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Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter, Randomized, Controlled Trial

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ABSTRACT

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) brings a serious impact on patients' quality of life, and has extremely high morbidity and mortality worldwide. Although there are many therapies being developed to alleviate symptoms and reduce mortality, few studies have supported which treatment method is the best. Traditional Chinese Medicine (TCM) has shown good potential in the prevention and treatment of AECOPD, especially in terms of supplementation and reduction of dosage of Western Medicine and side effects. The purpose of this study is to compare effectiveness of combination of TCM and Western Medicine with conventional therapy alone for AECOPD, and to ensure whether the combined therapy may reduce the use of systemic Glucocorticoid in AECOPD without influencing efficacy.

Methods and analysis: A multicenter, randomized, double-blind, placebo-controlled study was conducted to enroll a total of 360 eligible patients who will be randomized into Integrated Chinese and Western Medicine group A, B, and Western standard Medicine group C. After 5 days of intervention and 1 month of follow-up, the efficacy and safety of Xinjia Xuanbai Chengqi Decoction (XJXBCQ) in patients with AECOPD will be observed. The results of evaluation indicators include: clinical symptoms, biochemical indicators such as blood gas analysis, inflammatory markers, hospitalization time, TCM syndrome evaluation, biological indicators such as airway, intestinal flora sequencing.

Ethics and dissemination: This trail has been approved by the Ethics Committee of

China-Japan Friendship Hospital. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's post-study health status during follow-up.

Trial registration: Chinese Clinical Trial Registry, ID: ChiCTR1800016915. Registered on 3 July 2018.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, Comparative effectiveness research, Traditional Chinese Medicine

Article summary

Strengths and limitations of this study: (1) This study is designed as a randomized, double-blind, placebo-controlled, clinical, critical trial from the perspective of evidence-based medicine, that is considered to be the most definitive research method of treatment evaluation; (2) At the same time, this is a multi-center trial be carried out in four comprehensive Third-grade first-class hospitals across China, which improves the external validity and Representativeness of the sample and reduces the risk of selection bias; (3) Because clinical symptoms are often accompanied by a certain degree of subjectivity , we combine the core symptoms (cough phlegm, defecation, dyspnea) score and TCM syndrome score to ensure scientific objectivity; (4) In order to ensure quality, all staff in the study must complete the training of the standard operating procedures of the research program before recruitment; (5) As the main phase of the program will be performed during the hospital stay, practitioners will be

able to immediately identify and manage adverse reactions and guarantee the safety of participants. Practitioners will maintain good communication with the participants by phone after discharge.

However, the design of the program also has potential limitations, for example, the 5-day treatment period and the 1-month follow-up period are a bit short.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterized by airflow obstruction (FEV1<80% predicted and FEV1/FVC ratio<70%) that is not reversible. COPD is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. In China, the prevalence of COPD in people aged 40 years or older is 13.7%[2], more than 1 million people die and more than 5 million people disable of COPD each year.

Acute exacerbation of COPD (AECOPD)[3] is defined as acute worsening of respiratory symptoms(typically dyspnea, cough, increased sputum and/or purulent sputum) in patients with COPD, exceeding normal day-to-day variations and that may require a change in medication even hospitalization. Acute exacerbation is an important factor in the death of patients with COPD[4], and is also the main expenditure portion of medical expenses for COPD patients.

Traditional Chinese Medicine (TCM), with characteristic theory of syndrome differentiation and overall conditioning, implies its potential advantages in the treatment of COPD. TCM syndrome studies find that in addition to symptoms such as cough, phlegm, and wheezing, patients in acute exacerbation period are often accompanied by constipation, abdominal distension, and yellow greasy tongue coating. Based on TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", physicians use the method of Tongfu Xiere to AECOPD patients and usually achieve good results in clinical practice. Xinjia Xuanbai Chengqi Decoction (XJXBCQ), consists of Semen Armeniacae Amarum, Gypsum Fibrosum,

Fructus Trichosanthis, Radix et rhizoma rhei, Scutellariae Radix, Perillae Fructus, Radix Glycyrrhizae Preparata, Rhizoma Fagopyri Dibotryis and Radix Asteris, is evolved from the TCM classical prescription Xuan Bai Chengqi Decoction[5]. It has been widely used in AECOPD patients attached to the heat-phlegm and sthenic-fu syndrome, especially in combination with Western Medicine, not only can reduce the use of antibiotics, glucocorticoid, etc., but also decrease the side effects of modern routine medicine[6]. Despite this, there is not enough evidence to show the efficacy of XJXBCQ on patients with AECOPD. Hence, a more rigorously designed large-scale, multicenter, randomized trial is needed to assess the effectiveness of XJXBCQ on AECOPD. In conclusion, our aim is to conduct a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of XJXBCQ on AECOPD. The results of this trial will provide evidence that the XJXBCQ is an effective prescription for AECOPD. In view of the difficulty in assessing the quality of the decoction, we plan to use the XJXBCQ granules in the trial. The main purpose of this study is to evaluate the clinical symptoms, signs, blood gas analysis, serum inflammatory factors (IL-6[7], TNF-α, CRP[8], PCT), airway and intestinal microbes[9] of AECOPD hospitalized patients with XJXBCQ combined with Western Medicine; The secondary objective was to observe the effect of XJXBCQ combined with Western Medicine on reducing the use of glucocorticoid[10], the mortality, the hospitalized time, the requirement for invasive mechanical ventilation, and the re-admission rate of acute exacerbation within 30 days after discharge.

METHODS

Study design

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial that enrolled a total of 360 patients that will be randomly assigned to one of three groups: Integrated Chinese and Western Medicine Group A, Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. After 5 days of intervention, the effectiveness and safety of XJXBCQ in participants will be evaluated by comparing the various indicators of the three groups, including clinical symptoms, activity, biochemical indicators and biological indicators.

As the leading unit of the research, China-Japan Friendship Hospital is responsible for training the standard operating procedures of researchers and supervising the progress of all clinical sites. Other participating units include: Zhongshan Hospital affiliated to Fudan University, the First Affiliated Hospital of China Medical University, and Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University. Recruitment allocation: 180 cases will be from China-Japan Friendship Hospital, while the remaining three recruit 60 cases respectively. The flow chart of the trial is shown in Figure 1. This study protocol is registered with the China Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=28338). The Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 checklist is shown in Additional file 1.

Participants

Inclusion criteria

Patients must meet all of the following criteria: 1) Meet AECOPD diagnostic criteria; 2) AECOPD severity clinical grade I-II; 3) Comply with indications for antibiotic treatment recommended by *AECOPD Chinese Expert Consensus (Revised 2017)*; 4) Comply with the criteria for the heat-phlegm and sthenic-fu syndrome of TCM; 5) Age 40-80 years old, gender is not limited; 6) Provision of signed, informed consent.

Exclusion criteria

Patients who meet one or more of the exclusion criteria listed below will not be allowed: 1) Patients who with asthma, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer or any other airflow-limited disease with known causes and characteristic pathology; 2) Patients with coronary heart disease, hypertensive heart disease or heart valve disease, etc.; 3) Those need invasive mechanical ventilation; 4) Clinically confirmed or highly suspected pulmonary embolism; 5) Combine with diseases of severe cardiovascular, cerebrovascular, hepatorenal and hematopoietic or primary endocrine system[11]; 6) Those with intestinal obstruction requiring surgical intervention; 7) Pregnant or lactation period; 8) Mentally handicapped; 9) ALT, AST> 1.5 times the upper limit of normal reference or Scr> the upper limit of normal reference; 10) Need to combine immunosuppressant; 11) Taking oral or intravenous antibiotics before screening for more than 3 days in last 3 months; 12) Known to be allergic to the basic therapeutic drugs or other excipients prescribed through the research; 13) Known to be allergic to Chinese herbal medicinal ingredient prescription; 14) Those who have participated in or are participating in other clinical

trials within nearly 3 months; 15) Those who be considered inappropriate to participate in this clinical trial by the investigator.

Sample size

Since this research is an exploratory study, it has not yet relevant data to support the sample size calculation. So we primitively plan to recruit 360 AECOPD patients allocated as the ratio of 1:1:1, 120 per group, according to the objective conditions such as the research period and budget. The purpose is to initially evaluate the therapeutic effect and safety of Xinjia Xuanbai Chengqi Decoction on AECOPD, and provide basic data for further large-scale, multi-center clinical research.

Randomization

A block randomization method will be employed. We will select the appropriate length of the segment and use the SAS statistical software to generate a random sequence of 360 subjects (group A, group B, group C) according to the ratio of 1:1:1, listing the serial number as 001-360. The treatment allocation is that each center will be assigned a consecutive numbered medication on the basis of the random sequence. An independent clinical statistician will keep the random sequence which be saved as a file in a sealed envelope and record the method, process, result of entire produce, so as to be checked if necessary. In case there is a clinical emergency event, the individual's randomized code and group assignment can be identified as quickly as possible through the emergency envelope. Once any envelope has been opened,

whether intentional or not, it should be carefully recorded on the Case Report Form (CRF) and the patient will be withdrawn from the study.

Interventions

Program Description

Volunteers who meet the inclusion criteria will receive an information form and be required to provide written consent to participate in the trial. They will then undergo a physical screening test to determine if there are other comorbidities that may affect the trial. After successful screening, they will participate in the trial, get trial-specific identification (ID) numbers and be assigned to a group according to random sequence. A baseline measurement for each participant is then performed, including clinical symptoms scores and TCM syndrome scores, blood gas analysis (PH, PaO_2, $PaCO_2$), serum inflammatory markers (PCT, CRP, IL-6, TNF-α), induced sputum, stool sample, and so on. The research program flow is shown in Table 1. All outcome measurements will be taken by medical workers who are familiar with the management of these assessments and will be unaware of the participants' group assignments.

All participants will receive Standard Western Medicine treatment follow the *Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2018*, the *Chinese Medical Association Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised 2013)* and the *Accelerated Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD). (Updated 2017)*, including:

General treatment: controlled oxygen therapy, Venturi mask oxygen, NIV if requiring non-invasive ventilation;

Antibiotic: Levofloxacin and Sodium Chloride Injection, 0.5g, iv.gtt, qd;

Bronchodilator[12]: Compound Ipratropium Bromide Solution for Inhalation (Combivent), 500ug, inhal, tid.

Beside the above, Group A will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (2 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules (2 bags at a time, tid). Group B will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (1 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules (2 bags at atime, tid); Group C will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (2 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules Placebo (2 bags at a time, tid). The entire trial will go through 5 days.

Xinjia Xuanbai Chengqi Granules

Xinjia Xuanbai Chengqi Granules is a compound preparation of Chinese herbal medicine. The main components are shown in Table 2.

XJXBCQ Granules (2.5 g/bag, Batch number: 180605) are produced and packaged by Anhui Jiren Pharmaceutical Co., Ltd. that have China Pharmaceutical Production License (Number: Wan 20160083). The results of drug quality testing are consistent with the quality standards. XJXBCQ Granules will be administered orally, two bags at a time, three times a day for 5 days. All herbs were tested to the same standard.

Placebo

The placebo consists of starch without any active ingredient is produced by the same manufacturer as XJXBCQ Granules. It is a dextrin that matches as much as possible the appearance and taste of XJXBCQ Granules. The drug instructions for XJXBCQ Granules and placebo are completely consistent.

Combined medication regulations

Participants are allowed to remain their originally basic treatment taken before recruited; If one's condition deteriorates during the study and need to stay in the ICU or perform invasive mechanical ventilation, we will immediately deal with it; Those who need to adjust the antibiotic due to they can't tolerate LVFX or whose condition have not been alleviated but even aggravated after 3 days of treatment, the antibacterial therapy will be adjusted according to the regulations in *the Chinese Expert Consensus for the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) (Updated 2017)*. The reasons for adjustment of the antibacterial drug program need to be recorded in detail; Taking conventional treatment once right heart failure or heart rhythm disorders happened. In addition, other Chinese or Western medicines for phlegm and cough indications of COPD (except for for patients with COPD long-term basic treatment) should be prohibited.

Outcome measure

Because overall conditioning is the core values of TCM, there is no single indicator could be able to predict patients' recovery to evaluate effect of XJXBCQ Granules; thus, a comprehensive assessment is required to AECOPD [13].

Clinical symptoms (cough, phlegm, defecation, dyspnea) score: We will record the color[14], viscosity and amount of sputum[15] daily during the study. Scoring and grading constipation symptoms according to the severity of constipation score; The severity of dyspnea will be assessed by using a modified British Medical Research Council Respiratory Questionnaire (mMRC).

TCM syndrome score: Refer to *the Guidelines for TCM Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2011)* and *Guidelines for Clinical Research of New Traditional Chinese Medicine for Chronic Bronchitis (2002),* we conduct comprehensive evaluation on cough, phlegm, dyspnea, defecation, abdominal distension, fever from perspective of the heat-phlegm and sthenic-fu syndrome. Efficacy index (n) = [(pre-intervention scores − post-intervention scores)/ pre-intervention scores] × 100%

Clinical recovery: TCM clinical symptoms and signs disappeared or approximately disappeared, TCM scores decreased ≥90%;

Markedly effective: TCM clinical symptoms and signs are significantly improved, syndrome scores reduced ≥70%;

Effective: TCM clinical symptoms and signs are improved, syndrome scores reduced ≥30%;

Invalid: No TCM clinical symptoms or signs significantly improved and even

aggravated, syndrome scores reduced less than 30%.

Blood gas analysis: We will take arterial blood gas analysis (PH, PaO_2, $PaCO_2$) before and after intervention.

Serum inflammatory markers: Serum inflammatory markers include PCT, CRP, IL-6, TNF-α.

Induced sputum and stool sample: Induced sputum and stool sample will be collected at the baseline and Day 6. Due to TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", we also estimate microbial flora in induced sputum and stool sample of participants to explore the pathogenesis of AECOPD at the microbiological level by the 16S rRNA gene sequencing[16] and the whole-genome shotgun sequencing[17].

Theoretical discharge time: The theoretical discharge criteria[18] is: 1) Patients be considered that can adapt to family medicine; 2) patients can accept a stable inhalation therapy about long-acting bronchiectasis, β2 receptor agonist and/or an anticholinergic drug, with or without inhaled glucocorticoids. A short-acting β2 agonist[19] should be administered less than once every 4 hours; 3) Patients should be able to walk indoors if they have not been bedridden before; 4) Eating and sleep is good and not affected by dyspnea; 5) Stand at clinical stability for 12 ~ 24 h; 6) Arterial blood gas analysis should be stable for 12 ~ 24 h; 7) Patients or family members fully understand the correct use of stable period medicines; 8) Follow-up and home care plans have been arranged.

Mortality: All-cause mortality and COPD mortality will be calculated respectively

for the subjects during the study period.

Actual hospitalization time: Hospitalization time = discharge date - admission date + 1.

The proportion of patients requiring invasive mechanical ventilation during hospitalization: The proportion of patients requiring invasive mechanical ventilation during hospitalization = the number of patients with invasive mechanical ventilation during hospitalization / the total patients .

Proportion of patients transferred to ICU during hospitalization: Proportion of patients transferred to ICU during hospitalization = the number of patients transferred to ICU during hospitalization / the total patients.

Re-admission rate within 30 days after discharge: Judgment criteria for re-admission: subjects are hospitalized again due to COPD or other respiratory illnesses, excluding hospitalization for other illnesses or purposes. The follow-up will be finished and not continued if one is judged to be re-admitted to the hospital during the follow-up period. Re-admission rate = re-admitted patients / completed follow-up patients.

Safety assessment

The physical examination will be performed every day from the baseline to end of study. Blood routine, urine routine, liver function, renal function test and electrocardiogram will be performed at baseline and Day 6. Any adverse event occurs during the study will be observed and recorded in detail.

Quality control and data management

Prior to the study, the protocol had been reviewed and revised several times by clinicians, statistics, and methodologists. All staff members of the trial are required to participate in a series of trainings to ensure that the personnel involved fully understand the research protocol and standard operating procedures (SOPs) to guarantee accuracy and completeness of clinical data. Regular monitoring will be conducted by phone and email. All data will first be recorded by the assessor on a paper version of the case report form and then electronically dual-input into the EDC system. The monitor will periodically review the completion and compliance of the CRF. In order to maintain the objectivity of the data, we will ensure that observers and statisticians are unaware of it. The entire process will be monitored by an independent quality inspector. Beijing Qihuang Pharmaceutical Clinical Research Center is responsible for data management.

Statistical analysis

Full Analysis Set (FAS), Per Protocol Set (PPS), and Safety Analysis Set (SS) will be employed. FAS means an ideal set of all subjects (including all subjects randomized into the group and receiving at least one treatment) as close as possible to the principle of intentional analysis. Missing values for major variables, if once failure to observe whole data of case, we will carry-forward the last observation to the absence of test data, and the amount of subjects in each group to evaluate efficacy at the

endpoint will be corresponding to the beginning of trail. PPS refers to all cases that meet the stand protocol, have great compliance, use the trial medicine in the range of 80%-120%, complete the eCRF regulations, the main variables can be measured, the baseline variables are well-preserved, and have no significant violation to the protocol. SS refers to all subjects who accept at least one time treatment after randomization. For the continuous variables, the paired t-test will be used to compare the changes of clinical symptom scores pre- and post-intervention, and the covariance analysis model will be used for comparison between groups. The multiplier method will be used to calculate the quartiles (25%, 50%, 75%) of time from enrollment to events happened, and bilateral 95% confidence interval and the incidence rate at each time point after enrollment will be calculated yet. Kaplan-Meier curves will be plotted using the Log-rank test to compare theoretical hospital stay and actual hospital stay. For the two categorical variables, such as the recurrence rate of laboratory indicator, all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to the ICU during study, and the proportion of re-admission within 30 days after discharge, we will make comparison between groups and calculate the 95% confidence interval using a centrally stratified CMH $\chi 2$ test according to the classification, indicator, time point, quantity and percentage. Statistical analysis will be performed by SAS 9.4 software.

Patient and public involvement

Neither patients nor their family members were involved in the study design. The

results of the studies will be widely distributed in scientific reports as well as academic conferences to benefit policymakers, clinicians and patients.

Ethics and dissemination

This trail has been approved by the Ethics Committee of China-Japan Friendship Hospital. All volunteers will sign the informed consent, which is consistent with the ethical principles set forth in the Helsinki Declaration. Treatment expenses for participants during study will be reimbursed. Data usage will follow the rules of hospital's data oversight committee. Biological samples will be handled following the national guideline on biological waste management and disposal. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's post-study health status during follow-up.

DISCUSSION

Before conducting this experiment, we closely retrieved PubMed, Web of Science, Embase, CNKI (including China doctor/master's theses database and China Proceedings conference full-text database), Wan Fang Data, Vip Journal Integration Platform (VJIP), Chinese BioMedical (CBM) database (Sinomed), etc. and found no definite evidence for effect and safety of Xinjia Xuanbai Chengqi Decoction in the treatment of acute exacerbation of COPD. Therefore, we decide to conduct a multicenter, randomized, controlled clinical trial to closely study its effectiveness and

safety. Due to the lack of evidence on the effectiveness of XJXBCQ, we will apply Chinese medicine combined with Western medicine to treat AECOPD to ensure participants' compliance and ethical considerations, because antibiotics, bronchodilators, and glucocorticoids are first-line treatments to improve acute exacerbation of COPD according to guidelines.

COPD is a common, preventable disease, affecting millions worldwide. It seriously impairs patients' social activities, daily activities and quality of life[20]. The high economic burden of AECOPD to families and societies is growing year by year. The extensive clinical experience of using Chinese medicine in the prevention and treatment of COPD in China shows that Chinese medicine preparations are effective. Due to the complexity of the pathogenesis of COPD, the recent use of combination therapy has attracted more and more attention, providing new prospects for Traditional Chinese Medicine which be considered effective in improving clinical symptoms. TCM possess the advantages of being simple, convenient, efficient, inexpensive, and without serious adverse reactions. A systematic review suggested that Chinese medicine conspicuously improved the prognosis of patients with COPD but lack of high-quality research hinder the development of evidence-based recommendations for clinical practice. Therefore, we design this critical clinical trial, which has the following advantages: (1) This study is designed as a randomized, double-blind, placebo-controlled, clinical, critical trial from the perspective of evidence-based medicine, that is considered to be the most definitive research method of treatment evaluation; (2) At the same time, this is a multi-center trial be carried out

in four comprehensive Third-grade first-class hospitals across China, which improves the external validity and Representativeness of the sample and reduces the risk of selection bias; (3) Because clinical symptoms are often accompanied by a certain degree of subjectivity , we combine the core symptoms (cough phlegm, defecation, dyspnea) score and TCM syndrome score to ensure scientific objectivity; (4) In order to ensure quality, all staff in the study must complete the training of the standard operating procedures of the research program before recruitment; (5) As the main phase of the program will be performed during the hospital stay, practitioners will be able to immediately identify and manage adverse reactions and guarantee the safety of participants. Practitioners will maintain good communication with the participants by phone after discharge. However, the design of the program also has potential limitations, for example, the 5-day treatment period and the 1-month follow-up period are a bit short.

In conclusion, the aim of this study is to answer whether traditional Chinese medicine can supplement and reduce COPD Western medical treatments, reduce frequency of acute exacerbation of COPD, and provide objective data about effectiveness and safety. If the trial is successful, it will provide patients and physicians with a new option of combining XJXBCQ with Western Medicine for better disease remission, which can be implemented on a larger scale in clinical and community settings[21]. As an innovative and potentially cost-effective strategy, this approach can reduce the disease and financial burden of AECOPD. Given the high prevalence of COPD and serious consequences of acute exacerbations in this group of people, the results of this

study can be used to provide information on future international guidelines.

Trial status

Recruitment started in October 2018 and is expected to finish in March 2020, 18 months in total.

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Competing interests

None.

Funding

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Availability of data and materials

The data form the study will be available once the study is completed.

Authors' contributions

JJ and ZHC are co-first authors of this manuscript, contributing equally to the design, conduct of the trials and drafting the manuscript. All authors participated in the design of the study and performed the trial. ZH, ZY, CTH, and LX supervised and coordinated the clinical trial. JJ, LDM and JY are responsible for recruiting the participants. SZT and FJH participated in the statistical design. All authors read and approved the final manuscript.

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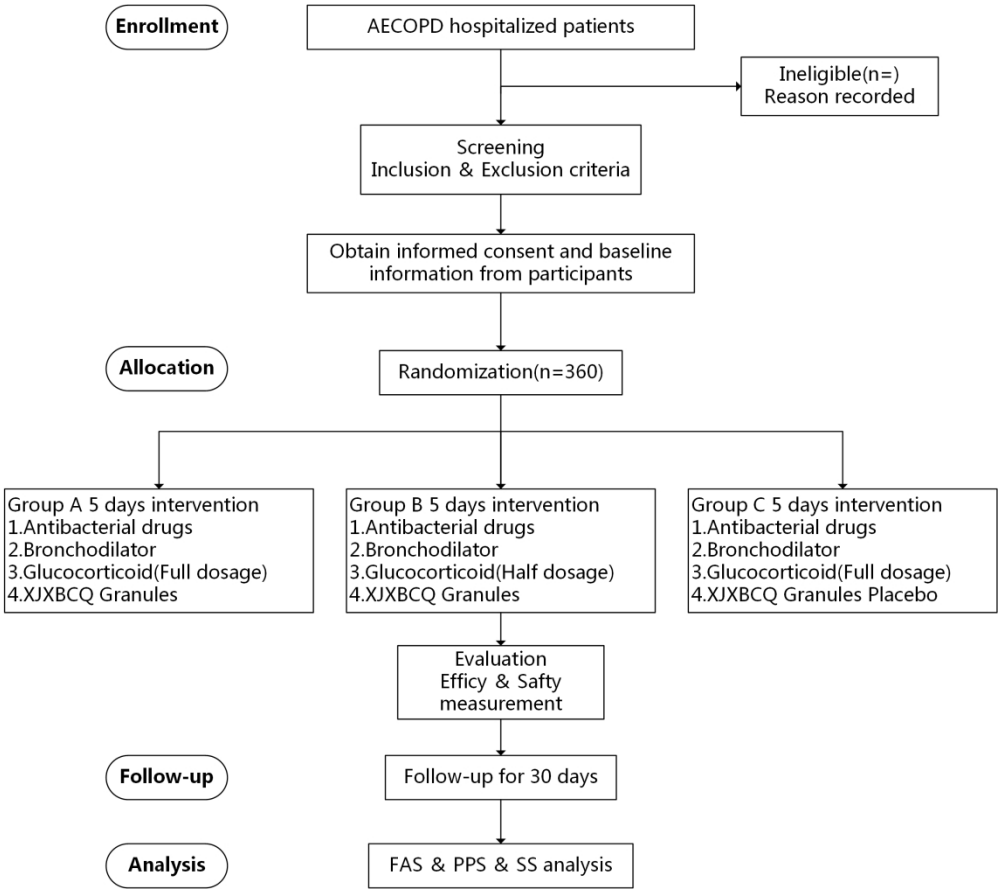
Table 1：Data collected from baseline to follow-up visits

	Study period									
	Enrollment	Allocation	Intervention						Post- Intervention	
	D-1	D0	D1	D2	D3	D4	D5	D6	Discharge	30 days after discharge
Enrollment:										
Consent form	√									
Basic information	√									
Inclusion & exclusion criteria	√									
Allocation		√								
Intervention:										
XJXBCQ+Budesonide (All)+ WST			√	√	√	√	√			
XJXBCQ+Budesonide (Half)+ WST			√	√	√	√	√			
XJXBCQ placebo+Budesonide (All)+ WST			√	√	√	√	√			

Outcome measure:											
Clinical symptoms score	√			√	√	√	√	√	√	√	
TCM syndrome score	√			√	√	√	√	√	√	√	
Blood gas analysis（PH、PaO2、PaCO2）	√							√			
Serum inflammatory markers（PCT、CRP、IL-6、TNF-α）	√					√			√		
Induced sputum & Stool sample	√							√			
Safety assessments:											
Adverse events recorded	√			√	√	√	√	√	√	√	√
Physical examination	√			√	√	√	√	√	√	√	
Blood & Urine routine	√							√			
Liver function（AST、ALT、Tbil、ALP、GGT）	√							√			
Kidney function（Scr、BUN、eGFR）	√							√			
ECG	√							√			

Table 2 Main components of Xinjia Xuanbai Chengqi Decoction

Chinese name	Latin name	Amount (g)
Ku Xing Ren	Semen Armeniacae Amarum	6g
Sheng Shi Gao	Gypsum Fibrosum	15g
Gua Lou	Fructus Trichosanthis	9g
Da Huang	Radix et rhizoma rhei	6g
Huang Qin	Scutellariae Radix	9g
Zi Su Zi	Perillae Fructus	9g
Zhi Gan Cao	Radix Glycyrrhizae Preparata	6g
Jin Qiao Mai	Rhizoma Fagopyri Dibotryis	10g
Zi Wan	Radix Asteris	9g



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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym A multicenter randomized controlled trial, 360 patients included, Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Full dosage of Glucocorticoid VS Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Half dosage of Glucocorticoid) VS Xinjia Xuanbai Chengqi Decoction placebo combined with western standard Medicine(Full dosage of Glucocorticoid).	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Chinese Clinical Trial Registry, ID: ChiCTR1800016915. Registered on 3 July 2018.	3
	2b	All items from the World Health Organization Trial Registration Data Set Not applicable.	No
Protocol version	3	Date and version identifier August 2018, version 1.2	No
Funding	4	Sources and types of financial, material, and other support The national key research and development project (2017YFC1309305)	21

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Jin Jin is from Beijing University of Chinese Medicine, Zhang Hong-chun and Li De-min are from Department of TCM Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, Jing Yue is from Wangjing Hospital of China Academy of Chinese Medical Sciences, Sun Zeng-tao is from Tianjin University of Traditional Chinese Medicine, Feng Ji-hong is from Affiliated Hospital of Tianjin University of TCM, Zhang Hong and Zhang Yan are from Department of Innovation and Transformation, National Center for Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine of the People's Republic of China,Cui Tian-hong and Lei Xiang are from Beijing Qihuang Medicine Clinical Research Center. JJ and ZHC are co-first author of this manuscript, contributing equally to the design, conduct the trials and draft the manuscript. All authors participated in the design of the study and performed the trial. ZH, ZY, CTH and LX supervised and coordinated the clinical trial. JJ, LDM and JY are responsible for recruiting the participants. SZT and FJH are participated in statistical design. All authors read and approved the final manuscript.	1,21
	5b	Name and contact information for the trial sponsor Zhang Hong-chun, Department of TCM Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, Ying Huayuan East Street, Chaoyang District, Beijing 100029, China. Fax: 0086-10-8463-3656;Email: 13701226664@139.com	1
	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 ZHC supervised and coordinated the clinical trial, conceived of the study and revised the manuscript critically for important intellectual content.	21

	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) China-Japan Friendship Hospital, Zhongshan Hospital affiliated to Fudan University, the First Affiliated Hospital of China Medical University, and Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University.	7
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 To observe the effect of Xinjia Xuanbai Chengqi Decoction combined with western medicine on the treatment of AECOPD. Common treatment of AECOPD is a 5-day high dose of Glucocorticoid plus Bronchodilator and/or Antibiotic,but whether this treatment is optimal is not known. the method of Tongfu Xiere has been widely used in AECOPD patients and usually achieve good results in clinical practice, especially in combination with Western Medicine, not only can reduce the use of antibiotics, glucocorticoid, etc., but also decrease the side effects of modern routine medicine. Despite this, there is not enough evidence to show the effectiveness.	5,6
	6b	Explanation for choice of comparators The comparator is Xinjia Xuanbai Chengqi Decoction placebo and Glucocorticoid for Glucocorticoid is considered to be effective in improving symptoms of AECOPD.	11
Objectives	7	Specific objectives or hypotheses Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Half dosage of Glucocorticoid is equivalent in the treatment of AECOPD, compared to Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Full dosage of Glucocorticoid), preferred to using western standard Medicine(Full dosage of Glucocorticoid) alone.	11

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) Three arms parallel group, 1:1:1, non-inferiority and superiority	7

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 China-Japan Friendship Hospital(Beijing), Zhongshan Hospital affiliated to Fudan University, Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University(Shanghai), and the First Affiliated Hospital of China Medical University (Shenyang).All of the hospital listed above is in China.	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) Inclusion criteria: 1) Meet AECOPD diagnostic criteria; 2) AECOPD severity clinical grade I-II; 3) Comply with indications for antibiotic treatment recommended by *AECOPD Chinese Expert Consensus (Revised 2017)*; 4) Comply with the criteria for the heat-phlegm and sthenic-fu syndrome; 5) Age 40-80 years old, gender is not limited; 6) Provision of signed, informed consent. Exclusion criteria: 1) Patients who with asthma, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer or other airflow-limited disease with known causes and characteristic pathology; 2) Patients with coronary heart disease, hypertensive heart disease, heart valve disease, etc.; 3) Those need invasive mechanical ventilation; 4) Clinically confirmed or highly suspected pulmonary embolism; 5) Combine with diseases of severe cardiovascular, cerebrovascular, hepatorenal and hematopoietic or primary endocrine system[12]; 6) Those with intestinal obstruction requiring surgical intervention; 7) Pregnant or lactation period; 8) Mental or mentally handicapped; 9) ALT, AST> 1.5 times the upper limit of normal reference or Scr> the upper limit of normal reference; 10) Need to combine immunosuppressants; 11) Taking oral or intravenous antibiotics before screening for more than 3 days; 12) Known to be allergic to the basic therapeutic drugs or any excipients prescribed through the research; 13) Known to be allergic to Chinese herbal medicinal ingredient prescription; 14) Those who have participated in or are participating in other clinical trials within nearly 3 months; 15) Those who be considered inappropriate to participate in this clinical trial by investigator. If applicable, eligibility criteria for study centres and individuals a physician will perform the interventions.	8,9

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Patients in intervention group will administrate Xinjia Xuanbai Chengqi Granule (2.5g/bag, two bags at a time) in 200 milliliter hot water as the instruction and take the solution orally three times a day for 5 days. While patients in the placebo group will take Xinjia Xuanbai Chengqi Granule placebo as the same way as the intervention group. Western medicine will be administrated as the standard operating procedure.	10,11
	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) When serious adverse effects occur, we will provide an appropriate treatment to the subject immediately and record the adverse effect and stop the subject to continue to take the given medicine.	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Since all participants are hospitalized and can be monitored by researchers at any time, adherence can be well guaranteed.	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Other Chinese or Western medicines for phlegm and cough indications of COPD (except for for patients with COPD long-term basic treatment) should be Prohibited.	12

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 Outcomes:1) Clinical symptoms and TCM syndrome score: be estimated at the baseline, Day 1, Day 2, Day 3, Day 4, Day 5 (Intervention period), Day 6 and discharge (Post-Intervention period);2) Blood gas analysis(PH、PaO_2、$PaCO_2$): be estimated at the baseline and Day 6;3) Serum inflammatory markers(PCT、CRP、IL-6、TNF-α): be estimated at the baseline, Day 3 and Day 6;4) Induced sputum and Stool sample: be estimated at the baseline and Day 6. Since AECOPD is defined as acute worsening of respiratory symptoms(typically dyspnea, cough, increased sputum and/or purulent sputum) in patients with COPD, the change of symptom score is very important to evaluate the clinical efficacy of XJXBCQ. AECOPD patients often present with changes in serum inflammatory markers such as PCT、CRP、IL-6、TNF-α and so on, serum inflammatory markers are also objective indicators for effectiveness of intervention. Due to TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", we also estimate microbial flora in induced sputum and stool sample of participants to explore the pathogenesis of AECOPD at the microbiological level.	12,13,14,15
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) Table 1 in the manuscript	25

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 Since this research is an exploratory study, it has not yet relevant data to support the sample size calculation. So we primitively plan to recruit 360 AECOPD patients allocated as the ratio of 1:1:1, 120 per group, according to the objective conditions such as the research period and budget. The purpose is to initially evaluate the therapeutic effect and safety of Xinjia Xuanbai Chengqi Decoction on AECOPD, and provide basic data for further large-scale, multi-center clinical research.	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size By poster in hospital and WeChat advertisement	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 Using the SAS statistical software to generate a random sequence of 360 subjects (group A, group B, group C) according to the ratio of 1:1:1, listing the serial number as 001-360.	9
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 The treatment allocation is that each center will be assigned a consecutive numbered medication on the basis of the random sequence. An independent clinical statistician will keep the random sequence which be saved in the form of a file in a sealed envelope and record the method, process, result of entire produce, so as to be checked if necessary.	9,10

Implement ation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions An independent clinical statistician will generate the allocation sequence, the care providers will enrol participants and The independent clinical statistician will assign participants to interventions.	9,10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how The investigator, doctors, nurses, outcome measuring person, statisticians and the participants have no idea about the group information until the end of the trial, when all statistics work are finished.	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial In case there is a clinical emergency event, the individual's randomized code and group assignment can be identified as quickly as possible through the emergency envelope. Once any envelope has been opened, whether intentional or not, it should be carefully recorded on the Case Report Form (CRF) and the patient will be withdrawn from the study.	9,10
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 China-Japan Friendship Hospital is responsible for training the standard operating procedures of researchers and supervising the progress of all clinical sites.	7
	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 Regular monitoring will be conducted by phone and email.	16

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 All data will first be recorded by the assessor on a paper version of the case report form and then electronically dual-input into the EDC system. The monitor will periodically review the completion and compliance of the CRF. In order to maintain the objectivity of the data, we will ensure that observers and statisticians are unaware of it. The entire process will be monitored by an independent quality inspector.	16
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 Statistical analysis will be performed by SAS 9.4 software. For the continuous variables, the paired t-test will be used to compare the changes of clinical symptom scores pre- and post-intervention, and the covariance analysis model will be used for comparison between groups. The multiplier method will be used to calculate the quartiles (25%, 50%, 75%) of time from enrollment to events happened, and bilateral 95% confidence interval and the incidence rate at each time point after enrollment will be calculated yet. Kaplan-Meier curves will be plotted using the Log-rank test to compare hospital stays and theoretical hospital stays.For the two categorical variables, such as the recurrence rate of laboratory indicator, all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to the ICU during study, and the proportion of re-admission within 30 days after discharge, we will make comparison between groups and calculate the 95% confidence interval using a centrally stratified CMH $\chi 2$ test according to the classification, indicator, time point, quantity and percentage.	16,17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) A subgroup analyses will be conducted when necessary.	16,17

	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) Missing values for major variables, such as failure to observe case data for complete test procedure, using the results of the last observation to carry-forward to the absence of test data, and the amount of subjects in each group to evaluate efficacy at the endpoint is consistent with the beginning of the trail.	16,17
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 Beijing Qihuang Pharmaceutical Clinical Research Center is responsible for data management and in charge of data entry, coding, security, and storage. They are independent from the sponsor and there are no competing interests.	16
	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 Not applicable.	No
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 At each visit, patients will be asked whether there are any adverse effects during the study period. When an adverse event was claimed, we will provide an appropriate treatment to the subject immediately and record the adverse effect. An emergency services will be provided in case of serious adverse events. In addition, we will test the patients' blood routine, urine routine, kidney and liver function.	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor One month at peak of recruitment and two months at plateau of recruitment. The process will be independent from investigators and the sponsor.	8

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval The trial protocol has been approved by the Ethics Committee of China-Japan Friendship Hospital, Beijing, China (approval Number 2018-56-K40-2), and we have got the oral permission of the other 3 centres and we will got formal approval number in this month.	18
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) No	No
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Investigators will invite patients to participate the trial, tell them in detail why we should take this trial and what kind of rights, obligations and risks they will have if they participate the trials. And investigators will give them a written informed consent. Only the patients fully understand and sign the informed consent, can they participant the trial.	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable.	No
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 The personal information will be collected to be used **only** in this trial, and we won't share or maintained the personal information when unnecessary.	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site We declared there were no competing interests for principal investigators for the overall trial and each study site	21
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 Statisticians.	16

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 Treatment expenses for participants during study will be reimbursed. We will give a certain amount of provision according to Institutional Review Board when necessary.	18
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 The results of the studies will be widely distributed in scientific reports as well as academic conferences to benefit policymakers, clinicians and patients.	17,18
	31b	Authorship eligibility guidelines and any intended use of professional writers No	No
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code We had no plans.	No
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates The consent materials had been approved by the Ethics Committee of China-Japan Friendship Hospital,	18
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 Not applicable.	No

*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

Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter, Randomized, Controlled Trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Acute exacerbation of chronic obstructive pulmonary disease, Comparative effectiveness research, Traditional Chinese Medicine

Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter, Randomized, Controlled Trial

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Word count：4087

ABSTRACT

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) brings a serious impact on patients' quality of life, and has extremely high morbidity and mortality worldwide. Although there are many therapies being developed to alleviate symptoms and reduce mortality, few studies have supported which treatment method is the best. Traditional Chinese Medicine (TCM) has shown good potential in the prevention and treatment of AECOPD, especially in terms of supplementation and reduction of dosage of Western Medicine and side effects. The purpose of this study is to compare effectiveness of combination of TCM and Western Medicine with conventional therapy alone for AECOPD, and to ensure whether the combined therapy may reduce the use of systemic Glucocorticoid in AECOPD without influencing efficacy.

Methods and analysis: A multicenter, randomized, double-blind, placebo-controlled study was conducted to enroll a total of 360 eligible patients who will be randomized into Integrated Chinese and Western Medicine group A, B, and Western standard Medicine group C. After 5 days of intervention and 1 month of follow-up, the efficacy

and safety of Xinjia Xuanbai Chengqi Decoction (XJXBCQ) in patients with AECOPD will be observed. The results of evaluation indicators include: clinical symptoms, biochemical indicators such as blood gas analysis, inflammatory markers, hospitalization time, TCM syndrome evaluation, biological indicators such as airway, intestinal flora sequencing.

Ethics and dissemination: This trail has been approved by the Ethics Committee of China-Japan Friendship Hospital. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's post-study health status during follow-up.

Trial registration: Chinese Clinical Trial Registry, ID: ChiCTR1800016915. Registered on 3 July 2018.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, Comparative effectiveness research, Traditional Chinese Medicine

Strengths and limitations of this study

- A randomized, double-blind, placebo-controlled, clinical, critical trial;
- A multi-center trial be carried out in four comprehensive Third-grade first-class hospitals across China, which improves the external validity and Representativeness of the sample and reduces the risk of selection bias;
- Because clinical symptoms are often accompanied by a certain degree of subjectivity , we combine the core symptoms (cough phlegm, defecation, dyspnea) score and TCM syndrome score to ensure scientific objectivity;
- As the main phase of the program will be performed during the hospital stay, practitioners will be able to immediately identify and manage adverse reactions and guarantee the safety of participants. Practitioners will maintain good communication with the participants by phone after discharge.
- The 5-day treatment period and the 1-month follow-up period may be a bit short.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterized by airflow obstruction (FEV1<80% predicted and FEV1/FVC ratio<70%) that is not reversible. COPD is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. In China, the prevalence of COPD in people aged 40 years or older is 13.7%[2], more than 1 million people die and more than 5 million people disable of COPD each year.

Acute exacerbation of COPD (AECOPD)[3] is defined as acute worsening of respiratory symptoms(typically dyspnea, cough, increased sputum and/or purulent sputum) in patients with COPD, exceeding normal day-to-day variations and that may require a change in medication even hospitalization. Acute exacerbation is an important factor in the death of patients with COPD[4], and is also the main expenditure portion of medical expenses for COPD patients.

Traditional Chinese Medicine (TCM), with characteristic theory of syndrome differentiation and overall conditioning, implies its potential advantages in the treatment of COPD. TCM syndrome studies find that in addition to symptoms such as cough, phlegm, and wheezing, patients in acute exacerbation period are often accompanied by constipation, abdominal distension, and yellow greasy tongue coating. Based on TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", physicians use the method of Tongfu Xiere to AECOPD patients and usually achieve good results in clinical practice. Xinjia Xuanbai Chengqi Decoction (XJXBCQ), consists of Semen Armeniacae Amarum, Gypsum Fibrosum,

Fructus Trichosanthis, Radix et rhizoma rhei, Scutellariae Radix, Perillae Fructus, Radix Glycyrrhizae Preparata, Rhizoma Fagopyri Dibotryis and Radix Asteris, is evolved from the TCM classical prescription Xuan Bai Chengqi Decoction[5]. It has been widely used in AECOPD patients attached to the heat-phlegm and sthenic-fu syndrome, especially in combination with Western Medicine, not only can reduce the use of antibiotics, glucocorticoid, etc., but also decrease the side effects of modern routine medicine[6]. Despite this, there is not enough evidence to show the efficacy of XJXBCQ on patients with AECOPD. Hence, a more rigorously designed large-scale, multicenter, randomized trial is needed to assess the effectiveness of XJXBCQ on AECOPD. In conclusion, our aim is to conduct a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of XJXBCQ on AECOPD. The results of this trial will provide evidence that the XJXBCQ is an effective prescription for AECOPD. In view of the difficulty in assessing the quality of the decoction, we plan to use the XJXBCQ granules in the trial. The main purpose of this study is to evaluate the clinical symptoms, signs, blood gas analysis, serum inflammatory factors (IL-6[7], TNF-α, CRP[8], PCT), airway and intestinal microbes[9] of AECOPD hospitalized patients with XJXBCQ combined with Western Medicine; The secondary objective was to observe the effect of XJXBCQ combined with Western Medicine on reducing the use of glucocorticoid[10], the mortality, the hospitalized time, the requirement for invasive mechanical ventilation, and the re-admission rate of acute exacerbation within 30 days after discharge.

METHODS

Study design

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial that enrolled a total of 360 patients that will be randomly assigned to one of three groups: Integrated Chinese and Western Medicine Group A, Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. After 5 days of intervention, the effectiveness and safety of XJXBCQ in participants will be evaluated by comparing the various indicators of the three groups, including clinical symptoms, activity, biochemical indicators and biological indicators.

As the leading unit of the research, China-Japan Friendship Hospital is responsible for training the standard operating procedures of researchers and supervising the progress of all clinical sites. Other participating units include: Zhongshan Hospital affiliated to Fudan University, the First Affiliated Hospital of China Medical University, and Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University. Recruitment allocation: 180 cases will be from China-Japan Friendship Hospital, while the remaining three recruit 60 cases respectively. The flow chart of the trial is shown in Figure 1. This study protocol is registered with the China Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=28338). The Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 checklist is shown in Additional file 1.

Participants

Patients with AECOPD attached to the heat-phlegm and sthenic-fu syndrome will be enrolled. Heat-phlegm and sthenic-fu syndrome is a typical syndrome type of traditional Chinese medicine based TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl". Referred to “Retention of Heat-Phlegm in the Lung” syndrome in *TCM Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease (2011)*, Heat-phlegm and sthenic-fu syndrome is defined as: Primary symptoms: cough, wheezing, chest distress, yellow and white sticky sputum, abdominal distension, constipation, red tongue, yellow and greasy fur, slippery or rapid pulse; Secondary symptoms: chest pain, facial blushing, thirst with desire to cold drinks, yellow urine, thick fur. Diagnosis: (1) cough or shortness of breath;(2) yellow and white sticky sputum with difficult expectoration;(3) abdominal distension or constipation;(4) facial blushing;(5) thirst with desire to cold drinks;(6) yellow urine;(7) red tongue, yellow and greasy fur, slippery or rapid pulse. The diagnosis should meet (1), (2) and (3), and two of (4), (5), (6) or (7). The first date of participant enrollment was 7 Jan 2019.

Inclusion criteria

Patients must meet all of the following criteria: 1) Meet AECOPD diagnostic criteria; 2) AECOPD severity clinical grade I-II[1,11]; 3) Comply with indications for antibiotic treatment recommended by *Chinese Expert Consensus on diagnosis and treatment of Accelerated Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)(Updated 2017)*; 4) Comply with the criteria for the heat-phlegm and sthenic-fu syndrome of TCM; 5) Age 40-80 years old, gender is not limited; 6)

Provision of signed, informed consent.

Exclusion criteria

Patients who meet one or more of the exclusion criteria listed below will not be allowed: 1) Patients who with asthma, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer or any other airflow-limited disease with known causes and characteristic pathology; 2) Patients with coronary heart disease, hypertensive heart disease or heart valve disease, etc.; 3) Those need invasive mechanical ventilation; 4) Clinically confirmed or highly suspected pulmonary embolism; 5) Combine with diseases of severe cardiovascular, cerebrovascular, hepatorenal and hematopoietic or primary endocrine system[12]; 6) Those with intestinal obstruction requiring surgical intervention; 7) Pregnant or lactation period; 8) Mentally handicapped; 9) ALT, AST> 1.5 times the upper limit of normal reference or Scr> the upper limit of normal reference; 10) Need to combine immunosuppressant; 11) Taking oral or intravenous antibiotics before screening for more than 3 days in last 3 months; 12) Known to be allergic to the basic therapeutic drugs or other excipients prescribed through the research; 13) Known to be allergic to Chinese herbal medicinal ingredient prescription; 14) Those who have participated in or are participating in other clinical trials within nearly 3 months; 15) Those who be considered inappropriate to participate in this clinical trial by the investigator.

Sample size

According to our pre-experiment, comparing symptom scores of patients before and

after treatment, the average score was 10.67±2.61 on admission, 4.33±1.97 on the 6th day of admission, and the difference value was 6.33±3.73. Excellent efficiency test will be conducted between Integrated Chinese and Western Medicine Group A and Western Standard Medicine Group C, meanwhile non-inferiority test will be conducted between Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. Cut-off point is defined as 1, so expected difference of excellent efficiency test should be more than 7.33(6.33+1), and which of non-inferiority test should be not less than 5.33(6.33-1). When the power=0.8, each of the three groups required 100 effective cases. Considering a 20% shedding rate, a total of 360 cases were needed in the three groups, with 120 cases in each group.

Randomization

A block randomization method will be employed. We will select the appropriate length of the segment and use the SAS statistical software to generate a random sequence of 360 subjects (group A, group B, group C) according to the ratio of 1:1:1, listing the serial number as 001-360. The treatment allocation is that each center will be assigned a consecutive numbered medication on the basis of the random sequence. An independent clinical statistician will keep the random sequence which be saved as a file in a sealed envelope and record the method, process, result of entire produce, so as to be checked if necessary. In case there is a clinical emergency event, the individual's randomized code and group assignment can be identified as quickly as possible through the emergency envelope. Once any envelope has been opened,

whether intentional or not, it should be carefully recorded on the Case Report Form (CRF) and the patient will be withdrawn from the study.

Interventions

Program Description

Volunteers who meet the inclusion criteria will receive an information form and be required to provide written consent to participate in the trial. They will then undergo a physical screening test to determine if there are other comorbidities that may affect the trial. After successful screening, they will participate in the trial, get trial-specific identification (ID) numbers and be assigned to a group according to random sequence. A baseline measurement for each participant is then performed, including clinical symptoms scores and TCM syndrome scores, blood gas analysis (PH, PaO_2, $PaCO_2$), serum inflammatory markers (PCT, CRP, IL-6, TNF-α), induced sputum, stool sample, and so on. The research program flow is shown in Table 1. All outcome measurements will be taken by medical workers who are familiar with the management of these assessments and will be unaware of the participants' group assignments.

All participants will receive Standard Western Medicine treatment follow the *Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2018*, the *Chinese Medical Association Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised 2013)* and the *Chinese Expert Consensus on diagnosis and treatment of Accelerated Exacerbation of Chronic Obstructive*

Pulmonary Disease (AECOPD)(Updated 2017), including: General treatment: controlled oxygen therapy, Venturi mask oxygen, NIV if requiring non-invasive ventilation;

Antibiotic: Levofloxacin and Sodium Chloride Injection, 0.5g, iv.gtt, qd;

Bronchodilator[13]: Compound Ipratropium Bromide Solution for Inhalation (Combivent), 500ug, inhal, tid.

Beside the above, Group A will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (2 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules (2 bags at a time, tid). Group B will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (1 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules (2 bags at atime, tid); Group C will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (2 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules Placebo (2 bags at a time, tid). The entire trial will go through 5 days.

Xinjia Xuanbai Chengqi Granules

Xinjia Xuanbai Chengqi Granules is a compound preparation of Chinese herbal medicine. The main components are shown in Table 2.

XJXBCQ Granules (2.5 g/bag, Batch number: 180605) are produced and packaged by Anhui Jiren Pharmaceutical Co., Ltd. that have China Pharmaceutical Production License (Number: Wan 20160083). The results of drug quality testing are consistent with the quality standards. XJXBCQ Granules will be administered orally, two bags at

a time, three times a day for 5 days. All herbs were tested to the same standard.

Placebo

The placebo consists of starch without any active ingredient is produced by the same manufacturer as XJXBCQ Granules. It is a dextrin that matches as much as possible the appearance and taste of XJXBCQ Granules. The drug instructions for XJXBCQ Granules and placebo are completely consistent.

Combined medication regulations

Participants are allowed to remain their originally basic treatment taken before recruited; If one's condition deteriorates during the study and need to stay in the ICU or perform invasive mechanical ventilation, we will immediately deal with it; Those who need to adjust the antibiotic due to they can't tolerate LVFX or whose condition have not been alleviated but even aggravated after 3 days of treatment, the antibacterial therapy will be adjusted according to the regulations in *the Chinese Expert Consensus for the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) (Updated 2017)*. The reasons for adjustment of the antibacterial drug program need to be recorded in detail; Taking conventional treatment once right heart failure or heart rhythm disorders happened. In addition, other Chinese or Western medicines for phlegm and cough indications of COPD (except for for patients with COPD long-term basic treatment) should be prohibited.

Outcome measure

Because overall conditioning is the core values of TCM, there is no single indicator could be able to predict patients' recovery to evaluate effect of XJXBCQ Granules; thus, a comprehensive assessment is required to AECOPD [14].

Clinical symptoms (cough, phlegm, defecation, dyspnea) score: We will record the color[15], viscosity and amount of sputum[16] daily during the study. Scoring and grading constipation symptoms according to the severity of constipation score; The severity of dyspnea will be assessed by using a modified British Medical Research Council Respiratory Questionnaire (mMRC).

TCM syndrome score: Refer to *the Guidelines for TCM Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2011)* and *Guidelines for Clinical Research of New Traditional Chinese Medicine for Chronic Bronchitis (2002),* we conduct comprehensive evaluation on cough, phlegm, dyspnea, defecation, abdominal distension, fever from perspective of the heat-phlegm and sthenic-fu syndrome. Efficacy index (n) = [(pre-intervention scores − post-intervention scores)/ pre-intervention scores] × 100%

Clinical recovery: TCM clinical symptoms and signs disappeared or approximately disappeared, TCM scores decreased ≥90%;

Markedly effective: TCM clinical symptoms and signs are significantly improved, syndrome scores reduced ≥70%;

Effective: TCM clinical symptoms and signs are improved, syndrome scores reduced ≥30%;

Invalid: No TCM clinical symptoms or signs significantly improved and even aggravated, syndrome scores reduced less than 30%.

Blood gas analysis: We will take arterial blood gas analysis (PH, PaO_2, $PaCO_2$) before and after intervention.

Serum inflammatory markers: Serum inflammatory markers include PCT, CRP, IL-6, TNF-α.

Induced sputum and stool sample: Induced sputum and stool sample will be collected at the baseline and Day 6. Due to TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", we also estimate microbial flora in induced sputum and stool sample of participants to explore the pathogenesis of AECOPD at the microbiological level by the 16S rRNA gene sequencing[17] and the whole-genome shotgun sequencing[18].

Theoretical discharge time: The theoretical discharge criteria[19] is: 1) Patients be considered that can adapt to family medicine; 2) patients can accept a stable inhalation therapy about long-acting bronchiectasis, β2 receptor agonist and/or an anticholinergic drug, with or without inhaled glucocorticoids. A short-acting β2 agonist[20] should be administered less than once every 4 hours; 3) Patients should be able to walk indoors if they have not been bedridden before; 4) Eating and sleep is good and not affected by dyspnea; 5) Stand at clinical stability for 12 ~ 24 h; 6) Arterial blood gas analysis should be stable for 12 ~ 24 h; 7) Patients or family members fully understand the correct use of stable period medicines; 8) Follow-up and home care plans have been arranged.

Mortality: All-cause mortality and COPD mortality will be calculated respectively for the subjects during the study period.

Actual hospitalization time: Hospitalization time = discharge date - admission date + 1.

The proportion of patients requiring invasive mechanical ventilation during hospitalization: The proportion of patients requiring invasive mechanical ventilation during hospitalization = the number of patients with invasive mechanical ventilation during hospitalization / the total patients .

Proportion of patients transferred to ICU during hospitalization: Proportion of patients transferred to ICU during hospitalization = the number of patients transferred to ICU during hospitalization / the total patients.

Re-admission rate within 30 days after discharge: Judgment criteria for re-admission: subjects are hospitalized again due to COPD or other respiratory illnesses, excluding hospitalization for other illnesses or purposes. The follow-up will be finished and not continued if one is judged to be re-admitted to the hospital during the follow-up period. Re-admission rate = re-admitted patients / completed follow-up patients.

Safety assessment

The physical examination will be performed every day from the baseline to end of study. Blood routine, urine routine, liver function, renal function test and electrocardiogram will be performed at baseline and Day 6. Any adverse event occurs

during the study will be observed and recorded in detail.

Quality control and data management

Prior to the study, the protocol had been reviewed and revised several times by clinicians, statistics, and methodologists. All staff members of the trial are required to participate in a series of trainings to ensure that the personnel involved fully understand the research protocol and standard operating procedures (SOPs) to guarantee accuracy and completeness of clinical data. Regular monitoring will be conducted by phone and email. All data will first be recorded by the assessor on a paper version of the case report form and then electronically dual-input into the EDC system. The monitor will periodically review the completion and compliance of the CRF. In order to maintain the objectivity of the data, we will ensure that observers and statisticians are unaware of it. The entire process will be monitored by an independent quality inspector. Beijing Qihuang Pharmaceutical Clinical Research Center is responsible for data management.

Statistical analysis

Full Analysis Set (FAS), Per Protocol Set (PPS), and Safety Analysis Set (SS) will be employed. FAS means an ideal set of all subjects (including all subjects randomized into the group and receiving at least one treatment) as close as possible to the principle of intentional analysis. Missing values for major variables, if once failure to observe whole data of case, we will carry-forward the last observation to the absence

of test data, and the amount of subjects in each group to evaluate efficacy at the endpoint will be corresponding to the beginning of trail. PPS refers to all cases that meet the stand protocol, have great compliance, use the trial medicine in the range of 80%-120%, complete the eCRF regulations, the main variables can be measured, the baseline variables are well-preserved, and have no significant violation to the protocol. SS refers to all subjects who accept at least one time treatment after randomization. For the continuous variables, the paired t-test will be used to compare the changes of clinical symptom scores pre- and post-intervention, and the covariance analysis model will be used for comparison between groups. The multiplier method will be used to calculate the quartiles (25%, 50%, 75%) of time from enrollment to events happened, and bilateral 95% confidence interval and the incidence rate at each time point after enrollment will be calculated yet. Kaplan-Meier curves will be plotted using the Log-rank test to compare theoretical hospital stay and actual hospital stay. For the two categorical variables, such as the recurrence rate of laboratory indicator, all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to the ICU during study, and the proportion of re-admission within 30 days after discharge, we will make comparison between groups and calculate the 95% confidence interval using a centrally stratified CMH $\chi 2$ test according to the classification, indicator, time point, quantity and percentage. Statistical analysis will be performed by SAS 9.4 software.

Patient and public involvement

Neither patients nor their family members were involved in the study design. The results of the studies will be widely distributed in scientific reports as well as academic conferences to benefit policymakers, clinicians and patients.

Ethics and dissemination

This trail has been approved by the Ethics Committee of China-Japan Friendship Hospital. All volunteers will sign the informed consent, which is consistent with the ethical principles set forth in the Helsinki Declaration. Treatment expenses for participants during study will be reimbursed. Data usage will follow the rules of hospital's data oversight committee. Biological samples will be handled following the national guideline on biological waste management and disposal. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's post-study health status during follow-up.

DISCUSSION

Before conducting this experiment, we closely retrieved PubMed, Web of Science, Embase, CNKI (including China doctor/master's theses database and China Proceedings conference full-text database), Wan Fang Data, Vip Journal Integration Platform (VJIP), Chinese BioMedical (CBM) database (Sinomed), etc. and found no definite evidence for effect and safety of Xinjia Xuanbai Chengqi Decoction in the treatment of acute exacerbation of COPD. Therefore, we decide to conduct a

multicenter, randomized, controlled clinical trial to closely study its effectiveness and safety. Due to the lack of evidence on the effectiveness of XJXBCQ, we will apply Chinese medicine combined with Western medicine to treat AECOPD to ensure participants' compliance and ethical considerations, because antibiotics, bronchodilators, and glucocorticoids are first-line treatments to improve acute exacerbation of COPD according to guidelines.

COPD is a common, preventable disease, affecting millions worldwide. It seriously impairs patients' social activities, daily activities and quality of life[21]. The high economic burden of AECOPD to families and societies is growing year by year. The extensive clinical experience of using Chinese medicine in the prevention and treatment of COPD in China shows that Chinese medicine preparations are effective. Due to the complexity of the pathogenesis of COPD, the recent use of combination therapy has attracted more and more attention, providing new prospects for Traditional Chinese Medicine which be considered effective in improving clinical symptoms. TCM possess the advantages of being simple, convenient, efficient, inexpensive, and without serious adverse reactions. A systematic review suggested that Chinese medicine conspicuously improved the prognosis of patients with COPD but lack of high-quality research hinder the development of evidence-based recommendations for clinical practice. Therefore, we design this critical clinical trial, which has the following advantages: (1) This study is designed as a randomized, double-blind, placebo-controlled, clinical, critical trial from the perspective of evidence-based medicine, that is considered to be the most definitive research method

of treatment evaluation; (2) At the same time, this is a multi-center trial be carried out in four comprehensive Third-grade first-class hospitals across China, which improves the external validity and Representativeness of the sample and reduces the risk of selection bias; (3) Because clinical symptoms are often accompanied by a certain degree of subjectivity , we combine the core symptoms (cough phlegm, defecation, dyspnea) score and TCM syndrome score to ensure scientific objectivity; (4) In order to ensure quality, all staff in the study must complete the training of the standard operating procedures of the research program before recruitment; (5) As the main phase of the program will be performed during the hospital stay, practitioners will be able to immediately identify and manage adverse reactions and guarantee the safety of participants. Practitioners will maintain good communication with the participants by phone after discharge. However, the design of the program also has potential limitations, for example, the 5-day treatment period and the 1-month follow-up period are a bit short.

In conclusion, the aim of this study is to answer whether traditional Chinese medicine can supplement and reduce COPD Western medical treatments, reduce frequency of acute exacerbation of COPD, and provide objective data about effectiveness and safety. If the trial is successful, it will provide patients and physicians with a new option of combining XJXBCQ with Western Medicine for better disease remission, which can be implemented on a larger scale in clinical and community settings[22]. As an innovative and potentially cost-effective strategy, this approach can reduce the disease and financial burden of AECOPD. Given the high prevalence of COPD and

serious consequences of acute exacerbations in this group of people, the results of this study can be used to provide information on future international guidelines.

Trial status

Recruitment started in October 2018 and is expected to finish in March 2020, 18 months in total.

Acknowledgements

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Competing interests

None.

Funding

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Availability of data and materials

The data form the study will be available once the study is completed.

Authors' contributions

JJ and ZHC are co-first authors of this manuscript, contributing equally to the design, conduct of the trials and drafting the manuscript. All authors participated in the design of the study and performed the trial. ZH, ZY, CTH, and LX supervised and coordinated the clinical trial. JJ, LDM, JY, ZJ, CQJ and LER are responsible for recruiting the participants. SZT and FJH participated in

the statistical design. All authors read and approved the final manuscript.

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Table 1：Data collected from baseline to follow-up visits

	Study period									
	Enrollment	Allocation	Intervention						Post- Intervention	
	D-1	D0	D1	D2	D3	D4	D5	D6	Discharge	30 days after discharge
Enrollment:										
Consent form	√									
Basic information	√									
Inclusion & exclusion criteria	√									
Allocation		√								
Intervention:										
XJXBCQ+Budesonide (All)+ WST			√	√	√	√	√			
XJXBCQ+Budesonide (Half)+ WST			√	√	√	√	√			
XJXBCQ placebo+Budesonide (All)+ WST			√	√	√	√	√			

Outcome measure:											
Clinical symptoms score	√			√	√	√	√	√	√	√	
TCM syndrome score	√			√	√	√	√	√	√	√	
Blood gas analysis（PH、PaO2、PaCO2）	√							√			
Serum inflammatory markers（PCT、CRP、IL-6、TNF-α）	√					√			√		
Induced sputum & Stool sample	√							√			
Safety assessments:											
Adverse events recorded	√			√	√	√	√	√	√	√	√
Physical examination	√			√	√	√	√	√	√	√	
Blood & Urine routine	√							√			
Liver function（AST、ALT、Tbil、ALP、GGT）	√							√			
Kidney function（Scr、BUN、eGFR）	√							√			
ECG	√							√			

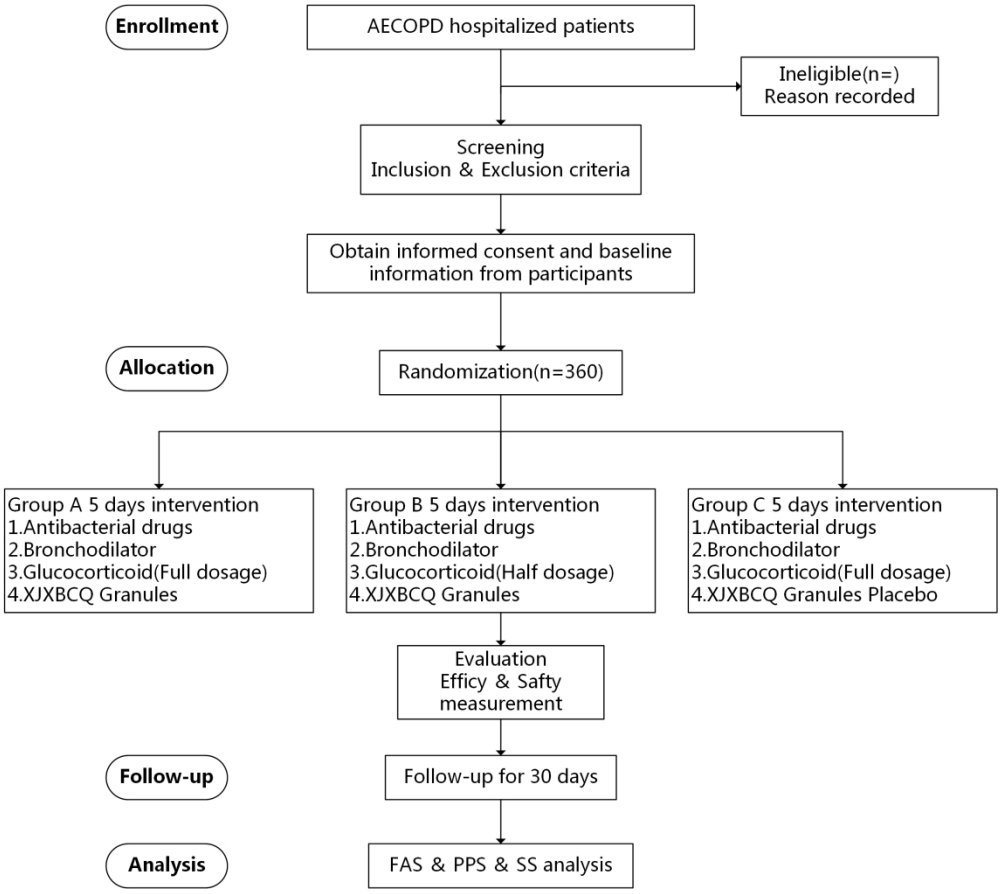
Table 2 Main components of Xinjia Xuanbai Chengqi Decoction

Chinese name	Latin name	Amount (g)
Ku Xing Ren	Armeniacae Semen Amarum	6g
Sheng Shi Gao	Gypsum Fibrosum	15g
Gua Lou	Trichosanthis Fructus	9g
Da Huang	Rhei Radix Et Rhizoma	6g
Huang Qin	Scutellariae Radix	9g
Zi Su Zi	Perillae Fructus	9g
Zhi Gan Cao	Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle	6g
Jin Qiao Mai	Fagopyri Dibotryis Rhizoma	10g
Zi Wan	Asteris Radix Et Rhizoma	9g

Figure legend

Figure 1 Study flow chart. FAS, Full Analysis Set; PPS, Per Protocol Set; SS, Safety Analysis Set.

Table 1 Basic information includes gender, height, weight, COPD history, other diseases combined and medical status, etc. XJXBCQ, Xinjia Xuanbai Chengqi Granules; WST, western standard treatment; TCM, Traditional Chinese Medicine.



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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym A multicenter randomized controlled trial, 360 patients included, Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Full dosage of Glucocorticoid VS Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Half dosage of Glucocorticoid) VS Xinjia Xuanbai Chengqi Decoction placebo combined with western standard Medicine(Full dosage of Glucocorticoid).	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Chinese Clinical Trial Registry, ID: ChiCTR1800016915. Registered on 3 July 2018.	3
	2b	All items from the World Health Organization Trial Registration Data Set Not applicable.	No
Protocol version	3	Date and version identifier August 2018, version 1.2	No
Funding	4	Sources and types of financial, material, and other support The national key research and development project (2017YFC1309305)	21

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Jin Jin is from Beijing University of Chinese Medicine, Zhang Hong-chun and Li De-min are from Department of TCM Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, Jing Yue is from Wangjing Hospital of China Academy of Chinese Medical Sciences, Sun Zeng-tao is from Tianjin University of Traditional Chinese Medicine, Feng Ji-hong is from Affiliated Hospital of Tianjin University of TCM, Zhang Hong and Zhang Yan are from Department of Innovation and Transformation, National Center for Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine of the People's Republic of China,Cui Tian-hong and Lei Xiang are from Beijing Qihuang Medicine Clinical Research Center. JJ and ZHC are co-first author of this manuscript, contributing equally to the design, conduct the trials and draft the manuscript. All authors participated in the design of the study and performed the trial. ZH, ZY, CTH and LX supervised and coordinated the clinical trial. JJ, LDM, JY, ZJ, CQJ and LER are responsible for recruiting the participants. SZT and FJH are participated in statistical design. All authors read and approved the final manuscript.	1,21
	5b	Name and contact information for the trial sponsor Zhang Hong-chun, Department of TCM Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, Ying Huayuan East Street, Chaoyang District, Beijing 100029, China. Fax: 0086-10-8463-3656;Email: 13701226664@139.com	1
	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 ZHC supervised and coordinated the clinical trial, conceived of the study and revised the manuscript critically for important intellectual content.	21

	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) China-Japan Friendship Hospital, Zhongshan Hospital affiliated to Fudan University, the First Affiliated Hospital of China Medical University, and Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University.	7
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 To observe the effect of Xinjia Xuanbai Chengqi Decoction combined with western medicine on the treatment of AECOPD. Common treatment of AECOPD is a 5-day high dose of Glucocorticoid plus Bronchodilator and/or Antibiotic,but whether this treatment is optimal is not known. the method of Tongfu Xiere has been widely used in AECOPD patients and usually achieve good results in clinical practice, especially in combination with Western Medicine, not only can reduce the use of antibiotics, glucocorticoid, etc., but also decrease the side effects of modern routine medicine. Despite this, there is not enough evidence to show the effectiveness.	5,6
	6b	Explanation for choice of comparators The comparator is Xinjia Xuanbai Chengqi Decoction placebo and Glucocorticoid for Glucocorticoid is considered to be effective in improving symptoms of AECOPD.	11
Objectives	7	Specific objectives or hypotheses Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Half dosage of Glucocorticoid is equivalent in the treatment of AECOPD, compared to Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Full dosage of Glucocorticoid), preferred to using western standard Medicine(Full dosage of Glucocorticoid) alone.	11

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) Three arms parallel group, 1:1:1, non-inferiority and superiority	7

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 China-Japan Friendship Hospital(Beijing), Zhongshan Hospital affiliated to Fudan University, Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University(Shanghai), and the First Affiliated Hospital of China Medical University (Shenyang).All of the hospital listed above is in China.	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) Inclusion criteria: 1) Meet AECOPD diagnostic criteria; 2) AECOPD severity clinical grade I-II; 3) Comply with indications for antibiotic treatment recommended by *AECOPD Chinese Expert Consensus (Revised 2017)*; 4) Comply with the criteria for the heat-phlegm and sthenic-fu syndrome; 5) Age 40-80 years old, gender is not limited; 6) Provision of signed, informed consent. Exclusion criteria: 1) Patients who with asthma, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer or other airflow-limited disease with known causes and characteristic pathology; 2) Patients with coronary heart disease, hypertensive heart disease, heart valve disease, etc.; 3) Those need invasive mechanical ventilation; 4) Clinically confirmed or highly suspected pulmonary embolism; 5) Combine with diseases of severe cardiovascular, cerebrovascular, hepatorenal and hematopoietic or primary endocrine system[12]; 6) Those with intestinal obstruction requiring surgical intervention; 7) Pregnant or lactation period; 8) Mental or mentally handicapped; 9) ALT, AST> 1.5 times the upper limit of normal reference or Scr> the upper limit of normal reference; 10) Need to combine immunosuppressants; 11) Taking oral or intravenous antibiotics before screening for more than 3 days; 12) Known to be allergic to the basic therapeutic drugs or any excipients prescribed through the research; 13) Known to be allergic to Chinese herbal medicinal ingredient prescription; 14) Those who have participated in or are participating in other clinical trials within nearly 3 months; 15) Those who be considered inappropriate to participate in this clinical trial by investigator. If applicable, eligibility criteria for study centres and individuals a physician will perform the interventions.	8,9

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Patients in intervention group will administrate Xinjia Xuanbai Chengqi Granule (2.5g/bag, two bags at a time) in 200 milliliter hot water as the instruction and take the solution orally three times a day for 5 days. While patients in the placebo group will take Xinjia Xuanbai Chengqi Granule placebo as the same way as the intervention group. Western medicine will be administrated as the standard operating procedure.	10,11
	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) When serious adverse effects occur, we will provide an appropriate treatment to the subject immediately and record the adverse effect and stop the subject to continue to take the given medicine.	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Since all participants are hospitalized and can be monitored by researchers at any time, adherence can be well guaranteed.	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Other Chinese or Western medicines for phlegm and cough indications of COPD (except for for patients with COPD long-term basic treatment) should be Prohibited.	12

	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 Outcomes:1) Clinical symptoms and TCM syndrome score: be estimated at the baseline, Day 1, Day 2, Day 3, Day 4, Day 5 (Intervention period), Day 6 and discharge (Post-Intervention period);2) Blood gas analysis(PH、PaO_2、$PaCO_2$): be estimated at the baseline and Day 6;3) Serum inflammatory markers(PCT、CRP、IL-6、TNF-α): be estimated at the baseline, Day 3 and Day 6;4) Induced sputum and Stool sample: be estimated at the baseline and Day 6. Since AECOPD is defined as acute worsening of respiratory symptoms(typically dyspnea, cough, increased sputum and/or purulent sputum) in patients with COPD, the change of symptom score is very important to evaluate the clinical efficacy of XJXBCQ. AECOPD patients often present with changes in serum inflammatory markers such as PCT、CRP、IL-6、TNF-α and so on, serum inflammatory markers are also objective indicators for effectiveness of intervention. Due to TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", we also estimate microbial flora in induced sputum and stool sample of participants to explore the pathogenesis of AECOPD at the microbiological level.	12,13,14,15
	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) Table 1 in the manuscript	25

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 Since this research is an exploratory study, it has not yet relevant data to support the sample size calculation. So we primitively plan to recruit 360 AECOPD patients allocated as the ratio of 1:1:1, 120 per group, according to the objective conditions such as the research period and budget. The purpose is to initially evaluate the therapeutic effect and safety of Xinjia Xuanbai Chengqi Decoction on AECOPD, and provide basic data for further large-scale, multi-center clinical research.	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size By poster in hospital and WeChat advertisement	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 Using the SAS statistical software to generate a random sequence of 360 subjects (group A, group B, group C) according to the ratio of 1:1:1, listing the serial number as 001-360.	9
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 The treatment allocation is that each center will be assigned a consecutive numbered medication on the basis of the random sequence. An independent clinical statistician will keep the random sequence which be saved in the form of a file in a sealed envelope and record the method, process, result of entire produce, so as to be checked if necessary.	9,10

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions An independent clinical statistician will generate the allocation sequence, the care providers will enrol participants and The independent clinical statistician will assign participants to interventions.	9,10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how The investigator, doctors, nurses, outcome measuring person, statisticians and the participants have no idea about the group information until the end of the trial, when all statistics work are finished.	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial In case there is a clinical emergency event, the individual's randomized code and group assignment can be identified as quickly as possible through the emergency envelope. Once any envelope has been opened, whether intentional or not, it should be carefully recorded on the Case Report Form (CRF) and the patient will be withdrawn from the study.	9,10
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 China-Japan Friendship Hospital is responsible for training the standard operating procedures of researchers and supervising the progress of all clinical sites.	7
	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 Regular monitoring will be conducted by phone and email.	16

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 All data will first be recorded by the assessor on a paper version of the case report form and then electronically dual-input into the EDC system. The monitor will periodically review the completion and compliance of the CRF. In order to maintain the objectivity of the data, we will ensure that observers and statisticians are unaware of it. The entire process will be monitored by an independent quality inspector.	16
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 Statistical analysis will be performed by SAS 9.4 software. For the continuous variables, the paired t-test will be used to compare the changes of clinical symptom scores pre- and post-intervention, and the covariance analysis model will be used for comparison between groups. The multiplier method will be used to calculate the quartiles (25%, 50%, 75%) of time from enrollment to events happened, and bilateral 95% confidence interval and the incidence rate at each time point after enrollment will be calculated yet. Kaplan-Meier curves will be plotted using the Log-rank test to compare hospital stays and theoretical hospital stays.For the two categorical variables, such as the recurrence rate of laboratory indicator, all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to the ICU during study, and the proportion of re-admission within 30 days after discharge, we will make comparison between groups and calculate the 95% confidence interval using a centrally stratified CMH $\chi 2$ test according to the classification, indicator, time point, quantity and percentage.	16,17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) A subgroup analyses will be conducted when necessary.	16,17

	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) Missing values for major variables, such as failure to observe case data for complete test procedure, using the results of the last observation to carry-forward to the absence of test data, and the amount of subjects in each group to evaluate efficacy at the endpoint is consistent with the beginning of the trail.	16,17
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 Beijing Qihuang Pharmaceutical Clinical Research Center is responsible for data management and in charge of data entry, coding, security, and storage. They are independent from the sponsor and there are no competing interests.	16
	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 Not applicable.	No
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 At each visit, patients will be asked whether there are any adverse effects during the study period. When an adverse event was claimed, we will provide an appropriate treatment to the subject immediately and record the adverse effect. An emergency services will be provided in case of serious adverse events. In addition, we will test the patients' blood routine, urine routine, kidney and liver function.	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor One month at peak of recruitment and two months at plateau of recruitment. The process will be independent from investigators and the sponsor.	8

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval The trial protocol has been approved by the Ethics Committee of China-Japan Friendship Hospital, Beijing, China (approval Number 2018-56-K40-2), and we have got the oral permission of the other 3 centres and we will got formal approval number in this month.	18
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) No	No
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Investigators will invite patients to participate the trial, tell them in detail why we should take this trial and what kind of rights, obligations and risks they will have if they participate the trials. And investigators will give them a written informed consent. Only the patients fully understand and sign the informed consent, can they participant the trial.	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable.	No
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 The personal information will be collected to be used **only** in this trial, and we won't share or maintained the personal information when unnecessary.	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site We declared there were no competing interests for principal investigators for the overall trial and each study site	21
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 Statisticians.	16

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 Treatment expenses for participants during study will be reimbursed. We will give a certain amount of provision according to Institutional Review Board when necessary.	18
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 The results of the studies will be widely distributed in scientific reports as well as academic conferences to benefit policymakers, clinicians and patients.	17,18
	31b	Authorship eligibility guidelines and any intended use of professional writers No	No
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code We had no plans.	No
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates The consent materials had been approved by the Ethics Committee of China-Japan Friendship Hospital,	18
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 Not applicable.	No

*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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Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter, Randomized, Controlled Trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Acute exacerbation of chronic obstructive pulmonary disease, Comparative effectiveness research, Traditional Chinese Medicine

Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter, Randomized, Controlled Trial

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ABSTRACT

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) brings a serious impact on patients' quality of life, and has extremely high morbidity and mortality worldwide. Although there are many therapies being developed to alleviate symptoms and reduce mortality, few studies have supported which treatment method is the best. Traditional Chinese Medicine (TCM) has shown good potential in the prevention and treatment of AECOPD, especially in terms of supplementation and reduction of dosage and adverse effect of Western Medicine. The purpose of this study is to compare effectiveness of combination of TCM and Western Medicine with conventional therapy alone for AECOPD, and to ensure whether the combined therapy may reduce the use of systemic glucocorticoid in AECOPD without influencing efficacy.

Methods and analysis: A multicenter, randomized, double-blind, placebo-controlled study was conducted to enroll a total of 360 eligible patients who will be randomized into Integrated Chinese and Western Medicine group A, B, and Western standard Medicine group C. After 5 days of intervention and 1 month of follow-up, the efficacy

and safety of Xinjia Xuanbai Chengqi Decoction (XJXBCQ) in patients with AECOPD will be observed. The results of evaluation indicators include: clinical symptoms, biochemical indicators such as blood gas analysis, inflammatory markers, hospitalization time, TCM syndrome evaluation, biological indicators such as airway, intestinal flora sequencing.

Ethics and dissemination: This trail has been approved by the Ethics Committee of China-Japan Friendship Hospital. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's post-study health status during follow-up.

Trial registration: Chinese Clinical Trial Registry, ID: ChiCTR1800016915. Registered on 3 July 2018.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, Comparative effectiveness research, Traditional Chinese Medicine

Strengths and limitations of this study

- A randomized, double-blind, placebo-controlled, clinical, critical trial;
- A multi-center trial be carried out in four comprehensive third-grade first-class hospitals across China, which improves the external validity and representativeness of the sample and reduces the risk of selection bias;
- Because clinical symptoms are often accompanied by a certain degree of subjectivity, we combine the core symptoms (cough, phlegm, defecation, dyspnea) score and TCM syndrome score to ensure scientific objectivity;
- As the main phase of the program will be performed during the hospital stay, practitioners will be able to immediately identify and manage adverse reactions to guarantee the safety of participants. Practitioners will maintain good communication with the participants by phone after discharge.
- The 5-day treatment period and the 1-month follow-up period may be a bit short.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterized by airflow obstruction (FEV1<80% predicted and FEV1/FVC ratio<70%) that is not reversible. COPD is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. In China, the prevalence of COPD in people aged 40 years or older is 13.7%[2], more than 1 million people die and more than 5 million people be disabled due to COPD each year.

Acute exacerbation of COPD (AECOPD)[3] is defined as acute worsening of respiratory symptoms(typically dyspnea, cough, increased sputum and/or purulent sputum) in patients with COPD, exceeding normal day-to-day variations that may require a change in medication even hospitalization. Acute exacerbation is an important factor in the death of patients with COPD[4], and is also the main expenditure portion of medical expenses for COPD patients.

Traditional Chinese Medicine (TCM), with characteristic theory of syndrome differentiation and overall conditioning, implies its potential advantages in the treatment of COPD. TCM syndrome studies find that in addition to symptoms such as cough, phlegm, and wheezing, patients in acute exacerbation period are often accompanied by constipation, abdominal distension, and yellow greasy tongue coating. Based on TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", physicians use the method of Tongfu Xiere to AECOPD patients and usually achieve good results in clinical practice. Xinjia Xuanbai Chengqi

Decoction (XJXBCQ), consists of Armeniacae Semen Amarum, Gypsum Fibrosum, Trichosanthis Fructus, Rhei Radix Et Rhizoma, Scutellariae Radix, Perillae Fructus, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle, Fagopyri Dibotryis Rhizoma and Asteris Radix Et Rhizoma is evolved from the TCM classical prescription Xuanbai Chengqi Decoction[5]. AECOPD is often treated with antibiotics, glucocorticoid, etc., with the risk of excessive dosage and unnecessary adverse effect[6], where TCM can play a complementary and alternative role. TCM has been widely used in AECOPD patients attached to the heat-phlegm and sthenic-fu syndrome, especially in combination with Western Medicine, not only can reduce the use of antibiotics, glucocorticoid, etc., but also decrease the adverse effect of modern routine medicine. Despite this, there is not enough evidence to show the efficacy of XJXBCQ on patients ofAECOPD. Hence, a more rigorously designed large-scale, multicenter, randomized trial is needed to assess the effectiveness of XJXBCQ on AECOPD. In conclusion, our aim is to conduct a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of XJXBCQ on AECOPD. The results of this trial will provide evidence that XJXBCQ is an effective prescription for AECOPD. In view of the difficulty in assessing the quality of the decoction, we plan to use the XJXBCQ granules in the trial. The main purpose of this study is to evaluate the clinical symptoms, signs, blood gas analysis, serum inflammatory factors (IL-6[7], TNF-α, CRP[8], PCT), airway and intestinal microbes[9] of AECOPD hospitalized patients with XJXBCQ combined with Western Medicine; The secondary objective was to observe the effect of XJXBCQ combined with Western

Medicine on reducing the use of glucocorticoid[10], the mortality, the hospitalized time, the requirement for invasive mechanical ventilation, and the re-admission rate of acute exacerbation within 30 days after discharge.

METHODS

Study design

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial that enrolled a total of 360 patients that will be randomly assigned to one of three groups: Integrated Chinese and Western Medicine Group A, Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. After 5 days of intervention, the effectiveness and safety of XJXBCQ in participants will be evaluated by comparing the various indicators of the three groups, including clinical symptoms, activity, biochemical indicators and biological indicators.

As the leading unit of the research, China-Japan Friendship Hospital is responsible for training the standard operating procedures of researchers and supervising the progress of all clinical sites. Other participating units include: Zhongshan Hospital affiliated to Fudan University, the First Affiliated Hospital of China Medical University, and Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University. Recruitment allocation: 180 cases will be from China-Japan Friendship Hospital, while the remaining three recruit 60 cases respectively. The flow chart of the trial is shown in Figure 1. This study protocol is registered with the China Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=28338). The Standard

Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 checklist is shown in Additional file 1.

Participants

Patients with AECOPD attached to the heat-phlegm and sthenic-fu syndrome will be enrolled. Heat-phlegm and sthenic-fu syndrome is a typical syndrome type of traditional Chinese medicine based TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl". Referred to “Retention of Heat-Phlegm in the Lung” syndrome in *TCM Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease (2011)*, Heat-phlegm and sthenic-fu syndrome is defined as: Primary symptoms: cough, wheezing, chest distress, yellow and white sticky sputum, abdominal distension, constipation, red tongue, yellow and greasy fur, slippery or rapid pulse; Secondary symptoms: chest pain, facial blushing, thirst with desire to cold drinks, yellow urine, thick fur. Diagnosis: (1) cough or shortness of breath;(2) yellow and white sticky sputum with difficult expectoration;(3) abdominal distension or constipation;(4) facial blushing;(5) thirst with desire to cold drinks;(6) yellow urine;(7) red tongue, yellow and greasy fur, slippery or rapid pulse. The diagnosis should meet (1), (2) and (3), and two of (4), (5), (6) or (7). The first date of participant enrollment was 7 Jan 2019.

Inclusion criteria

Patients must meet all of the following criteria: 1) Meet AECOPD diagnostic criteria; 2) AECOPD severity clinical grade I-II[1,11]; 3) Comply with indications for antibiotic

treatment recommended by *Chinese Expert Consensus on diagnosis and treatment of Accelerated Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)(Updated 2017)*; 4) Comply with the criteria for the heat-phlegm and sthenic-fu syndrome of TCM; 5) Age 40-80 years old, gender is not limited; 6) Provision of signed, informed consent.

Exclusion criteria

Patients who meet one or more of the exclusion criteria listed below will not be allowed: 1) Patients who with asthma, pneumonia, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer or any other airflow-limited disease with known causes and characteristic pathology; 2) Patients with coronary heart disease, hypertensive heart disease or heart valve disease, etc.; 3) Those need invasive mechanical ventilation; 4) Clinically confirmed or highly suspected pulmonary embolism; 5) Combine with diseases of severe cardiovascular, cerebrovascular, hepatorenal and hematopoietic or primary endocrine system[12]; 6) Those with intestinal obstruction requiring surgical intervention; 7) Pregnant or lactation period; 8) Mentally handicapped; 9) ALT, AST> 1.5 times the upper limit of normal reference or Scr> the upper limit of normal reference; 10) Need to combine immunosuppressant; 11) Taking oral or intravenous antibiotics before screening for more than 3 days in last 3 months; 12) Known to be allergic to the basic therapeutic drugs or other excipients prescribed through the research; 13) Known to be allergic to Chinese herbal medicinal ingredient prescription; 14) Those who have participated in or are participating in other clinical trials in last 3 months; 15) Those who be

considered inappropriate to participate in this clinical trial by the investigator.

Sample size

According to our pre-experiment, comparing symptom scores of patients before and after treatment, the average score was 10.67±2.61 on admission, 4.33±1.97 on the 6th day of admission, and the difference value was 6.33±3.73. Excellent efficiency test will be conducted between Integrated Chinese and Western Medicine Group A and Western Standard Medicine Group C, meanwhile non-inferiority test will be conducted between Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. Cut-off point is defined as 1, so expected difference of excellent efficiency test should be more than 7.33(6.33+1), and which of non-inferiority test should be not less than 5.33(6.33-1). When the power=0.8, each of the three groups required 100 effective cases. Considering a 20% shedding rate, a total of 360 cases were needed in the three groups, with 120 cases in each group.

Randomization

A block randomization method will be employed. We will select the appropriate length of the segment and use the SAS statistical software to generate a random sequence of 360 subjects (group A, group B, group C) according to the ratio of 1:1:1, listing the serial number as 001-360. The treatment allocation is that each center will be assigned a consecutive numbered medication on the basis of the random sequence. An independent clinical statistician will record the method, process, result of entire

produce and keep the random sequence which be saved as a file in a sealed envelope , so as to be checked if necessary. In case there is a clinical emergency event, the individual's randomized code and group assignment can be identified as quickly as possible through the emergency envelope. Once any envelope has been opened, whether intentional or not, it should be carefully recorded on the Case Report Form (CRF) and the patient will be withdrawn from the study.

Interventions

Program Description

Volunteers who meet the inclusion criteria will receive an information form and be required to provide written consent to participate in the trial. They will then undergo a physical screening test to determine if there are other comorbidities that may impact the trial. After successful screening, they will participate in the trial, get trial-specific identification (ID) numbers and be assigned to a group according to random sequence. A baseline measurement for each participant is then performed, including clinical symptoms scores and TCM syndrome scores, blood gas analysis (PH, PaO_2, $PaCO_2$), serum inflammatory markers (PCT, CRP, IL-6, TNF-α), induced sputum, stool sample, and so on. The research program flow is shown in Table 1. All outcome measurements will be taken by medical workers who are familiar with the management of these assessments and will be unaware of the participants' group assignments.

All participants will receive Standard Western Medicine treatment follow the *Global*

Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2018, the *Chinese Medical Association Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised 2013)* and the *Chinese Expert Consensus on diagnosis and treatment of Accelerated Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)(Updated 2017)*, including:

General treatment: controlled oxygen therapy, venturi mask oxygen, NIV if requiring non-invasive ventilation;

Antibiotic: Levofloxacin and Sodium Chloride Injection, 0.5g, iv.gtt, qd;

Bronchodilator[13]: Compound Ipratropium Bromide Solution for Inhalation (Combivent), 500ug, inhal, tid.

Beside the above, Group A will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (2 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules (2 bags at a time, tid). Group B will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (1 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules (2 bags at a time, tid); Group C will be given Budesonide Suspension for Inhalation (PULMICORT RESPULES, 1 mg) (2 at a time, bid) and Xinjia Xuanbai Chengqi (XJXBCQ) Granules Placebo (2 bags at a time, tid). The entire trial will go through 5 days.

Xinjia Xuanbai Chengqi Granules

Xinjia Xuanbai Chengqi Granules is a compound preparation of Chinese herbal medicine. The main components are shown in Table 2.

XJXBCQ Granules (2.5 g/bag, Batch number: 180605) are produced and packaged by Anhui Jiren Pharmaceutical Co., Ltd. that have China Pharmaceutical Production License (Number: Wan 20160083). The results of drug quality testing are consistent with the quality standards from *Pharmacopoeia of the People's Republic of China 2015*. XJXBCQ Granules will be administered orally, two bags at a time, three times a day for 5 days. All herbs were tested to the same standard.

Placebo

The placebo consists of starch without any active ingredient is produced by the same manufacturer as XJXBCQ Granules. It is a dextrin that matches as much as possible the appearance and taste of XJXBCQ Granules. The drug instructions for XJXBCQ Granules and placebo are completely consistent.

Comorbidities and exacerbations regulation

Participants are allowed to remain their originally basic treatment (such as medicine for hypertension or diabetes)taken before recruited; If one's condition deteriorates during the study and need to stay in the ICU or perform invasive mechanical ventilation, we will immediately deal with it; Those who need to adjust the antibiotic due to they can't tolerate LVFX or whose condition have not been alleviated but even aggravated after 3 days of treatment, the antibacterial therapy will be adjusted according to the regulations in *the Chinese Expert Consensus for the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) (Updated*

2017). The reasons for adjustment of the antibacterial drug program need to be recorded in detail; Taking conventional treatment once right heart failure or heart rhythm disorders happened. In addition, other Chinese or Western medicines for phlegm and cough indications of COPD (except those for patients with COPD long-term basic treatment) should be prohibited.

Outcome measure

Because overall conditioning is the core values of TCM, there is no single indicator could be able to predict patients' recovery to evaluate effect of XJXBCQ Granules; Thus, a comprehensive assessment is required to AECOPD [14].

Clinical symptoms (cough, phlegm, defecation, dyspnea) score: We will record the color[15], viscosity and amount of sputum[16] daily during the study. Scoring and grading constipation symptoms according to the severity of constipation score; The severity of dyspnea will be assessed by using a modified British Medical Research Council Respiratory Questionnaire (mMRC).

TCM syndrome score: Refer to *the Guidelines for TCM Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2011)* and *Guidelines for Clinical Research of New Traditional Chinese Medicine for Chronic Bronchitis (2002),* we conduct comprehensive evaluation on cough, phlegm, dyspnea, defecation, abdominal distension, fever from perspective of the heat-phlegm and sthenic-fu syndrome. The evaluation criteria of TCM syndrome score are shown in Table 3. Efficacy index (n) = [(pre-intervention scores－post-intervention scores)/ pre-intervention scores] × 100%

Clinical recovery: TCM clinical symptoms and signs disappeared or approximately disappeared, TCM scores decreased ≥90%;

Markedly effective: TCM clinical symptoms and signs are significantly improved, syndrome scores reduced ≥70%;

Effective: TCM clinical symptoms and signs are improved, syndrome scores reduced ≥30%;

Invalid: No TCM clinical symptoms or signs significantly improved and even aggravated, syndrome scores reduced less than 30%.

Blood gas analysis: We will take arterial blood gas analysis (PH, PaO_2, $PaCO_2$) before and after intervention.

Serum inflammatory markers: Serum inflammatory markers include PCT, CRP, IL-6, TNF-α.

Induced sputum and stool sample: Induced sputum and stool sample will be collected at the baseline and Day 6. Due to TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", we also estimate microbial flora in induced sputum and stool sample of participants to explore the pathogenesis of AECOPD at the microbiological level by the 16S rRNA gene sequencing[17] and the whole-genome shotgun sequencing[18].

Theoretical discharge time: The theoretical discharge criteria[19] is: 1) Patients be considered that can adapt to family medicine; 2) Patients can accept a stable inhalation therapy about long-acting bronchiectasis, β2 receptor agonist and/or an anticholinergic drug, with or without inhaled glucocorticoids. A short-acting β2

agonist[20] should be administered less than once per 4 hours; 3) Patients should be able to walk indoors if they were not bedridden before; 4) Eating and sleep is good and not influenced by dyspnea; 5) Stay at clinical stability for 12 ~ 24h; 6) Arterial blood gas analysis should be stable for 12 ~ 24h; 7) Patients or family members fully understand the correct use of stable period medicines; 8) Follow-up and home care plans have been arranged.

Mortality: All-cause mortality and COPD mortality will be calculated respectively for the subjects during the study period.

Actual hospitalization time: Hospitalization time = discharge date - admission date + 1.

The proportion of patients requiring invasive mechanical ventilation during hospitalization: The proportion of patients requiring invasive mechanical ventilation during hospitalization = the number of patients with invasive mechanical ventilation during hospitalization / the total patients .

Proportion of patients transferred to ICU during hospitalization: Proportion of patients transferred to ICU during hospitalization = the number of patients transferred to ICU during hospitalization / the total patients.

Re-admission rate within 30 days after discharge: Judgment criteria for re-admission: subjects are hospitalized again due to COPD or other respiratory illnesses, excluding hospitalization for other illnesses or purposes. The follow-up will be finished and not continued if one is judged to be re-admitted to the hospital during the follow-up period. Re-admission rate = re-admitted patients / completed follow-up

patients.

Safety assessment

The physical examination will be performed every day from the baseline to end of study. Blood routine, urine routine, liver function, renal function test and electrocardiogram will be performed at baseline and Day 6. Any adverse event occurs during the study will be observed and recorded in detail.

Quality control and data management

Prior to the study, the protocol had been reviewed and revised several times by clinicians, statistics, and methodologists. All staff members of the trial are required to participate in a series of trainings to ensure that the personnel involved fully understand the research protocol and standard operating procedures (SOPs) to guarantee accuracy and completeness of clinical data. Regular monitoring will be conducted by phone and email. All data will first be recorded by the assessor on a paper version of the case report form and then electronically dual-input into the EDC system. The monitor will periodically review the completion and compliance of the CRF. In order to maintain the objectivity of the data, we will ensure that observers and statisticians are unaware of it. The entire process will be monitored by an independent quality inspector. Beijing Qihuang Pharmaceutical Clinical Research Center is responsible for data management.

Statistical analysis

Full Analysis Set (FAS), Per Protocol Set (PPS), and Safety Analysis Set (SS) will be employed. FAS means an ideal set of all subjects (including all subjects randomized into the group and receiving at least one treatment) as close as possible to the principle of intentional analysis. Missing values for major variables, if once fail to observe whole data of case, we will carry-forward the last observation to the absence of test data, and the amount of subjects in each group to evaluate efficacy at the endpoint will be corresponding to the beginning of trail. PPS refers to all cases that meet the stand protocol, have great compliance, use the trial medicine in the range of 80%-120%, complete the eCRF regulations, the main variables can be measured, the baseline variables are well-preserved, and have no significant violation to the protocol. SS refers to all subjects who accept at least one time treatment after randomization. For the continuous variables, the paired t-test will be used to compare the changes of clinical symptom scores pre- and post-intervention, and the covariance analysis model will be used for comparison between groups. The multiplier method will be used to calculate the quartiles (25%, 50%, 75%) of time from enrollment to events happened, and bilateral 95% confidence interval and the incidence rate at each time point after enrollment will be calculated yet. Kaplan-Meier curves will be plotted using the Log-rank test to compare theoretical hospital stay and actual hospital stay. For the two categorical variables, such as the recurrence rate of laboratory indicator, all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to the ICU during study, and the proportion of re-admission

within 30 days after discharge, we will make comparison between groups and calculate the 95% confidence interval using a centrally stratified CMH $\chi 2$ test according to the classification, indicator, time point, quantity and percentage. Statistical analysis will be performed by SAS 9.4 software.

Patient and public involvement

Neither patients nor their family members were involved in the study design. The results of the studies will be widely distributed in scientific reports as well as academic conferences to benefit policymakers, clinicians and patients.

Ethics and dissemination

This trail has been approved by the Ethics Committee of China-Japan Friendship Hospital. All volunteers will sign the informed consent, which is consistent with the ethical principles set forth in the Helsinki Declaration. Treatment expenses for participants during study will be reimbursed. Data usage will follow the rules of hospital's data oversight committee. Biological samples will be handled following the national guideline on biological waste management and disposal. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's post-study health status during follow-up.

DISCUSSION

Before conducting this experiment, we closely retrieved PubMed, Web of Science, Embase, CNKI (including China doctor/master's theses database and China Proceedings conference full-text database), Wan Fang Data, Vip Journal Integration Platform (VJIP), Chinese BioMedical (CBM) database (Sinomed), etc. and found no definite evidence for effect and safety of Xinjia Xuanbai Chengqi Decoction in the treatment of acute exacerbation of COPD. Therefore, we decide to conduct a multicenter, randomized, controlled clinical trial to closely study its effectiveness and safety. Due to the lack of evidence on the effectiveness of XJXBCQ, we will apply TCM combined with Western Medicine to treat AECOPD to ensure participants' compliance and ethical considerations, because antibiotics, bronchodilators, and glucocorticoids are first-line treatments to improve acute exacerbation of COPD according to guidelines.

COPD is a common, preventable disease, influencing millions worldwide. It seriously impairs patients' social activities, daily activities and quality of lives[21]. The high economic burden of AECOPD to families and societies is growing year by year. The extensive clinical experience of using Chinese medicine in the prevention and treatment of COPD in China shows that TCMpreparations are effective. Due to the complexity of the pathogenesis of COPD, the recent use of combination therapy has attracted more and more attention, providing new prospects for Traditional Chinese Medicine which be considered effective in improving clinical symptoms. TCM possess the advantages of being simple, convenient, efficient, inexpensive, and without serious adverse reactions. A systematic review suggested that Chinese

medicine conspicuously improved the prognosis of patients with COPD but lack of high-quality research hinder the development of evidence-based recommendations for clinical practice. Therefore, we design this critical clinical trial, which has the following advantages: (1) This study is designed as a randomized, double-blind, placebo-controlled, clinical, critical trial from the perspective of evidence-based medicine, that is considered to be the most definitive research method of treatment evaluation; (2) At the same time, this is a multi-center trial be carried out in four comprehensive third-grade first-class hospitals across China, which improves the external validity and representativeness of the sample and reduces the risk of selection bias; (3) Because clinical symptoms are often accompanied by a certain degree of subjectivity , we combine the core symptoms (cough phlegm, defecation, dyspnea) score and TCM syndrome score to ensure scientific objectivity; (4) In order to ensure quality, all staff in the study must complete the training of the standard operating procedures of the research program before recruitment; (5) As the main phase of the program will be performed during the hospital stay, practitioners will be able to immediately identify and manage adverse reactions to guarantee the safety of participants. Practitioners will maintain good communication with the participants by phone after discharge. However, the design of the program also has potential limitations, for example, the 5-day treatment period and the 1-month follow-up period are a bit short.

In conclusion, the aim of this study is to answer whether traditional Chinese medicine can supplement and reduce COPD Western medical treatments, reduce frequency of

acute exacerbation of COPD, and provide objective data about effectiveness and safety. If the trial is successful, it will provide patients and physicians with a new option of combining XJXBCQ with Western Medicine for better disease remission, which can be implemented on a larger scale in clinical and community settings[22]. As an innovative and potentially cost-effective strategy, this approach can reduce the disease and financial burden of AECOPD. Given the high prevalence of COPD and serious consequences of acute exacerbations in this group of people, the results of this study can be used to provide information on future international guidelines.

Trial status

Recruitment started in October 2018 and is expected to finish in March 2020, 18 months in total.

Acknowledgements

The authors would like to acknowledge Beijing Qihuang Pharmaceutical Clinical Research Center for managing the trail, Anhui Jiren Pharmaceutical Co., Ltd for produce and package of granules. Most especially, we would like to thank the patients with AECOPD who participate in this study.

Competing interests

None.

Funding

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Availability of data and materials

The data form the study will be available once the study is completed.

Authors' contributions

JJ and ZHC are co-first authors of this manuscript, contributing equally to the design, conduct of the trials and drafting the manuscript. All authors participated in the design of the study and performed the trial. ZH, ZY, CTH, and LX supervised and coordinated the clinical trial. JJ, LDM, JY, ZJ, CQJ and LER are responsible for recruiting the participants. SZT and FJH participated in the statistical design. All authors read and approved the final manuscript.

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Table 1: Data collected from baseline to follow-up visits

	Study period									
	Enrollment	**Allocation**	**Intervention**						**Post- Intervention**	
	D-1	D0	D1	D2	D3	D4	D5	D6	Discharge	30 days after discharge
Enrollment:										
Consent form	√									
Basic information	√									
Inclusion & exclusion criteria	√									
Allocation		√								
Intervention:										
XJXBCQ+Budesonide (All)+ WST			√	√	√	√	√			

XJXBCQ+Budesonide (Half)+ WST			√	√	√	√	√			
XJXBCQ										
placebo+Budesonide (All)+ WST			√	√	√	√	√			
Outcome measure:										
Clinical symptoms score	√		√	√	√	√	√	√	√	
TCM syndrome score	√		√	√	√	√	√	√	√	
Blood gas analysis（PH、PaO2、PaCO2）	√						√			
Serum inflammatory markers（PCT、CRP、IL-6、TNF-α）	√				√		√			
Induced sputum & Stool sample	√						√			
Safety assessments:										
Adverse events recorded	√		√	√	√	√	√	√	√	√
Physical examination	√		√	√	√	√	√	√	√	
Blood & Urine routine	√						√			
Liver function（AST、ALT、Tbil、ALP、GGT）	√						√			
Kidney function（Scr、	√						√			

BUN、eGFR)		
ECG	√	√

Table 2: Main components of Xinjia Xuanbai Chengqi Decoction

Chinese name	Latin name	Amount (g)
Ku Xing Ren	Armeniacae Semen Amarum	6g
Sheng Shi Gao	Gypsum Fibrosum	15g
Gua Lou	Trichosanthis Fructus	9g
Da Huang	Rhei Radix Et Rhizoma	6g
Huang Qin	Scutellariae Radix	9g
Zi Su Zi	Perillae Fructus	9g
Zhi Gan Cao	Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle	6g
Jin Qiao Mai	Fagopyri Dibotryis Rhizoma	10g
Zi Wan	Asteris Radix Et Rhizoma	9g

Table 3: Evaluation criteria of TCM syndrome score

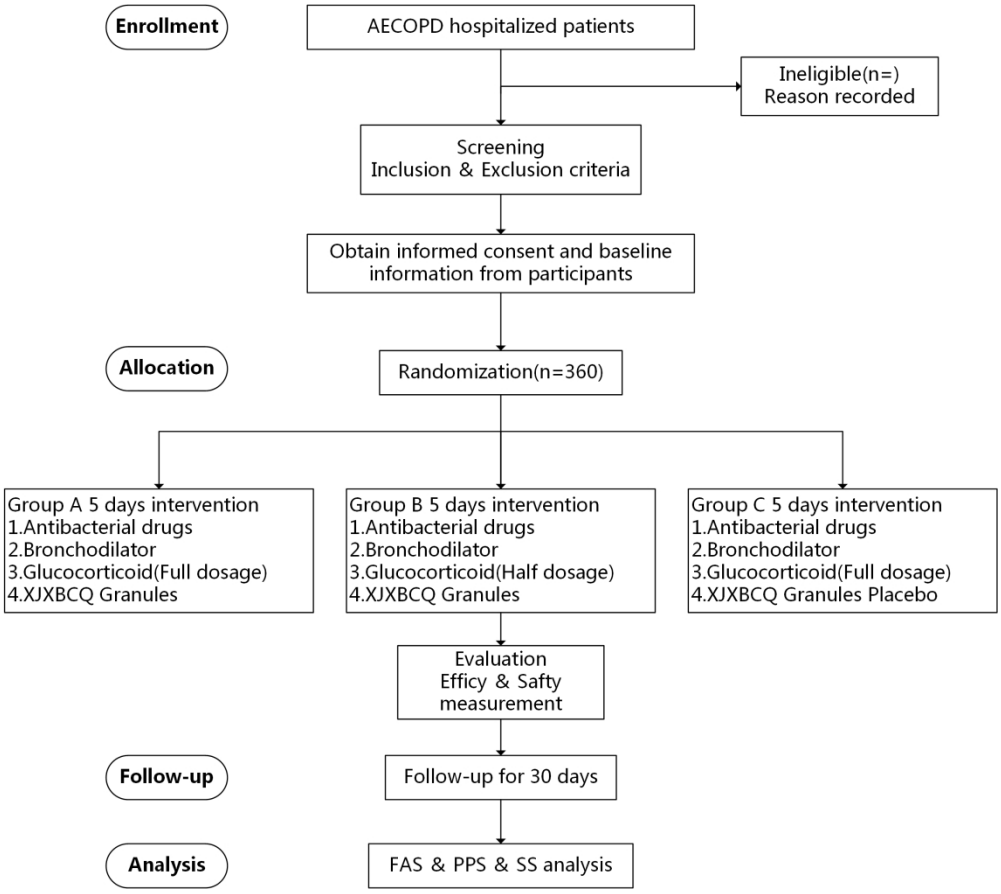
syndrome	**Normal (0)**	**Mild (3)**	**Moderate (6)**	**Severe (9)**
cough	Not significant	In the morning only	Occasionally at any time	Frequently
phlegm	Not significant	10~50ml in 24h or dilute white sputum	50~100ml in 24h or sticky yellow sputum easily	＞1000ml in 24h or sticky yellow sputum difficultly

			expectorated	expectorated
dyspnea	Not significant	Occasionally but not impacting sleep or activity	Accompanying with activity but improved after rest	Too drastic to be supine position or sleep or do other activities
constipation	Not significant	Dry stool once a day	Very dry and once two days	Very hard and once several days
abdominal distension	Not significant	A little	Occasional	Continuous
fever	Not significant	37.5~38..0℃	38.1~39.0℃	＞39.0℃

Figure legend

Figure 1 Study flow chart. FAS, Full Analysis Set; PPS, Per Protocol Set; SS, Safety Analysis Set.

Table 1 Basic information includes gender, height, weight, COPD history, other diseases combined and medical status, etc. XJXBCQ, Xinjia Xuanbai Chengqi Granules; WST, western standard treatment; TCM, Traditional Chinese Medicine.



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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym A multicenter randomized controlled trial, 360 patients included, Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Full dosage of Glucocorticoid VS Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Half dosage of Glucocorticoid) VS Xinjia Xuanbai Chengqi Decoction placebo combined with western standard Medicine(Full dosage of Glucocorticoid).	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Chinese Clinical Trial Registry, ID: ChiCTR1800016915. Registered on 3 July 2018.	3
	2b	All items from the World Health Organization Trial Registration Data Set Not applicable.	No
Protocol version	3	Date and version identifier August 2018, version 1.2	No
Funding	4	Sources and types of financial, material, and other support The national key research and development project (2017YFC1309305)	21

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Jin Jin is from Beijing University of Chinese Medicine, Zhang Hong-chun and Li De-min are from Department of TCM Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, Jing Yue is from Wangjing Hospital of China Academy of Chinese Medical Sciences, Sun Zeng-tao is from Tianjin University of Traditional Chinese Medicine, Feng Ji-hong is from Affiliated Hospital of Tianjin University of TCM, Zhang Hong and Zhang Yan are from Department of Innovation and Transformation, National Center for Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine of the People's Republic of China,Cui Tian-hong and Lei Xiang are from Beijing Qihuang Medicine Clinical Research Center. JJ and ZHC are co-first author of this manuscript, contributing equally to the design, conduct the trials and draft the manuscript. All authors participated in the design of the study and performed the trial. ZH, ZY, CTH and LX supervised and coordinated the clinical trial. JJ, LDM, JY, ZJ, CQJ and LER are responsible for recruiting the participants. SZT and FJH are participated in statistical design. All authors read and approved the final manuscript.	1,21
	5b	Name and contact information for the trial sponsor Zhang Hong-chun, Department of TCM Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, Ying Huayuan East Street, Chaoyang District, Beijing 100029, China. Fax: 0086-10-8463-3656;Email: 13701226664@139.com	1
	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 ZHC supervised and coordinated the clinical trial, conceived of the study and revised the manuscript critically for important intellectual content.	21

	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) China-Japan Friendship Hospital, Zhongshan Hospital affiliated to Fudan University, the First Affiliated Hospital of China Medical University, and Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University.	7
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 To observe the effect of Xinjia Xuanbai Chengqi Decoction combined with western medicine on the treatment of AECOPD. Common treatment of AECOPD is a 5-day high dose of Glucocorticoid plus Bronchodilator and/or Antibiotic,but whether this treatment is optimal is not known. the method of Tongfu Xiere has been widely used in AECOPD patients and usually achieve good results in clinical practice, especially in combination with Western Medicine, not only can reduce the use of antibiotics, glucocorticoid, etc., but also decrease the side effects of modern routine medicine. Despite this, there is not enough evidence to show the effectiveness.	5,6
	6b	Explanation for choice of comparators The comparator is Xinjia Xuanbai Chengqi Decoction placebo and Glucocorticoid for Glucocorticoid is considered to be effective in improving symptoms of AECOPD.	11
Objectives	7	Specific objectives or hypotheses Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Half dosage of Glucocorticoid is equivalent in the treatment of AECOPD, compared to Xinjia Xuanbai Chengqi Decoction combined with western standard Medicine(Full dosage of Glucocorticoid), preferred to using western standard Medicine(Full dosage of Glucocorticoid) alone.	11

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) Three arms parallel group, 1:1:1, non-inferiority and superiority	7

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 China-Japan Friendship Hospital(Beijing), Zhongshan Hospital affiliated to Fudan University, Ruijin Hospital affiliated to School of Medicine, Shanghai Jiao Tong University(Shanghai), and the First Affiliated Hospital of China Medical University (Shenyang).All of the hospital listed above is in China.	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) Inclusion criteria: 1) Meet AECOPD diagnostic criteria; 2) AECOPD severity clinical grade I-II; 3) Comply with indications for antibiotic treatment recommended by *AECOPD Chinese Expert Consensus (Revised 2017)*; 4) Comply with the criteria for the heat-phlegm and sthenic-fu syndrome; 5) Age 40-80 years old, gender is not limited; 6) Provision of signed, informed consent. Exclusion criteria: 1) Patients who with asthma, bronchiectasis, cystic fibrosis, pulmonary tuberculosis, lung cancer or other airflow-limited disease with known causes and characteristic pathology; 2) Patients with coronary heart disease, hypertensive heart disease, heart valve disease, etc.; 3) Those need invasive mechanical ventilation; 4) Clinically confirmed or highly suspected pulmonary embolism; 5) Combine with diseases of severe cardiovascular, cerebrovascular, hepatorenal and hematopoietic or primary endocrine system[12]; 6) Those with intestinal obstruction requiring surgical intervention; 7) Pregnant or lactation period; 8) Mental or mentally handicapped; 9) ALT, AST> 1.5 times the upper limit of normal reference or Scr> the upper limit of normal reference; 10) Need to combine immunosuppressants; 11) Taking oral or intravenous antibiotics before screening for more than 3 days; 12) Known to be allergic to the basic therapeutic drugs or any excipients prescribed through the research; 13) Known to be allergic to Chinese herbal medicinal ingredient prescription; 14) Those who have participated in or are participating in other clinical trials within nearly 3 months; 15) Those who be considered inappropriate to participate in this clinical trial by investigator. If applicable, eligibility criteria for study centres and individuals a physician will perform the interventions.	8,9

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Patients in intervention group will administrate Xinjia Xuanbai Chengqi Granule (2.5g/bag, two bags at a time) in 200 milliliter hot water as the instruction and take the solution orally three times a day for 5 days. While patients in the placebo group will take Xinjia Xuanbai Chengqi Granule placebo as the same way as the intervention group. Western medicine will be administrated as the standard operating procedure.	10,11
	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) When serious adverse effects occur, we will provide an appropriate treatment to the subject immediately and record the adverse effect and stop the subject to continue to take the given medicine.	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Since all participants are hospitalized and can be monitored by researchers at any time, adherence can be well guaranteed.	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Other Chinese or Western medicines for phlegm and cough indications of COPD (except for for patients with COPD long-term basic treatment) should be Prohibited.	12

	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 Outcomes:1) Clinical symptoms and TCM syndrome score: be estimated at the baseline, Day 1, Day 2, Day 3, Day 4, Day 5 (Intervention period), Day 6 and discharge (Post-Intervention period);2) Blood gas analysis(PH、PaO_2、$PaCO_2$): be estimated at the baseline and Day 6;3) Serum inflammatory markers(PCT、CRP、IL-6、TNF-α): be estimated at the baseline, Day 3 and Day 6;4) Induced sputum and Stool sample: be estimated at the baseline and Day 6. Since AECOPD is defined as acute worsening of respiratory symptoms(typically dyspnea, cough, increased sputum and/or purulent sputum) in patients with COPD, the change of symptom score is very important to evaluate the clinical efficacy of XJXBCQ. AECOPD patients often present with changes in serum inflammatory markers such as PCT、CRP、IL-6、TNF-α and so on, serum inflammatory markers are also objective indicators for effectiveness of intervention. Due to TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl", we also estimate microbial flora in induced sputum and stool sample of participants to explore the pathogenesis of AECOPD at the microbiological level.	12,13,14,15
	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) Table 1 in the manuscript	25

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 Since this research is an exploratory study, it has not yet relevant data to support the sample size calculation. So we primitively plan to recruit 360 AECOPD patients allocated as the ratio of 1:1:1, 120 per group, according to the objective conditions such as the research period and budget. The purpose is to initially evaluate the therapeutic effect and safety of Xinjia Xuanbai Chengqi Decoction on AECOPD, and provide basic data for further large-scale, multi-center clinical research.	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size By poster in hospital and WeChat advertisement	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 Using the SAS statistical software to generate a random sequence of 360 subjects (group A, group B, group C) according to the ratio of 1:1:1, listing the serial number as 001-360.	9
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 The treatment allocation is that each center will be assigned a consecutive numbered medication on the basis of the random sequence. An independent clinical statistician will keep the random sequence which be saved in the form of a file in a sealed envelope and record the method, process, result of entire produce, so as to be checked if necessary.	9,10

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions An independent clinical statistician will generate the allocation sequence, the care providers will enrol participants and The independent clinical statistician will assign participants to interventions.	9,10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how The investigator, doctors, nurses, outcome measuring person, statisticians and the participants have no idea about the group information until the end of the trial, when all statistics work are finished.	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial In case there is a clinical emergency event, the individual's randomized code and group assignment can be identified as quickly as possible through the emergency envelope. Once any envelope has been opened, whether intentional or not, it should be carefully recorded on the Case Report Form (CRF) and the patient will be withdrawn from the study.	9,10
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 China-Japan Friendship Hospital is responsible for training the standard operating procedures of researchers and supervising the progress of all clinical sites.	7
	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 Regular monitoring will be conducted by phone and email.	16

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 All data will first be recorded by the assessor on a paper version of the case report form and then electronically dual-input into the EDC system. The monitor will periodically review the completion and compliance of the CRF. In order to maintain the objectivity of the data, we will ensure that observers and statisticians are unaware of it. The entire process will be monitored by an independent quality inspector.	16
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 Statistical analysis will be performed by SAS 9.4 software. For the continuous variables, the paired t-test will be used to compare the changes of clinical symptom scores pre- and post-intervention, and the covariance analysis model will be used for comparison between groups. The multiplier method will be used to calculate the quartiles (25%, 50%, 75%) of time from enrollment to events happened, and bilateral 95% confidence interval and the incidence rate at each time point after enrollment will be calculated yet. Kaplan-Meier curves will be plotted using the Log-rank test to compare hospital stays and theoretical hospital stays.For the two categorical variables, such as the recurrence rate of laboratory indicator, all-cause mortality, the proportion of mechanical ventilation, the proportion of patients transferred to the ICU during study, and the proportion of re-admission within 30 days after discharge, we will make comparison between groups and calculate the 95% confidence interval using a centrally stratified CMH $\chi 2$ test according to the classification, indicator, time point, quantity and percentage.	16,17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) A subgroup analyses will be conducted when necessary.	16,17

	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) Missing values for major variables, such as failure to observe case data for complete test procedure, using the results of the last observation to carry-forward to the absence of test data, and the amount of subjects in each group to evaluate efficacy at the endpoint is consistent with the beginning of the trail.	16,17
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 Beijing Qihuang Pharmaceutical Clinical Research Center is responsible for data management and in charge of data entry, coding, security, and storage. They are independent from the sponsor and there are no competing interests.	16
	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 Not applicable.	No
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 At each visit, patients will be asked whether there are any adverse effects during the study period. When an adverse event was claimed, we will provide an appropriate treatment to the subject immediately and record the adverse effect. An emergency services will be provided in case of serious adverse events. In addition, we will test the patients' blood routine, urine routine, kidney and liver function.	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor One month at peak of recruitment and two months at plateau of recruitment. The process will be independent from investigators and the sponsor.	8

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval The trial protocol has been approved by the Ethics Committee of China-Japan Friendship Hospital, Beijing, China (approval Number 2018-56-K40-2), and we have got the oral permission of the other 3 centres and we will got formal approval number in this month.	18
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) No	No
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Investigators will invite patients to participate the trial, tell them in detail why we should take this trial and what kind of rights, obligations and risks they will have if they participate the trials. And investigators will give them a written informed consent. Only the patients fully understand and sign the informed consent, can they participant the trial.	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable.	No
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 The personal information will be collected to be used **only** in this trial, and we won't share or maintained the personal information when unnecessary.	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site We declared there were no competing interests for principal investigators for the overall trial and each study site	21
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 Statisticians.	16

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 Treatment expenses for participants during study will be reimbursed. We will give a certain amount of provision according to Institutional Review Board when necessary.	18
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 The results of the studies will be widely distributed in scientific reports as well as academic conferences to benefit policymakers, clinicians and patients.	17,18
	31b	Authorship eligibility guidelines and any intended use of professional writers No	No
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code We had no plans.	No
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates The consent materials had been approved by the Ethics Committee of China-Japan Friendship Hospital,	18
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 Not applicable.	No

*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.