

Evaluation of the efficacy and health economics of Bufeì Yishen Formula on patients with frequent acute exacerbations of chronic obstructive pulmonary disease in stable stage: Study protocol for a multi-center, randomized, double-blind, placebo-controlled trial

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) has a high incidence and mortality rate globally. Frequent acute exacerbation of chronic obstructive pulmonary disease (AECOPD) can lead to progressive decline in lung function, gradual deterioration of the disease condition, and even pose a serious threat to patients' lives. However, current treatment measures still need further improvements to reduce the frequency of AECOPD and improve the quality of life of COPD patients. Traditional Chinese medicine (TCM) has certain advantages in treating COPD.

Objective: This study aims to evaluate the efficacy and safety of the Bufei Yishen (BFYS) formula on patients with frequent AECOPD in stable stage and explore its value in health economics.

Methods: This is a multi-center, randomized, double-blind, placebo-controlled trial. A total of 848 eligible patients will participate in the study. The participants will be randomly assigned to the experimental group and the control group at a 1:1 ratio. Both groups will receive health education and biomedical treatments according to relevant guidelines. In addition, the experimental group will take the BFYS granules for 52 weeks, while the control group will take the corresponding BFYS placebos. The primary outcome is the frequency of AECOPD. The secondary outcomes include the number of AECOPD leading to hospitalization or death, the time of the first AECOPD episode, the severity of AECOPD, the duration of AECOPD, the mortality rate, lung function, clinical symptoms and signs, six-minute walk distance (6MWD), COPD Assessment Test (CAT), and 36-item Short-Form (SF-36). Safety will be assessed by blood routine, urine routine, liver function, kidney function, and electrocardiogram. Outcomes will be measured at each visit (day 0 and weeks 13, 26, 39, and 52). Adverse events should be observed and recorded in time throughout the study. Besides, we will evaluate the value of health economics of the BFYS formula through cost-effectiveness analysis methods.

Results: This trial will scientifically assess the clinical efficacy and safety of the BFYS formula in treating patients with frequent AECOPD in stable stage. Moreover, through cost-effectiveness analysis and other analytical methods, this study will estimate the advantages of health economics of the BFYS formula. Thus, the TCM diagnosis and treatment scheme for patients with frequent AECOPD in stable phase will be established.

Conclusions: Therefore, we could draw the conclusion that BFYS formula plays a therapeutic role in COPD through multi-component, multi-pathway, and multi-target. The clinical efficacy of BFYS formula will be confirmed by the results of this trial.

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Original Manuscript

Evaluation of the efficacy and health economics of Bufei Yishen Formula on patients with frequent acute exacerbations of chronic obstructive pulmonary disease in stable stage: Study protocol for a multi-center, randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) has a high incidence and mortality rate globally. Frequent acute exacerbation of chronic obstructive pulmonary disease (AECOPD) can lead to progressive decline in lung function, gradual deterioration of the disease condition, and even pose a serious threat to patients' lives. However, current

treatment measures still need further improvements to reduce the frequency of AECOPD and improve the quality of life of COPD patients. Traditional Chinese medicine (TCM) has certain advantages in treating COPD. Therefore, this study aims to evaluate the efficacy and safety of the Bufe Yishen (BFYS) formula on patients with frequent AECOPD in stable stage and explore its value in health economics.

Methods: This is a multi-center, randomized, double-blind, placebo-controlled trial. A total of 848 eligible patients will participate in the study. The participants will be randomly assigned to the experimental group and the control group at a 1:1 ratio. Both groups will receive health education and biomedical treatments according to relevant guidelines. In addition, the experimental group will take the BFYS granules for 52 weeks, while the control group will take the corresponding BFYS placebos. The primary outcome is the frequency of AECOPD. The secondary outcomes include the number of AECOPD leading to hospitalization or death, the time of the first AECOPD episode, the severity of AECOPD, the duration of AECOPD, the mortality rate, lung function, clinical symptoms and signs, six-minute walk distance (6MWD), COPD Assessment Test (CAT), and 36-item Short-Form (SF-36). Safety will be assessed by blood routine, urine routine, liver function, kidney function, and electrocardiogram. Outcomes will be measured at each visit (day 0 and weeks 13, 26, 39, and 52). Adverse events should be observed and recorded in time throughout the study. Besides, we will evaluate the value of health economics of the BFYS formula through cost-effectiveness analysis methods.

Discussion: This trial will scientifically assess the clinical efficacy and safety of the BFYS formula in treating patients with frequent AECOPD in stable stage. Moreover, through cost-effectiveness analysis and other analytical methods, this study will estimate the advantages of

health economics of the BFYS formula. Thus, the TCM diagnosis and treatment scheme for patients with frequent AECOPD in stable phase will be established.

Trial registration: The number of protocol version is V1.0, version date is December 27th, 2023. This study was registered at ClinicalTrials.gov on March 22, 2024 (No.NCT06326658). <https://clinicaltrials.gov/ct2/show/NCT06326658>.

Keywords: Bufe Yishen formula, frequent acute exacerbations of chronic obstructive pulmonary disease, randomized controlled trial, protocol

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by persistent airflow restriction and respiratory symptoms(1). It has a high incidence and mortality rate globally(2-4). Epidemiological studies showed that the prevalence of COPD among people over 40 years old in China was 13.7%(2). It seriously affects patients' labor capacity and quality of life(5-7). What's worse, according to the statistical data, COPD became the third leading cause of death globally in 2019, resulting in 3.23 million deaths per year and placing a heavy burden on society(8).

Frequent acute exacerbation of chronic obstructive pulmonary disease (AECOPD) refers to two or more acute exacerbations in the past year(9). The interval should be more than 4 weeks since the end of treatment for the previous acute exacerbation, or more than 6 weeks since the prior acute exacerbation in untreated patients. The quality of daily life of patients with AECOPD is significantly decreased, labor capacity is weakened, clinical symptoms are aggravated, and lung function is decreased. AECOPD not only increases the economic burden of families and society but also is closely related to increased mortality(10). At present, biomedical treatments of AECOPD are still dominated by oxygen therapy, respiratory support therapy, anti-inflammatory, anti-infection, relieving cough and phlegm, and ameliorating spasms and asthma(11). Although these treatment measures can alleviate the disease to a

certain extent, there are still many problems, such as bacterial resistance caused by the abuse of antibiotics, and complications caused by glucocorticoids. Therefore, further research is urgently needed to reduce the frequency of AECOPD.

Traditional Chinese medicine (TCM) has a certain curative effect on this disease(12-14). Previous syndrome study has shown that qi deficiency of lung and kidney is a common syndrome of patients with frequent AECOPD in stable phase. Based on years of clinical experience, our team formulated Bufeiyishen (BFYS) formula with the effect of tonifying lung and kidney, eliminating phlegm and promoting blood circulation. Our prior clinical studies have shown that BFYS formula could effectively attenuate clinical symptoms, improve lung function, enhance exercise tolerance, and improve patients' quality of life(15, 16). Meanwhile, previous animal experiments have found that BFYS formula can also significantly improve lung function, reduce pathological injury of lung tissue, and inhibit inflammation in COPD rats(17-20).

In order to obtain a high level of evidence-based support, we will conduct a multi-center, randomized, double-blind, placebo-controlled trial. It will confirm the efficacy and safety of BFYS formula in the treatment of patients with frequent AECOPD in stable phase, and evaluate the health economics value of BFYS formula.

Methods and analysis

Study design

This is a multi-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of BFYS formula in the treatment of patients with frequent AECOPD in stable stage. A total of 848 eligible patients will participate in this study. We will explain the purpose, interventions, examinations, and follow-up procedures of the trial to each participant. After signing the informed consent, they will be randomly divided into experimental group and control group at a 1:1 ratio. Then, all subjects will receive BFYS

granules or placebos for 52 weeks. In order to assess the condition of acute exacerbation, laboratory indicators, quality of life scores, etc., all participants need to return to the hospital at weeks 13, 26, 39, and 52. The flow chart of this trial is demonstrated in **Figure 1**. This protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines(21) (**Additional file 1**).

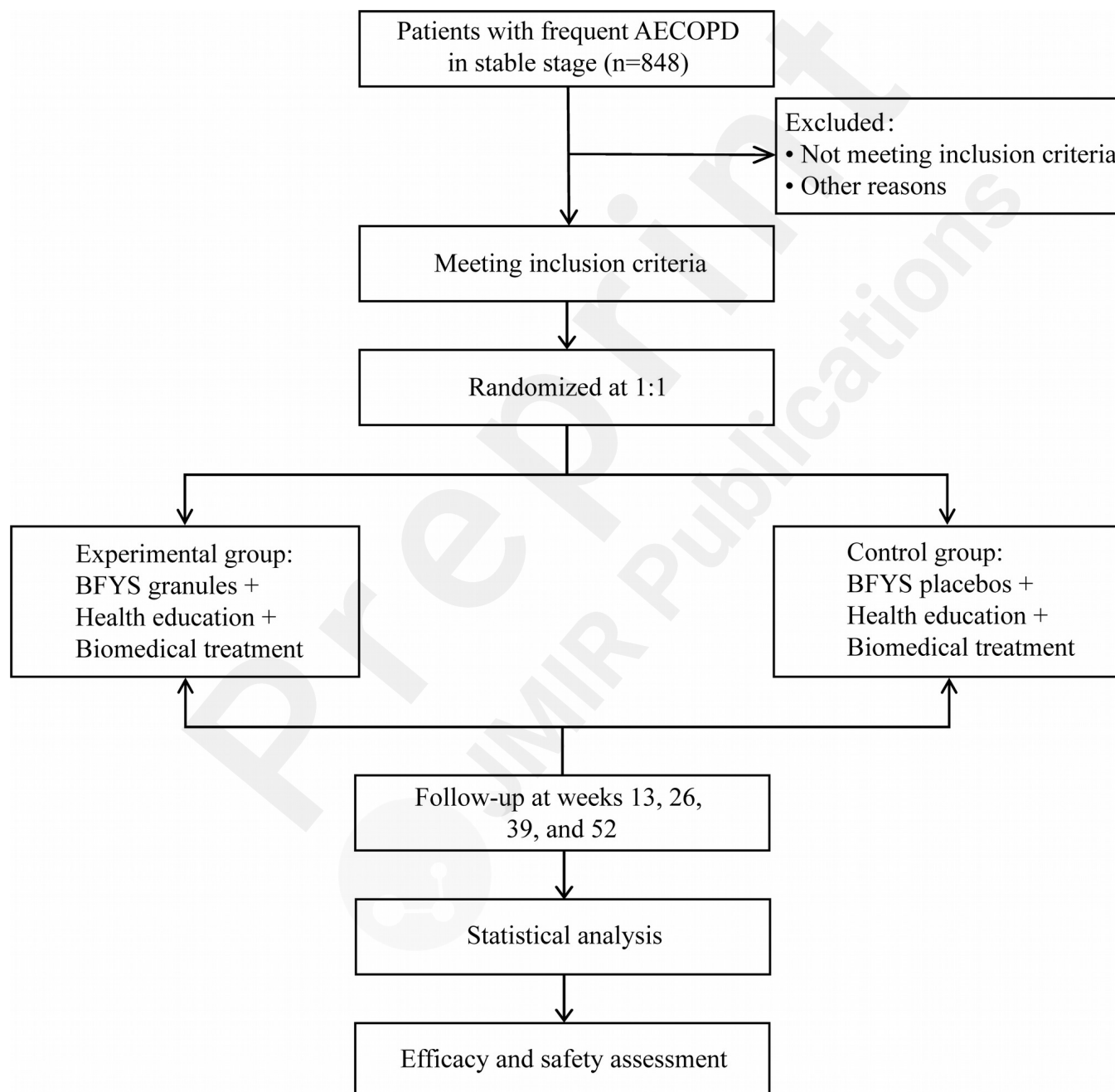


Fig.1 The flow chart for this trial

Sample size

The number of acute exacerbations is the main evaluation outcome. According to the data in previous studies, the annual number of acute exacerbations in the experimental group and the control group was 0.648 times (to be published) and 1.08 times (22), respectively. The α and β of the hypothesis test are set as 0.05 and 0.1, and the sample size ratio of the experimental group and control group is 1:1. The sample size of each group is about 359 cases by using PASS software. After adding a 15% dropout rate, the result is 423 cases per group. Due to the central blocked randomization (4-digit block number), each group needs to recruit 424 participants. A total of 848 subjects will be enrolled in this trial.

Study institutions

Patients will be recruited from thirteen hospitals with sufficient experience of randomized controlled trials (RCTs), including the First Affiliated Hospital of Henan University of Chinese Medicine, the First Affiliated Hospital of Anhui University of Chinese Medicine, Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, the Second Affiliated Hospital of Liaoning University of Chinese Medicine, the First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Shaanxi Hospital of Traditional Chinese Medicine, Kunming Hospital of Chinese Medicine, Jiangyin Hospital of Traditional Chinese Medicine, Xiangyang Hospital of Traditional Chinese Medicine, Qingdao Hospital of Chinese Medicine, Wuhan Hospital of Integrated Chinese and Western Medicine, and Zhuhai Hospital of Integrated Chinese and Western Medicine.

Participant recruitment

This study focuses on patients with frequent AECOPD in the stable phase. Participants will be recruited from thirteen hospitals mentioned above. Printed recruitment posters will be displayed in the outpatient clinics and wards of these hospitals. Meanwhile, we will also use the internet and WeChat to briefly introduce our study to attract potential participants. The

recruitment is scheduled from September 2024 to September 2025. Participants who meet the criteria will be enrolled in this trial, and then they will accept random allocation, treatment, and follow-up according to the protocol.

Inclusion criteria

Patients enrolled in this trial are required to meet the following criteria:

1. Patients diagnosed with COPD in stable stage;
2. Patients with moderate or severe frequent AECOPD;
3. People aged between 40 and 80 years old;
4. Patients with 4-week stable disease condition before enrollment;
5. Not participate in clinical trials of other drugs within 1 month before enrollment;
6. Patients treated with double bronchodilator or triple inhalation for at least 3 months before enrollment;
7. Participants underwent a washout period of 2 weeks before enrollment;
8. Participate in this trial voluntarily and sign the informed consent form.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

1. Patients with other respiratory diseases, including but not limited to asthma, active tuberculosis, bronchiectasis, pulmonary hypertension, pulmonary embolism, pneumothorax, pleural effusion, interstitial lung disease, or other pulmonary diseases requiring intervention;
2. Patients with severe or acute cardiovascular or cerebrovascular diseases, including acute cardiovascular and cerebrovascular events, malignant arrhythmias, unstable angina pectoris, uncontrolled hypertension, etc.;
3. Patients with severe liver or kidney disease (severe liver diseases refer to cirrhosis, portal hypertension, and bleeding from varicose veins, severe kidney diseases refer to kidney diseases requiring dialysis or kidney transplantation);

4. Patients with abnormal liver or kidney function. The value of either Alanine Transaminase (ALT) or Aspartate Transaminase (AST) exceeds 1.5 times the upper limit of the normal, or the value of Serum creatinine (Scr) exceeds the upper limit of the normal;
5. Tumor patients who have undergone surgical resection, radiotherapy, or chemotherapy in the past five years;
6. Patients with mobility problems caused by severe osteoarthropathy, neuromuscular disease, or peripheral vascular disease;
7. Patients who are prohibited from participating in 6-minute walking test (6MWT), such as resting heart rate greater than 120 times per minute, systolic blood pressure greater than 180mmHg, or diastolic blood pressure greater than 100mmHg, etc.;
8. Patients with cognitive or mental disorders;
9. Patients with oral glucocorticoids within 2 weeks before enrollment;
10. Participants who had taken Chinese herbal preparation prohibited during the study period within 2 weeks before enrollment;
11. People known to be allergic to therapeutic drugs;
12. Pregnant women, lactating women, and people who cannot use effective contraceptive measures.

Withdrawal/discontinuation criteria

Patients with any of the following conditions will be withdrawn or discontinued from this study early:

1. Serious adverse events or allergies occurred after taking BFYS formula;
2. Participants who cannot take medication according to the protocol or comply with the follow-up procedures of this trial;
3. Participants unblinded halfway through the study;
4. Patients who request to withdraw from this study;

The researchers need to record the reasons for participants' withdrawal in detail. In addition, it is necessary to document the last time of taking their medication and conduct a final assessment before they withdraw or discontinue.

Interventions

Both the experimental group and control group will accept health education and biomedical treatments according to relevant guidelines(11). Health education refers to improving patients' and their families' understanding of COPD. Biomedical treatments include the triple inhalation therapy of inhaled corticosteroids (ICS)/long-acting beta 2-agonist (LABA)/long-acting muscarinic antagonist (LAMA), rofumilast, theophylline, etc(9).

At the same time, the experimental group will be given BFYS granules additionally, while the control group will receive BFYS placebos. BFYS granules and placebos are prepared by Jiangyin Tianjiang Pharmaceutical Co., Ltd. (Jiangsu, China). The ingredients of placebos include five percent of BFYS granules and maltodextrin. The appearance, weight, color, and smell of the placebos are the same as BFYS granules. All drugs meet national quality standards. The drug components of BFYS granules are shown in **Table 1**.

The packaging bags of TCM granules and placebos will indicate the specification (6.5g/pack), usage, and dosage. Patients should take two packages orally twice a day. The treatment will last for 52 weeks and the drug will be distributed every 13 weeks. Medications not taken by patients will be collected at the next follow-up visit.

Table 1 Components of BFYS granules

Chinese name	Latin name	Parts of the substances	Dosage (g)
Ren Shen	<i>Radix Ginseng</i>	Root	9
Zhi Huang Qi	<i>Astragali Radix</i>	Root	15
Jiu Yu Rou	<i>Fructus Corni</i>	Sarcocarp	12

Gou Qi Zi	<i>Lycii Fructus</i>	Fruit	12
Cu Wu Wei Zi	<i>Schisandrae Chinensis Fructus</i>	Fruit	9
Zhi Yin Yang Huo	<i>Epimedium brevicornu Maxim</i>	Whole herb	9
Zhe Bei Mu	<i>Fritillaria thunbergii Miq</i>	Bulb	9
Chi Shao	<i>Paeoniae Radix Rubra</i>	Root	9
Di Long	<i>Pheretima</i>	Drying body	12
Chao Zi Su Zi	<i>Perilla frutescens</i>	Seed	9
Ai Di Cha	<i>Japanese Ardisia Herb</i>	Dried whole grass	15
Chen Pi	<i>Citrus reticulata Blanco</i>	Peel of fruit	12

Randomization, blinding and unblinding

Patients who met inclusion criteria and signed informed consent will be assigned using a block randomization. The block size will be 4. The researchers are responsible for recruiting participants and uploading their information. After a two-week washout period, statisticians use SAS software to randomly divide the participants into two groups, generate random numbers, and upload them to a central randomization system for storage.

This study is a double-blind trial. All participants and researchers (except those who assign treatments) will be blinded to the group information. Independent researchers place the random numbers and corresponding treatment assignments in the opaque envelopes. The drug preparation personnel prepare the drugs, pack them respectively, and code them according to the random numbers. Apart from this, the researchers who assign treatments and the drug preparation personnel are no longer responsible for other processes of the trial. The researchers distribute the drugs to the participants whose random numbers match the drug

codes. The results of the blind method will be saved by the project manager, drug preparation personnel, and statisticians separately.

After all data are entered and the blind data are reviewed, the database will be locked.

Unblinding will be performed by the project manager and the statistician to identify the interventions corresponding to the random numbers. Next, statistician will analyze the data of the clinical trial. In case of emergency, the researcher will report it to the project manager and decide whether to open the envelope. The over 20% of emergency unblinding rate indicates trial failure.

Outcomes

Primary outcome

The primary outcome of this study is the frequency of AECOPD after the interventions.

AECOPD refers to the process of acute attack characterized by dyspnea and/or increased coughing and expectoration(11). The frequency will be recorded at every visit, and the total number in the 52-week treatment period will be calculated. A lower number in a given period indicates better efficacy.

Secondary outcomes

Secondary outcomes include the following indicators:

1. The number of AECOPD leading to hospitalization or death. Hospitalization or death due to AECOPD should be recorded in the study diary in time. The frequencies should be recorded every 13 weeks during the study period.
2. The attack time of the first AECOPD means the number of days between the first medication and the first AECOPD.
3. The severity of AECOPD. It can be classified as mild, moderate, or severe(23). Mild means that patients only need to be treated with short-acting bronchodilators alone. Moderate refers to patients requiring short-acting bronchodilators and antibiotics, with or without oral

corticosteroids. Severe means that the patients require hospitalization or treatment in the emergency room or intensive care unit. Results will be recorded at every visit.

4. Duration of AECOPD. The duration of acute exacerbation is the time from the beginning of an acute exacerbation to the stabilization of the disease condition. It will be noted at every visit.

5. Mortality. At the end of the study, the mortality of the two groups will be measured. It includes the mortality due to acute exacerbation and the all-cause mortality. The mortality due to AECOPD=(number of mortality due to AECOPD during the intervention)/ (number of subjects in each group) and all-cause mortality=(number of mortality during the intervention)/ (number of subjects in each group).

6. Lung function. This test includes forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1 predicted (FEV1%pred), and FEV1/FVC. It will be conducted before the study and every 13 weeks during the study period.

7. Clinical symptoms and signs include cough, phlegm, wheezing, chest tightness, fatigue, cyanosis, body temperature, etc. The score of each item is rated from 0 to 3. The total score is the sum of each item. The higher the score, the worse the disease status. It should be evaluated before the trial and every 13 weeks after the start of the trial.

8. Six-minute walking distance (6MWD). The total distance of the patient across a flat surface in six minutes can reflect the patient's movement ability. The greater the distance, the better the patient's ability to exercise(24). 6MWD will be tested before the study and every 13 weeks during the study period.

9. Quality of life. COPD assessment Test (CAT) and 36-item short-form health survey (SF-36) are used to assess the quality of life of patients. The higher the SF-36 value, the better the quality of life(25). While the higher the CAT value, the worse the quality of life(26). These

questionnaires will be evaluated before the trial and every 13 weeks after the initiation of the trial.

Safety outcomes

On the one hand, we will measure the physical signs at each visit, such as temperature, breathing, heart rate, and blood pressure. On the other hand, laboratory tests to assess safety involve blood routine, urine routine, liver function, kidney function, and electrocardiogram (ECG), which are tested once every 13 weeks. Chest CT will be conducted before the trial.

Adverse events

Adverse events include abnormal clinical symptoms, signs, diseases, and laboratory tests. It can be classified as mild, moderate, or severe according to the severity. Adverse events will be recorded in detail on Case Report Form (CRF), including the severity, time of occurrence, duration, use of experimental drugs, treatment measures, results, etc.

Health economics evaluation

Effect evaluation indicators include the number of AECOPD, the number of AECOPD leading to hospitalization and death, etc. Costs include the direct costs and indirect costs of the patient for diagnosis and treatment. It involves the cost of total hospitalization, total outpatient, vaccine prevention, health care, and psychological treatment.

The cost-effectiveness analysis method is adopted to assess the cost saved by each unit of effectiveness improvement of BFYS formula. Moreover, we will build a micro-simulation model of COPD cost-effectiveness evaluation based on Monte Carlo simulation, and conduct basic analysis and sensitivity analysis of the model.

The schedule of enrollment, interventions, and outcomes is shown in **Table 2**.

Table 2 The schedule of enrollment, interventions, and outcomes

Study Period

	Enrollment	Baseline	Post-allocation			
Time Point	Day -14 to 0	Day 0	Week 13	Week 26	Week 39	Week 52
Visit	Screening stage	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Enrollment:						
General information	×					
Demographic information	×					
Informed consent	×					
Eligibility screen	×					
Randomization		×				
Interventions						
BFYS formula	13g/time, twice a day					
BFYS placebo	13g/time, twice a day					
Outcomes						
Number of AECOPD			×	×	×	×
Number of AECOPD leading to hospitalization or death			×	×	×	×
Time of the first AECOPD episode			×	×	×	×
Severity of AECOPD			×	×	×	×
Duration of AECOPD			×	×	×	×
Mortality			×	×	×	×
Lung function		×	×	×	×	×
Clinical symptoms and signs		×	×	×	×	×

6MWT	×	×	×	×	×
CAT, SF-36	×	×	×	×	×
Blood routine	×	×	×	×	×
Urine routine	×	×	×	×	×
Liver function	×	×	×	×	×
Kidney function	×	×	×	×	×
ECG	×	×	×	×	×
Chest CT	×				
Adverse events		×	×	×	×
Health costs	×	×	×	×	×

Quality control

In order to ensure the quality of this trial, we will establish a quality control committee and a data monitoring committee (DMC). Quality control experts will conduct quality control assessments monthly to ensure the quality of the study. Besides, the researchers are professionally trained and have obtained Good Clinical Practice (GCP) certificates to ensure the quality of the research data and the benefits of the subjects. Last but not least, improving subjects' compliance is another important measure of quality control.

Data collection and management

We will use the CRF for data collection. It includes general information, laboratory examinations, health questionnaires, health costs, etc. Researchers should ensure that the CRF and medical records are filled out accurately and completely. Any incorrect records should not be blotted out. It should be re-filled with the correct records, as well as the researcher's signature and date of the day.

All research data will be handled, stored, and destroyed based on relevant policies. The

medical records will be locked in cabinets that hold information about the participants. Then, all the information collected will be entered into a computer with restricted access and only researchers could access it. What's more, in order to guarantee patient's privacy, data storage and transmission will be protected with a password.

Statistical analysis

SPSS 24.0 software will be used for statistical analysis in this study. The Per Protocol Set (PPS) will be used for the analysis of clinical efficacy, and the Safety Set (SS) will be used for safety analysis. The missing data will be filled by the method of the last observation carried forward. The measurement data are expressed by mean $\pm$ standard deviation or median (interquartile range), while the enumeration data are described by frequency (ratio). We will firstly assess whether the experimental and control groups are comparable through the analysis of baseline data. In terms of the analysis of clinical efficacy, the Chi-square test will be used for enumeration data, while analysis of variance (ANOVA) and T test are used for measurement data. The paired samples t-test and independent samples t-test will be used for intragroup comparison and intergroup comparison of measurement data, respectively. $P < 0.05$ is considered statistically significant.

In terms of safety analysis, we will list the frequency table of abnormal laboratory indicators. In addition, we will present a detailed table of adverse events. Then, the incidence of adverse events and serious adverse events during the intervention period will be calculated.

Ethics and dissemination

This study has been approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine (No.2024HL-043-01). The study process will be supervised by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine. Any modification to the study protocol requires the agreement of the Ethics Committee. Participants need to sign the informed consent form before participating in

the trial. They will be informed of the details of the trial, including the purpose, methods, potential benefits and risks, etc. Meanwhile, they will also be informed that their research data is confidential. We will answer any questions they may have. More importantly, participants could withdraw at any time without giving a reason and their medical benefits will not be compromised.

The results will be published in a peer-reviewed journal after the end of the study. The data of this trial will be disseminated publicly through conferences and publications.

Discussion

AECOPD is the important cause of the progression and deterioration of COPD. The occurrence of frequent acute exacerbations makes the patients' quality of life worse, lung function declines faster, and even increases the risk of death(9). Frequent hospitalizations can also impose a heavy financial burden on patients and society(27). Therefore, reducing the frequency of acute exacerbations is the important goal of COPD management. However, there are few therapeutic regimens and related studies to reduce the frequency of AECOPD. So many patients seek the solutions from TCM. TCM has a long history and rich experience in treating COPD. It has achieved good therapeutic effects in reducing the frequency of acute exacerbations, improving lung function, and ameliorating quality of life (28-31).

Based on years of clinical experience, our team formulated BFYS formula for the treatment of COPD. Previous animal experiments have found that BFYS formula may play a beneficial role in COPD by improving airway epithelial cell aging, protecting the airway epithelial barrier in COPD rats, inhibiting the inflammatory response, and immune regulation, etc(17-20). Therefore, we could draw the conclusion that BFYS formula plays a therapeutic role in COPD through multi-component, multi-pathway, and multi-target. The clinical efficacy of BFYS formula will be confirmed by the results of this trial.

In this study, a multi-center, randomized, double-blind, placebo-controlled trial will be

conducted. It will confirm the effects of BFYS formula on acute exacerbations, exercise ability, lung function, and quality of life on patients with frequent AECOPD in stable stage. The results will provide a high-level evidence-based basis for the TCM treatment of frequent AECOPD. Moreover, this study will clarify the health economic value of BFYS formula through the method of cost-effectiveness analysis.

However, this study has some limitations. First of all, the intervention period of this trial is up to 52 weeks. Long-term medication and follow-up procedures may affect patients' compliance. Hence, during the study, various measures should be taken to improve patients' compliance as much as possible, such as regular follow-up and partial reduction of medical expenses. Secondly, the trial includes patients with moderate or severe frequent AECOPD, which may not be representative of all frequent AECOPD patients. Further evaluation of the suitability of BFYS formula for frequent AECOPD patients of different severity is needed in the future.

Trial status

The recruitment will start from September 2024 and is expected to be completed in September 2025. The preparations for the recruitment of subjects have been completed.

Supplementary Information

Details of the SPIRIT 2013 checklist could be viewed in Additional file 1.

Abbreviations

AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; ALT: Alanine Transaminase; ANOVA: analysis of variance; AST: Aspartate Transaminase; BFYS: Bufei Yishen; CAT: COPD assessment Test; COPD: Chronic obstructive pulmonary disease; CRF: Case Report Form; DMC: data monitoring committee; ECG: Electrocardiogram; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; GCP: Good Clinical Practice; ICS: Inhaled corticosteroids; LABA: Long-acting beta 2-agonist; LAMA: Long-acting

muscarinic antagonist; PPS: Per Protocol Set; RCT: Randomized controlled trial; Scr: Serum creatinine; SF-36: 36-item short-form health survey; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SS: Safety Set; TCM: Traditional Chinese medicine; 6MWD: 6-minute walking distance; 6MWT: 6-minute walking test.

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We gratefully acknowledge the efforts of all researchers and the cooperation of all subjects.

Author contributions

XQH contributed to the manuscript writing. WMH is responsible for the design and implementation of the trial. LZG contributes to the subjects recruitment. CT is the statistician for this study. LJS contributed to the top-level design and guidance of the project. All the authors have read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The protocol of this study is approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine (Ethics approval number: 2024HL-043-01). Any change will be submitted to the Ethics Committee. Subjects can only participate in this clinical trial after they fully understand and voluntarily sign informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Files

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