



## Study Protocol

# Thinking and Practice in the Design of Clinical Trial Schemes for the Treatment of COVID-19 with Traditional Chinese Medicine: A Study Protocol



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## Abstract

**Background and objectives:** This study aimed to determine the key points in the design of clinical trial protocols for coronavirus disease 2019 (COVID-19) following the PICOS principle.

**Methods:** A randomized, double-blind, placebo-controlled study of Cangma Huadu Granules in the treatment of mild COVID-19 will be carried out.

**Discussion:** We recommend a randomized controlled trial as the study type. The inclusion criteria should not only define the diagnostic criteria of Western medicine and the syndrome types of Chinese medicine but also define the course of the disease. The definition of high-risk groups in the exclusion criteria needs to specify the diseases and laboratory test indicators to avoid excluding patients with common underlying diseases. Preclinical studies on the experimental product and the traditional Chinese medicine theory of indications should be outlined to clarify the trial rationale. A placebo combined with basic treatment is recommended as a control. Outcomes can refer to the core outcome set for clinical trials on COVID-19, and it is recommended to set the main outcome indicators around the clinical symptoms. In addition, homogeneous Chinese medicine during the experiment should be avoided, and the online registration should be completed in a timely manner.

**Trial Registration:** Chinese Clinical Trial Registry, ChiCTR2300070933. Registered on 26 April 2023, [www.chictr.org.cn](http://www.chictr.org.cn).

## Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease. With the continuous mutations in severe acute respiratory syndrome coronavirus 2, the transmission rate and immune evasion ability of the Omicron variant have increased.<sup>1,2</sup>

**Keywords:** Evidence-based medicine; COVID-19; Clinical trials; Cangma Huadu Granules.

**Abbreviations:** COS, core outcome set; COS-COVID, core outcome set for clinical trials on COVID-19; COVID-19, coronavirus disease 2019; TCM, traditional Chinese medicine.

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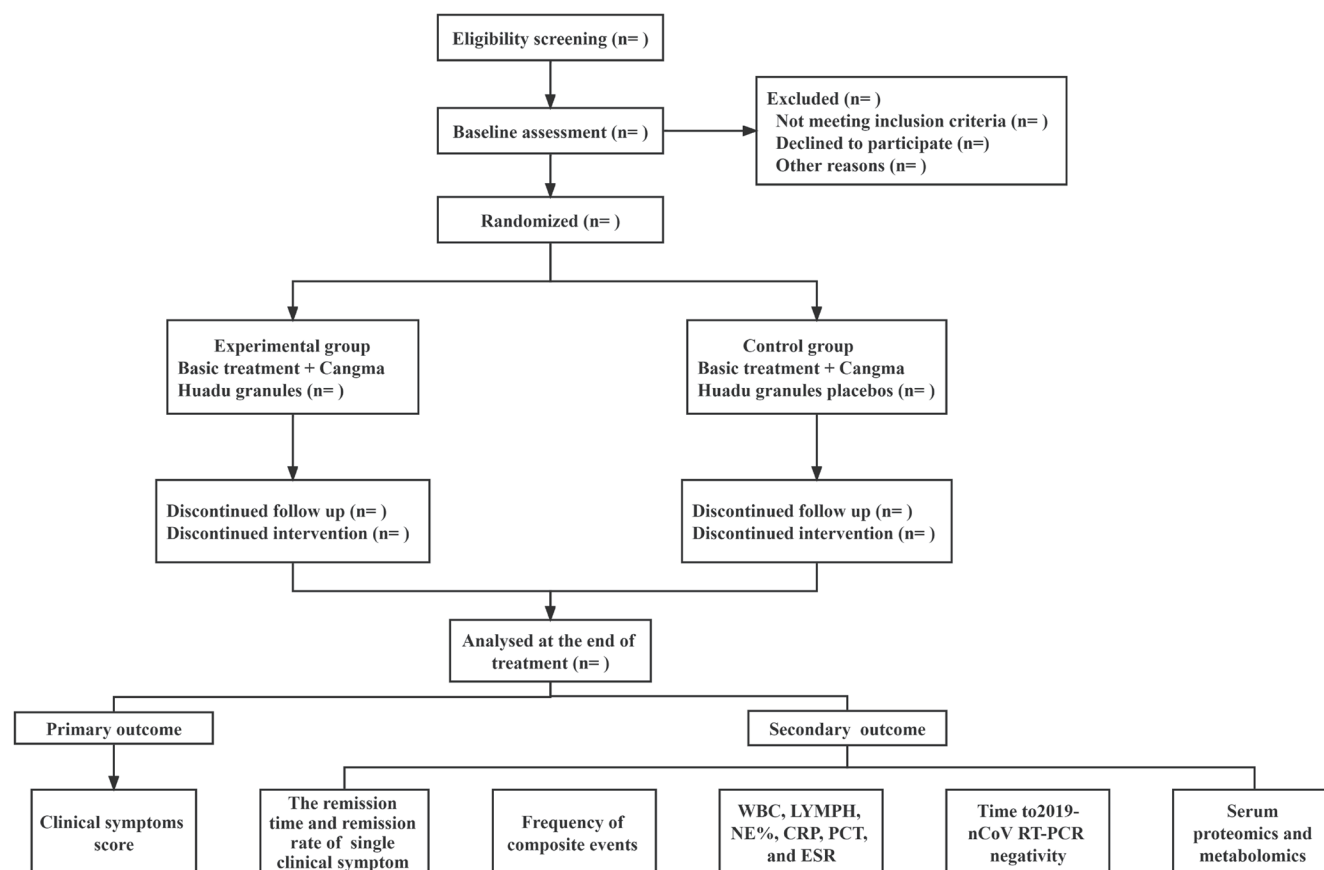
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This virus may coexist with humans for a long time, and the disease caused by it will gradually evolve into a common respiratory infectious disease. Many scientific studies focusing on COVID-19 have been carried out, and clinical studies on the treatment of COVID-19 by traditional Chinese medicine (TCM) have emerged one after another. However, many clinical trials of treatments for COVID-19 have problems such as unclear target populations, low randomization rates, and similar interventions with similar populations.<sup>3</sup> This study aimed to determine the key points in the design of clinical trial protocols for coronavirus disease 2019 (COVID-19) following the PICOS principle using a randomized, double-blind, placebo-controlled study of Cangma Huadu Granules in the treatment of mild COVID-19 as an example.

## Methods

### Research design

In the design of the clinical trial scheme, the study type needs to be



**Fig. 1. Flowchart of the trial.** Parts include composite events as well as patients converted to the ordinary, severe, or critical type during treatment.

defined first. The purpose of the study and the strength of the demonstration should be considered when selecting the trial type. The purpose of this study is to evaluate the efficacy and safety of Cangma Huadu granules in the treatment of mild COVID-19; this study type is a therapeutic study. Therapeutic studies often use randomized controlled trials to evaluate efficacy.<sup>4</sup> In randomized controlled trials, randomization effectively avoids the influence of confounding factors, and the setting of the control identifies the differences between the treatment factors and the nontreatment factors and makes the nonresearch measures equal between the experimental group and control group, ensuring the scientific and rigorous conclusions of the study.<sup>5</sup> The setting of the blind method can eliminate the subjective psychological influence of the subjects and researchers.<sup>6</sup> Randomized controlled trials provide the best evidence for evaluating the effectiveness of medical interventions.<sup>7</sup> Therefore, this study is a multicenter, randomized, double-blind, placebo-controlled clinical trial: (1) The trial will be conducted simultaneously in three hospitals. (2) A stratified randomization method with central stratification will be used. Random numbers will be generated by programming through the PROC PLAN procedure of SAS statistical software. The random assignment sequence will be placed in sequentially coded, sealed, light-opaque envelopes. After the investigator determines the subject's eligibility, he will open the envelope in sequence and assign the subject to the corresponding study group. (3) The study is blind to both the researchers and subjects. (4) The treatment regimen of the experimental group is basic treatment + Cangma Huadu granules; the control group is basic treatment + placebo. (5) This study

is a prospective exploratory clinical trial, and there are no relevant literature reports. Therefore, the minimum sample size principle will be adopted, and the 10% shedding rate will be calculated. A total of 66 subjects, including 33 in the experimental group and 33 in the control group, are planned to be included. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Beijing Hospital of Traditional Chinese Medicine (No. SL-2022BL02-089-02). Informed consent was obtained from all study participants, the trial registration number in the Chinese clinical trial registry is ChiCTR2300070933 ([www.chictr.org.cn](http://www.chictr.org.cn)) (Fig. 1).

### Participants

The external validity and universality of a clinical trial depend in part on the eligibility criteria of the participants. Therefore, reasonable inclusion and exclusion criteria are a prerequisite to ensure the scientific nature and smooth development of clinical trials. In choosing the inclusion criteria, the first concern should be the description of the diagnostic criteria. The definition of the disease should be rigorous and clear, not simply and broadly referring to the name "novel coronavirus infection," but clearly citing the latest, recognized, and authoritative relevant guidelines. In addition, the course of the disease should be determined. In practice, patients usually have clinical symptoms first and then undergo antigen or nucleic acid testing while the disease is progressing. It is not practical to calculate the course of disease from the time of the laboratory test report. Therefore, the course of the disease should be set from the earliest onset of symptoms. The inclusion

criteria of this study were set as follows: (1) Patients who meet the diagnostic criteria for mild cases in the Diagnosis and Treatment Protocol for Novel Coronavirus Infection (Trial Version 6).<sup>8</sup> (2) The disease course (calculated from the time of the first symptom onset) was  $\leq 48$  h. (3) Damp constraint in the lung pattern and clinical manifestations of fever, fatigue, sore body, sore throat, chest tightness, suffocation, loss of appetite, nausea, vomiting, loose stool, or sticky stool. The tongue is light red, and the coating is either white and greasy or thin and yellow. The pulse is slippery and rapid, or soggy. (4) Age  $\geq 18$  years old and  $\leq 65$  years old, male or female. (5) The informed consent form was voluntarily signed. The exclusion criteria should be set to exclude conditions that affect the efficacy of the study drug and increase the risk. The exclusion criteria are not the opposite of the inclusion criteria; however, they complement the inclusion criteria, listing confounding factors and special circumstances that lead to bias in the results on the basis of meeting the inclusion criteria.<sup>9,10</sup> The exclusion criteria in this study were set as follows: (1) Patients who have the following risk factors: women who are pregnant or puerperal; chronic lung diseases; diseases of the nervous system and neurodevelopmental disorders; heart disease, excluding high blood pressure without any other heart-related symptoms; diseases of the blood system; endocrine system diseases, excluding hemoglobin A1c  $< 8\%$ ; kidney disease, creatinine clearance  $\leq 60$  mL/min or maintenance dialysis; liver disease, excluding asymptomatic abnormal liver function with aspartate aminotransferase or alanine aminotransferase levels elevated less than 50% of the upper limit of normal; impaired immune system; body mass index  $\geq 30$ ; heavy smokers. (2) Patients who have received or are receiving Western medicines that have anti-COVID-19 effects. (3) Antipyretic and analgesic drugs were used 6 h before enrollment. (4) A Chinese medicine with a similar efficacy to the test drug was used 6 h before enrollment. (5) Patients with severe allergic constitution. (6) Mentally ill persons, or others unable or unwilling to cooperate. (7) Participants in other trials within the last 3 months.

Thus, the diagnostic criteria included in the inclusion criteria should be based on authoritative clinical guidelines. At the same time, TCM clinical trials should pay attention to the setting of TCM syndrome differentiation and typing, and the selection of syndrome types should be determined according to the composition and efficacy of the drugs. The exclusion criteria should be based on meeting the inclusion criteria to exclude those with treatment contraindications, high-risk groups with severe diseases, and the groups who have received the same efficacious drug treatment. It should be noted that since the participants of this study have mild cases, the elderly, patients with serious underlying diseases, and obese patients are clearly excluded from this study according to the setting of severe/critical high-risk groups in the Diagnosis and Treatment Protocol for Novel Coronavirus Infection (Trial Version 6).<sup>8</sup> At the same time, considering exclusion criteria that are too strict is neither scientific nor conducive to the inclusion of subjects. In the exclusion criteria, the severity of underlying diseases was set more clearly, which is conducive to avoiding the exclusion of patients with general underlying diseases.

### Intervention

In the design of the TCM clinical trial scheme, the formulation of intervention measures should be combined with TCM theory and modern research results in order to clarify the source basis and to formulate ideas. A guideline for reporting randomized controlled trials of herbal interventions suggests that preclinical work (animal studies, case reports, and observational studies) on herbal

products and the TCM theory of indications should be outlined to clarify the trial rationale.<sup>11,12</sup> COVID-19 belongs to the category of “Wen Yi” in TCM. The disease is mainly located in the lungs and can affect the spleen, stomach, heart, and kidneys of patients. Based on the rich clinical practice, Professor Qingquan Liu believes that “dampness” is the core pathogenic factor of COVID-19; therefore, Cangma Huadu was created.<sup>13</sup> Cangma Huadu is composed of Ephedra sinica Stapf, Atractylodes lancea (Thunb.) DC., Pogostemon cablin (Blanco) Benth. and another TCM, which has the effects of clearing heat, dampening the spleen, and detoxifying. These herbs in Cangma Huadu have anti-inflammatory, anti-allergic, and other pharmacological effects.<sup>14–16</sup> In addition, animal experiments have shown that Cangma Huadu can effectively reduce the release of inflammatory cytokines (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6) in the serum induced by a novel coronavirus (HCoV-229E) and influenza virus (H1N1/FM1), and inhibit the expression of phosphorylated nuclear factor kappa B p65/nuclear factor kappa B p65 in the lung of mice.<sup>13,17</sup> Therefore, the intervention measures of this study were set as basic treatment + Cangma Huadu granules, one bag/time, two times/day, and a course of treatment for 7 days.

### Comparison

In clinical randomized controlled trials, for diseases without effective treatment, placebos can be used to compare the new therapies to build evidence.<sup>18–20</sup> In randomized controlled trials, placebo controls help to control for the placebo effect, spontaneous remission, statistical regression to the mean, etc.<sup>21,22</sup> Placebo-controlled trials are considered the gold standard for determining the efficacy of new treatments.<sup>23</sup>

In addition, the use of placebos also needs to consider the risk of disease, clinical practice, and ethical issues. With regard to the treatment needs of COVID-19 and the health considerations of patients, the control measures in this study were combined with basic treatment on the basis of placebo treatment. According to the “Diagnosis and Treatment Protocol for Novel Coronavirus Infection (version 6),” the basic treatment in this study was set as follows:<sup>8</sup> ensure adequate energy and nutrition intake of patients, pay attention to water and electrolyte balance, and maintain internal environment stability; standard effective oxygen therapy measures should be given according to the condition, including a nasal catheter, oxygen mask, and nasal high-flow oxygen therapy; those with underlying diseases should be given corresponding treatment.

### Outcomes

In 2020, the Core Outcome Measures in Effectiveness Trials (COMET) Initiative developed a core outcome set (COS) for clinical trials on COVID-19 (COS-COVID) to tackle the outcome issues. COS-COVID recommended the most important outcomes according to the different clinical classifications of COVID-19. COS-COVID includes the following outcomes for the mild type and the ordinary type: length of hospital stay; score of clinical symptoms; composite events; and time to reverse transcription–polymerase chain reaction negativity for the virus that causes COVID-19.<sup>24</sup> Based on the efficacy of the investigational products, we believe that Cangma Huadu has an advantage in alleviating COVID-19-related clinical symptoms (e.g., fever, cough, sputum, dry throat, and sore throat). Referring to COS-COVID and combining it with the investigational product characteristics, we set up the primary outcomes around “clinical symptoms.” According to the symptoms of COVID-19, we developed a clinical symptom scoring scale (Table 1). The primary outcomes are recovery rate,

**Table 1. Symptom assessment rating scale**

Item	0	1	2	3
Fever	<37.2°C	37.2–38.0°C	38.1–39.0°C	>39.0°C
Cough	None	Once in a while	Between mild and severe	Frequent, affecting normal life
Expectoration	None	Once in a while	Between mild and severe	Frequent, affecting normal life
Dry throat	None	Mild	Between mild and severe	Severe, affecting normal life
Sore throat	None	Mild	Between mild and severe	Severe, affecting normal life
Fatigue	None	Mild	Between mild and severe	Severe, affecting normal life
Muscle or body aches	None	Mild	Bearable	Unbearable
Rate your sense of taste in the last 24 h	Normal	Diminution	None	N/A
Rate your sense of smell in the last 24 h	Normal	Diminution	None	N/A
Stuffy nose	None	Mild	One side of the nasal cavity is completely stuffy	Bilateral nasal cavity is completely stuffy
Runny nose	None	Mild	Between mild and severe	Severe, affecting normal life
Headache	None	Mild	Bearable	Unbearable
How many times did you vomit (throw up) in the last 24 h?	None	1–2 times	3–4 times	5 or more times
How many times did you have diarrhea (loose or watery stools) in the last 24 h?	None	1–2 times	3–4 times	5 or more times

prominent effective rate, and effective rate of the main clinical symptoms (fever, cough, sputum, dry throat, and sore throat). The following definitions will be used: recovery, after 7 days of treatment, the main clinical symptoms disappeared without recurrence; prominent effectiveness, after 7 days of treatment, the body temperature returned to normal, and the scores of other major clinical symptoms decreased by more than two-thirds; effectiveness, after 7 days of treatment, the body temperature returned to normal but still fluctuated, and the scores of other major clinical symptoms decreased by one-third to two-thirds; ineffectiveness, after 7 days of treatment, the condition did not change or worsen.

Secondary outcomes are contained in randomized controlled trials to provide additional information concerning treatment benefits beyond those offered by the primary endpoint.<sup>4</sup> Secondary outcomes can include outcomes that help to understand the overall benefit of treatment, variables that help to comprehend the mechanism of action of experimental drugs, and outcome measures of secondary hypotheses.<sup>25,26</sup> The secondary outcomes of this study are as follows: (1) the remission time and remission rate of every single clinical symptom on days 3, 5, and 7 of treatment (symptom remission: symptom score changed from 2 or 3 to 0 or 1 and remained for at least 24 h); (2) the proportion of patients that converted to the ordinary, severe, and critical types during treatment; (3) the time to reverse transcription–polymerase chain reaction negativity for the virus that causes COVID-19; (4) numerical difference of laboratory indicators (white blood cell count, lymphocyte count, neutrophil percentage, C-reactive protein, procalcitonin, and erythrocyte sedimentation rate) before and after treatment; and (5) serum proteomics and metabolomics tests.

Safety outcomes need to be designed according to the experimental drug compositions and pharmacotoxicological studies. Cangma Huadu is composed of *Ephedra sinica* Stapf, *Sophorae Tonkinensis* Radix et Rhizoma, and other TCMs. *Ephedra* herb extract has the effect of exciting the heart and constricting blood vessels, which can cause excitement, arrhythmias, and insomnia.<sup>27</sup>

As the main active ingredient of *Sophorae Tonkinensis* Radix et Rhizoma, high doses of matrine have hepatotoxicity and neurotoxicity.<sup>28,29</sup> Therefore, the safety outcomes of this study should collect data on the subjects' liver and kidney function, cardiac function, and all adverse events. In this study, the safety outcomes are as follows: (1) all adverse events (especially cardiovascular, nervous, and digestive symptoms); (2) vital signs: blood pressure, heart rate, respiration, and pulse; and (3) routine blood tests, routine urine tests, routine stool tests, cardiac function, liver and kidney function, and an electrocardiogram.

### Concomitant medication

In clinical trials, concomitant medications can affect the evaluation of efficacy, which has a great impact on the scientific nature of the whole trial. When setting up concomitant medications, care should be taken to avoid combining drugs that have a homogeneous effect on efficacy. In addition, remedial treatment in case of aggravation needs to be specified. In our study, herbal medicines and Chinese patented medicines with anti-cold and anti-influenza properties are prohibited during the trial period. Moreover, patients with a high fever (axillary temperature of  $\geq 38.5^{\circ}\text{C}$  and lasting for more than 4 h or  $\geq 39^{\circ}\text{C}$  and lasting for more than 2 h) can be given ibuprofen (0.2–0.4 g each time, repeated administration at an interval of 4–6 h), and patients with severe cough and sputum can be given ambroxol hydrochloride tablets (30 mg each time, 3 times a day). The cause of taking combined drugs, drug name, frequency, dosage, start and end time of medication, and outcome should be recorded. The use of ibuprofen and ambroxol hydrochloride tablets is a remedy to be used after treatment with the experimental drug failed, so this condition is included in the analysis as an “ineffective” case.

### Discussion

As demonstrated in clinical practice, TCM has played an important



role in the treatment of COVID-19. However, clinical trials can provide objective and scientific evidence for the efficacy and safety of TCM in the treatment of COVID-19. Taking a randomized, double-blind, placebo-controlled study of Cangma Huadu Granules in the treatment of mild COVID-19 as an example, we discussed the design of study type, subjects, intervention, comparison, outcomes, and concomitant medication in the trial. The type of study is closely related to the demonstration strength of the research. A randomized controlled trial is the best regimen to evaluate therapeutic studies, maximum avoiding the influence of various biases and confounding factors. Therefore, we recommend preferred randomized controlled trials as the study type. Furthermore, the subjects determined the external validity and universality of the trial. For the study of mild COVID-19, attention should be paid to the exclusion of high-risk groups, while avoiding the total exclusion of patients with other underlying diseases. Therefore, the definition of high-risk groups in the exclusion criteria needs to specify the diseases and laboratory test indicators. The course of the disease in mild cases also needs to be defined. If the time from the first symptom to enrollment is too long, the patient will have a tendency to recover or worsen. In clinical trials of TCM, the TCM theory about the intervention is often ignored. We consider it necessary to outline preclinical studies of experimental products and theories of TCM to clarify the rationale for the trials. At present, there is still a lack of specific drugs for the treatment of COVID-19, and the treatment of mild COVID-19 is mainly basic treatment. For randomized controlled trials of mild COVID-19, we recommend using a placebo as a control. It helps controls the placebo effect and helps the investigator to observe the efficacy and adverse effects of the trial drug more objectively. The formulation of outcomes can refer to COS-COVID. The treatment of COVID-19 by TCM starts from the symptoms. The practice has proved that TCM has a good effect on relieving the clinical symptoms of COVID-19. Taking relieving clinical symptoms as the main outcome index can reflect the superiority of traditional Chinese medicine. In addition, the use of homogeneous Chinese medicines during the experiment should be avoided. There are still many other aspects that must be paid attention to in the research design, but we analyzed the key links of the trial design of TCM treatment for COVID-19, hoping to provide references and suggestions for clinical researchers.

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## Conflict of interest

Two of the authors, Xiaolong Xu and Qingquan Liu, are editorial board members of *Future Integrative Medicine*. The other authors have declared that no competing interests exist.

## Author contributions

ZXL and YD: Original draft preparation; XLX and QQL: Reviewing and Editing.

## Ethical statement

This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Beijing Hospital of Traditional Chinese Medicine (No. SL-2022BL02-089-02). Informed consent was obtained from all study participants, the trial registration number in the Chinese clinical trial registry is ChiCTR2300070933 (www.chictr.org.cn).

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