the nonrandomized XTSJ granule group.

Blinding

This study is a double-blind RCT. The number of group and treatment will be sealed in envelop separately in emergency letter. The treatment and group information also will be blinded to both participates and investigators until the entire study is completed. The placebo was made as same appearance as the XTSJ granule. Both active drug and placebo are provided by Guangdong Yifang Pharmaceutical. The Active drug and placebo use the same box and label. The drug administrator will receive standardized training so that he can instruct patient clearly about the way to take the medicine. The evaluation of clinical efficacy was done by independent research members without knowing of the allocation information.

Diagnostic criteria

Discharge Criteria of Covid-19 pneumonia is based on Covid-19 Pneumonia Diagnosis and Treatment Program (Trial Version 7) [2]. The patients who meet the below criteria can be discharged.

- (1) body temperature returned to normal for more than 3 days.
- (2) respiratory symptoms improved significantly.
- (3) lung imaging showed significant improvement of acute exudative lesions.
- (4) Nucleic acid was tested negative from sputum, Nasopharyngeal swabs or other respiratory tract specimens at least two consecutive times (sampling time at least 24 hours apart).

Diagnostic criteria for TCM syndrome differentiation

Qi deficiency and phlegm stasis syndrome: Qi deficiency and phlegm stasis syndrome of Covid-19 pneumonia refers to "Guiding Principles of Clinical Research on Traditional Chinese Medicine and New Drugs" and relevant literatures. Diagnose is made meeting at least three main symptoms and three secondary symptoms below, combining with tongue and pulse.

- (1) Main symptoms: shortness of breath, cough and sputum, fatigue, sweating, defecation weakness.

(2) Secondary symptoms: bloating, belching, anorexia, vomiting, loose stools, insomnia.

(3) Tongue and pulse: Pale or dark red tongue or with ecchymosis, greasy tongue fur, deep-feeble pulse, or small-uneven pulse.

Inclusion criteria

(1) Has diagnosis history of Covid-19 pneumonia.

(2) Meet the discharge criteria of "Covid-19 Pneumonia Diagnosis and Treatment Program (Trial Version 7)".

(3) Meet the criteria of Qi deficiency and phlegm stasis syndrome in TCM.

(4) Aged between 18–70 years old.

(5) Lung CT scan shows the lesion is not absorbed within 14 days, scores ≥ 2 .

(6) Can understand and sign informed consent.

Exclusion criteria

(1) Patients with severe primary and / or secondary cardiovascular, cerebrovascular, urogenital, endocrine, digestive, neurological and hematological diseases, tumors, or tuberculosis.

(2) Patients with pulmonary hypertension, congestive heart failure, deep vein thrombosis, unstable fractures, or other diseases.

(3) Those who have participated or are participating in other clinical trials within one month.

(4) Patients with mental disorders who cannot express their feelings.

(5) Female patients during pregnancy, lactation, or pregnancy preparation period.

(6) Other situations that cannot be included in this study.

Termination criteria

Participants have the right to discontinue to be investigated anytime even without any reason. subject withdrew from the study might due to dissatisfaction of treatment, intolerance of treatment, personal reasons, or economy issues et al.

Intervention

The participates in both experimental group and control group are administrated respiratory training as basic rehabilitation treatment following Covid-19 Pneumonia Rehabilitation Program for Discharged Patients (Trial)[13]. The medicine intervention will last for 28 days. Investigators will distribute medicine to patients every two weeks. The investigator should record the amount of distributed, taken and returned

medicine. Medication rate (actual dose/predicted dose) < 80% or > 120% is considered as poor compliance. The investigator should timely record all required information on the case report form.

(1) Xiao Tan San Jie(XTSJ) granule: Huangqi (Astragalus) 20 g, Hongjingtian (Rhodiola) 15 g, Xuanshen (Scrophulariaceae) 15 g, Zhebei (Fritillaria) 20 g, Muli (Raw oyster) 30 g, Dilong (Earthworm) 10 g, Jiangcan (Bombyx Batryticatus) 10 g, Haigeqiao (Concha meretricis sea cyclinae) 15 g, Dongguazi (Winter melon seed) 20 g, Chuanxiong (Ligusticum chuanxiong hort)15 g, Ezhu (Curcuma aeruginosa Roxb) 15 g, Taoren (Semen Persicae) 10 g, Jiegeng (Platycodon grandiflorus) 10 g, Baijiezi (Semen sinapis) 6 g, Tinglizi (Eruca sativa Mill) 10 g. The medicine which is made into granules (14.5 g per bag) is dissolved in warm water, and will be taken two times per day for 28 days.

(2) Placebo granule: 5% XTSJ, lactose, maltodextrin and food coloring. It is basically as the same as the XTSJ granule in terms of traits, color, and smell. It will be dissolved in warm water and be taken two times per day for 28 days.

(3) Respiratory training in Covid-19 Pneumonia Rehabilitation Program for Discharged Patients (Trial):

a. ACBT [14]: ACBT is a cycle of breathing control (BC), thoracic expansion exercises (TEE, bigger deep breaths), and forced expiration technique (FET, huffing). BC is relaxed normal breathing using the lower chest. This helps to relax the airways for the next stage of deep breathing. TEE are three-to-four deep, full breaths where your lungs are slowly filled to full expansion. Hold your breath for 1–2 seconds, then exhale passively and easily. The FET is a combination of breathing control and one or two forced expirations (FET that should be performed by opening your mouth, keeping the back of your throat open and breath out sputum). Pay attention to cover up mouse using mask.

b. Breathing pattern training: It Includes adjusting breathing rhythm (aspiration: exhalation = 1: 2), abdominal breathing training, and lip contraction breathing training, etc.

c. Respiratory rehabilitation exercises: It includes neck flexion and extension, chest expansion, turning, waist rotation, side body, squatting, leg raising, leg opening, ankle pump and other series of exercises according to the physical condition of the patient.

(4). Combination therapy.

a. If the participant has other diseases at the same time, and there is not necessary to terminate the previous medicine or treatment.

b. Participants are not allowed to take other Chinese and Western medicines which is special for the recovery stage of Covid-19, or Chinese and Western medicines that might have interaction effects on the efficacy of XTSJ granule.

c. The participants should report detailed information about the concomitant medication to investigators during the trial. The investigators should record and explain it in the case report, including the disease

name, medicine, dose, usage, time of use, etc.

Outcome assessment

Primary Outcome

(1) Scores of lung CT scan

Two senior radiologists read and analyze the CT performance and score it independently without aware of the allocation information. When the conclusions are not consistent, they should reach an agreement through consultation and review by the cardiothoracic doctor with the professional title.

(2) CT performance analysis includes (Table 3):

Table 3
Lung CT Scan.

Location		Scores	Feature	Location		Scores	Feature		
Right lung	Upper lobe		Ground-glass opacities <input type="checkbox"/>	Left lung	Upper lobe		Ground-glass opacities <input type="checkbox"/>		
			Consolidation <input type="checkbox"/>				Consolidation <input type="checkbox"/>		
			Fibrosis <input type="checkbox"/>				Fibrosis <input type="checkbox"/>		
	Middle lobe		Ground-glass opacities <input type="checkbox"/>					Fibrosis <input type="checkbox"/>	
			Consolidation <input type="checkbox"/>						
			Fibrosis <input type="checkbox"/>			Lower lobe		Ground-glass opacities <input type="checkbox"/>	
	Lower lobe		Ground-glass opacities <input type="checkbox"/>				Consolidation <input type="checkbox"/>		
			Consolidation <input type="checkbox"/>				Fibrosis <input type="checkbox"/>		
			Fibrosis <input type="checkbox"/>						
	Others: Pleural effusion <input type="checkbox"/> Pneumothorax <input type="checkbox"/> Tumor <input type="checkbox"/>					Others: Pleural effusion <input type="checkbox"/> Pneumothorax <input type="checkbox"/> Tumor <input type="checkbox"/>			

(1) the location and density of the lesion: Record the location of the lesion according to the lung lobes (left upper lobe, left lower lobe, right upper lobe, right middle lobe, right lower lobe), and record whether there is any lesion away from pleural. The Density of lesion is recorded as ground glass density or partially consolidated ground glass density.

(2) The number of lung lobes involved in lesions.

Use semi-quantitative method for scoring: Use the visual method to evaluate the involvement of each lobe in units of a single lobe (0 points, no involvement; 1 point, < 5% involvement; 2 points, 5% ~ 25%; 3 points, 26% ~ 49%; 4 points, 50–75%; 5 points, > 75% involvement), the sum of all lung lobes' scores is recorded as a total score, ranging from 0 (no involvement) to 25 (maximum involvement).

(3) Primary outcome will also be evaluated by following categories:

a. High improvement: CT score decreased by $\geq 70\%$ ((CT scores before treatment-CT scores after treatment)/CT scores before treatment X100%).

b. Moderate improvement: CT score reduced by $\geq 30\%$.

c. No improvement: CT score decreased by less than 30%.

The observation is made before the intervention and on the fourth weekend of the intervention.

Secondary Outcomes

(1) Pulmonary function assessment: (vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), maximal voluntary ventilation (MVV), Maximal mid-expiratory flow curve (MMF) (Table 5).

Table 4
Scores of Qi Deficiency and Phlegm Stasis Syndrome Scale.

Main Symptoms	0 points	2 points	4 points	6 points
Chest tightness	Not at all <input type="checkbox"/>	Slightly <input type="checkbox"/>	Obviously, sometimes sign-like breath <input type="checkbox"/>	Severely, sign all the time <input type="checkbox"/>
Shortness of breath	Not at all <input type="checkbox"/>	After fatigue <input type="checkbox"/>	After normal activities <input type="checkbox"/>	After a little activity even in resting state <input type="checkbox"/>
Cough	Not at all <input type="checkbox"/>	Occasionally <input type="checkbox"/>	Often <input type="checkbox"/>	Frequently and severely <input type="checkbox"/>
Phlegm	Not at all <input type="checkbox"/>	Occasionally and small amount <input type="checkbox"/>	Sometimes and not too much <input type="checkbox"/>	Frequently and large amount <input type="checkbox"/>
Fatigue	Not at all <input type="checkbox"/>	Slightly, can finish moderate physical activities <input type="checkbox"/>	Sometimes, hard to finish daily activities <input type="checkbox"/>	Continually even at rest, cannot finish daily activities <input type="checkbox"/>
Sweating	Not at all <input type="checkbox"/>	Sweating slightly after activities <input type="checkbox"/>	Sweating after light activities <input type="checkbox"/>	Sweating heavily even at rest <input type="checkbox"/>
Weak Bowel movements	Not at all <input type="checkbox"/>	Slightly difficult bowel movement, occasionally bloating <input type="checkbox"/>	Moderately difficult bowel movement, sometimes bloating <input type="checkbox"/>	Difficult bowel movement, always bloating <input type="checkbox"/>
Secondary symptoms	0 points	1 point	2 points	3 points
Bloating	Not at all <input type="checkbox"/>	Slightly <input type="checkbox"/>	Often, especial after eating <input type="checkbox"/>	Severe all the time <input type="checkbox"/>
Belching	Not at all <input type="checkbox"/>	Occasionally <input type="checkbox"/>	Sometimes <input type="checkbox"/>	Frequently <input type="checkbox"/>
Scores:				
Investigator: Date ☐ year mm dd				

Main Symptoms	0 points	2 points	4 points	6 points
Anorexia	Not at all <input type="checkbox"/>	Decrease of appetite, normal food intake <input type="checkbox"/>	Poor appetite, food intake reduces 1/3 <input type="checkbox"/>	No appetite, food intake reduces over 1/2 <input type="checkbox"/>
Nausea and vomiting	Not at all <input type="checkbox"/>	Occasionally <input type="checkbox"/>	Often <input type="checkbox"/>	Frequently <input type="checkbox"/>
Diarrhea	Not at all <input type="checkbox"/>	Occasionally <input type="checkbox"/>	Frequently, especially after eating greasy food <input type="checkbox"/>	All the time <input type="checkbox"/>
Insomnia	Not at all <input type="checkbox"/>	Occasionally <input type="checkbox"/>	Often <input type="checkbox"/>	All the time <input type="checkbox"/>
Tongue and Pulse				
Scores:				
Investigator: Date ☐ year mm dd				

Table 5
Pulmonary Function Test.

Spirometry	Actual
Vital Capacity (VC)	
Forced Vital Capacity (FVC)	
Forced Expiratory Volume in One Second (FEV ₁)	
Maximal voluntary ventilation (MVV)	
Maximal Mid-expiratory Flow curve(MMF)	

Observation start before the intervention and on the fourth weekend of the intervention.

(2_ Change of symptoms of Covid-19: Scores of Visual Analogue Scale (VAS) of Covid-19 symptoms (Table 6).

Table 6
Visual Analogue Scale (VAS) of Covid-19
Symptoms.

Symptom severity	1	2	3	4	5	6	7	8	9	10
	(no symptom) (moderate) (a great deal)									
Fever										
Cough										
Fatigue										
Congestion										
Running nose										
Sore throat										
Muscle or body aches										
Nausea or vomiting										
Diarrhea										

Observation is made before the intervention and on the second and fourth weekend of the intervention.

(3) Improvement of TCM symptoms: Scores of Qi Deficiency and Phlegm Stasis syndrome scale (Table 4).

Observation is made before the intervention and on the second and fourth weekend of the intervention.

(4) Improvement of quality of life assessment: Scores of St. George's Respiratory Questionnaire (SGRQ) [15].

Observation is made before the intervention and on the second and fourth weekend of the intervention.

Safety outcomes

The Safety outcomes will be performed before intervention as baseline, and on the second and fourth weekend of the intervention.

(1) Hematuria test.

(2) Electrocardiogram (ECG).

(3) Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT).

(4) Renal function: blood urea nitrogen (BUN), uric acid (UA), and β 2-microglobulin.

Adverse events

(1) Observation and records of adverse events: Once an adverse event occurs, the investigator should record the type of the adverse event, time of occurrence, severity, duration, measures which are taken and the outcome. Investigator also should make a preliminary judgment about the relevance of adverse events and treatment medicine.

(2) Management of adverse events: Once an adverse event occurs, it must be dealt with as soon as possible to ensure the life and health safety of the participants. At the same time investigator should report to the main investigator, main researcher and ethics committees, sponsors within 24 hours.

(3) Follow-up of adverse events: All adverse events will be followed up until they are properly resolved.

Statistical analysis

Center for evidence-based Chinese medicine in Beijing University of Chinese Medicine (BUCM), as the independent data management and statistical analysis department, will perform data analysis for this study. The data collected by clinical researchers from three medical centers (ChiBi, DongHu, XiHu) will be sent to another independent statistic center (DAP Software). Data entry procedure will use DAP EDC system with audit trail function to ensure any revisions for database could be documented and tracked.

Statistical SPSS 20.0 (IBM Corp., Armonk, NY.) and R 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) will be used for data analysis. The primary analysis is to be conducted in the intention-to-treat (ITT) population. All statistical tests are 2-sided tests, and $P < 0.05$ will be considered statistically significant. Continuous data will be presented with mean \pm SD, and n (percentage) for categorical data. We will evaluate the effectiveness mainly by primary outcome through both continuous and categorical data type. For continuous type, considering that the baseline and site are essential to the change of lung CT score, analysis of covariance (ANCOVA) using baseline score and site as covariates will be performed to analyze the score change from baseline to week 4. Interactions between site and group will also be tested. Mean difference and 95%CI will be also presented. For categorical type, the distribution of three improvement types (high, moderate, and no) between groups will be compared using Wilcoxon Rank Sum test. The difference of rate for each category between groups accompanying with 95% will be also calculated.

As for the analyses for secondary outcomes, descriptive and inferences methods will depend on the data type and distribution. For continuous data, when normal distribution is met, student t test will be used and Wilcoxon Rank Sum test could be the alternative when the normality presumption is violated. For categorical data, Chi-square test or Fisher exact test will be performed. For ranked data, we will use Wilcoxon Rank Sum test to compare the difference between groups.

Quality control

(1) During the screening and enrollment of participants, investigator should control the mixed factors and strictly follow the inclusion criteria.

(2) During the process of trial, participants should be managed and tracked properly to ensure that all participants can complete the trial procedures as required.

(3) Data is double-blind entered to ensure the quality of data entry.

(4) Raw data is backed up to prevent data corruption.

Discussion

After discharge, patients with Covid-19 are left with varying degrees of lung function damage or interstitial pneumonia, and even irreversible pulmonary fibrosis. The symptoms still exist for long time including fatigue, anorexia, shortness of breath and coughing, which seriously decrease the prognosis quality of patients. There is still no evidence and confidence to use any current available medicine to address above problems.

From the perspective of TCM, these symptoms could be differentiated as the syndrome of qi deficiency and phlegm coagulation. This study uses XTSJ granule to facilitate the progress of patients' recovery from the Covid-19. As far as we know, this trial is the first RCT which mainly focuses on the treatment of Covid-19 patients during convalescence. Therefore, better evidence is expected to be produced to support future clinical decisions on management of same kinds of patients.

We report transparently and will update our protocol accordingly if any. More detailed contents about statistical analysis plan will also be reported by publication or attachment as an independent document when we submit the final results.

Current Status

The current protocol version is v1.0 which was finalized on April 1,2020. After registration and carefully drafting, we submitted this protocol on Sep.17 2020. At the time of submission, 129 patients had been recruited. The expected total sample size is 132. The recruitment started from April 20, 2020 and was estimated to be completed on Oct.1,2020.

Declarations

Ethics approval and consent to participate

Ethics Committee of Beijing University of Chinese Medicine approved this project No. 2020BZHILL0111. Written, informed consent including publication of identifying images and clinical details will be obtained from all participants.

Availability of data and materials

The materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes after the final research article has been published.

Competing Interests

There is no any conflict of interests about the authorship. The funding part has no role on the study design, carrying out, data management, statistical analysis, interpretation on the results and writing manuscript.

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Authors' contributions

YL, JH(Junwen Han),YZ contributed equally to this paper as co-first authors.

QW, YL, JW, LL(Lingru Li), YZ, YZ designed this protocol; YZ, JH(Jiangming He), GZ, LL(Li Liu), YW prepared the data collection and management. YL, JH(Junwen Han), YZ wrote the protocol. All of the authors have read and approved the final manuscript.

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