BMJ Open CUPID: a protocol of a randomised controlled trial to identify characteristics of similar Chinese patent medicines

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ABSTRACT

Introduction: Traditional Chinese medicine (TCM) has accumulated some experience in curing stable angina pectoris (SAP) and efficacy has been demonstrated. Chinese patent medicines, known as modern dosage forms of TCM, can attain the desired effect in clinical application only with the guidance of TCM syndrome theory. However, due to their use by a large number of persons with little knowledge of TCM theories and practices, their efficacy and reputation have been seriously affected.

Method and analysis: Two common syndrome types of SAP in TCM, ‘qi deficiency and blood stasis’ and ‘qi stagnation and blood stasis’, will be studied in 144 subjects from four TCM hospitals in Tianjin in China using a partial crossover design. The two syndromes will be broken down into six symptom combinations; patients will select a combination of the most distressing to them, and then will be randomised into two groups. Each group, on the basis of routine medication, will be administered one kind of Chinese patent drug: Qishen yiqi Dripping Pills or Compound Danshen Dripping Pills. The treatment characteristics of the two medicines will be evaluated with the COME-PRO method developed by our research team.

Ethics and dissemination: This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number TJUTCM-EC20130005). The study is safe and reliable.

Trial registration number: Chinese clinical trials register ChiCTR-TTRRC-14004406.

BACKGROUND

Chinese patent medicines for stable angina pectoris

Stable angina pectoris (SAP) is a common coronary artery disease, its occurrence and mortality rate are on the rise. Though a number of methods are available for its control, it is still an area of high concern, especially for a series of relevant clinical symptoms associated with this disease.1 In China, traditional Chinese medicine (TCM) is a prevailing comparative and alternative medicine.2 3 In the past few years, TCM researchers have conducted substantial researches on the aetiology/pathogenesis and clinical treatment of SAP and have accumulated certain experiences.4 5 As some studies have shown, ‘qi deficiency and blood stasis’ and ‘qi stagnation and blood stasis’ are the two most common TCM syndromes of SAP.6 7 Chinese patent medicines can improve the clinical symptoms of SAP patients, reduce the number of attacks, increase blood supply to coronary arteries, improve myocardial ischemia, and resist oxidation and thrombus formation.8 9

At present, more than 70% of SAP patients in China are using Chinese patent medicines,9 and responding well to the treatment. Due to the lack of direct comparative effectiveness evidence about similar Chinese patent medicines, it is difficult for doctors to choose the optimal Chinese patent medicine for each patient. Needless to say, this increases the rate of irrational use and adverse events for Chinese patent medicines.

Rational use of TCM

‘Syndrome differentiation and treatment’ is the core of TCM theory.10 TCM practitioners will summarise the major complaints of patients, differentiate their syndrome types

Strengths and limitations of this study

▪ PIO+PRO: evaluation by combination of PIO and PRO. Patients select symptom type and evaluate the efficacy by themselves, with a popular ‘patient-centred evaluation’ in modern medicine.
▪ TCM syndrome+symptom (combinations): evaluation by combination of TCM syndrome and symptom (combinations). To find the efficacy of Chinese patent medicines by breaking down TCM syndromes into different symptoms or symptom combinations.
▪ The practicability and feasibility of the methodology in this study needs to be tested in practice.
based on an overall consideration and then prescribe medicines for them. Chinese patent medicines are the modern TCM medicine in different dosage forms, processed from different herbs under the guidance of TCM theories. However, according to investigations, 98% of users of Chinese patent medicines are persons ignorant of TCM theory and practice in China, giving rise to irrational use of these medicines and consequently limited efficacy. Thus, it is very important to identify and explain the efficacy of similar Chinese patent medicines in a simpler and clearer method.

Identifying characteristics of Chinese patent medicines
At the end of the 1990s, the concept of ‘personalised medicine’ was proposed and applied to the field of tutor treatment, representing the trend of medical development. The core of ‘syndrome differentiation and treatment’ of TCM is personalised diagnosis and treatment; identifying characteristics of Chinese patent medicines will help screen out the most effective medicine for individual patient.

COME-PIO (Comparative Effectiveness Research for similar Chinese patent medicines based on Patient Important Outcomes), built in the early stage by our research team, is a method for finding the characteristics of Chinese patent medicines. This method breaks the TCM syndrome down into multiple symptom combinations, then makes a comparison at the level of symptom or symptom combinations, and finally gives an individuality analysis based on the consolidated results among the comparison of different medicines and syndromes. This method now has integrated advanced analytical technologies, such as comparative effectiveness research (CER), patient important outcome (PIO), patient report outcome (PRO), minimal clinically important differences (MCID) and correspondence analysis (CA), and is adopted in this study.

Two common Chinese patent medicines for SAP
Qishenyiqi Dripping Pills (QSYQ) and Compound Danshen Dripping Pills (FFDS) are two common Chinese patent medicines for treating SAP. The main ingredients of QSYQ are astragalus, salvia miltiorrhiza, pseudo-ginseng and rosewood heart wood; and the main ingredients of FFDS are salvia miltiorrhiza, pseudoginseng and borneol. The two medicines are in the same dosage form.

Objective of this study
This study will explain and differentiate the efficacy of QSYQ and FFDS from the perspective of improvement in patients’ symptoms or symptom combinations, so as to promote rational use of them in clinical practice. The CUPID-based clinical trial model for personality identification of similar Chinese patent medicines will be designed and built in this study.

METHODS
Research type
This is a randomised controlled, double-blind and double-dummy, partial crossover design.

Intervention
This study comprises three stages (figure 1):
- First treatment (14 days): randomised controlled trial design is adopted
  - Group 1: Routine medication + A (QSYQ + FFDS placebo)
  - Group 2: Routine medication + B (FFDS + QSYQ placebo)
- Wash-out phase (3 days): all subjects enter the wash-out period, during which the first efficacy analysis is given
Group 1: Routine medication + QSYQ placebo + FFDS placebo  
Group 2: Routine medication + FFDS placebo + QSYQ placebo  
- Crossover of treatment (14 days): subjects for whom the medicine is found ineffective in the first efficacy analysis will enter the crossover trial for further observation.  
  - Group 1': Routine medication + B (FFDS + QSYQ placebo)  
  - Group 2': Routine medication + A (QSYQ + FFDS placebo).

Routine medication  
Routine medications include aspirin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-receptor blockers, statins, nitrates and drugs for improving myocardial metabolism. In addition, participants cannot use the banned drugs listed in table 1 during the treatment period.

Randomisation  
Patients are assigned randomly by the stratified blocked randomisation method (1:1); the stratification factor is syndrome pattern and symptom combination. The syndrome criteria of ‘qi deficiency and blood stasis’ and ‘qi stagnation and blood stasis’ are based on the basic components of the symptom combination; each combination comprises primary symptoms and secondary symptoms (primary symptoms are fixed, secondary symptoms are decided by the patients themselves). A third party statistician works out the Random Assignment Table using SAS V9.1 (table 2).

Allocation concealment  
A random number table generated by simulation of SAS statistical software is used for allocation concealment. Original copies of the blind codes are sealed in the lightproof envelope; one is kept by the major research unit and the other by the applicant of the trial. They are not allowed to be opened before formal statistical analysis. Drug blinding is carried out by the randomised group made up of members not involved in this trial; and the whole process is given strict supervision and quality control.

Blindness  
This trial adopts the double-blind method. The trial drug and simulator for use are both provided by the manufacturer; they are basically identical in appearance, shape, colour and packaging, and are accompanied by a qualified drug inspection report. The principal investigators, clinical research assistants, drug administrators, patients and statisticians will be blinded.

In case of emergencies or necessary rescue of patients, persons-in-charge of the participating units shall immediately report to the clinical research associate and major investigators; unblinding can be performed only upon their approval. Once the allocation is unblinded,
the operation and record-taking must observe the requirements of the trial.

Sample size
The sample size was calculated on the basis of literature research. It was assumed that the means of the Seattle angina questionnaire (SAQ) scores of the groups taking QSYQ and taking FFDS were 82 and 80, respectively, with the same SD (SD=4).

A total of 144 patients, 72 in each group, should be recruited in order to show a significant difference between the two groups, with a significance level of 0.05, 80% power and a drop-out rate of 15% using the PASS software.

Screening of participants

 Screening condition
Patients participation in this trial is voluntary and they should select the symptom types by themselves; physicians should note the criteria met and diagnose syndrome types.

 Diagnosis criteria
SAP (I–III): diagnostic criteria refer to WHO for nomenclature and criteria for diagnosis of ischaemic heart disease and the Canadian Cardiovascular Society classification standard in 1972.21
‘Qi and blood stasis’ and ‘qi deficiency and blood stasis’ syndrome: syndrome differentiation criteria refer to the Guidelines for Clinical Research of Chinese Medicine (new drug) in 2002.22

 Inclusion criteria
Patients aged between 40 and 75.
Patients have signed informed consent forms.
Patients diagnosed with SAP.
Patients with SAP of grade I, II or III.
Patients with ‘qi deficiency and blood stasis’ or ‘qi stagnation and blood stasis’ syndromes.

 Exclusion criteria
Patients younger than 40 or older than 75 years.
Patients do not conform to diagnostic standards of Western medicine; TCM pattern is diagnostic.
Patients with infraction angina or Prinzmetal variant angina.
Patients with other organ dysfunction and other diseases involving the heart.
Patients with uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg).
Patients who have received percutaneous coronary intervention for no more than 3 months.
Patients with a cardiac pacemaker.
Patients with a history of allergy to the control drug or investigational drug.
Patients with liver and kidney dysfunction.
Patients with tumours, autoimmune disease or blood disease, or pregnant or lactating women who should not be included in the trial as adjudged by the recruiting personnel.
Presence of active peptic ulcers and other haemorrhagic disease.
Patients involved in another clinical trial now or in the past 3 months.

Termination criteria
Patients withdraw of their own accord for any reason. Serious adverse events occurring during the trial. Major mistakes or serious deviations identified in the clinical trial protocol in the process of execution (though the plan is good), making it difficult to evaluate the efficacy of the drug.
Trial is cancelled by the authority.

Study setting
We will prepare to collect cases from the first hospital and Baokang Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Wuqing hospital of TCM in China.

Registration and enrolment

 Registration of patients
Two months prior to the trial, 144 SAP subjects qualified for inclusion will be gathered from four hospitals of Tianjin City (72 cases of ‘qi stagnation and blood stasis’, 72 cases of ‘qi deficiency and blood stasis’); basic data of the patients, including name, sex, age, type of syndrome and contact, will be registered.

Centralised enrolment
The patients will be enrolled into groups altogether on the same day when the trial has commenced. Inclusion

| Table 2  | The two syndrome types and six symptom combination groups involved in this trial |
|----------|---------------------------------------------------------------------------------|
| Number of symptom combination | Type of symptom combination | Syndrome differentiation |
| Combination 1 | +shortness of breath | qi deficiency and blood stasis syndrome |
| Combination 2 | +fatigue | qi deficiency and blood stasis syndrome |
| Combination 3 | +palpitations | qi deficiency and blood stasis syndrome |
| Combination 4 | +spontaneous perspiration | qi deficiency and blood stasis syndrome |
| Combination 5 | +chest coerces bloated | qi stagnation and blood stasis syndrome |
| Combination 6 | +pain | qi stagnation and blood stasis syndrome |

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conditions of patients will be confirmed again based on inclusion criteria. Patients meeting inclusion conditions are randomised into one of two groups based on their syndrome and symptom types.

Index of end point
Score of SAQ: 19 questions in all, including physical limitation, anginal stability, anginal frequency, treatment satisfaction, and understanding of illness. The higher the score, the better the life quality and functional status of the organism will be.23

Score of Likert scale (LS): this scale contains a series of statements that expresses the positive and negative attitudes towards the test items and asks the respondents to express their degree of satisfaction. The answer of each respondent will be awarded certain points to show his or her degree of approval or disapproval of each statement.24

Follow-up
A total of four follow-up points are arranged in this trial: the first visit is day 0 after enrolment; the second visit is day 14±1; the third visit is day 17±1, and the fourth visit is day 31±1.

Data are captured based on the CRF (table 3).

Measurement tools (MCID)25
Extract the SAQ values of Likert scale 7 of all patients in the interval of (0, +1), the calculated mean value is marked as \( \bar{x}_0 \); extract the SAQ value of Likert scale 7 in the interval of (+2, +3), the calculated mean value is marked as \( \bar{x}_1 \) (figure 2).

Calculation formula for MCID:

\[
MCID = \sqrt{\frac{\sum (x_1 - \bar{x}_1)^2 + \sum (x_0 - \bar{x}_0)^2}{n - 1}} \times (1 - r)
\]

(N represents the sample size; r represents the reliability coefficient of SAQ scale).

Compare SAQ value of each patient against MCID, which is regarded as the valid measurement scale. Results of comparisons show the efficacy on relevant symptoms or symptom combinations; values above MCID indicate effectiveness, values below MCID indicate ineffectiveness.

STATISTICAL ANALYSIS
Baseline balance
Baseline demographic characteristics will be reported as mean and SD for continuous data and number/percentage for categorical data. Intergroup comparability is crucial to options of statistical methods. In this study, comparability will be checked by t test or \( \chi^2 \) test where appropriate. In case of incomparability, baseline-adjusted methods will be used.

First treatment period
After the first treatment period, the SAQ scores will be compared between the two groups using the t test or Mann–Whitney U test according to the normality of the sample distribution indicated by the Kolmogorov–Smirnov test. A two-tailed value of \( p<0.05 \) will be considered statistically significant. Moreover, all patients will be

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**Table 3** Follow-up

| Items                                      | Visit                  |
|--------------------------------------------|------------------------|
|                                            | 1 0 day                |
|                                            | 2 14±1 days            |
|                                            | 3 17±1 days            |
|                                            | 4 31±1 days            |
| Medical history                            | √                       |
| Inclusion/exclusion criteria                | √                       |
| Informed consent form                      | √                       |
| Syndrome differentiation                    | √                       |
| Symptom combination                        | √                       |
| Random allocation                          | √                       |
| General information                        | √                       |
| History of medical treatment and allergies | √                       |
| Taking drugs currently                     | √                       |
| Drug distribution                          | √                       |
| Drug recovery                              | √                       |
| Combination drugs                          | √                       |
| Compliance judgement                       | √                       |
| Evaluation index                           | √                       |
| SAQ score                                  | √                       |
| 7-point LS score                           | √                       |
| Safety observation                         | √                       |
| Vital signs                                | √                       |
| Adverse event                              | √                       |

LS, Likert scale; SAQ, Seattle angina questionnaire.
divided into different subgroups by single symptom combination or multiple symptom combinations. The SAQ scores will be compared between the two groups, in order to differentiate the characteristics of the two medicines.

After the crossover treatment period
The individual results of the first treatment period and the crossover treatment period are compared; CA is adopted to compare the curative effects of A and B on symptoms, symptom combinations and SAP-related TCM syndrome.

Curative effect of treatment A(B) on single symptom combination
Establish corresponding relationship between symptom 1–6 and two outcomes: A is effective and B is ineffective (B is effective and A is ineffective); both A and B are ineffective.

Curative effect of treatment A(B) on symptom combinations
List all possible multiple symptom combinations and establish corresponding relationship between different symptom combinations and the two outcomes: A is effective and B is ineffective (B is effective and A is ineffective); both A and B are ineffective.

Curative effect of treatment A(B) on TCM syndrome
Merge the symptom according to different TCM syndromes and establish corresponding relationship between different symptom combinations and the two outcomes: A is effective and B is ineffective (B is effective and A is ineffective); both A and B are ineffective.

Plot the corresponding distribution (Biplot)
In this study, SPSS V.16.0 will be used to perform CA. The relative distances between different points will be calculated with the Biplot method; these will be the differences between treatment A and treatment B.

SAFETY
Standard operating procedures of adverse events
Standard operating procedures (SOPs) for the management of adverse events (AEs) must be worked out in order to guarantee that AEs are under control. Clinical research associates (CRAs) will participate in AE management and SOP drafting so that they can manage AEs during clinical testing in a scientific and standardised manner.

Recording of AEs
When observing efficacy, pay attention to the occurrence of AEs and adverse reactions and record them in detail; serious AEs arising out of the trial must be reported in good time to the person-in-charge of the project and the ethics committee.

Rating of AE severity
The correlation between AE and drug is estimated according to 5-grade criteria (tables 4 and 5).

Analysis of AEs
The $\chi^2$ test is used to compare the incidence of AEs of drug A and B, and the correlation between AE and drug is analysed.

Drug management
We will establish a trial drug management and register system. Trial drug management personnel must have passed good clinical practice (GCP) training and obtained a qualification certificate; they must possess the capability of managing clinical trial drugs. A central drug administrator takes charge of the overall allocation of all trial drugs; drug administrators of sub-centres take charge of the allocation and recovery of the drugs of their own centres. The whole process of acceptance, storage, allocation, use, counting and recovery of the trial drug are monitored by the CRA, Ethics Committee and Quality Control Committee, so as to ensure the safety and stability of the trial drugs.

| Table 4: Severity grading and definition |
|-----------------|-----------------|
| **Severity Grading** | **Definition** |
| Mild | Short-lasting and mild symptoms, no pain caused to patients, bearable, daily activities not affected |
| Moderate | Overt symptoms but bearable, daily activities affected |
| Severe | Severe symptoms, daily activities seriously affected |
Table 5  Determination of correlation between adverse event and drug

| Criteria                                      | Definitely relevant | Probably relevant | Probably irrelevant | Definitely irrelevant | Unable to decide |
|-----------------------------------------------|--------------------|-------------------|--------------------|----------------------|------------------|
| Within the reasonable post-dosage time sequence | +                  | +                 | −                  | −                    | −                |
| Within known types of reaction of suspected drug | +                  | −                 | +                  | −                    | −                |
| Symptoms improved after withdrawal of drug    | −                  | +                 | −                  | −                    | −                |
| Reactions recur after repeated administration | +                  | −                 | −                  | −                    | −                |
| Related to other treatment                    | −                  | +                 | +                  | +                    | −                |

‘+’ means YES; ‘−’ means NO; ‘?’ means unclear situation.

DATA MANAGEMENT

Management software
This trial plans to use Oracle Clinical (OC) software for online data updating, data tracing and dynamic management at the same time, with the support of the check function of this software.26

Data recording
All data of the trial are subject to remote recording. Investigators will enter relevant data via the internet; such a pattern contributes to improved quality and efficiency of the clinical study.

Data examination
The data administrator performs a logic check and automatic comparison of data information using the check function of OC software, checks the result values are inconsistent with the case report forms, and checks one-by-one with the original case report forms and make corrections, so as to ensure the data in the database are consistent with the results of the case report form. This enables traceability, accuracy, completeness and timeliness of data.

Data exporting
After the trial, the data administrator will export the data in the form of data interexchange code and statistical analysts will extract relevant data from the database according to the code and program for statistical analysis.

QUALITY ASSURANCE

Compliance of investigators
Before the trial, all investigators must be trained as per the trial and technical requirements. The prime investigator is responsible for examining the case inclusion criteria of their units, deciding the end point and adverse events, handling serious AEs, controlling the trial quality of their own units, and confirming the completion of trial.27

Compliance of subjects
Subjects will receive trial drugs, transportation fees and necessary healthcare instructions (diet, mental adjustment) for free. Subjects are required to maintain appropriate physical activities and control daily exercises, in order to guarantee inter-group comparability. The dosage and remaining amount of drug shall be recorded; the drug counting method is used to monitor compliance.

Monitoring
An Independent Data Monitor Committee (IDMC) composed of clinical experts, statisticians and relevant workers will provide regular monitoring of this trial. CRAs are required to monitor various units regularly; CRAs shall rigidly examine case report forms to ensure consistency with the original data, and they shall trace the source or directly visit the subjects when necessary; CRAs shall identify problems timely and feed back the solution to investigators within the shortest time.

DISCUSSION

Chinese patent medicines have definite advantages in treating SAP, particularly in improving symptoms of patients. In the past, many SAP patients have expressed their great satisfaction with Chinese patent medicines. Use of Chinese patent medicines is one of the major clinical practices based on ‘syndrome differentiation and treatment’ under the guidance of TCM. However, due to improper use by many non-TCM persons, irrational clinical use of Chinese patent medicines is frequently reported, which has seriously affected their clinical efficacy.

The CUPID-based clinical trial model built in this trial for identification of individual characteristics of similar Chinese patent medicines explains and distinguishes the efficacy of QSYQ and FDSD from a more intuitive angle of patients’ symptoms or symptom combination, thus contributing to wider and more definite and rational use of Chinese patent medicines; this method provide direct evidence of the efficacy of these medicines by asking patients to choose their symptom types and evaluate the efficacy on their symptoms. A partial crossover trial design is used for classification evaluation of drugs and symptoms; the COME-PIO method is used to achieve ‘reduced dimension decomposition, multidimensional comparison and degree progress analysis’ of the TCM syndrome, enabling the expression of the efficacy of Chinese patent medicines in a more comprehensible way.

The CUPID model embodies advanced analysis technologies such as PIO, PRO, MCID and CA, and will provide a methodological reference for identifying the
characteristic of Chinese patent medicines. Meanwhile, it will facilitate differentiated use of Chinese patent medicines by non-physicians and improve the use efficiency of Chinese patent medicines.

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Contributors All authors have contributed to the overall design of this study, and been involved in the ongoing management of the trial. HBC plotted the study, participated in its design and coordination, prepared the protocol, wrote the manuscript, and undertook the staff management. NL participated in the design and coordination of the study, and wrote the manuscript. JBZ was in charge of sample size and all statistical works of trial. HXC, XL and WM collected and analysed the data and critically revised the manuscript. HCS conceived of and designed the study, obtained financial support and wrote the manuscript. ZL and HW were responsible for data management and developing, overseeing the qualitative components of the trial. All authors have read and approved the final manuscript.

Competing interests None.

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