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

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.