Project number: 2017YFC1700602

A Multicenter, Double-blind, Randomized, Placebo-controlled Clinical Trial of Shenbai Granules in Reducing Recurrence of Colorectal Adenoma

Sponsor: Affiliated Hospital of Nanjing University of Chinese Medicine

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Synopsis

Title	A multicenter, double-blind, randomized, placebo-controlled clinical trial of Shenbai Granules in reducing recurrence of colorectal adenoma
Participating units	1. Affiliated Hospital of Nanjing University of Chinese Medicine 2. Guangdong Provincial Hospital of Traditional Chinese Medicine 3. Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine 4. Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine 5. the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine 6. Affiliated Hospital of Naval Military Medical University 7. Beijing Friendship Hospital, Capital Medical University 8. the First Affiliated Hospital of Nanjing Medical University 9. Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University
Purpose	1. To evaluate the efficacy and safety of Shenbai Granules in reducing recurrence of colorectal adenoma 2. To provide high-quality, internationally recognized, evidence-based medical evidence for the clinical guidelines of traditional Chinese medicine in the prevention and treatment of colorectal adenoma
Design	Prospective, multicenter, double-blind, randomized, placebo-controlled clinical trial
Sample size	Total 400: Shenbai Granules group, 200; Placebo group, 200
Test Population	Patients aged 18-70 years who have undergone complete polypectomy within the recent 6 months and pathologically confirmed colorectal adenomatous polyps
Administration Plan	**Treatment group:** Shenbai Granules, 1 pack/time, 2 times a day, for 6 months **Control group:** placebos, 1 pack/time, 2 times a day, for 6 months
Effectiveness Indicators	**Primary indicator:** The adenoma detection rate during follow-up for 2 years **Secondary indicator:** (1) The detection rate of any polypoid lesions during follow-up for 2 years (2) The detection rate of high-risk adenomas during follow-up for 2 years

	(3) The detection rate of sessile serrated lesions during follow-up for 2 years
Safety indicators	1. Physical examination 2. Laboratory test (blood and urine routine, liver and kidney function) 3. Adverse events
Statistical Analysis	General information will be analyzed with ITT data, effectiveness with mITT and PPS data respectively, and safety with SS data.

Study visits flow chart

Study phase / Project	Screening period	Treatment period			
	Baseline (-1m to 0)	**Visit 1 (3m ± 1w)**	**Visit 2 [a] (12m ± 2w)**	**Visit 3 (15m ± 2w)**	**Visit 4 [b] (24m ± 2w)**
Obtaining informed consent form	•				
Demographics	•				
Determination of inclusion and exclusion criteria	•				
Filling in general information	•				
Concomitant disease and medication before treatment	•				
Physical examinations	•	•	•	•	•
Colonoscopy and polypectomy [c]	•		•		•
Histological diagnosis	•		•		•
Boston score	•		•		•
withdrawal time	•		•		•
Blood routine	•	•	•	•	
Urine routine	•	•	•	•	
Liver function	•	•	•	•	
Renal function	•	•	•	•	
Urine pregnancy test (women)	•		•		
Distribution of trial granules	•		•		
Recovery of trial granules		•		•	
Adverse events		•	•	•	•

Concurrent medication records	•	•	•	•	•
Reason for dropouts		•	•	•	•

[a] The first subsequent colonoscopy should be performed around 1 year after baseline colonoscopy.

[b] The second subsequent colonoscopy should be performed around 2 years after baseline colonoscopy.

[c] Each colonoscopy should have adequate bowel preparation, reach the ileocecal region and have a withdrawal time of more than 6 minutes. All polyps detected should be removed and evaluated completely.

1. Background

Colorectal cancer (CRC) is one of the most common malignant tumors that threaten human health, and its morbidity and mortality are increasing year by year. Colorectal adenoma (CRA) is the precancerous lesion of CRC. Endoscopy has become an important treatment for CRA. But endoscopic polypectomy does not reduce the recurrence and cancerization rate of adenoma. At present, measures such as increasing dietary fiber, smoking cessation, and appropriate supplementation of calcium and vitamin D are used to prevent the recurrence of CRA. However, there is no established chemopreventive agent for the prevention of recurrent CRA.

With the innovative development of the "preventive treatment for disease" theory of traditional Chinese medicine (TCM), the clinical and mechanism studies on the prevention and treatment of CRC have gradually become a research focus. Under the guidance of Professor Zhou Zhongying, a famous TCM master, our research team combined clinical practice to propose “accumulation of dampness and heat, deficiency of spleen and Qi" as the basic pathogenesis of CRA and established the TCM formula "Shenbai Granules (SBG)" (*Sophorae flavescentis* radix, *Hedyotis diffusa*, *Codonopsis* radix, *Atractylodis macrocephalae* rhizoma, Coicis semen, *Coptidis* rhizoma, Mume fructus and *Zingiberis rhizome praeparatum*). The combination of the whole formula has the functions of beneficial Qi, invigorating spleen, clearing heat and dampness. Previous studies have found that Shenbai Granules could significantly reduce the recurrence of CRA and promote the apoptosis of colorectal cancer cells.

Therefore, we plan to conduct a multicenter, randomized, double-blind clinical study to enroll patients diagnosed with adenoma after colonoscopic resection. After obtaining informed consent, the treatment group will receive SBG, and the control group will receive SBG mimic as placebo. The efficacy and safety of SBG will be evaluated by adenoma detection rate (ADR) and adverse events, as well as clinical symptoms. This study aims to provide high-quality, internationally recognized, evidence of evidence-based medicine for the development of clinical guidelines.

2. Study objectives

The primary objective is to evaluate the efficacy and safety of SBG in reducing recurrence of CRA. The secondary objective is to provide high-quality, internationally recognized, evidence-based medical evidence for the clinical guidelines of TCM in the prevention and treatment of CRA.

3. Study design

3.1 Design guidelines

The study will be conducted in accordance with the ethical and moral principles, namely the Declaration of Helsinki, the SPIRIT Statement, as well as the principles of scientificity, the principles of Good Clinical Practice and current laws and regulations.

3.2 Study type

A multicenter, randomized, double-blind, placebo-controlled clinical trial design is adopted.

3.3 Sample size

According to the literature search and previous research results, the average detection rate of recurrent adenomas without agent intervention for patients after polypectomy is 52%. We hope that ADR will be reduced by 34% after intervention of SBG. With a significance level (alpha) of 5% and power of 90%, the patient number needed is160 in each group. Allowing for 20% of participants to drop out, the target number of participants to be randomly assigned is 400.

3.4 Randomization method

The stratified block randomization method is used, and the following design is completed by an independent third-party organization.

(1) Design and specify the block length;

(2) Generate the block number and random numbers within the block, and conduct one-to-one correspondence between the random numbers with the trial granules number;

(3) Allocate the cases to the treatment and placebo groups within the block in a 1:1 ratio, and finally obtain the result of block randomization; and generate the randomization list and blinding codes.

3.5 Blinding procedures

A double-blind design is used in this study for the investigators and subjects. The blinding codes are separately sealed and stored by the independent third-party organization. Trial granules are randomly coded as subject unique identification codes, and used by each clinical site according to the assigned drug numbers and in the order of case enrollment. Clinical monitors and investigators must be blinded at all times.

3.6 Control selection

Since there is no internationally recognized standard treatment for the prevention and treatment of CRA, we chose the SBG mimic as a control drug.

3.7 Multicenter

There are 8 hospitals participating in screening and recruiting patients in this clinical trial. These hospitals include: 1) Affiliated Hospital of Nanjing University of Chinese Medicine, 2) Guangdong Provincial Hospital of Traditional Chinese Medicine, 3) Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 4) Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 5) the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, 6) Affiliated Hospital of Naval Military Medical University, 7) Beijing Friendship Hospital, Capital Medical University, 8) the First Affiliated Hospital of Nanjing Medical University.

4. Selection of subjects

4.1 Diagnostic criteria

The criteria are established according to the *Integrated colorectal Oncology*:

Colorectal adenoma (CRA): Colonoscopy reveals colonic and (or) rectal polyps, and pathological diagnosis is adenomatous polyps, including tubular adenoma, villous adenoma, and tubulovillous adenoma.

Tubular adenoma (microscopically): Adenoma is mainly composed of mucin-secreting epithelium with varying degrees of dysplasia. The epithelium is tall columnar and arranges in a glandular tubular structure, which is separated by the lamina propria stroma. The glands are generally more regular, sometimes also can appear different degrees of branching and irregular shape. The nuclei of the epithelial cells are large and hyperchromatic, and the nuclei are pen-rod shaped and closely arranged. In mild atypia, the nuclei are arranged at the base of the epithelium, and with the increase of atypia, the nuclei shift upward to form pseudostratified structures.

Villous adenoma (microscopically): The villi are branching and growing vertically to the mucosa, the center of the villi is a central cord, and there is fibrovascular stroma. The surface epithelium is the same as that of tubular adenoma, but the general atypia is more obvious.

Tubulovillous adenoma (microscopically): The tumor tissue is composed of a mixture of glandular tubular, papillary or villous structures, of which villous or papillary structures account for 1/5-4/5 of adenomas. If the villous structure comprises less than 1/5 or more than 4/5 of the adenoma, it is

classified as tubular or villous, respectively.

[Reference]

[1] Jingyuan Fang. Integrated colorectal Oncology [M]. Beijing: People's Medical Press,2015,205-206.

4.2 Inclusion criteria

(1) Patients underwent colonoscopy within the last 6 months, and all polyps detected have been removed;
(2) Meet the diagnostic criteria for CRA;
(3) Between 18 and 70 years of age (inclusive);
(4) Those who have been fully informed and signed the informed consent.

4.3 Exclusion criteria

(1) Colonoscopy suggests poor cleanliness and the Boston score is less than 6, or it is no cecal intubation, or withdrawal time is less than 6 minutes;
(2) Patients with hereditary polyposis such as familial adenomatous polyposis, MUTYH-associated polyposis, Peutz-Jeghers syndrome, serrated polyposis syndrome, etc;
(3) There is reliable evidence that the tumor has invaded the muscularis propria mucosa, or deep submucosal invasion is suspected;
(4) Combined with colorectal malignant tumor or previous history of colorectal malignant tumor;
(5) Colonoscopy is highly suggestive of inflammatory bowel disease;
(6) Pregnant and lactating women;
(7) Women of appropriate age who have recently planned to have children;
(8) Unstable vital signs, or severe heart, lung, cerebrovascular disease, or liver and kidney dysfunction (ALT, AST > 2 × upper limit of normal; Serum creatinine and blood urea nitrogen > 1.5 × upper limit of normal) who can not tolerate colonoscopy and clinical intervention;
(9) Loss of follow-up due to frequent changes in work environment or other circumstances;
(10) Chemopreventive drugs (aspirin, folic acid, vitamin D, calcium, etc.) with potential for the treatment of colorectal adenoma have been used;
(11) Patients participating in other clinical trials.

4.4 Withdrawal criteria

(1) If the patient has severe gastrointestinal symptoms during the study period, the study can be stopped according to the investigator's judgment. Or if the patient's colonoscopy showed deterioration of intestinal polyps, the study can be stopped, and the ineffective case can be treated.
(2) The adverse drug reactions have occurred during the study, or other serious adverse events, according to the judge to stop the case of clinical studies.
(3) Significant deviation has come up in the implementation of study protocol, such as poor adherence, difficult to evaluate drug effect.
(4) The patient is unwilling to continue the clinical trial, and offer to withdraw from the trial to the doctor in charge.

4.5 Dropout and management of cases

Dropout cases are defined as all the subjects who had completed the informed consent form and are screened and qualified to enter the randomized trial, regardless of when or for reasons, but have not completed the observation period specified by the study.

When the subjects drop out, the researchers should contact the subjects as much as possible by visiting their home, making follow-up appointments, telephone calls, and letters to ask the reasons, record the time of the last medication, and complete the evaluation items that can be completed.

For patients who withdraw from the study due to adverse events or ineffective treatment during the study, researchers should take corresponding measures according to the actual situation of patients.

The study data of the dropped cases should be properly preserved, not only for archival purposes, but also for the statistics of the full analysis set. No additional information is required for drop-out patients.

5. Intervention

5.1 Health education

(1) Increasing dietary fiber intake of vegetables, such as the cruciferous food;
(2) Reducing the intake of red meat and processed meat products;
(3) To give up smoking and drinking;
(4) Body weight control;
(5) Reasonable physical exercise.

5.2 Grouping and medication

SBG group: SBG granules (provided by Jiangyin Tianjiang Pharmaceutical Co., LTD), orally, 1 sachet once, diluted in 150-200 ml of boiling water, 2 times a day.

Placebo group: Placebo (provided by Jiangyin Tianjiang Pharmaceutical Co., LTD), 1 sachet once, diluted in 150-200 ml of boiling water, 2 times a day.

5.3 Duration of treatment

In the first year, the trial granules will be started after enrollment for 3 months; In the second year, the trial granules will be started in the first 3 months; Each participant should have completed 6 months of trial granules.

5.4 Composition of Shenbai Granules

Chinese name (pinyin name)	**Latin name**	**Original plant and medicinal part**	**Dose (g)**
Ku Shen	*Sophorae flavescentis* radix	Dried root of *Sophora flavescens* Ait.	4.5
Bai Hua She She Cao	*Hedyotis diffusa*	Dried whole plant of *Hedyotis diffusa* Willd.	10
Dang Shen	*Codonopsis* radix	Dried root of *Codonopsis pilosula* (Franch.) Nannf.	7.5
Bai Zhu	*Atractylodis macrocephalae* rhizoma	Dried root and stem of *Atractylodes macrocephala* koidz.	6
Yi Yi Ren	Coicis semen	Dried mature kernel of *Coix lacryma-jobi* L.Vra. *mayuen* (Roman.) Stapf.	10
Huang Lian	*Coptidis* rhizoma	Dried root and stem of *Coptis chinensis* Franch.	1.5
Wu Mei	Mume fructus	Dried near-ripe fruit of *Prunus*	4.5

		mume (Sieb.) Sieb.et Zucc.	
Pao Jiang	*Zingiberis rhizome praeparatum*	Fried product of the dried root and stem of *Zingiber officinale* Rose.	3

According to the recommended prescription of Professor Zhou Zhongying, the master of TCM.

5.5 Composition of placebo

It contains 5% SBG content, and the remaining ingredients are flavoring agents, starch and coloring agents. It is the same with SBG in appearance, smell and dosage form.

5.6 Drug packaging, distribution, storage and label

(1) The SBG and SBG mimetic agents used in the study are uniformly produced by Jiangyin Tianjiang Pharmaceutical Co., LTD. The special personnel of the research group will conduct drug management. The drug receipt form are signed by two people in duplicate.

(2) Drugs should be stored at room temperature, away from light, dry, and kept by special personnel, special counters, and locked.

(3) The doses are packaged in one medium package for each visit use, and in one large package for all visits. The special label for investigational study should be applied to identify the investigational drug. The labels must bear the information of "For clinical trial use only", and include the drug name, drug number and other information.

(4) The distribution and recovery of each drug should be recorded on a special record sheet.

(5) At the end of the study, the remaining drugs will be collected, and the drug recovery sheet should be signed by both parties. They should be handed over to the principal investigator after study.

Drug No.: _____

A multicenter, double-blind, randomized, placebo-controlled clinical trial of Shenbai Granules in reducing recurrence of colorectal adenoma (Project number: 2017YFC1700602)（For clinical trial use only）

Usage and dosage: 1 bag once, diluted in 150-200 ml of boiling water. 2 times a day

Dosage form: Granule formulation

Product batch No.:

Production date:

Storage: Sealed and kept in a cool and dry place

Jiangyin Tianjiang Pharmaceutical Co., LTD

5.7 Toxic and side effects of SBG and drug contraindications

(1) The Chinese herbs used in SBG are all included in the *Pharmacopoeia of the People's Republic of China*.

(2) The doses used are all within the range prescribed by the *Pharmacopoeia of the People's Republic of China*.

(3) *Sophorae flavescentis* radix and *Coptidis* rhizome are big bitter cold. Overdose is easy to damage the spleen and stomach, so patients who have deficiency and cold of spleen and stomach should not be included.

5.8 Rules for concomitant medications

In addition to trial granules, physicians should ask patients to bring in all medications they are taking at follow-up visits during the observation period to check for concomitant medications. The name of the drug (or other treatment), the amount, the frequency and duration of use of the drug or other treatment that must be continued for a co-morbid condition must be recorded in the study's medical record for analysis and report in the summary.

Medications with potential for the treatment of CRA (aspirin, folic acid, vitamin D, calcium) were prohibited.

6. Observation indicators

6.1 General observation

(1) Demographic characteristics: sex, age, job, address, phone, etc.

(2) Vital signs: temperature, resting heart rate, respiration, blood pressure (systolic pressure, diastolic blood pressure).

(3) Chronic disease related information.

6.2 Effectiveness indicators

(1) Primary indicator

Adenoma detection rate (ADR): the ratio of the number of patients with new adenoma detected by colonoscopy to the total number of cases in this group during follow-up for 2 years.

(2) Secondary indicator

① The detection rate of any polypoid lesions: the ratio of the number of patients with any polypoid lesions detected by colonoscopy to the total number of cases in this group during follow-up for 2 years.

②The detection rate of high-risk adenomas: the ratio of the number of patients with high-risk adenomas detected by colonoscopy to the total number of cases in this group during follow-up for 2 years.

③The detection rate of sessile serrated lesions: the ratio of the number of patients with sessile serrated lesions detected by colonoscopy to the total number of cases in this group during follow-up for 2 years.

Colonoscopy will be performed around 1 year and 2 years after baseline colonoscopy. When new polyps are found, endoscopic resection will be performed immediately, and the excised tissue will be retrieved for histological examination.

6.3 Safety indicators

(1) Physical examination at each visit.

(2) Laboratory test: Blood routine, urine routine, liver function (alanine aminotransferase, aspartate aminotransferase), renal function (serum creatinine, blood urea nitrogen) will be rechecked before clinical intervention, every visit after taking medicine.

(3) Adverse events: recording the conditions of adverse events occurring in the whole process from before and after the treatment, and in the observation period.

7. Adverse events

7.1 Definition

Adverse Event (AE): defined as all adverse medical events that occurred after the participant received test medicines, which may be presented as symptoms and signs, diseases or abnormalities in the laboratory test, but may not have the causality with the test medicines.

Note: In this study, AE does not include the following conditions: diseases, situations or abnormalities in the laboratory test that previously existed before the screening, or were detected but not further deteriorate; abnormalities with clinical significance in the laboratory test or in the observation that were related to the studied disease, which were not included in the AE or SAE unless the conditions of patients were more serious than the expectation judged by the investigator.

It is up to the investigator to decide whether an abnormal result of the laboratory test or other observed abnormalities is with clinical significance.

Serious Adverse Event (SAE): referring to the death, life threatening, permanent or severe disability or loss of function that occurred after the participant received the test medicines, and the participant is required to treat in hospital or extent the hospitalization time, as well as the adverse medical events including congenital abnormalities, birth defects, etc.

Significant Adverse Event: referring to any adverse events except for SAE that leads to the adoption of directed medical measurement (such as drug withdrawal, dose reduction and symptomatic therapy) and obvious abnormalities in the hematological or other laboratory tests.

Drug-related Adverse Reaction: referring to any reaction unexpected or harmful to human body that was associated with test medicines in the clinical trial. There is at least one of the reasonable possibilities for the causality between test medicines and adverse events, i.e. could not exclude the correlation.

7.2 Judgment of the level of adverse events

All adverse events occurring during the trial will be judged for the severity according to CTCAEv5.0

Level 1: mild; no symptom or slight; only seen in clinic or diagnosis; no treatment is needed

Level 2: moderate; minor, local or non-invasive treatment is required; instrumental common daily activities appropriate to the age are limited*

Level 3: severe or important in medical meaning but not immediate life threatening; leading to stay or extension in hospital; causing disability; self-caring common daily activities are limited**

Level 4: life-threatening; emergent treatment is required

Level 5: AE-associated death

The semicolon (;) used in the description of the level means “or”.

Not all adverse events include all levels. Therefore, there are fewer than five levels for some adverse event to choose.

*instrumental common daily activities refer to cooking, shopping food or clothes, playing telephone, and making finance, etc.

**self-caring common daily activities refer to bathing, taking on/off clothes, eating, washing, taking medicine, etc. but without being bedridden.

7.3 Judgment for the causality with medicines

The relationship between adverse events and trial granules will be assessed according to the following 6-point classification criteria by the WHO-Uppsala Monitoring Centre (WHO-UMC) rating method: certain, likely, possible, unlikely, unclassified, unclassifiable.

Causal criteria for adverse events

Causality term	Assessment criteria
Certain	1. Event or laboratory test abnormality, with plausible time relationship to drug intake 2. Cannot be explained by disease or other drugs 3. Response to withdrawal plausible (pharmacologically, pathologically) 4. Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) 5. Rechallenge satisfactory, if necessary
Likely	1. Event or laboratory test abnormality, with reasonable time relationship to drug intake 2. Unlikely to be attributed to disease or other drugs 3. Response to withdrawal clinically reasonable 4. Rechallenge not required
Possible	6. Event or laboratory test abnormality, with reasonable time relationship to drug intake 7. Could also be explained by disease or other drugs 8. Information on drug withdrawal may be lacking or unclear
Unlikely	9. Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) 10. Disease or other drugs provide plausible explanations
Unclassified	11. Event or laboratory test abnormality 12. More data for proper assessment needed, or 13. Additional data under examination
Unclassifiable	14. Report suggesting an adverse reaction 15. Cannot be judged because information is insufficient or contradictory 16. Data cannot be supplemented or verified

7.4 Disposal of adverse events

(1) Observation and recording

Researchers should ask patients to truly report their condition changes after medication and avoid leading questions.

Any adverse reaction during the study should fill in the "adverse event form", and follow up investigation, record the treatment process and results in detail, until the laboratory examination returned to normal and the symptoms and signs disappeared. According to the severity of adverse reactions, the follow-up methods can be selected by hospitalization, outpatient service, home visit, telephone, communication and other forms.

(2) Medical management

When adverse reactions are found, the investigators should make decisions on diagnosis and treatment according to the patient's condition, and decide whether to discontinue the observation. In case of serious adverse events, the unit undertaking the clinical research must take necessary measures immediately to protect the safety of the subjects.

(3) Report

The investigators complete the serious adverse event report Form, and report it to the responsible institution and the ethics committee of their institution within 24 hours, and sign and date the report. The responsible unit of the project should timely inform the participating units and ensure that all the reporting procedures required by laws and regulations are met.

8. Quality control and warranty

8.1 Measures to prevent possible bias

Investigators should perform their duties and strictly follow the clinical research protocol and adopt standard operating procedures to ensure the implementation of the quality control and quality assurance system of the clinical research.

The sponsor shall employ 3 to 5 supervisors, who should have medical background, protect the rights and interests of the subjects participating in the clinical research, ensure the authenticity, accuracy and completeness of the research data recording and reporting, and ensure that the research complies with the designed research protocol and relevant regulations. The number of monitor visits should meet the needs of clinical research quality control. Monitors informed the project leader of the monitoring results after each visit.

The main measures for the possible bias in this study are as follows: to strengthen the training and monitoring of the researchers for the possible bias in the implementation of the study protocol in multi-center study; In view of the bias of researchers in the selection of subjects, a randomized design is adopted. In view of the bias of the researchers in the evaluation of the efficacy, the isolated evaluation is adopted, and the evaluation doctors are always blinded.

8.2 Measures to improve compliance of subjects

(1) Researchers should carefully implement informed consent so that subjects can fully understand the requirements of the study and cooperate with the study. The physical and chemical examination fee is provided by the project fund.

(2) Drug counting method is used to monitor the medication compliance of subjects. Compliance = (actual dosage/supposed dosage) ×100%. Adherence of less than 80% or more than 120% was considered to be a major protocol violation.

(3) Patients will be reminded by telephone 2 days before the scheduled visit. The medicine is distributed by special personnel.

8.3 Investigator Training

Each research unit is responsible for organizing experts to train investigators on the study protocol before the start of the clinical study. Sign the investigator statement.

8.4 Quality control measures of test indicators

The laboratories of each participating hospital should establish standard operating procedures and quality control procedures for colonoscopy examination and laboratory observation indicators. The national legal units of measurement must be adopted for all laboratory tests in each participating hospital.

Laboratory test results must be printed on a computer with the date, test item, result, and normal range. Data should be traceable.

9. Data administration

9.1 Case Report Form (CRF)

In view of the fact that most outpatient medical records of hospitals in China are brought by patients, in order to preserve the primary data of clinical research completely, a special “Case Report Form” is designed for this study.

9.2 Data record

Requirements for CRF: ①Investigators must write CRF while treating subjects to ensure that the data are timely, complete, accurate and true. ②Any evidenced correction in the medical records of the study should only be underlined, and the revised data should be circumscribed and dated by the investigators, and the original records should not be erased or overwritten. ③ The laboratory results of both outpatients and inpatients should be filled in the "Physical and Chemical Examination Result Report Form" to the CRF. The original laboratory tests of subjects are pasted on the CRF.

Review of study medical records: After the end of the observation course for each subject, the researcher should submit the study medical record, informed consent and patient medication record card to the project leader of the unit within 3 working days for review, signature and storage, and timely deal with and record any problems found.

Data are reported using electronic CRF (Electronic Data Capture, EDC). The project leader of each center designates someone to undertake the work of “EDC entry clerk”, which is responsible for the record of the first review of the research medical records and the registration and filling of the electronic CRF. The investigator must promptly hand over the study medical records to the “EDC entry clerk” after completing each subject observation. The “EDC entry clerk” must first review: whether the project record of the study medical record is complete and report on time.

9.3 Data monitoring

The monitoring frequency should meet the quality control requirements of clinical research. Monitors review each study record and complete “Monitor review pages” on a case-by-case basis.

Two monitors should 100% check the consistency of source data and electronic CRF data in the way of reading, and complete the “data consistency check report”. If any errors are found in the data, the “Data Consistency Check Error Correction report” shall be submitted for correction by the electronic CRF data manager.

9.4 Data checking and blinding review

A database is established, including numerical ranges and logical checks. If there are any doubts, the query list will be filled out, and the questions in the query list will be answered by the researcher. Complete the data inspection report. The list of questions should be kept properly. After the blinded review report is completed, the database is locked. Documents related to quality control should be preserved, such as the original records of data consistency check, numerical range and logic check, the original records of blind review, and the records of questions communicated between researchers and monitors.

10. Statistical analysis

10.1 Statistical analysis plan and statistical software

Software SAS9.4 is used for statistical analysis.

The plan of statistical analysis will be made after the start of the study, and affirmed before the lock of the database. The plan will provide the content involved in all the statistical analysis, including the definition of dataset used for analysis, and statistical description and analytic methods used for different indicators, etc.

10.2 Selection of data sets for analysis

Full Analysis Set (FAS) refers to the ideal set of participants approaching as closely as possible to the analytic principle of intentionality (including all the cases randomized into the group, receiving at least one treatment of trial medicines, and having the evaluating data after administration). The missing data of the efficacy index in the visiting period will be supplemented with the method of Last Observation Carry Forward (LOCF).

Per Protocol Set (PPS) refers to the set of participants who meet the inclusion criteria in the trial treatment protocol, have good compliance, have not used the combined medicines that seriously affect the evaluation of efficacy, and not tremendously violated the trial protocol.

Safety Analysis Set (SS) refers to all cases that received at least one treatment with trial medicines after randomization, and had the data for safety evaluation post administration.

The division of statistical analytic dataset will be finalized in the conference of data review.

10.3 Content of Statistical analysis

The actual number of subjects in the two groups, dropout and exclusion cases, demographic and other baseline characteristics, compliance, efficacy analysis and safety analysis.

10.4 Statistical analysis methods

(1) Descriptive statistical analysis: qualitative indicators are described by frequency table, percentage or constituent ratio. Quantitative indicators are described as mean, standard deviation, or median, lower quartile (Q1), upper quartile (Q3), minimum value, and maximum value.

(2) Comparative analysis of the two groups: Chi-square test, Fisher's exact test, Wilcoxon rank sum test, CMHχ^2 test, WLS covariance are used for qualitative data. Quantitative data with normal distribution are tested by t test (homogeneity of variance test between groups, 0.05 is used as the test level, Satterthwaite method is used to correct the t test when the variance is not equal). Non-normal distribution is tested by Wilcoxon rank sum test, Wilcoxon signed rank sum test; GLM covariance. Two-sided test is used to test the hypothesis, and the test statistics and their corresponding P values are presented. $P \leq 0.05$ is considered statistically significant, and $P \leq 0.01$ is considered highly statistically significant.

11. Ethics

11.1 Ethical review

The clinical trial protocol is submitted to the ethics committee for approval before implementation. If the protocol is revised during the implementation of the clinical trial, it needs to be submitted to the ethics committee again for approval. If important new information related to the trial drug is found, the informed consent form have to be revised in writing to the ethics committee for approval, and then the consent is obtained from the subjects again.

This study is reviewed and approved by the Institutional Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine before the start of the trial. When necessary (such as serious adverse events), the ethics committee should hold a meeting in time for review, and the review conclusion should be reported.

11.2 Benefits and risks

Subjects and society will likely benefit from this research. Such benefits include the potential for improvement in the subject's condition and the possibility that the study could lead to the development of a new treatment that could be used in other patients with similar conditions. Subjects receive free fees for study-related examinations during the study, registration fees at follow-up. Subjects will have access to good medical care for the duration of the study.

11.3 Recruitment of subjects

The relevant information is released through the recruitment notice in the hospital → interested persons sign up → read the study introduction → sign the informed consent form → physical examination → screening → qualified persons sign the informed consent form → selected subjects are randomly divided into two groups. Recruitment notices and study briefs need to be submitted to the ethics committee for review.

11.4 Medical care and protection of subjects

Investigators at the Affiliated Hospital of Nanjing University of Chinese Medicine are responsible for the medical care of the subjects, make relevant medical decisions, and ensure that the subjects receive appropriate treatment in the event of adverse events during the trial.

11.5 Protection of subject privacy

Only investigators and monitors involved in clinical trials may have access to subjects' personal medical records. Data will be processed in a “data anonymization” manner, omitting information that could identify individual subjects.

11.6 The process of informed consent

The detailed information about the clinical trial should be explained, including the purpose of the trial, the trial procedure, the possible benefits and risks, and the rights and obligations of the subjects, etc., so that the subjects can fully understand and have sufficient time to consider, give consent after the questions have been answered satisfactorily, and sign the "informed consent" before starting the clinical trial. When each patient signs the informed consent form, the doctor will give his contact number to the patient, so that the patient can find the doctor at any time if his condition changes.

12. Summary and data preservation

Each research center is equipped with special file cabinets, and special personnel are responsible for keeping and sorting out the trial documents and related data. Special cabinets for trial drugs are set up, and special persons are responsible for drug registration, distribution and recovery. Investigators should submit the study medical records, informed consent forms, and patient medication record cards to the principal investigator of their centers within 3 days after the end of the observation course of each study case. Study data are uploaded to the data management center in accordance with relevant regulations. After the end of the study, all the research data are stored centrally in the project undertaking unit. The study is summarized by the blinded evaluators, and all the original data related to the study are saved by the research group and archived after the conclusion of the project.

13. Task allocation

Randomization is stratified by center, with block randomization. The study is conducted simultaneously in 8 hospitals including the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine (team leader), Beijing Friendship Hospital Affiliated to Capital Medical University, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Guangdong Provincial Hospital of Traditional Chinese Medicine, the First Affiliated Hospital of Nanjing Medical University, Shuguang

Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Changhai Hospital Affiliated to Naval Medical University, and the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine. The random arrangement of 400 subjects to receive treatment is generated by an independent third-party with the help of SAS statistical analysis system. The basic information of the cases is input by each member unit, and the eligible cases are automatically assigned to the treatment group or the control group and received corresponding treatment.

Hospital	**Planned number of cases assigned**
Affiliated Hospital of Nanjing University of Chinese Medicine	112
Guangdong Provincial Hospital of Traditional Chinese Medicine	84
Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine	52
Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine	76
the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine	48
Affiliated Hospital of Naval Military Medical University	16
Beijing Friendship Hospital, Capital Medical University	8
the First Affiliated Hospital of Nanjing Medical University	4
Total	400