BMJ Open

Shufeng Jiedu capsule for acute exacerbation of chronic obstructive pulmonary disease: a protocol of multicentre, randomised, double-blind, placebo-controlled trial

Ruyu Xia ,[1] Yutong Fei,[1] Lishan Zhang,[2] Zhijun Jie,[3] Xiaoyun Fan,[4] Mengyuan Dai,[5] Michael Moore ,[6] Merlin Willcox ,[6] Xiaoyang Hu,[6] Nick Francis ,[6] Changhao Liang ,[1] Guanghe Fei,[5] Jianping Liu[1]

To cite: Xia R, Fei Y, Zhang L, *et al*. Shufeng Jiedu capsule for acute exacerbation of chronic obstructive pulmonary disease: a protocol of multicentre, randomised, double-blind, placebo-controlled trial. *BMJ Open* 2023;**13**:e070864. doi:10.1136/bmjopen-2022-070864

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-070864).

GF and JL contributed equally.

Received 07 December 2022
Accepted 20 August 2023

For numbered affiliations see end of article.

Correspondence to
Dr Jianping Liu; liujp@bucm.edu.cn and Dr Guanghe Fei; guanghefei@126.com

ABSTRACT

Introduction Chronic obstructive pulmonary disease (COPD) represents one of the leading causes of death worldwide. Published clinical trials suggest that the Chinese patent herbal medicine Shufeng Jiedu capsule (SFJD) is safe and may be effective for treating acute exacerbations of COPD (AECOPD). However, these effects have been reported with low or very low certainty evidence. This trial aims to evaluate the effectiveness and safety of SFJD for AECOPD.

Methods and analysis This study is designed as a multicentre, randomised, double-blind, placebo-controlled trial. Three hundred patients with moderate or severe hospitalised AECOPD will be recruited in Beijing, Shanghai and Hefei. Participants will be randomly assigned to SFJD and usual care or placebo and usual care at a ratio of 1:1. SFJD and placebo will be administered orally four capsules three times daily for 7 consecutive days followed by an 8-week follow-up period. The primary outcome will be COPD symptom severity as measured by the EXAcerbation of Chronic Pulmonary Disease Tool score. Secondary outcomes include clinical symptoms, quality of life, length of hospital stay, a total dose of antibiotics, the frequency of recurrence of AECOPD, haematological biomarkers, death and adverse events. This study will answer the question of whether SFJD was safe to use and will improve symptoms in people with AECOPD, and will therefore reduce the necessity for antibiotics, the risk and duration of admission to hospital, and the risk of recurrence.

Ethics and dissemination The ethics committee of the first affiliated hospital of Anhui Medical University, Beijing University of Chinese Medicine affiliated Dongzhimen hospital and fifth people's hospital of Shanghai Fudan University approved the study protocol. Informed written consent will be obtained from all the participants. The results of this trial will be disseminated at academic conferences and in peer-reviewed publications.

Trial registration number ISRCTN99049821.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The current trial will be a multicentre randomised placebo-controlled double-blind parallel group trial.
⇒ This trial will investigate the effectiveness and safety of Shufeng Jiedu capsule for acute exacerbation of chronic obstructive pulmonary disease.
⇒ The aim of this trial will be to analyse whether Shufeng Jiedu capsule will improve symptoms in people with acute exacerbation of chronic obstructive pulmonary disease, and will therefore reduce the necessity for antibiotics, the risk and duration of admission to hospital, and the risk of recurrence.
⇒ The target sample size will be 300 participants (150 administered with placebo and 150 with the Shufeng Jiedu capsule).

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, causing 6% of total deaths in 2019.[1] The prevalence of COPD is up to 13.7% in the Chinese population aged 40 years or older.[2] Acute worsening of respiratory symptoms necessitating additional therapy is known as an acute exacerbation of chronic obstructive pulmonary disease (AECOPD).[3] Each patients with COPD experience 0.5–3.5 episodes of acute exacerbations on average each year.[4] AECOPD leads to increased need for hospitalisation and risk of death in patients with COPD.[5 6] AECOPD accounts for the largest proportion of the total COPD burden in the healthcare system. The most frequent causes of AECOPD are respiratory infections brought on by viruses or bacteria and non-infectious environmental factors such air pollution.[5 7] A systematic review has shown that the prevalence of bacterial infection was approximately 50% in patients

with AECOPD.[8] A real-world study in China found that 86.2% of hospitalised patients with AECOPD received antibiotic treatment, and the median antibiotic therapy duration (9.0 days) was significantly longer than international guidelines, which suggests overuse of antibiotics in patients with AECOPD.[9]

Chinese herbal medicine (CHM) has a long history of treating respiratory tract infections. Chinese patent herbal medicine accounts for 62.8% or higher in the market of medications for respiratory tract diseases in China.[10] An oral Chinese patent herbal medicine called Shufeng Jiedu capsule (SFJD) is commonly used to treat acute respiratory tract infections in China.[11] SFJD is made up of eight common Chinese herbs, including *Reynoutria japonica* Houtt. (Polygonaceae), *Forsythia suspensa* (Thunb.) Vahl (Oleaceae), *Isatis indigotica* (Brassicaceae), *Bupleurum chinense* DC. (Apiaceae), *Patrinia scabiosifolia f. scabiosifolia* (*Caprifoliaceae*), *Verbena officinalis* L. (Verbenaceae), *Phragmites australis subsp. australis* (Poaceae) and *Glycyrrhiza uralensis* Fisch. ex DC. (Fabaceae). Preclinical studies suggested that SFJD may have a broad-spectrum antibacterial, antiviral, anti-inflammatory, antipyretic and immunomodulatory effects.[12–18] A published systematic review found SFJD plus usual care is associated with a significant decrease in the treatment failure rate (from 20.1% to 8.3%) and length of hospital stay (mean difference −4.32 days) for AECOPD when compared with usual care alone.[19] However, trials included in this systematic review were with low or very low certainty due to high risk of bias, mainly with inadequate blinding, and the insufficient number of participants in each trial.

This randomised, multicentre, double-blind, placebo-controlled trial is designed to evaluate the therapeutic effectiveness and safety of SFJD in patients with AECOPD. The Standard Protocol Items: Recommendations for Interventional Trials guidelines have been used to develop the protocol for this trial (see online supplemental file 1).[20]

METHODS AND ANALYSIS

Aims of the study

The main aim of this study is to evaluate the effectiveness and safety of SFJD in addition to conventional treatment for AECOPD.

Trial design

This clinical trial is designed as a multicentre, double-blind, parallel-group, randomised and placebo-controlled trial. The trial will include 300 participants with AECOPD. Informed consent will be taken by trained investigators. Before enrolment, every eligible patient must sign a written consent form for trial participation. Then, participants will be randomised to either SFJD and usual care group or placebo and usual care group at a 1:1 ratio. For both groups, SFJD and placebo will be administered orally for consecutive 7 days (1 week) followed by an 8-week follow-up period. This clinical trial is registered at ISRCTN registry in October 2021 with an identifier (ISRCTN99049821). Figure 1 displays the trial's flow diagram.

Trial setting

The study will be simultaneously conducted in three centres, namely the first affiliated hospital of Anhui medical university, Beijing University of Chinese Medicine affiliated Dongzhimen hospital and fifth people's hospital of Shanghai Fudan University. Participants will be recruited through posters in the hospitals. A brief summary of the eligible participants and details on how they are involved in the trial will be included in the poster information. The trial protocol, in addition its benefits and risks will be discussed with eligible patients by researchers.

Participants

Inclusion criteria

The participants who are included must meet all the following criteria: (1) aged 40 years and older; (2) diagnosis of COPD according to Global Strategy for the Diagnosis, Management, and Prevention of COPD[21] or diagnosis of COPD in clinical record; (3) current acute exacerbation of COPD with at least one of the following: increased sputum purulence, increased sputum volume, or increased breathlessness[21]; (4) moderate or severe hospitalised acute exacerbation of COPD (forced expiratory volume in 1 s (FEV1) % range from 30% to 80%); (5) willing and able to comply with all study procedures, and has signed the informed consent form.

Exclusion criteria

Patients who meet one or more of the following criteria will be excluded:

1. Pleural empyema, a primary diagnosis of bronchiectasis, cystic fibrosis, chronic neurological disorder preventing clearance of pulmonary secretions, severe pulmonary illness (eg, needed mechanical ventilation treatment, or necessity for admission to intensive care unit), or other active chronic respiratory disease.
2. Confirmed or suspected respiratory tract infections attributable to sources other than acute exacerbation of COPD, non-infectious causes of pulmonary infiltrates.
3. Patients who require concomitant antimicrobial or systemic antifungal therapy for any reason.
4. Infections or conditions requiring concomitant systemic corticosteroids.
5. Previous treatment with an antimicrobial or corticosteroids for treatment of this acute exacerbation of COPD more than 72 hours leading up to admission.
6. Using other traditional Chinese medicine as therapy for this acute exacerbation of COPD.
7. Probenecid administration within 3 days prior to initiation of the study treatment regimen or requirement for concomitant therapy with probenecid.

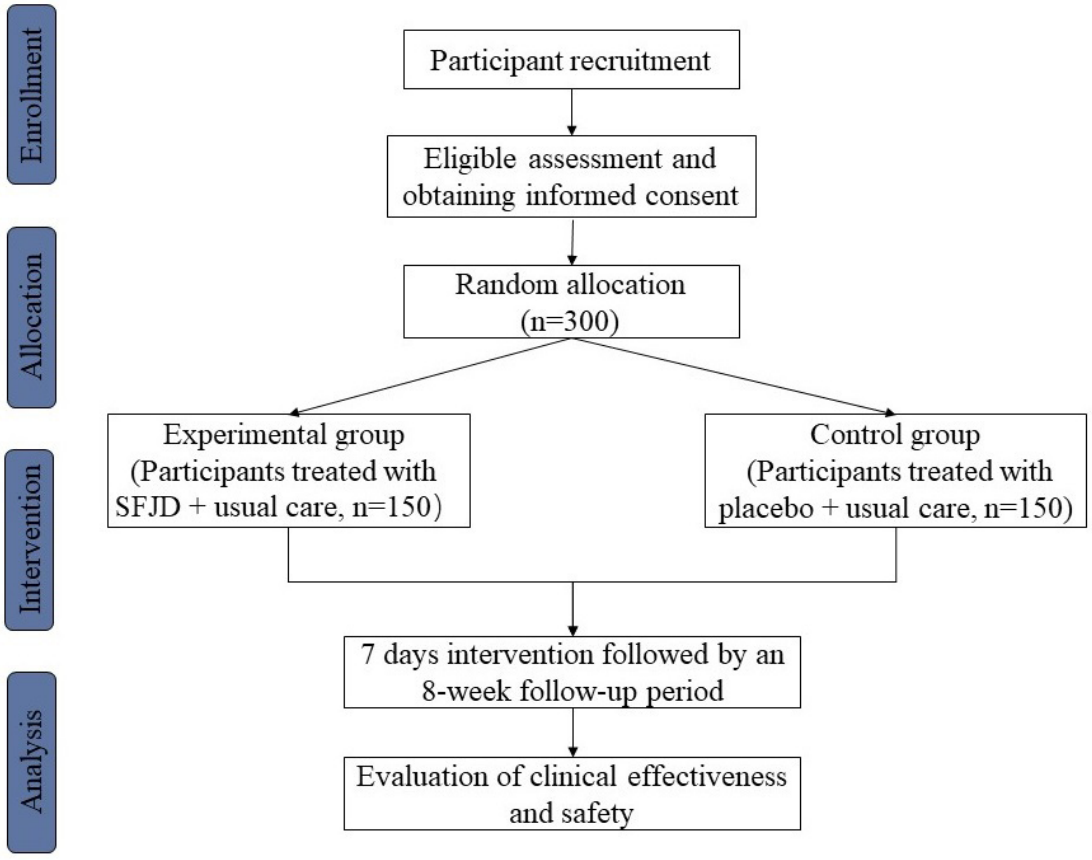

Figure 1 Study flow chart.

8. Hospitalised within 14 days prior to onset of symptoms.
   a. Tests indicate severe liver disease, impaired renal function, haematological or immunological disease.
9. History of epilepsy or seizure disorder.
10. Carcinoma or immediately life-threatening disease, or life expectancy of less than or equal to 3 months.
11. History of any hypersensitivity or allergic reaction to SFJD or components of SFJD.
12. Pregnant or lactating women, and women not using an effective form of contraception.
13. Previously recruited into another drug trial within the last 6 weeks.
14. Involved in the planning and/or conduct of the study.

Criteria for participants who discontinue the trial

Patients are free to withdraw from the research project for any reason at any time, and the reason will be recorded in the case report form (CRF). Reasons for premature discontinuation of the trial may include, but are not limited to patient decision, severe non-compliance to study protocol, safety or insufficient therapeutic effect. Those patients who discontinue prematurely from the trial should always be asked about the reasons and the presence of any adverse events. Adverse events should also be followed. The end of treatment assessment, the day of meeting discharge criteria assessment and follow-up assessments should be performed.

Intervention

Eligible patients will be randomly assigned to the SFJD group (4×520 mg capsules, orally three times daily for seven consecutive days) or the placebo group (same appearance and taste, 4×520 mg capsules, orally three times daily for seven consecutive days).

The SFJD consists of eight Chinese medicinal herbs (see background section above and Table 1). The quality of these herbs and preparation method was in accordance with the Chinese Pharmacopoeia.[22] The detailed manufacturing procedure of SFJD is available on the website of the China Patent Inquiry System and carried out in strict compliance with the standards of Good Manufacturing Practice (GMP). The ratio of individual herbs contained in the SFJD formula together with the extraction solvent are listed in table 1. SFJD has been approved by the China Food and Drug Administration for the treatment of acute upper respiratory tract infection in 2009. It has been widely used for respiratory tract infections including AECOPD. A published systematic review found low certainty evidence suggesting possible benefits (57% reduction in the risk of treatment failure, reduction of 4 days in hospital stay) from SFJD in combination with usual care for patients with AECOPD, compared with usual care.[19] The current study evaluates the effects of SFJD in patients with AECOPD.

Table 1 Ratio of individual herb contained in the Shufeng Jiedu capsule (SFJD)

Pharmaceutical name	Extraction solvent	Proportion of formula
Polygoni Cuspidati Rhizoma Et Radix	70% ethanol	16.67%
Forsythiae Fructus	Water	13.33%
Isatidis Radix	70% ethanol	13.33%
Bupleuri Radix	Water	13.33%
Patriniae Herba	Water	13.33%
Verbenae Herba	Water	13.33%
Phragmitis Rhizoma	Water	10%
Glycyrrhizae Radix Et Rhizoma	Water	6.7%
Volatile oils of *Forsythiae Fructus* and *Bupleuri Radix*		approx. 1 µL per capsule

Placebo capsules were designed matching SFJD in size, weight, colour, taste and smell, consisting of corn dextrin (79.66%), caramel (4.62%), food additive lemon yellow (0.35%), compound colourant chocolate brown (0.05%), compound colourant gardenia yellow (0.19%), compound colourant Cocoa Brown (0.23%), naringin (9.62%), anhydrous citric acid (0.96%), menthol (0.96%), FA-10101 sauce flavour essence (2.88%) and MCK135C ginger powder base (0.48%).

All patients will be treated with usual care according to the 2019 Global Strategy for Prevention, Diagnosis and Management of COPD.[21] The following are recommended usual care according to the clinical condition of the patient：

- Combination therapy with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS) (aerosol inhalation of budesonide 1 mg+salbutamol 2.5 mg+2 mL normal saline (two times a day)) or oral/intravenous methylprednisolone (40 mg, four times a day) for 5 days.
- Bronchodilators: inhaled short-acting beta agonists or short-acting muscarinic antagonist, LABA/ICS or long-acting muscarinic antagonist/ICS.
- Oxygen therapy.
- Antibiotics.

Indicators of using antibiotics: antibiotics should be considered when three cardinal symptoms (increase in dyspnoea, sputum volume and sputum purulence) occur; or two of the cardinal symptoms occur, if increased purulence of sputum is one of the two symptoms.

Indicators of antibiotic cessation: doctors can end antibiotic treatment based on their clinical experiences when the patients meet the following criteria (one of the three): dyspnoea, purulent sputum and sputum volume decrease to baseline normal, procalcitonin < 0.25 ng/mL (decrease by 80%), C-reactive protein < 5 mg/L.

Experimental medication preparation and quality control

Anhui Jiren Pharmaceutical Co. (Bozhou, China) is in charge of SFJD and placebo production and quality control (batch no.: 3210601 and 3230401). The production date and expiry date of the first batch of experimental medications (batch no.: 3210601) are June 2021 and May 2023, respectively. The production date and validity period of the second batch of experimental medications (batch no.: 3230401) are April 2023 and March 2025, respectively. The entire production process fully meets GMP requirements. Intermediate products are tested to ensure quality. After finishing the packaging, a sample will be further tested by the laboratory to ensure that the quality meets the expected requirements.

Randomisation, allocation concealment and blinding

The Centre for Evidence-based Chinese Medicine at Beijing University of Chinese Medicine (CEBCM-BUCM) generated the randomisation sequence using centre-based stratification and block randomisation with a fixed block size by the R V.4.1.1 software. The SFJD or placebo will be randomly assigned to the eligible participants at a 1:1 ratio. To reduce selection bias, allocation concealment will be carried out applying the 'coding the drug packaging' approach.[23–25] Participants will be assigned a participant identification number, which will be used for subject identification throughout the study. As closely as possible, the placebo's appearance, flavour and specification will resemble SFJD. The outside package for both placebo and SFJD will be the same. Both participants and investigators will be kept blinded to the allocation until the research is completed. To ensure concealment, the block sizes will not be disclosed.

Only if there is a serious adverse event relevant to the research medication, the assignment code will be broken. The clinician can ask the clinical research associate or the principal investigator to disclose the intervention the participant received if they suffer a serious adverse event or require emergency rescue during the trial. The date and reason for breaking the blinding code should be recorded in the CRF. The participant will be listed as a withdrawal case whenever it is chosen to disclose the intervention they got.

Furthermore, the outcome data collectors and adjudicators were both blinded to the interventions allocation. Also, statisticians will be blinded to the group assignment when analysing the data.

Outcomes

Primary outcomes

COPD symptom severity, measured using EXAcerbation of Chronic Pulmonary Disease Tool (EXACT-PRO) score. We will compare the scores after treatment (day 8) between groups.

Secondary outcomes

- Clinical symptoms measured using COPD Assessment Test scores after treatment; EXACT-PRO scores at day of meeting discharge criteria and three follow-up time points; EXACT-PRO frequency and duration of symptom-defined events, and severity of symptoms.
- Quality of Life measured using St Georges Respiratory Questionnaire and EuroQol-5 Dimensions (EQ-5D) after treatment; EQ-5D scores at day of meeting discharge criteria and three follow-up time points.
- Length of hospital stay measured using the duration from admission to meeting discharge criteria.
- A total dose of antibiotics measured using defined daily dose.
- The frequency of recurrence of acute exacerbations of COPD during follow-up 8 weeks (including medical consultation or readmission).
- Haematological biomarkers (full blood count, inflammation factors) absolute value and change from baseline at end of treatment.
- Death during hospitalisation or follow-up.
- Safety measured using adverse event and adverse drug reaction.
- Change in bacteria identified in sputum samples from baseline to day of meeting discharge criteria

Patient timelines for participants

Study day 1 is defined as the day that the study drug is first administered, baseline assessments for study eligibility will occur within 24 hours prior to administration of the first dose of the study treatment regimen and continues for a treatment duration of 7 days. An end of treatment outcome assessment will occur on day 8, followed by four follow-up assessment timepoints (day of meeting discharge criteria, 14 days, 28 days and 56 days after meeting discharge criteria). The compliance of the participants will be improved by regular telephone follow-up. Table 2 shows the treatment and outcome measurement schedule.

Sample size

We calculated the sample size referring to the EXACT-PRO data of a previous trial.[26] A limited number of studies have compared CHM treatment to placebo in patients with AECOPD, and a limited number of studies have measured EXACT-PRO in patients with AECOPD. Rhee *et al*[26] found that the mean EXACT-PRO score on day 7 (42 points, SD 11) was significantly lower than on day 1 (mean 46.7 points, SD 11.9) for moxifloxacin groups of treatment of moderate AECOPD (FEV1% was 49.1±17.2 in the moxifloxacin group, it corresponds to the moderate and severe GOLD degree, similar to the severity of our trial included patients with AECOPD). It is thus assumed that the mean EXACT-PRO score after treatment in our control group population will be 42 points, SD of EXACT-PRO score after treatment in 2 groups both will be 11. We interviewed three patients who met the inclusion criteria, who thought that the difference of four points of EXACT-PRO would make a difference in their life. Sample-size calculation was performed with PASS V.15. With a one-sided type 1 error of 0.025, 120 patients per group have to be recruited to reject the null-hypothesis with 80% power and a 4 points difference between two groups. Allowing for a dropout of 20%, we will recruit a total of 300 patients.

Data collection and management

Investigators will be trained in standard operating procedures for trial execution. According to the original observation records, investigators at all sites will finish the CRFs completely and correctly in a timely manner, and entered into EpiData Software. Both the treatment period and the follow-up phase will be performed for data collecting. Before the analysis and evaluation, all samples and data are anonymised. All electronic data will be stored in password-protected files on designated computers that researchers can access. CEBCM-BUCM will be responsible for data management. Interim analyses will not be performed.

The trial quality control

The following rules apply to trial quality control: (1) all three centres have significant experience in treating AECOPD, the designated personnel from three centres are in charge of monitoring the trial; (2) the designated CEBCM-BUCM personnel assisted with supervising the entire trial.

The following are included content of quality control: (1) ensure participant protection and informed consent; (2) confirm that the protocol is being followed during the trial process; (3) confirm the data's accuracy, truth and completeness; and (4) confirm that the adverse events are timely recorded and reported.

Statistical analysis

Data analysis will be performed by the designated CEBCM-BUCM personnel in accordance with the trial statistical analysis plan (developed by CEBCM-BUCM). SPSS/SAS software will be used for data statistical analysis. All analyses will follow the intention-to-treat (ITT) principle, which covers all patients who were randomly assigned. ITT will be used to analyse baseline characteristics. Data from participants who drop out from trial will be implemented by the last observation carried forward method. The primary analysis is to be conducted in the ITT population. Along with the ITT analysis, the per-protocol set (PPS) analysis will be performed. When ITT analysis results contradict with PPS analysis results, ITT analysis results will be given preference, and we will

Table 2 Schedule for treatment and outcome measurement

Assessments	Baseline	Intervention (days 1–7)	End of treatment (day 8)	Day of meeting discharge criteria*	Follow-up†		
					Meeting discharge criteria +14 days	Meeting discharge criteria +28 days	Meeting discharge criteria +56 days
Informed consent	√						
EXACT PRO	√	√	√	√	√	√	√
CAT	√	√	√	√	√	√	√
Prior admission/after discharge/ medication	√				√	√	√
Lung function	√			√			
Pulse oximetry	√	√	√	√			
12-lead ECG	√			√			
Chest X-ray or CT scan	√						
Laboratory tests (liver and kidney function, PCT, CRP, IL-6, full blood count, urine test)	√			√			
SGRQ	√		√				
EQ-5D	√	√	√	√	√	√	√
Sputum smear and sputum culture	√			√			
Blood for culture (when temperature>38.5 ℃)							
Record adverse events	√	√	√	√	√	√	√
Administer drug		√	√	√			
Number of visits and admissions					√	√	√

*'Day of meeting discharge criteria' could be before/after end of treatment.
†After the patients meeting discharge criteria, they would fill in the EXACT PRO, CAT, EQ-5D in the patient diary every day until the end of the follow-up period.
CAT, COPD Assessment Test; CRP, C-reactive protein; EQ-5D, EuroQol-5 Dimensions; EXACT PRO, EXAcerbation of Chronic Pulmonary Disease Tool; IL, interleukin; PCT, procalcitonin; SGRQ, St Georges Respiratory Questionnaire.

explore potential reasons for lack of compliance. The safety evaluation will make use of safety set.

Statistical description and statistical analysis methods

The baseline characteristics of the patients will be described by group, using the most appropriate statistics. Regarding continuous outcomes, we will evaluate normality assumptions. Mean and SD will be used to present continuous outcomes that follow a normal distribution, and median and IQR will be used to present continuous outcomes that do not. Quantitative variables will typically be summarised using frequencies and percentages for appropriate categorisations and may also be summarised using descriptive statistics.

For the outcomes, between-group comparisons will be performed using an independent two-sample *t*-test or the Wilcoxon rank-sum test for continuous outcomes. For count data, the χ^2 test or Fisher's exact probability will be required, whereas, for ranked data, the Wilcoxon rank-sum test will be used.

95% CIs will be provided with treatment effect estimates. It will be considered statistically significant when two-tailed p values less than 0.05.

Ethics and dissemination

The Good Clinical Practice Guideline and the declaration of Helsinki will both be followed during the course of this trial. The protocol has been approved by medical ethics committee of first affiliated hospital of Anhui Medical University, Beijing University of Chinese Medicine affiliated Dongzhimen hospital and fifth people's hospital of Shanghai Fudan University. The sponsor of this trial, CEBCM-BUCM, will audit this trial. The primary investigators will discuss and communicate any necessary changes to the trial protocol. The Medical Ethics Committee will also receive an approval request for the updated protocol.

Results of this trial will be disseminated at academic conferences and published in a peer-reviewed journal. Additional documents (statistical analysis plan) may be available. Authorship will be granted to authors who make important contributions.

Patient and public involvement

When calculating the sample size, we estimate minimal clinically important difference of EXACT-PRO based on patient perspective, as we did not find any previous studies on this. Trial participants will not be informed of the trial results directly. However, the final results of this trial will be published.

DISCUSSION

AECOPD may necessitate hospitalisation or emergency department visits and may lead to acute respiratory failure. In the treatment of AECOPD, bronchodilators are frequently used in together with antibiotics, systemic corticosteroids. Guidelines recommend these treatments, which have been confirmed by data from randomised controlled trials.[21 27] However, antibiotics are not always needed, and their excessive use promotes the development of antibiotic resistance.[28]

There are some clinical trials comparing the effect of SFJD plus conventional drugs with conventional drugs alone for the treatment of AECOPD.[29–31] However, none of the trials used placebo, and the majority of trials had an unclear risk of attrition bias. This placebo-controlled multicentre trial will analyse the effect of SFJD on different outcomes in the treatment of AECOPD. The Trial Management Committee is responsible for designing the study and study protocol, maintenance of the quality of study conduct, ongoing monitoring of adverse events and writing study publications. CEBCM-BUCM will regularly review the recruitment rates, follow-up rates and safety aspects of the study.

High-quality evidence regarding the effectiveness and safety of SFJD will be provided, and if effective and safe, this has the potential to be implemented in routine care to relieve the symptoms of AECOPD and reduce the necessity for antibiotics.

Author affiliations
[1]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China
[2]Respiratory Department, Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital, Beijing, China
[3]Department of Respiratory and Critical Care Medicine, Shanghai Fifth People's Hospital, Fudan University, Shanghai, China
[4]Department of Geriatric Respiratory and Critical Care, First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
[5]Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
[6]Primary Care Research Centre, School of Primary Care, Population Sciences and Medical Education, University of Southampton, Southampton, UK

Twitter Nick Francis @nickafrancis

Contributors J-PL, RX, YF and G-HF designed the trial protocol. LZ, ZJ, XF, MD, MM, MW, XH, NF and CL put forward suggestions on the revision of this protocol, especially professional knowledge of COPD and CHM involved in this protocol. RX drafted the manuscript. All authors approved the final manuscript.

Funding This work was supported by the National Key Research and Development Project (grant no. 2018YFE0102300). The funding sources had no role in the design, decision to publish or preparation of the manuscript.

Competing interests The authors declare that they have the following possible conflicts of interest. However, these conflicts of interest did not actually influence the design, and the reporting of this study. The Beijing University of Chinese Medicine obtained funding from the Ministry of Science and Technology of the People's Republic of China for a project investigating the use of Chinese herbal medicine for the treatment of chronic obstructive pulmonary disease. The other partners in the project are the University of Southampton, Anhui Jiren Pharmaceutical Co. (manufacturer of SFJD, providing the trial medication/placebo for free), and Phoenix Medical. The project is part of the "UK-China collaboration to tackle antimicrobial resistance", funded by the UK and Chinese governments. Ruyu Xia, Yutong Fei, Lishan Zhang, Mengyuan Dai, Guanghe Fei and Jianping Liu received this research funding from Ministry of Science and Technology of the People's Republic of China; Michael Moore, Merlin Willcox, and Xiaoyang Hu received this research funding from Innovate-UK.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used and/or analyzed after completing the current study will be available from the corresponding author by reasonable requests.

ORCID iDs
Ruyu Xia http://orcid.org/0000-0001-9828-5195
Michael Moore http://orcid.org/0000-0002-5127-4509
Merlin Willcox http://orcid.org/0000-0002-5227-3444
Nick Francis http://orcid.org/0000-0001-8939-7312
Changhao Liang http://orcid.org/0000-0001-6292-4514

REFERENCES

1 WHO. Global health estimates: the top 10 causes of death. 2020. Available: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
2 Wang C, Xu J, Yang L, *et al*. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China pulmonary health [CPH] study): a national cross-sectional study. *The Lancet* 2018;391:1706–17.
3 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). 2021. Available: https://staging.goldcopd.org/2021-gold-reports/ [Accessed 23 Sep 2022].
4 Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) panel. Expert consensus on diagnosis and treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in China (2017 updated). *Int J Respir* 2017;37:1041–57.
5 Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007;29:1224–38.
6 Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, *et al*. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005;60:925–31.
7 Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *Lancet* 2007;370:786–96.
8 Moghoofei M, Azimzadeh Jamalkandi S, Moein M, *et al*. Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Infection* 2020;48:19–35.

9 Ma Y, Huang K, Liang C, *et al*. Real-world antibiotic use in treating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in China: evidence from the ACURE study. *Front Pharmacol* 2021;12:649884.
10 Li RY. The market of respiratory system medicine exceeded 100 billion yuan in 2015, patent Chinese medicine became the leader. 2022. Available: https://www.jiemian.com/article/717433.html [Accessed 23 Sep 2022].
11 Huang Z, Pan X, Zhou J, *et al*. Chinese herbal medicine for acute upper respiratory tract infections and reproductive safety: a systematic review. *Biosci Trends* 2019;13:117–29.
12 Bao Y, Gao Y, Cui X. Effect of Shufeng Jiedu capsules as a broad-spectrum antibacterial. *Biosci Trends* 2016;10:74–8.
13 Xia L, Shi Y, Su J, *et al*. Shufeng Jiedu, a promising herbal therapy for moderate COVID-19: antiviral and anti-inflammatory properties, pathways of bioactive compounds, and a clinical real-world pragmatic study. *Phytomedicine* 2021;85:153390.
14 Ji S, Bai Q, Wu X, *et al*. Unique synergistic antiviral effects of Shufeng Jiedu capsule and oseltamivir in influenza A viral-induced acute exacerbation of chronic obstructive pulmonary disease. *Biomed Pharmacother* 2020;121:109652.
15 Li Y, Chang N, Han Y, *et al*. Anti-inflammatory effects of Shufeng Jiedu capsule for upper respiratory infection via the ERK pathway. *Biomed Pharmacother* 2017;94:758–66.
16 Yuan Y, Liao Q, Xue M, *et al*. Shufeng Jiedu capsules alleviate lipopolysaccharide-induced acute lung inflammatory injury via activation of GPR18 by verbenalin. *Cell Physiol Biochem* 2018;50:629–39.
17 Yang Z-H, Wang B, Ma Q, *et al*. Potential mechanisms of action of Chinese patent medicines for COVID-19: a review. *Front Pharmacol* 2021;12:668407.
18 Tao Z, Meng X, Han Y-Q, *et al*. Therapeutic mechanistic studies of Shufeng Jiedu capsule in an acute lung injury animal model using quantitative proteomics technology. *J Proteome Res* 2017;16:4009–19.
19 Xia R-Y, Hu X-Y, Fei Y-T, *et al*. Shufeng Jiedu capsules for treating acute exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *BMC Complement Med Ther* 2020;20:151.
20 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
21 Singh D, Agusti A, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019;53:1900164.
22 Chinese Pharmacopoeia Comission. *Pharmacopoeia of the people's republic of China*. Beijing: China Medical Science Press, 2020: 1784.
23 Li J. Allocation concealment: why and how? *Chin J Evid Based Med* 2004;4:714–5.
24 Wang JL. Clinical epidemiology: clinical research design, measurement and evaluation. 4th edn. Shanghai: Shanghai Science and Technology Publishers, 2014: 94–5.
25 Flower A, Witt C, Liu J, *et al*. GP-TCM unabridged guidelines for randomised controlled trials investigating Chinese herbal medicine (CHM). *Eur J Integr Med* 2014;6:186–210.
26 Rhee CK, Chang JH, Choi EG, *et al*. Zabofloxacin versus moxifloxacin in patients with COPD exacerbation: a multicenter, double-blind, double-dummy, randomized, controlled, phase III, non-inferiority trial. *Int J Chron Obstruct Pulmon Dis* 2015;10:2265–75.
27 Wedzicha JA, Miravitlles M, Hurst JR, *et al*. Management of COPD exacerbations: a European respiratory society/American thoracic society guideline. *Eur Respir J* 2017;49:1600791.
28 Stolz D, Tamm M. Discriminate use of antibiotics for exacerbation of COPD. *Curr Opin Pulm Med* 2009;15:126–32.
29 Zhang LG, Li Y. Study on Shufeng Jiedu capsules for acute exacerbation of chronic obstructive pulmonary disease and its affect on patients' status of nutrition. *Beijing Med J* 2015;37:974–6.
30 Hu HZ, Xiong L, Yang SC, *et al*. Effect of Shufeng Jiedu capsule as adjuvant therapy for acute exacerbation of chronic obstructive pulmonary disease. *J Pract Tradit Chin Medi* 2018;34:961–2.
31 Tian TL, Rong L, Qu XK, *et al*. Effect of Shufeng Jiedu capsule on inflammatory regulation in acute exacerbation of chronic obstructive pulmonary disease. *J Emerg Tradit Chin Med* 2018;27:1814–6.