

# Efficacy and safety of Guhong injection for treating the Coronary microvascular disease: study protocol for a randomized controlled trial

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## Study protocol

**Keywords:** Guhong injection, Coronary microvascular disease, Randomized controlled trial, Inflammatory response, Endothelial function

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# Abstract

**Background:** Coronary microvascular disease (CMVD) refers to cardiovascular diseases with normal coronary angiography but evidence of myocardial ischemia or microcirculation lesions, often presenting as angina pectoris attack. Coronary artery of microtubules dysfunction is one of the pathogenesis of coronary heart disease, but the occurrence and development and the current of CMVD intervention therapy remains to be further researched. Chinese traditional medicine (TCM) has advantages in the treatment of cardiovascular diseases, therefore, this article describes an ongoing randomized controlled clinical trial, based on the theory of TCM, for the purpose of evaluating the efficacy and safety of Guhong injection, a Chinese patent medicine, compared with placebo in patients suffering from CMVD. **Methods/design:** This is a multicenter, randomized, parallel arm, open-label, double-blind, placebo-controlled clinical trial. A total of 260 eligible patients will be allocated and randomly assigned, in a ratio of 1:1, to either the experimental group or the control group. The treatment course is 10 consecutive days, with a 8-week follow-up. The primary outcome is the frequency of angina attacks, Secondary outcomes include myocardial metabolites, ecg changes, quantitative score of TCM syndromes, inflammatory response and endothelial function indicators. **Discussion:** This trial is strictly designed in accordance with principles and regulations issued by the China Food and Drug Administration (CFDA). The results will provide high quality evidence on the efficacy and safety of Guhong injection in the treatment of CMVD. **Trial registration:** Chinese Clinical Trials Registry, ChiCTR1900022902. Registered on 27 April 2019. **Keywords:** Guhong injection, Coronary microvascular disease, randomized controlled trial, inflammatory response, endothelial function

## Background

CMVD is a clinical syndrome with objective evidence of exertional angina or myocardial ischemia caused by structural or functional abnormalities of the precoronary and arterioles under the influence of multiple pathogenic factors. In the past 20 years, a large number of studies have shown that coronary microcirculation structural and functional abnormalities can be found in non-occlusive coronary artery diseases, but in people with high risk factors of coronary heart disease, as well as in cardiomyopathy and occlusive coronary artery diseases, which have important predictive and therapeutic target values [1, 2]. Currently, there are still no large sample epidemiological data on CMVD, but some clinical studies with small sample have shown that the incidence of CMVD is up to 45%~60% in patients with myocardial ischemia symptoms but coronary angiography showing non-obstructive lesions, and the major cardiovascular events and all-cause mortality in these patients are significantly higher than the control group [3]. It is generally believed that the pathogenesis of CMVD is complex nowadays. Endothelial injury, inflammatory factors, various vascular substances, and microembolism may all lead to changes in microvascular structure and function, and the pathophysiological mechanism of different types of CMVD is not completely the same in clinical practice [4-6]. At present, the treatment regime of western medicine mainly includes anti-thrombus, lipid regulation, plaque stabilization and vascular dilation, etc, but it is still an urgent problem to be solved in clinical practice [7], Many patients still have repeated angina attacks

under the current drug treatment regimen, causing anxiety and restlessness in the psychology, which has a huge impact on life and work.

TCM has the advantage of multi-target and multi-link therapeutic effect and less adverse reactions, especially on the treatment of cardiovascular and cerebrovascular diseases with many years of history and has been widely studied and confirmed. TCM treatment depends on different kinds of pathogenesis, blood stasis is generally considered as one of the most important pathogenesis of coronary heart disease, so promoting blood circulation and removing blood stasis is an extremely important treatment [8]. In recent years, the research of TCM in the prevention and treatment of CMVD has shown a good application prospect, but this is still not universally agreed treatment.

Redflower is one of the most famous traditional Chinese medicines and is considered to be essential for promoting blood circulation and removing blood stasis [9]. Guhong injection is made with red flower extracts and acetylglutamide, of them redflower extracts contain active ingredients such as redflower glycosides and redflower yellow pigment (Table 1). Clinical pharmacology research results show that Guhong injection can inhibit platelet aggregation, prevent thrombosis, expansion of coronary artery, reduce myocardial oxygen consumption, improve microcirculation, alleviate ischemia-reperfusion injury, anti oxygen free radicals [10]. Accordingly, this study intends to use Guhong injection by peripheral intravenous drip on the treatment of CMVD to demonstrate its efficacy and safety, and explore its mechanism of action from the perspective of inflammatory response and endothelial function, so as to provide a basis for the treatment of coronary artery microvascular dysfunction with integrated Chinese and western medicine.

**Table 1 Pharmacological effects of each ingredient in Guhong injection**

<b>Ingredient</b>	<b>Pharmacological effects</b>
Redflower glycosides	Resist myocardial ischemia, resist platelet aggregation
Redflower yellow pigment	Protect heart muscle, resist oxidation, resist inflammation
Acetylglutamide	Activate nerve cell

## Methods/design

### Study design

This study is a multicenter, parallel, prospective, double-blind, randomized, placebo-controlled clinical trial. A total of 260 patients will be enrolled and randomly divided into the treatment and placebo groups. All patients will receive 10 consecutive days of treatment and follow up for 8 weeks. Efficacy and safety data will be collected throughout the study. Flowchart is Fig. 1.

### Ethics

This trial has been successfully registered in the China Clinical Trial Registry (ChiCTR1900022902). Additionally, the study will be strictly conducted in accordance with the Helsinki Declaration, Good Clinical Practice (GCP) guidelines and laws. The research protocol, informed consent, and recruitment posters were reviewed and approved by the Ethics Committee of the Guangdong Provincial Hospital of

Traditional Chinese Medicine (No. BF2018-180-01). The researchers in all six trial centers are well-trained and qualified medical staff. All eligible patients will be fully informed and totally understand about this protocol and will sign an informed consent form(ICF) prior to participation. All participants can receive all exams and treatments for free, and their privacy, data and security will be greatly protected.

## **Participants and recruitment**

We will recruit patients who meet the criteria for inclusion by advertising on hospital notice boards, posting recruitment information in network communication groups or being recommended by outpatient and inpatient doctors. A total of 260 eligible participants will be recruited in the following 6 hospitals: (1) Guangdong Provincial Hospital of Traditional Chinese Medicine ,(2) Guizhou Provincial Hospital of Traditional Chinese Medicine ,(3) Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, (4) Foshan Traditional Chinese Medicine Hospital ,(5) Shenzhen longgang district hospital of traditional Chinese medicine,(6) Yangjiang people's hospital. These six trial centers are all first-class hospitals in China, with advanced cardiovascular interventional departments, excellent medical teams and many inpatient beds. Especially the Guangdong Provincial Hospital of traditional Chinese medicine, which has the largest number of outpatients among the hospitals of TCM in China and rich experience and achievements in the research of integrated Chinese and western medicine. So the first center will be recruited 80 patients, and 36 for each of the remaining centers.

## **Inclusion criteria**

For inclusion, participants should fulfill all the following criteria:

1. Coronary angiography or coronary CT (computed tomography) indicated the absence of unstable plaque or coronary stenosis <50% and the presence of clinical symptoms of stable angina pectoris. [11].
2. Aged between 35 and 75, regardless of gender.
3. Willingness to participate the trial and to sign the informed consent form,with high compliance and cooperative attitude.

## **Exclusion criteria**

Participants with any of the following conditions will be excluded:

1. Psychopaths ,pregnant or lactating women.
2. Patients with myocardial infarction,heart failure,stroke,arterial dissection,arterial embolization, tumors, severe hematologic diseases,endocrine diseases or pneumonia and other infections.
3. Patients with liver and kidney dysfunction.( Expression of aminotransferase [ALT] and aspartate aminotransferase [AST] was 1.5 times higher than higher than the normal upper limit, abnormal serum creatinine,positive urine protein qualitative test).
4. Patients who are allergic to Guhong injection.

5. Participated in other clinical trials and took actual experimental drugs within 3 months.
6. Patients who are not considered to meet the criteria by the researchers.

### **Withdrawal criteria**

The withdrawal criteria include the following:

1. Experiencing serious complications or rapid deterioration of the condition during the trial, including angina attack frequency increased significantly, myocardial ischemia continued to worsen, myocardial infarction, arrhythmia and other changes.
2. Serious adverse events occurred, which should be stopped according to the doctor's judgment.
3. Participants with important deviations in the implementation of the program, such as poor compliance and difficulty in evaluating drug effects.
4. Quitting the clinical trial voluntarily.

### **Sample size**

A previous study for Guhong injection in the treatment of angina pectoris [12] showed that the effective rate of the conventional treatment group (33 cases) was 81.82%, while that of the Guhong injection plus conventional treatment group (33 cases) was 93.94%. According to the literature, it was assumed that the efficient rate of Guhong injection group was from 81.82% to 93.94%, and the sample size was calculated based on the parameter  $\alpha = 0.05$  (bilateral test) and  $\beta = 0.2$ . By comparing the effective rate of the two groups according to the following sample size estimation formula:  $N = [\pi_t (1 - \pi_t) / k + \pi_c (1 - \pi_c)] (\mu_{1-\alpha/2} + \mu_{1-\beta})^2 / (\pi_t - \pi_c)$ ; we calculated that 111 patients should be recruited for each group. Taking into consideration of an attrition rate of <15%, the eligible participants in each group should be >130. Ultimately, we determined the final sample size to be 130 (N=260 in total).

### **Randomization and blinding**

A total of 260 participants will be randomly assigned to the Guhong group and control group in the ratio of 1:1 by the method of using 260 opaque envelopes. Each envelope will be stuffed with a piece of paper. There are 260 pieces of papers in total, half of which were written with the notes of "20ml Guhong injection plus 250ml 0.9% sodium chloride, ivd, qd", and the other half were written "270ml 0.9% sodium chloride, ivd, qd". After all opaque envelopes were stuffed and sealed, they will be mixed evenly and distributed to each trial center.

When a sub-center accepts an eligible participant, the investigators will write the baseline information (including the subject's hospital ID number, name, age, gender) on the cover of the envelope. Both investigators and participants will be blinded. Only drug administrators and dispensing nurses are responsible for opening the envelope to know the the group allocation and perform interventions according to the written instructions on the paper, but they won't be involved in recruitment, recommendation, data collection and analysis. Both Guhong injection and placebo are administered

using a photophobic infusion set to avoid the subjects being aware of the group information. All investigators, outcome assessors and data analysts will be blinded to collect and summarize data just based on subject's baseline information until the completion of the visit and analysis.

### **Emergency unblinding**

If an emergency occurs, the patient group assignment should be unblinded and known from drug administrators or dispensing nurses and corresponding emergency measures will be taken. Researchers will report this special situation to the center's principal within 24 hours. At the same time, the cause of unblinding, the time of emergency, the solution and the result must be filled in case report form (CRF). Once the participant's allocated intervention during the trials has been revealed, the case will be withdrawn and the data will be recorded on day 10 of the trial evaluation.

### **Unblinding after the study**

When all trials are completed and all data is locked, the unblinding process will be conducted in the presence of the researchers.

### **Interventions**

On the basis of conventional western medicine treatment, the Guhong group will be given 20ml intravenous infusion of Guhong injection that was diluted with 250ml 0.9% sodium chloride injection once a day, while the control group will be given 270ml 0.9% sodium chloride injection as placebo treatment once a day. (Guhong injection is provided by China tonghua guhong pharmaceutical co.LTD. The production batch number is 20190306 and each bottle has a capacity of 5ml. The drug distributed to each center will be labeled with the statement of "for trial only" and the information of name, dosage, dosing plan, indications, storage conditions, expiration date, manufacturer and so on. Each center has an independent manager responsible for receiving, handling, storing and distributing medications.) The course of treatment was 10 days. On the day of enrollment and at the end of treatment, the clinical symptoms and signs of angina pectoris will be recorded, the quantitative table of TCM syndrome will be scored, the electrocardiogram will be examined, and the indicators of inflammation, endothelial function, myocardial metabolites and related biochemical tests will be conducted. Moreover, patients will be followed up for 8 weeks after the end of treatment, including the angina pectoris improvement and TCM syndrome quantitative score. During the entire study period, participants will be visited a total of 4 times by investigators. Specific research process details are provided in Table 2.

**Table 2 Study schedule for patients**

	Study period			
	Enrollment	Allocation	Post-allocation	Check-out
Visits	Visit 1	Visit 2	Visit 3	Visit 4
Time point(day)	-0.5	1	10	66
<b>Enrollment</b>				
ICF signature	X			
Basic information	X			
Coronary angiography or coronary CT	X			
Symptoms and signs	X		X	X
<b>Interventions</b>				
Guhong injection group		**	**	
Placebo-control group		**	**	
<b>Safety and efficacy assessment</b>				
Frequency of angina	X		X	X
TCM symptoms and sign scores	X		X	X
Electrocardiogram	X		X	
Inflammation test	X		X	
Endothelial function test	X		X	
Myocardial metabolism test	X		X	
Blood routine test	X		X	
Urine and fecal routine test	X		X	
Liver and kidney function test	X		X	
Adverse events recording	X	X	X	X
<b>Others</b>				
Randomized allocation	X			
Drug distribution	X			
Concomitant treatment		X		X
Distribute patient diary cards		X		X
Quality control and monitoring		X	X	X

## Concomitant treatments and forbidden drugs

During the study period, participants with other diseases are allowed to continue corresponding treatment of western medicine, such as hypertension, diabetes, hyperlipidemia, et al. And the name, dosage and duration of any concomitant medication must be carefully recorded in the case report form (CRF), and any other western medicine or Chinese medicine that may affect the research results will be prohibited. Once banned drugs are used, patients will be dropped out of the study and their data will not be used according to the signed informed consent.

## Efficacy assessment

### Primary outcome

The criteria for therapeutic efficiency evaluation is based on the principles for clinical research reports on cardiovascular drugs formulated by the National Health and Pharmaceutical Bureau of China [13] by comparing the angina attack frequency and ECG changes before and after treatment in the two groups of participants. Specific evaluation criteria are shown in table 3.

**Table 3. Evaluation criteria on the Therapeutic efficiency**

Three graded criteria	Detailed description	Classification
Significant improvement	Angina attacks disappeared or significantly improved, decreased by 80%;ECG returned to normal or substantially normal	Significant effective
Improvement	Angina attacks improved or the frequency of angina attacks decreased by 50-80%;The descending ST segment of the ECG rose $\geq 0.05\text{mV}$ , and the ascending ST segment fell $\geq 0.05\text{mV}$ , but still did not return to normal;,Or the T-wave of the main ECG lead changed from flat to upright;Or the T-wave changed from inverted to shallow by more than 50%	Effective
No improvement	No change or even aggravation of angina attacks, no decrease or even increase of the frequency of angina pectoris attacks,no change or even aggravation of ECG ST-T	No effect

## Secondary outcomes

Secondary outcomes include changes in TCM symptoms and signs scores(Table 4), the average frequency of angina pectoris ,ECG,the indicators of inflammation,endothelial function and myocardial metabolism.

## Change in TCM symptoms and signs scores

The TCM syndromes scoring system used in the study follows the Guidelines of clinical research on the treatment of coronary heart disease (chest pain) with New Chinese Medicine [14], in which all symptoms and signs scores are graded (Table 4). A total of 9 kinds of symptoms include: chest pain, chest tightness, breathless, palpitations, mental fatigue, aversion to cold and cold limbs, lumbar and knee soreness, spontaneous sweating and insomnia.The score is 0 point for asymptomatic, 1 point for mild, 2 point for moderate, and 3 point for severe. The total score ranged from 0 to 27. The lower the score, the milder the symptoms.

**Table 4 Symptom and sign scoring system**

Symptom or sign	Score			
	Asymptomatic(0)	Mild(1)	Moderate(2)	Severe(3)
Chest pain(angina)	None	Occasionally, self-medication	Frequently, obvious when moving	Sustained, can't insist on work
Breathless	000	000	000	000
Palpitations	000	000	000	000
Chest tightnes	000	000	000	000
Mental fatigue	000	000	000	000
Aversion to cold And cold limbs	000	000	Frequently, Need to add clothes	Severe,can't ease when adding clothes
Lumbar and knee Soreness	000	000	000	000
Spontaneous sweating	000	Occasionally, aggravate when moving	Frequently, when a little activity	Severe, when no movement
Insomnia	000	Mild, difficult to sleep, but hardly affected	Moderate, can't sleep for hours	Severe, can't sleep all night

### The average frequency of angina pectoris

The average frequency of angina pectoris from the first day of enrollment to the end of treatment and at 8 weeks of follow-up will be recorded in the CRF.Each participant will be instructed to record any change in the symptom of angina pectoris in their patient diary every day.

### Indicators of inflammation, endothelial function and myocardial metabolism

Indicators of inflammation, endothelial function and myocardial metabolism of participants before and after treatment will be tested in this study. Inflammatory indicators include hypersensitive c-reactive protein (hs-CRP), interleukin-6(IL-6) Tumor necrosis factor-alpha(TNF- $\alpha$ ). Endothelial function indexes include nitric oxide (NO) and endothelin-1 (ET-1) Thromboxane A2 (TXA2). Myocardial metabolism indicators include cardiac troponin I (cTn I), creatine kinase isoenzyme (CK - MB). Inflammatory reaction plays a significant role in the occurrence and development of coronary heart disease angina pectoris. TNF- $\alpha$  is the initiation factor of inflammatory response, which stimulates the synthesis and release of pro-inflammatory response factors (IL-6 and CRP), leading to the aggravation of inflammatory response and the formation of thrombus.[15,16] NO and ET-1 are the two most important vasoactive factors and the sensitive indicator of endothelial dysfunction in human body[17], NO can relax blood vessels [18], while

ET-1 can promote vasoconstriction [19]. After vascular endothelial injury, TXA2 will promote platelet aggregation and vasoconstriction [20]. As for c Tn I and CKMB, they are ideal metabolites for early myocardial injury [21].

### **Safety evaluation**

Liver and kidney function, blood routine, urine routine, fecal routine and electrocardiogram before and after treatment will be detected to assess the drug safety and adverse reactions.

### **Data management and statistical analysis**

The drug clinical research center of Guangzhou university of TCM will be responsible for the data statistical analysis. Two independent data administrators are in charge of reading the CRFs and recording data on the EpiData 3.1 software. And Clinical research assistants (CRA) and investigators will re-check and review the accuracy and consistency of data. After entering and reviewing, the database will be locked and the statistical analysis will be performed only with the permission of the sponsor, the principal investigator and the investigators.

The full analysis set (FAS) is the primary analysis set, in which patients should be dosed with Guhong injection or placebo for 10 days with clinical observation record in the study. All subjects without any major protocol deviations will be included in the per-protocol set (PPS). Efficacy assessment will be performed through FAS and PPS. Safety evaluation will be conducted for those who have been treated at least once, which is defined as the safety set (SS).

All continuous data and normal distribution data are represented by mean  $\pm$  standard deviation, while median and range for non-normal data. Classified data are expressed in frequency counts and percentages. Baseline balance between groups will be determined by chi-square test or anova. All the indicator about angina attack frequency, inflammation, endothelial function and myocardial metabolites will be estimated and compared by the log-rank test. A Kaplan-meier survival curves will be constructed and the median time will be provided separately for each group with a two-sided 95% confidence interval. Analysis of variance (ANOVA) and Bonferroni method will be used to compare the TCM symptom and sign scores of the two groups. All collected data will be processed by professional statisticians using SAS 9.2 software; a two-sided P value of  $<0.05$  is considered statistically significant

### **Quality control and monitoring**

All case report forms (CRFs) are designed in strict accordance with relevant requirements of GCP which be filled out by trained researchers to ensure consistency and reduce bias. If there is any ambiguity in the completion process, the results will be determined by the team members of the whole center after discussion. Each trial center has a project leader to control the quality, and all survey researchers are trained to be qualified and familiar with the process. In the process of clinical research, measures should be taken to ensure patient compliance according to the possible causes of losing to follow up, and designated special cardiologists will visit each center regularly to check the original documents and CRFs,

and supervise the study to ensure it complies with the protocol. Any shortcomings or problems found by inspectors should be improved.

### **Interim analyses and stopping guidelines**

When the trial was nearly halfway done, an interim analysis of the collected data will be performed. And only the sponsor and the principal investigator will have access to these interim results and decide whether or not to make the final decision to terminate the trial. The guidelines for stopping the trial are listed as follows: (1) The efficacy and safety of the studied drug have been confirmed; (2) The expected inter-group effect difference cannot be achieved; (3) There was an intolerable adverse drug reaction.

## **Discussion**

Many studies have confirmed that coronary microcirculation plays an important role in regulating coronary blood flow and myocardial perfusion [22]. However, it cannot be developed in coronary angiography, so it is easy to be neglected in clinical work. Therefore, while we focus on the prevention and treatment of coronary artery disease, we should pay enough attention to CMVD, and this part of the population is not in the minority. To date, there are no drugs or methods on the treatment of CMVD that have been proved to be effective by extensive clinical studies [23]. However, TCM has been used for cardiovascular and cerebrovascular diseases with thousands of years in China. What's more, many Chinese medicines have been developed by combining the historical therapeutic experience of TCM with modern pharmacological research, and their efficacy and safety have been repeatedly confirmed by studies. But it is a pity that not a few of these studies have limitations of general quality and low quantity [24], so it is hard to popularize and apply globally.

As a Chinese medicine developed by famous domestic pharmaceutical groups, Guhong injection has been proved to be effective and has been used on the treatment of cardiovascular and cerebrovascular diseases in clinical practice for many years. In order to demonstrate the efficacy and safety of Guhong injection for CMVD, and to investigate its mechanism of action from the perspective of inflammation and endothelial function, we applied for this multicenter, double-blind, placebo-controlled randomized clinical trial in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and the "One study, one primary outcome" clinical trial methodology published by the CFDA [25] for purpose of obtaining high-quality evidence for clinical extension. Moreover, the protocol presents a detailed and practical methodology for future clinical trials of developing TCM.

### **Trial status**

The study is currently in the process of continuing to enroll participants in six trial centers. And the protocol version number is 1.0 and the date is November 1, 2018. Our recruitment period will be from December 19, 2018 to December 19, 2020.

## **Abbreviations**

ALT: aminotransferase; AST: Aspartate aminotransferase; CMVD :coronary microvascular disease; TCM:Chinese traditional medicine; CFDA:China Food and Drug Administration; ChiCTR-IPR:China Clinical Trial Registry; cTnI:troponin I; CRF:case report form; CK-MB:creatin kinase isoenzyme; CRA:Clinical research assistants; CONSORT: consolidated Standards of Reporting Trials; CRO: Contract Research Organization; ET-1:and endothelin-1; FAS:full analysis set; GCP: Good Clinical Practice; hs-CRP: hypersensitive c-reactive protein;IL-6 :interleukin-6; ICF:informed consent form;PPS :per-protocol set; SS :afety set; TNF- $\alpha$ :Tumor necrosis factor-alpha; TXA2: Thromboxane A2.

## Declarations

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### Availability of data and materials

All data will be made available.

### Authors' contributions

ZJ, ZS, and CH contributed to the design and development of the trial. CB is the principal investigator of this study. ZJ drafted the initial manuscript, and ZS revised it carefully. DX and CY participated in the design and coordination of the trial as well as in recruiting patients. All authors reviewed the content and approved the final version.

### Competing interests

The authors declare that they have no competing interests.

### Consent for publication

Not applicable.

## **Ethics approval and consent to participate**

The protocol, informed consent form, and recruitment poster were reviewed and approved by the Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine (No. BF2018-180-01), the Ethics Committee of the Guizhou Provincial Hospital of Traditional Chinese Medicine, the Ethics Committee of the Second Affiliated Hospital of Guizhou University of TCM, the Ethics Committee of the Foshan TCM Hospital, the Ethics Committee of the Shenzhen Longgang District Hospital of TCM, the Ethics Committee of the Yangjiang People's Hospital. Written informed consent will be obtained from each participant prior to enrollment.

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## Figures

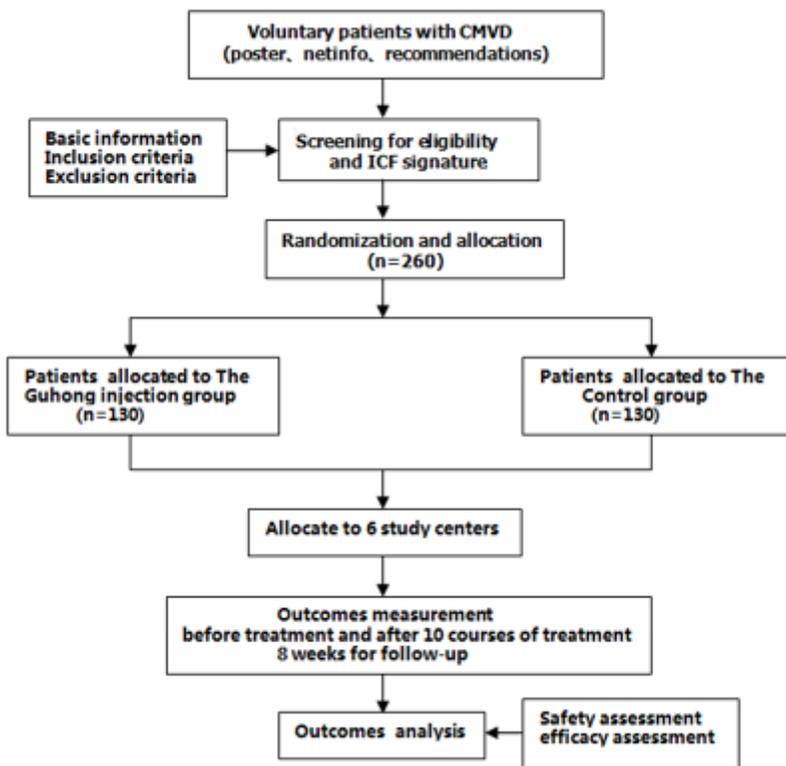


Figure 1

Study flow chart. ICF informed consent form.

## Supplementary Files

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