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Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

Running title： Efficacy and safety of Xueshuantong injection in patients with UA

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Abstract

Objective: Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection having the potential to treat ACS. This clinical trial aims to examine the efficacy and safety of XST.

Design: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial.

Setting and Participants: A total of 1200 participants with UA will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with one-twentieth dose in the control group.

Interventions: All participants will receive the conventional treatment. XST group will be treated via intravenous drip with 500 mg XST diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days, while the patients in control group will be treated via intravenous drip with 25 mg XST diluted with 250–500 mL of 5% glucose injection or sodium chloride injection.

Primary and secondary outcome measures: The primary outcome will include the incidence of composite endpoints for major adverse cardiovascular events(MACE), including cardiovascular death, nonfatal myocardial infarction, and revascularization. The secondary outcomes, the efficacy of angina pectoris will be observed and the myocardial injury markers will be monitored.

Results: The efficacy assessment and MACE will be observed, and angina pectoris

will be examined at the start and end of the run-in period. All AEs will be recorded, regardless of severity, to assess the safety of XST. The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

Conclusions: Clinical evidence for the efficacy and safety of XST in reducing the incidence of MACE in patients with UA.

Trial registration: This study was registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn/) with the ID ChiCTR180001591.

Key words: Acute coronary syndrome, clinical trial, traditional Chinese herbal injection, unstable angina

Strengths and limitations of this study

- This is a randomized, double-blind, placebo-controlled and multicenter trial to assess the efficacy and safety of Xuanshuantong injection(lyophilized) in patients with unstable angina
- A multicenter trial is carried out in 17 medical centers across China, which can improves the external validity and representativeness of the sample and reduces the risk of selection bias.
- A long-term follow-up (1, 3, and 6 months) will be conducted after the supervised intervention.
- The treatment period of 7-14 days may be a bit short.

1.Introduction

Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Reduced blood flow to the heart muscle is the most common cause of UA because the coronary arteries are narrowed by atherosclerosis, leading to the rupture of coronary blood vessels and hence blood clotting, which blocks the flow of blood to the heart muscle. The risk factors for UA include diabetes, obesity, family history of heart disease, high blood pressure, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, male sex, and use of any form of tobacco[1, 2]. With the wide application of percutaneous coronary intervention (PCI) in patients with ACS, current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after ACS management with PCI. However, the greatest anti-ischemic benefit of potent antiplatelet drugs over the less-potent clopidogrel occurs early, while most excess bleeding events occur during chronic treatment. It is related to the efforts of physicians to reduce the adverse incidence of cardiovascular events, promote the patient's early recovery, and improve their health-related quality of life.

Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection comprising a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and People's Republic of China Pharmacopoeia, respectively. It has been

reported to have anti-inflammatory effects that correct endothelial dysfunction *in vivo*[3] and *in vitro*[4]. Clinically, as a common medicine in China's Grade-A Tertiary Hospital, XST has been reported to be beneficial in treating ACS[5, 6]. In preliminary studies, including small samples, XST reduced the incidence of major adverse cardiovascular events (MACE). The high-quality trials and evidence are needed to prove the efficacy of XST. This randomized, parallel, controlled, double-blind, and multicenter clinical trial aims to examine the efficacy and safety of XST in patients with UA. The results of this trial may provide clinical evidence for treating patients with UA.

2. Method and design

2.1 Study design

This randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial will be conducted in 17 medical centers in China: The First Affiliated Hospital of Guangzhou University of Chinese Medicine, The First Affiliated Hospital of the Henan University of Chinese Medicine, Luoyang No. 1 Hospital of Traditional Chinese Medicine, Shanxi Fenyang Hospital, The First Affiliated Hospital of Henan University of Science and Technology, Zhengzhou People's Hospital, Zhengzhou Central Hospital, Ruikang Hospital Affiliated to Guangxi University of Traditional Chinese Medicine, Nanjing Hospital of Chinese Medicine, Shuguang Hospital Affiliated to Shanghai University of Chinese Medicine, Changsha Fourth Hospital,

The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Affiliated Hospital of Tianjin Academy of Chinese Medicine, Tianjin Beichen District Hospital of Traditional Chinese Medicine, and Wenzhou Hospital of Traditional Chinese Medicine. A total of 1200 patients with UA who met the selection will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with 1/20th dose in the control group.

All the visits will be recorded in electronic care report forms through the Electronic Data Capture system, which is accessed online via the Internet for data collection and management. The protocol of this study was developed in accordance with the standard protocol project: Interventional Trial Recommendations guidelines[7].

2.2 Ethics

This study has been approved by the ethics committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (approval number: ZYYEC[2017]002) and registered on the Chinese Clinical Trial Registry with the ID ChiCTR1800015911.

2.3 Study population

Patients will be included after written informed consent and enrolled in the study when the inclusion and exclusion criteria are met (Table 1).

2.3.3 Withdrawal criteria

1. Patients with some comorbidities, complications, or special physiological changes during the trial
2. Patients with poor compliance in the trial; the use of the drug not reaching 80% (except for those recovered in advance) or exceeding 120% of the prescribed amount
3. Patients with blindness or emergency unblinding during the trial
4. Patients with serious adverse events and those not appropriate to continue the test
5. Patients failing to use the test drug
6. Patients misdiagnosed or not matching the inclusion criteria and accidentally included
7. Patients with no follow-up records
8. Patients failing to comply with the treatment during the trial, changing the medicines, or adding nonspecified therapeutic medications by themselves, especially those medications that may affect the evaluation of the test drug, affecting the validity and safety.

2.4 Study setting and recruitment

Between December 2018 and December 2020, 1200 patients will be recruited at the 17 centers mentioned earlier through the official website of the hospitals, posters, and networks. The physicians will diagnose the participants, and the research assistants will manage the recruitment.

2.5 Randomization

After the recruitment is completed, statistical analysis system software will be used to generate the random arrangement of 1200 people in 2 groups (XST and placebo groups) with the method of central stratified regional group randomization. The randomization numbers will be kept in opaque sealed envelopes. The physicians and patients will not be aware of the grouping and intervention.

2.6 Blinding

This study has a double-blind design, with a very low dose used as control. The number of cases in the study and control groups will be in the ratio of 1:1. The blinding work will be completed by statisticians. To ensure the blinding of investigators and participants to study treatment, the study drug or placebo will be provided in identical packaging and labeling. Due to some natural variability in the color of the study drug, which is batch dependent, the color of the placebo will be matched to be the same as the average color of the study drug. Study drug and placebo will be labeled with a unique label letter that will be used to assign treatment to the patient but will not indicate treatment allocation to investigators or participants. No member of the study team and their extended staff, except for pharmacists and biostatisticians, will have access to the randomization scheme during the conduct of the study. In the event of a medical emergency, where breaking the blind is required

to provide medical care to the participant, the investigator will obtain the treatment assignment from the trial pharmacists.

2.7 Sample size calculation

MACE will be used as the effect index according to the statistical requirements of the optimal validity test design.

Based on the expert advice combined with clinical practical considerations and according to the loss rate of less than 20% estimated beforehand, the study sample was 1200 cases (600 cases in each group), assuming that the incidence of MACE was 12% after dual antiplatelet therapy for 6 months, which was reduced by 6% after lyophilization (alpha = 0.05; power = 0.9).

2.8 Interventions

All participants will receive dual antiplatelet therapy (aspirin 100 mg/d + clopidogrel 75 mg/d) and anticoagulation therapy (unfractionated heparin) according to the 2014 American College of Cardiology/American Heart Association Guidelines for the Diagnosis and Treatment of Non-ST-Segment Acute Coronary Syndrome, and in accordance with the guidelines to accept statins, angiotensin-converting enzyme inhibitors, beta-blockers, and nitrates. Patients with mild UA will undergo a standardized baseline assessment before the treatment, including detailed medical history, physical examination, and laboratory testing. Meanwhile, the following

treatments will be given to different groups:

(1) XST treatment group: The patients will be treated via an intravenous drip with 500 mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days.

(2) Control group: The patients will be treated via an intravenous drip with 25 mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days.

The experimental drugs will be distributed by a drug administrator and injected by trained nurses.

Patients who continue to use the drug for more than 7 days until discharge will end the medication and move directly to the follow-up period. The efficacy and safety of XST will be assessed after treatment for 7–14 days and follow-up for 1, 3, and 6 months (Figs. 1 and Table 2).

2.7 Outcome measurements

2.7.1 Primary outcomes

The primary endpoints will include the incidence of composite endpoints for MACE, including cardiovascular death, nonfatal myocardial infarction, and revascularization.

The primary endpoint is the time from the enrollment to the end of the study (including the medication observation period and follow-up period) when any of the

MACE events occur for the first time. Patients without MACE during the study will be defined as censored at the end of the study. For patients who quit the trial early due to reasons other than MACE, the time of occurrence is defined as censoring at the time of early termination. Deaths not due to cardiovascular diseases or that occur after the MACE will not be evaluated.

2.7.2 Secondary outcomes

The efficacy of angina pectoris will be observed at the time of enrollment and at the end of treatment.

Myocardial injury markers [serum creatine kinase MB; cardiac troponin T/cardiac troponin I (cTnI)/high-sensitivity troponin I] will be monitored.

2.7.3 Safety assessment

The observation of vital signs; testing of blood and urine samples, renal function, and liver function; electrocardiograms; and physical examinations will be examined at the start and end of the run-in period. The researchers will record the abnormal changes at any time. An adverse event (AE) is any adverse medical event that occurs during the trial. Patients will be required to report all AEs at each visit. All AEs will be recorded, regardless of severity, to assess the safety of XST.

If an AE occurs, the researchers will have to determine whether to stop the observation and proceed with the diagnosis and corresponding treatment. If any

severe AE occurs, the researchers must take immediate action to ensure the safety of the participants. They must also report to the ethics committee within 24 h. The responsible staff from The First Affiliated Hospital of Guangzhou University of Chinese Medicine must promptly notify other participating centers and initiate any necessary legal procedures.

2.8 Follow-up

All included participants will be evaluated for the occurrence of MACE after 1, 3, and 6 months through phone calls after the end of the medication. The trial will be ended if the following endpoints occur: death, nonfatal myocardial infarction, or revascularization (including PCI and CABG). The academic research on hemorrhage in Europe and the United States proposed a unified definition of hemorrhage type 3–5.

The occurrence of the MACE must be recorded in an original supporting document, including but not limited to a copy of the discharge summary, a copy of the medical record, or other documents that can be used to verify the occurrence of the MACE and the date of its occurrence.

2.9 Statistical analysis

2.9.1 Enrollment and case completion

The completion of the trial at each center must be recorded and described. All

cases of shedding must be listed.

2.9.2 Baseline comparability analysis

The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

2.9.3 Analysis of efficacy

(1) Baseline comparability analysis: This includes the description of demographic data, symptoms, and general conditions. The *t* test or nonparametric statistical method will be used for quantitative data. Qualitative data will be determined using the chi-square test, Fisher's exact probability method, CMH test, and Wilcoxon rank-sum test.

(2) Primary and secondary outcomes: The incidence of composite endpoints for MACE and the efficacy of angina pectoris will be compared between the two groups and analyzed using the chi-square or Fisher exact tests and two-sample *t* tests or Wilcoxon rank-sum test. The laboratory data on myocardial injury markers will be analyzed for the changes before and after the intervention. The average value of each laboratory data after the treatment will be compared.

(3) For cases of rejection and shedding, statistical descriptions will be performed one by one. Adverse reactions will be statistically described. The incidence of adverse reactions will be compared using the chi-square or Fisher exact tests.

3. Discussion

XST is a traditional Chinese herbal injection consisting of a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and the People's Republic of China Pharmacopoeia, respectively. *T*otal saponins, isolated from the root and rhizome of *P. notoginseng,* are the main components of XST.

P. notoginseng is known for promoting blood circulation, preventing thrombosis, and dilating blood vessels. It is widely applied to treat acute cerebral infarction, stroke, and coronary heart disease in clinical practice[8, 9]. Gan et al.[10] evaluated the efficacy and safety of the *P. notoginseng* extract via intracoronary injection for treating the post-PCI slow-reflow phenomenon in patients with ST-segment elevation myocardial infarction and its impact on patients' prognosis. They found that coronary injection with tirofiban and XST was more effective in improving the coronary blood flow and showed no increase in the incidence of hemorrhagic complications compared with the injection with tirofiban only. *P. notoginseng* has been found to be beneficial to patients with UA. The use of the extract has been recommended for patients with UA in clinical practice as a complementary and alternative therapy[11]. However, more randomized controlled trials with reliable designs, large samples, and long-term observations are needed for further evaluations.

The meta-analysis of XST injection combined with routine basic treatment was superior to routine basic treatment alone in alleviating clinical symptoms, with statistically significant differences between the groups. XST injection combined with routine basic treatment could alleviate UA pectoris. However, due to the low quality of included studies, further well-designed, multicenter, and large-scale RCTs are still needed to evaluate the efficacy of XST injection [14]. Moreover, the total revenue from XST in the Chinese market in 2013 was over $700 million [15]. Therefore, the enormous consumption requires stricter and accurate evidence on its safety. However, many reports of XST were case reports, and hence large-sample and high-level evidence for the efficacy and safety of XST is still lacking. Therefore, this study will be conducted to investigate the efficacy and safety of XST in reducing the incidence of MACE in patients with UA. The findings of this study will provide clinical evidence for the use of XST in reducing the incidence of MACE in patients with UA.

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injection (lyophilized) in reducing the incidence of MACE in patients with unstable angina: A randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy" (no. 10600216) and the second batch of national TCM clinical research base project (no. 2018131).

Trial status

Currently the participants are being enrolled for the trial.

Conflicts of interest

All authors declare no any conflicts of interest.

Author contribution

XSX, LHL and YZQ carried out the studies, LJH, DJ, HY and LY participated in collecting data, and drafted the manuscript. LWJ, LLM and LQQ performed the statistical analysis and participated in its design. TYQ, YTH, HX and LWJ participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

Patient Consent Form

All participants provided written informed consent.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Flowchart of the study procedure.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
● Patients diagnosed with coronary heart disease who met at least one of the following diagnostic criteria[1]: (1) a clear history of myocardial infarction (MI); (2) prior coronary revascularization; (3) coronary angiography or coronary angiography suggesting at least one coronary artery stenosis with catheter stenosis ⩾50%; (4) cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging to confirm myocardial ischemia in the patient having coronary heart disease	◆ Patients with cardiac function class IV (New York Heart Association cardiac function grading); or patients at a high risk of UA short-term risk stratification ◆ ◆ Patients with uncontrolled grade III hypertension having systolic blood pressure ⩾180 mm Hg and/or diastolic blood pressure ⩾110 mm Hg; severe cardiopulmonary insufficiency; severe arrhythmia; severe primary diseases of the liver, kidney, and hematopoietic system; or serious diseases (such as tumors) and mental diseases ◆ Patients also having other clinical conditions that might increase the risk of bleeding, such as a history of important organ bleeding in the last 6 months (such as intracerebral hemorrhage and upper gastrointestinal bleeding), decreased platelet count, abnormal coagulation function, and recent active bleeding ◆ Patients with abnormal function indexes of the liver and kidney
● Patients complying with the diagnosis of UA and having at least one of the following conditions: (1) electrocardiograph with a transient or persistent ST-segment depression of 0.1 mV and even more on one or more leads; (2) Thrombolysis In Myocardial	

Infarction (TIMI) risk score[9] ⩾3 ● Patients receiving dual antiplatelet therapy (aspirin + clopidogrel) ● Patients aged 40–75 years, irrespective of sex ● Patients willing to accept the drug treatment and provide written informed consent, conforming to the relevant regulations of Good Clinical Practice	[blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level more than two times the upper normal reference range; glomerular filtration rate (GFR) <60 mL/(min × 1.73 m²)]. Simplified Modification of Diet in Renal Disease formula[4]: GFR [mL/(min × 1.73 m²)] = 186.3 × serum creatinine (Scr)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 female); Scr in mg/dL and age in years ◆ Patients who planned to undergo revascularization [PCI or coronary artery bypass grafting (CABG)] recently ◆ Patients allergic to a variety of foods, or with known allergy to study drugs, including their components ◆ Patients pregnant, preparing for pregnancy, or lactating ◆ Patients participating in other clinical trials during the same period ◆ Patients considered inappropriate to participate in this study

Table 2. Study schedule of assessments

	Study period			
	Enrollment	**Allocation**	**Intervention**	**Follow-up**
Time point	**-2 week**	**0**	**7-14 days**	**1,3 and 6 months**
ENROLLMENT:	**X**			
Eligibility screen	**X**			
Informed consent	**X**			
Allocation		**X**		
INTERVENTIONS:				
SXT treatment			**X**	
Placebo treatment			**X**	
ASSESSMENTS:				
MACE			**X**	**X**
CK-MB		**X**	**X**	
cTnT		**X**	**X**	
cTnI		**X**	**X**	
hsTnI		**X**	**X**	
Adverse events			**X**	**X**

Abbreviations: CK-MB, creatine kinase MB; MACE, major adverse cardiac events; cTn, cardiac troponin; hsTn, high-sensitivity Troponin; UA, unstable angina.

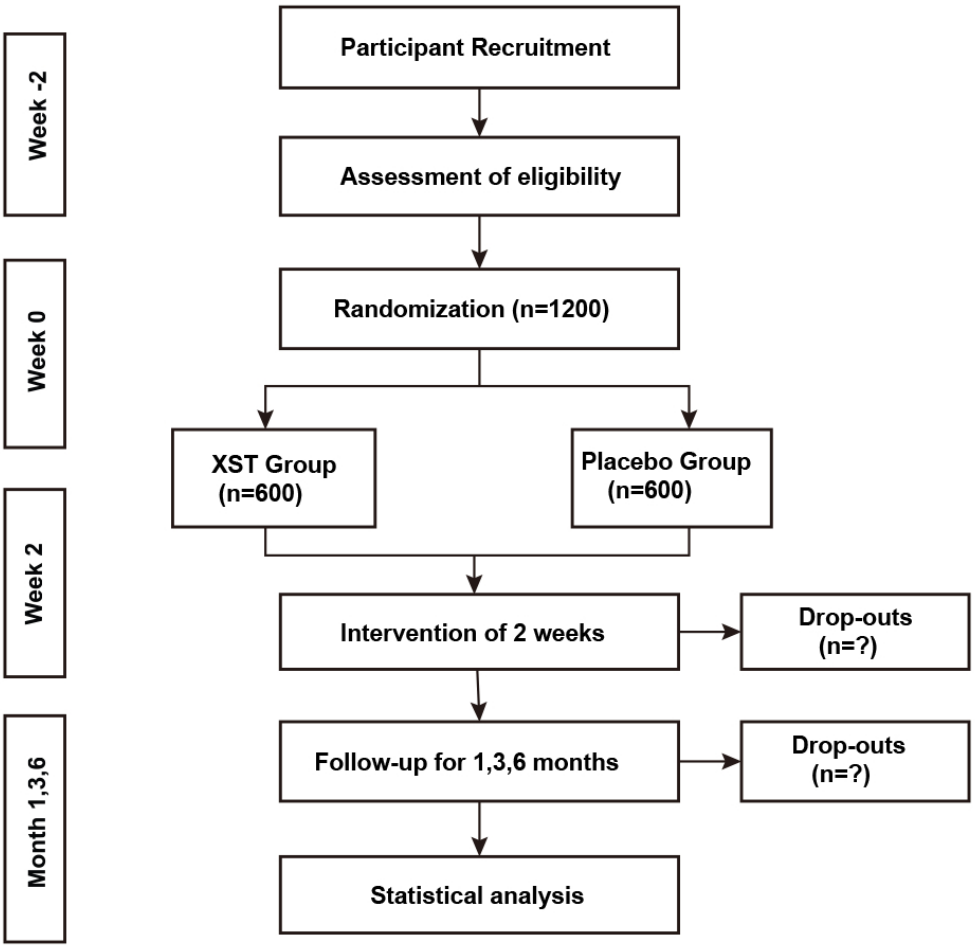

fig 1

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist Item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8-9
Sample size	7a	How sample size was determined	8-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8-10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8-10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8-10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8-10

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	6
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

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Efficacy and safety of Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

Running title：Efficacy and safety of Xueshuantong injection in patients with UA

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List of abbreviation

ACS, Acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass grafting; cTn, cardiac troponin; CK-MB, creatine kinase MB; HDL-C, low high-density lipoprotein cholesterol; LDL-C, high low-density lipoprotein cholesterol; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; hsTn, high-sensitivity troponin; UA, unstable angina

Abstract

Introduction: Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection having the potential to treat ACS. However, no clinical trial has been performed in this field. This clinical trial aims to examine the efficacy and safety of XST.

Methods and Analysis: This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial. A total of 1200 participants with UA will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with one-twentieth dose in the control group. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectoris will be examined at the start and end of the run-in period. All AEs will be recorded, regardless of severity, to assess the safety of XST. The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

Ethics and Dissemination: This trial has been approved by Research Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine, China (approval number: ZYYEC [2017] 0021). Written informed consent will be obtained from all participants. The results of this trial will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration: This study was registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn/) with the ID ChiCTR1800015911.

Key words: Acute coronary syndrome, clinical trial, traditional Chinese herbal injection, unstable angina

Strengths and limitations of this study:

1. This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial.
2. The trial will be conducted in 17 medical centers with 1200 participants.
3. In our study, to better implement the blind method, the extremely low dose 25mg is used as the control group.
4. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectoris will be examined at the start and end of the run-in period.
5. Our experiments will be conducted in different regions of China, and whether similar effects are available to other ethnic groups and regions remains uncertain.

Introduction

Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Reduced blood flow to the heart muscle is the most common cause of UA because the coronary arteries are narrowed by atherosclerosis, leading to the rupture of coronary blood vessels and hence blood clotting, which blocks the flow of blood to the heart muscle. The risk factors for UA include diabetes, obesity, family history of heart disease, high blood pressure, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, male sex, and use of any form of tobacco[1, 2]. With the wide application of percutaneous coronary intervention (PCI) in patients with ACS, current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after ACS management with PCI. However, the greatest anti-ischemic benefit of potent antiplatelet drugs over the less-potent clopidogrel occurs early, while most excess bleeding events occur during chronic treatment. It is related to the efforts of physicians to reduce the adverse incidence of cardiovascular events, promote the patient's early recovery, and improve their health-related quality of life.

Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection comprising a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and People's Republic of China Pharmacopoeia, respectively. It has been reported to have anti-inflammatory effects that correct endothelial dysfunction *in vivo*[3] and *in vitro*[4]. Clinically, as a common medicine in China's Grade-A Tertiary Hospital, XST has been reported to be beneficial in treating ACS[5, 6]. In preliminary studies, including small samples, XST has been found to platelet aggregation inhibition, anti-myocardial ischemia, anti-inflammation, anti-oxidation, protecting endothelial cells, which could reduce the incidence of major adverse cardiovascular events (MACE)[7]. As the primary component[8], Panax notoginseng, has been extensively verified that it can ameliorate ischemia-reperfusion (IR)-induced injury in cardiovascular and neuronal systems

mainly by upregulating the activity of estrogen receptor α -dependent phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and nuclear factor erythroid-2-related factor 2 (NRF2) pathways and downregulating nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. The high-quality trials and evidence are needed to prove the efficacy of XST. This randomized, parallel, controlled, double-blind, and multicenter clinical trial aims to examine the efficacy and safety of XST in patients with UA. The results of this trial may provide clinical evidence for treating patients with UA.

2. Method and design

2.1 Study design

This randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial will be conducted in 17 medical centers in China: The First Affiliated Hospital of Guangzhou University of Chinese Medicine, The First Affiliated Hospital of the Henan University of Chinese Medicine, Luoyang No. 1 Hospital of Traditional Chinese Medicine, Shanxi Fenyang Hospital, The First Affiliated Hospital of Henan University of Science and Technology, Zhengzhou People's Hospital, Zhengzhou Central Hospital, Ruikang Hospital Affiliated to Guangxi University of Traditional Chinese Medicine, Nanjing Hospital of Chinese Medicine, Shuguang Hospital Affiliated to Shanghai University of Chinese Medicine, Changsha Fourth Hospital, The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Affiliated Hospital of Tianjin Academy of Chinese Medicine, Tianjin Beichen District Hospital of Traditional Chinese Medicine, and Wenzhou Hospital of Traditional Chinese Medicine. A total of 1200 patients with UA who met the selection will be enrolled in a 1:1 ratio, with 600 patients included in the XST

treatment group and 600 in the control group.

All the visits will be recorded in electronic care report forms through the Electronic Data Capture system, which is accessed online via the Internet for data collection and management. The protocol of this study was developed in accordance with the standard protocol project: Interventional Trial Recommendations guidelines[9].

2.2 Ethics

This study has been approved by the ethics committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (approval number: ZYYEC[2017]002) and 17 other medical centers， which have been approved by the ethics committee by the respective medical centers. The trial has been registered on the Chinese Clinical Trial Registry with the ID ChiCTR1800015911.

2.3 Patient and public involvement

This clinical trial was designed to evaluate the efficacy and safety of XST in patients with UA. Clinically, XST has been found to be beneficial in treating ACS, which had been widely used in China's Grade-A Tertiary Hospital. More high-quality trials and evidence are needed to prove the efficacy of XST. The outcome measures used in this trial were considered as important endpoints in clinical practice. The participants of this trial will be recruited from 17 medical centers in China. However, patients were not directly involved in the design, recruitment, or conduct of the study. After the trial completes, the results of this study will be disseminated to the public through academic conferences and peer-reviewed journals. Once the manuscript is published, the results will be briefly summarized in a simple language and inform all trial participants through the telephone. The burden of intervention will not be assessed

by the trial participants.

2.4 Study population

Patients will be included after written informed consent and enrolled in the study when the inclusion and exclusion criteria are met (Table 1).

2.4.1 Withdrawal criteria

1. Patients with some comorbidities, complications, or special physiological changes during the trial
2. Patients with poor compliance in the trial; the use of the drug not reaching 80% (except for those recovered in advance) or exceeding 120% of the prescribed amount
3. Patients with blindness or emergency unblinding during the trial
4. Patients with serious adverse events and those not appropriate to continue the test
5. Patients failing to use the test drug
6. Patients misdiagnosed or not matching the inclusion criteria and accidentally included
7. Patients with no follow-up records
8. Patients failing to comply with the treatment during the trial, changing the medicines, or adding nonspecified therapeutic medications by themselves, especially those medications that may affect the evaluation of the test drug, affecting the validity and safety.

2.5 Study setting and recruitment

Between December 2018 and December 2020, 1200 outpatients or inpatient will be recruited at the 17 centers mentioned earlier through the official website of the

hospitals, posters, and networks. The physicians will diagnose the participants, and the research assistants will manage the recruitment.

2.6 Randomization

On the day of enrollment, statistical analysis system software will be used to generate the random arrangement of 1200 people in 2 groups (XST and placebo groups) with the method of central stratified regional group randomization. The randomization numbers will be kept in opaque sealed envelopes. The physicians and patients will not be aware of the grouping and intervention.

2.7 Blinding

This study has a double-blind design. Because XST was lyophilized powder form in this study, which was a kind of white or light yellow amorphous powder or loose solid, and was dissolved with an appropriate amount of injection sodium chloride injection before use, there were color changes and a small amount of powder precipitation. Therefore, in order to better implement the blind method, an extremely low dose (25mg) was used as the control group, which is invalid for UA from our previous pharmacokinetic experiment, did not increase the efficacy of the experimental group.

The number of cases in the study and control groups will be in the ratio of 1:1. The blinding work will be completed by statisticians. To ensure the blinding of investigators and participants to study treatment, the study drug or placebo will be provided in identical packaging and labeling. Due to some natural variability in the color of the study drug, which is batch dependent, the color of the placebo will be matched to be the same as the average color of the study drug. Study drug and placebo will be labeled with a unique label letter that will be used to assign treatment

to the patient but will not indicate treatment allocation to investigators or participants. No member of the study team and their extended staff, except for pharmacists and biostatisticians, will have access to the randomization scheme during the conduct of the study. In the event of a medical emergency, where breaking the blind is required to provide medical care to the participant, the investigator will obtain the treatment assignment from the trial pharmacists.

2.8 Sample size calculation

MACE will be used as the effect index according to the statistical requirements of the optimal validity test design.

Based on the expert advice combined with clinical practical considerations and according to the loss rate of less than 20% estimated beforehand, the study sample was 1200 cases (600 cases in each group), assuming that the incidence of MACE was 12% after dual antiplatelet therapy for 6 months, which was reduced by 6% after lyophilization (alpha = 0.05; power = 0.9).

2.9 Interventions

All participants will receive dual antiplatelet therapy (aspirin 100 mg/d + clopidogrel 75 mg/d) and anticoagulation therapy (unfractionated heparin) according to the 2014 American College of Cardiology/American Heart Association Guidelines for the Diagnosis and Treatment of Non-ST-Segment Acute Coronary Syndrome, and in accordance with the guidelines to accept statins, angiotensin-converting enzyme inhibitors, beta-blockers, and nitrates. Patients with mild UA will undergo a standardized baseline assessment before the treatment, including detailed medical history, physical examination, and laboratory testing. Meanwhile, the following treatments will be given to different groups:

(1) XST treatment group: The patients will be treated via an intravenous drip with 500 mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days.

(2) Control group: The patients will be treated via an intravenous drip with 25 mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days.

The experimental drugs will be distributed by a drug administrator and injected by trained nurses.

Patients will be admitted to the hospital on the day of registration for the first intervention, and patients who discharge will move directly to the follow-up period. The efficacy and safety of XST will be assessed after treatment for 7–14 days and follow-up for 1, 3, and 6 months (Figs. 1 and Table 2).

2.10 Outcome measurements

2.10.1 Primary outcomes

The primary endpoints will include the incidence of composite endpoints for MACE, which is a commonly used indicator to evaluate the prognosis of patients with coronary heart disease or UA [10], including cardiovascular death, nonfatal myocardial infarction, and revascularization.

The primary endpoint is the time from the enrollment to the end of the study (including the medication observation period and follow-up period) when any of the MACE events occur for the first time. The researchers will record through telephone interviews, in-patient and outpatient medical records of patients, and information provided by their family members. Patients without MACE during the study will be defined as censored at the end of the study. For patients who quit the trial early due to reasons other than MACE, the time of occurrence is defined as censoring at the time

of early termination. Deaths not due to cardiovascular diseases or that occur after the MACE will not be evaluated.

2.10.2 Secondary outcomes

The efficacy of angina pectoris will be observed at the time of enrollment and at the end of treatment, including the frequency of angina attack, the clinical manifestations, ECG and laboratory examination.

Myocardial injury markers [serum creatine kinase MB; cardiac troponin T/cardiac troponin I (cTnI)/high-sensitivity troponin I] will be monitored, in order to observe changes in myocardial injury during treatment and to assess efficacy and safety during treatment.

2.10.3 Safety assessment

An adverse event (AE) is any adverse medical event that occurs during the trial. The researchers will record the observation of vital signs, testing of blood and urine samples, renal and liver function at the start and end of the run-in period, and recorded abnormal changes and AEs at any time.

In view of the particularity of the disease, the condition of the participants may change significantly during the observation, including the need for hospitalization for the deterioration of the disease, or even life-threatening. Since cardiovascular death, non-fatal myocardial infarction, and revascularization were the endpoints of this study, the above events would not be reported as serious adverse events (and described in the study history). Known adverse reaction of the XST: systemic injury: fever, chills, anaphylactic reaction, anaphylactic shock, etc.; the respiratory system damage: chest tightness, breathing difficulties, shortness of breath, asthma, laryngeal edema, etc.; skin and its appendages damage: rash, pruritus, dermatitis exfoliating;heart rate and

arrhythmia: palpitations, tachycardia, etc.; central and peripheral nervous system damage: dizziness, headache, convulsions, tremor, etc.; gastrointestinal system damage: nausea, vomiting, etc.; cardiovascular system damage: cyanosis, flushing, decreased blood pressure, elevated blood pressure, etc.; other damage: blood in the urine, abnormal liver function, etc.

Patients will be required to report all AEs at each visit. All AEs will be recorded, regardless of severity, to assess the safety of XST.

If an AE occurs, the researchers will have to determine whether to stop the observation and proceed with the diagnosis and corresponding treatment. If any severe AE occurs, the researchers must take immediate action to ensure the safety of the participants. They must also report to the ethics committee within 24 h. The responsible staff from The First Affiliated Hospital of Guangzhou University of Chinese Medicine must promptly notify other participating centers and initiate any necessary legal procedures.

2.11 Follow-up

All included participants will be evaluated for the occurrence of MACE after 1, 3, and 6 months through phone calls after the end of the medication. The trial will be ended if the following endpoints occur: death, nonfatal myocardial infarction, or revascularization (including PCI and CABG). The academic research on hemorrhage in Europe and the United States proposed a unified definition of hemorrhage type 3–5.

The occurrence of the MACE must be recorded in an original supporting document, including but not limited to a copy of the discharge summary, a copy of the medical record, or other documents that can be used to verify the occurrence of the MACE and the date of its occurrence.

2.12 Statistical analysis

2.12.1 Enrollment and case completion

The completion of the trial at each center must be recorded and described. All cases of shedding must be listed.

2.12.2 Baseline comparability analysis

The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

2.12.3 Analysis of efficacy

(1) Baseline comparability analysis: This includes the description of demographic data, symptoms, and general conditions. The *t* test or nonparametric statistical method will be used for quantitative data. Qualitative data will be determined using the chi-square test, Fisher's exact probability method, CMH test, and Wilcoxon rank-sum test.

(2) Primary and secondary outcomes: The incidence of composite endpoints for MACE and the efficacy of angina pectoris will be compared between the two groups and analyzed using the chi-square or Fisher exact tests and two-sample *t* tests or Wilcoxon rank-sum test. The laboratory data on myocardial injury markers will be analyzed for the changes before and after the intervention. The average value of each laboratory data after the treatment will be compared.

(3) For cases of rejection and shedding, statistical descriptions will be performed one by one. Adverse reactions will be statistically described. The incidence of adverse reactions will be compared using the chi-square or Fisher exact tests.

3. Discussion

XST is a traditional Chinese herbal injection consisting of a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and the People's Republic of China Pharmacopoeia, respectively. *T*otal saponins, isolated from the root and rhizome of *P. notoginseng,* are the main components of XST.

P. notoginseng is known for promoting blood circulation, preventing thrombosis, and dilating blood vessels. It is widely applied to treat acute cerebral infarction, stroke, and coronary heart disease in clinical practice[11, 12]. Wang et al.[13]found that in a rat model of middle cerebral artery occlusion-reperfusion ,administration of XST combined with salvianolate lyophilized(SLI) injection not only significantly decreased neurological deficit scores and infarct volumes,and increased regional cerebral blood flow. Gan et al.[14] evaluated the efficacy and safety of the *P. notoginseng* extract via intracoronary injection for treating the post-PCI slow-reflow phenomenon in patients with ST-segment elevation myocardial infarction and its impact on patients' prognosis. They found that coronary injection with tirofiban and XST was more effective in improving the coronary blood flow and showed no increase in the incidence of hemorrhagic complications compared with the injection with tirofiban only. *P. notoginseng* has been found to be beneficial to patients with UA. The use of the extract has been recommended for patients with UA in clinical practice as a complementary and alternative therapy[15]. However, more randomized controlled trials with reliable designs, large samples, and long-term observations are needed for further evaluations.

The meta-analysis of XST injection combined with routine basic treatment was superior to routine basic treatment alone in alleviating clinical symptoms, with statistically significant differences between the groups. XST injection combined with routine basic treatment could alleviate UA pectoris. However, due to the low quality of included studies, further well-designed, multicenter, and large-scale RCTs are still needed to evaluate the efficacy of XST injection [16]. Moreover, the total revenue from

XST in the Chinese market in 2013 was over $700 million [17]. Therefore, the enormous consumption requires stricter and accurate evidence on its safety. However, many reports of XST were case reports, and hence large-sample and high-level evidence for the efficacy and safety of XST is still lacking. Therefore, this study will be conducted to investigate the efficacy and safety of XST in reducing the incidence of MACE in patients with UA. The findings of this study will provide clinical evidence for the use of XST in reducing the incidence of MACE in patients with UA.

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Contributors

ZY and WL wrote the study protocol. SX, HL, TY and YT developed the original study design. XH, JL, YH, JD, YL and WL were all involved in the revision of the study design and contributed in the review process of the protocol manuscript. YT and QL are jointly responsible for the collection of data and administration of study participants. LL provides methodological guidance on research statistics. ZY is the principal investigator and responsible for the funding and overall management of the trial.

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Disclaimer

The funders have no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Trial status

Currently the participants are being enrolled for the trial.

Conflicts of interest

All authors declare no conflicts of interest.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
● Patients who meet all the following requirements ● Patients diagnosed with coronary heart disease who met at least one of the following diagnostic criteria[1]: (1) a clear history of myocardial infarction (MI); (2) prior coronary revascularization; (3) coronary angiography or coronary angiography suggesting at least one coronary artery stenosis with catheter stenosis ⩾50%; (4) cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging to confirm myocardial ischemia in the patient having coronary heart disease	◆ Patients with cardiac function class IV (New York Heart Association cardiac function grading); or patients at a high risk of UA short-term risk stratification ◆ Patients with uncontrolled grade III hypertension having systolic blood pressure ⩾180 mm Hg and/or diastolic blood pressure ⩾110 mm Hg; severe cardiopulmonary insufficiency; severe arrhythmia; severe primary diseases of the liver, kidney, and hematopoietic system; or serious diseases (such as tumors) and mental diseases ◆ Patients also having other clinical conditions that might increase the risk of bleeding, such as a history of important organ bleeding in the last 6 months (such as intracerebral

● Patients complying with the diagnosis of UA and having at least one of the following conditions: (1) electrocardiograph with a transient or persistent ST-segment depression of 0.1 mV and even more on one or more leads; (2) Thrombolysis In Myocardial Infarction (TIMI) risk score[18] ⩾3 ● Patients receiving dual antiplatelet therapy (aspirin + clopidogrel) ● Patients aged 40–75 years, irrespective of sex ● Patients willing to accept the drug treatment and provide written informed consent, conforming to the relevant regulations of Good Clinical Practice	hemorrhage and upper gastrointestinal bleeding), decreased platelet count, abnormal coagulation function, and recent active bleeding ◆ Patients with abnormal function indexes of the liver and kidney [blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level more than two times the upper normal reference range; glomerular filtration rate (GFR) <60 mL/(min × 1.73 m²)]. Simplified Modification of Diet in Renal Disease formula: GFR [mL/(min × 1.73 m²)] = 186.3 × serum creatinine (Scr)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 female); Scr in mg/dL and age in years ◆ Patients who planned to undergo revascularization [PCI or coronary artery bypass grafting (CABG)] recently ◆ Patients allergic to a variety of foods, or with known allergy to study drugs, including their components ◆ Patients pregnant, preparing for pregnancy, or lactating ◆ Patients participating in other clinical trials during the same period ◆ Patients considered inappropriate to

	participate in this study

Table 2. Study schedule of assessments

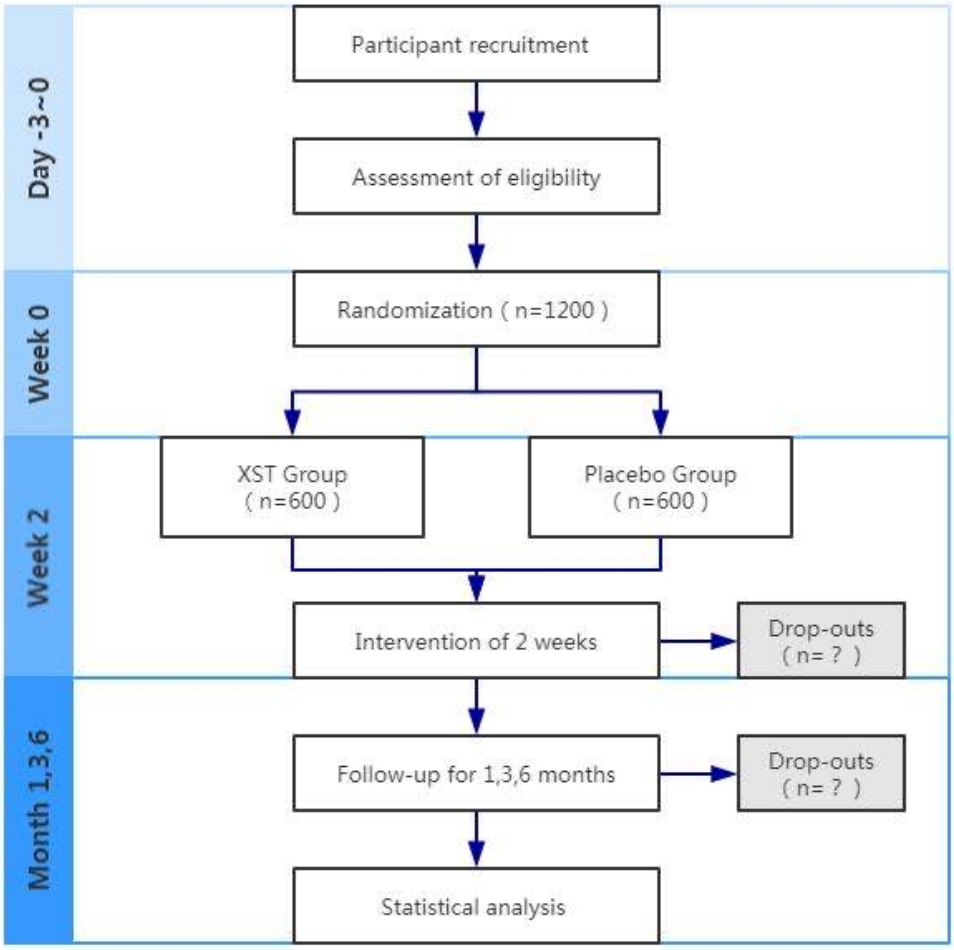
Abbreviations: CK-MB, creatine kinase MB; MACE, major adverse cardiac events; cTn, cardiac troponin; hsTn, high-sensitivity Troponin; UA, unstable angina.

	Study period			
	Enrollment	**Allocation**	**Intervention**	**Follow-up**
Time point	**-3 ~ 0 days**	**0**	**7 ~ 14 days**	**1, 3 and 6 months**
ENROLLMENT:	X			
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
SXT treatment			X	
Placebo treatment			X	
ASSESSMENTS:				
MACE			X	X

CK-MB		X	X	
cTnT		X	X	
cTnI		X	X	
hsTnI		X	X	
Adverse events			X	X

Figure legends

Figure 1. Flowchart of the study procedure.



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17-18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	5,6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8 21-22
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	23-24
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	23-24
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8,17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of High-Dose Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

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Secondary Subject Heading:	Complementary medicine
Keywords:	CARDIOLOGY, Adult cardiology < CARDIOLOGY, Coronary heart disease

	< CARDIOLOGY

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Efficacy and safety of High-Dose Xueshuantong injection (lyophilized) in reducing the incidence of major adverse cardiovascular events in patients with unstable angina: A protocol of a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial based on dual antiplatelet therapy

Running title：Efficacy and safety of Xueshuantong injection in patients with UA

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List of abbreviation

ACS, Acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass grafting; cTn, cardiac troponin; CK-MB, creatine kinase MB; HDL-C, low high-density lipoprotein cholesterol; LDL-C, high low-density lipoprotein cholesterol; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; hsTn, high-sensitivity troponin; UA, unstable angina

Abstract

Introduction: Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection having the potential to treat ACS. However, no clinical trial has been performed in this field. This clinical trial aims to examine the efficacy and safety of XST.

Methods and Analysis: This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial. A total of 1200 participants with UA will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group and 600 with one-twentieth dose in the control group. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectoris will be examined at the start and end of the run-in period. All AEs will be recorded, regardless of the severity, to assess the safety of XST. The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

Ethics and Dissemination: This trial has been approved by the Research Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine, China (approval number: ZYYEC [2017] 0021). Written informed consent will be obtained from all participants. The results of this trial will be disseminated to the public through academic conferences and peer-reviewed journals.

Trial registration: This study was registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn/) with the ID ChiCTR1800015911.

Key words: Acute coronary syndrome, clinical trial, traditional Chinese herbal injection, unstable angina

Strengths and limitations of this study:

1. This is a randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial.
2. The trial will be conducted in 17 medical centers with 1200 participants.

3. In our study, to better implement the blind method, the extremely low dose 25mg is used as the control group.

4. The efficacy assessment and major adverse cardiovascular events (MACE) will be observed, and the frequency of angina attack, angina pectorals will be examined at the start and end of the run-in period.

5. Our experiments will be conducted in different regions of China, and whether similar effects are available to other ethnic groups and regions remains uncertain.

Introduction

Unstable angina (UA), referred to as acute coronary syndrome (ACS), causes unexpected chest pain. Reduced blood flow to the heart muscle is the most common cause of UA because the coronary arteries are narrowed by atherosclerosis, leading to the rupture of coronary blood vessels and hence blood clotting, which blocks the flow of blood to the heart muscle. The risk factors for UA include diabetes, obesity, family history of heart disease, high blood pressure, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, male sex, and use of any form of tobacco[1, 2].With the wide application of percutaneous coronary intervention (PCI) in patients with ACS, current guidelines recommend potent platelet inhibition with prasugrel or ticagrelor for 12 months after ACS management with PCI. However, the greatest anti-ischemic benefit of potent antiplatelet drugs over the less-potent clopidogrel occurs early, while most excess bleeding events occur during chronic treatment. It is related to the efforts of physicians to reduce the adverse incidence of cardiovascular events, promote the patient's early recovery, and improve their health-related quality of life.

Xueshuantong injection (lyophilized) (XST) is a traditional Chinese herbal injection comprising a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and People's Republic of China Pharmacopoeia, respectively. It has been reported to have anti-inflammatory effects that correct endothelial dysfunction *in vivo*[3] and *in vitro*[4]. Clinically, as a common medicine in China's Grade-A Tertiary Hospital,XST has been reported to be beneficial in treating ACS[5, 6]. In preliminary studies, including small samples, XST has been found to platelet aggregation inhibition, anti-myocardial ischemia, anti-inflammation, anti-oxidation, protecting endothelial cells, which could reduce the incidence of major adverse cardiovascular events (MACE)[7].The recent study found that XST inhibits platelet activation and suppresses leukocytes adhesion

to injured endothelial cells (ECs) under controlled shear stress in vitro, which not only dose-dependent and showed stronger anti-platelet activation and adhesion effect under low shear stress[8]. XST also played an effect in fighting against thrombosis induced by k-carrageenan in rats. High dose could significantly increase the microcirculatory blood flow perfusion of the tail and significantly inhibit platelet aggregation rate[9]. Besides, XST could significantly inhibit platelet piezo1 protein expression which may improve blood flow and antithrombotic. The Meta-analysis reported that Xueshuantong Injection combined with routine basic treatment (RBT) can alleviate unstable angina pectorals, especially for frequency relief of angina, frequency reduction of nitroglycerin and the effective rate is more than 80%. It can significantly reduce blood high-sensitivity C-reactive protein(hs-CRP), fibrinogen(FIB) concentration[10]. As the primary component[11], Panax notoginseng, has been extensively verified that it can ameliorate ischemia-reperfusion (IR)-induced injury in cardiovascular and neuronal systems mainly by upregulating the activity of estrogen receptor α -dependent phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and nuclear factor erythroid-2-related factor 2 (NRF2) pathways and downregulating nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways. Therefore, high-quality trials and evidence are needed to prove the efficacy of XST. This randomized, parallel, controlled, double-blind, and multicenter clinical trial aims to examine the efficacy and safety of XST in patients with UA. The results of this trial may provide clinical evidence for treating patients with UA.

2. Method and design

2.1 Study design

This randomized, parallel-arm, controlled, double-blind, and multicenter clinical trial will be conducted in 17 medical centers in China: The First Affiliated Hospital of

Guangzhou University of Chinese Medicine, The First Affiliated Hospital of Henan University of Chinese Medicine, Luoyang No. 1 Hospital of Traditional Chinese Medicine, Shanxi Fenyang Hospital, The First Affiliated Hospital of Henan University of Science and Technology, Zhengzhou People's Hospital, Zhengzhou Central Hospital, Ruikang Hospital Affiliated to Guangxi University of Traditional Chinese Medicine, Nanjing Hospital of Chinese Medicine, Shuguang Hospital Affiliated to Shanghai University of Chinese Medicine, Changsha Fourth Hospital, The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Affiliated Hospital of Tianjin Academy of Chinese Medicine, Tianjin Beichen District Hospital of Traditional Chinese Medicine, and Wenzhou Hospital of Traditional Chinese Medicine. A total of 1200 patients with UA who met the selection will be enrolled in a 1:1 ratio, with 600 patients included in the XST treatment group (high-dose, 500mg) and 600 in the control group (extremely low dose, 25mg).

All the visits will be recorded in electronic case report forms through the Electronic Data Capture system, which is accessed online via the Internet for data collection and management. The protocol for this study was developed in accordance with the standard protocol project: Interventional Trial Recommendations guidelines[12].

2.2 Ethics

This study has been approved by the ethics committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (approval number: ZYYEC[2017]002) and 17 other medical centers: the Ethics Committee of Drug Clinical Trials of Zhengzhou People's Hospital（approval number: YW201800501）,

the Ethics Committee of Shanxi Fenyang Hospital（approval number: 2018002）, the Ethics Committee of Ruikang Hospital Affiliated to Guangxi University of Traditional Chinese Medicine（approval number: RK201709）, the Ethics Committee of Changsha Fourth Hospital （approval number: CSSDSYY-LL-SC-2017-03-03）, the Ethics Committee of The First Affiliated Hospital of the Henan University of Chinese Medicine（approval number: 2018HL-046-01）, the Ethics Committee of the Second Affiliated Hospital of Heilongjiang University of Chinese Medicine (approval number: 2015R000774), the Ethics Committee of The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine （approval number: HN-LL-2017-018-01）, the Medical Ethics Committee of Luoyang NO.1 Hospital of TCM (approval number: 2018-01), the Ethics Committee of Zhengzhou Central Hospital (approval number: 2018-006-02), the Ethics Committee of Tianjin Beichen District Hospital of Traditional Chinese Medicine（approval number: BCZYK201901）, the Ethics Committee of Nanjing Hospital of Chinese Medicine （approval number: 2017NJL033）, the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Chinese Medicine（approval number: 2017-563-46-01）, the Ethics Committee of Affiliated Hospital of Tianjin Academy of Chinese Medicine（approval number: LLSY207-04）, the Ethics Committee of The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine （approval number: EC.AT/03.19-02/08.0）, the Ethics Committee of The First Affiliated Hospital of Henan University of Science and Technology （approval number: 2018-0020）and the Ethics Committee of Wenzhou Hospital of Traditional Chinese Medicine （approval number: WTCM-H-2017024-2018-002）.The trial has been registered on the Chinese Clinical Trial Registry with the ID ChiCTR1800015911.

2.3 Patient and public involvement

This clinical trial was designed to evaluate the efficacy and safety of high-dose

XST in patients with UA. Clinically, XST has been found to be beneficial in treating ACS, which had been widely used in China's Grade-A Tertiary Hospital. More high-quality trials and evidence are needed to prove the efficacy of XST. The outcome measures used in this trial were considered as important endpoints in clinical practice. The participants in this trial will be recruited from 17 medical centers in China. However, patients were not directly involved in the design, recruitment, or conduct of the study. After the trial completes, the results of this study will be disseminated to the public through academic conferences and peer-reviewed journals. Once the manuscript is published, the results will be briefly summarized in a simple language and inform all trial participants through the telephone. The burden of intervention will not be assessed by the trial participants.

2.4 Study population

Patients will be included after written informed consent and enrolled in the study when the inclusion and exclusion criteria are met (Table 1).

2.4.1 Withdrawal criteria

1. Patients with some comorbidities, complications, or special physiological changes during the trial
2. Patients with poor compliance in the trial; the use of the drug not reaching 80% (except for those recovered in advance) or exceeding 120% of the prescribed amount
3. Patients with blindness or emergency unblinding during the trial
4. Patients with serious adverse events and those not appropriate to continue the test
5. Patients failing to use the test drug
6. Patients misdiagnosed or not matching the inclusion criteria and accidentally included
7. Patients with no follow-up records

8. Patients failing to comply with the treatment during the trial, changing medicines, or adding non specified therapeutic medications by themselves, especially those medications that may affect the evaluation of the test drug, affecting the validity and safety.

2.5 Study setting and recruitment

Between December 2018 and December 2020, 1200 outpatients or inpatient will be recruited at 17 centers mentioned earlier through the official website of the hospitals, posters, and networks. Physicians will diagnose the participants, and the research assistants will manage the recruitment.

2.6 Randomization

On the day of enrollment, statistical analysis system software will be used to generate the random arrangement of 1200 people in 2 groups (XST and placebo groups) with the method of central stratified regional group randomization. The randomization numbers will be kept in opaque sealed envelopes. Physicians and patients will not be aware of the grouping and intervention.

2.7Blinding

This study has a double-blind design. Because XST was lyophilized powder form in this study, which was a kind of white or light yellow amorphous powder or loose solid, and was dissolved with an appropriate amount of injection sodium chloride injection before use, there were color changes and a small amount of powder precipitation. Therefore, in order to better implement the blind method, an extremely low dose (25mg) was used as the control group, which is invalid for UA from our

previous pharmacokinetic experiment, did not increase the efficacy of the experimental group.

The number of cases in the study and control group will be in the ratio of 1:1. The blinding work will be completed by statisticians. To ensure the blinding of investigators and participants to study treatment, the study drug or placebo will be provided in identical packaging and labeling. Due to some natural variability in the color of the study drug, which is batch dependent, the color of the placebo will match the same as the average color of the study drug. Study drug and placebo will label with a unique label letter that will be used to assign treatment to the patient but will not indicate treatment allocation to investigators or participants. No member of the study team and their extended staff, except for pharmacists and biostatisticians, will have access to the randomization scheme during the conduct of the study. In the event of a medical emergency, where breaking the blind is required to provide medical care to the participant, the investigator will obtain the treatment assignment from the trial pharmacists.

2.8 Sample size calculation

MACE will be used as the effective index according to the statistical requirements of the optimal validity test design.

Based on the expert advice combined with clinical practical considerations and according to the loss rate of less than 20% estimated beforehand, the study sample was 1200 cases (600 cases in each group), assuming that the incidence of MACE was 12% after dual antiplatelet therapy for 6 months, which was reduced by 6% after lyophilization (alpha = 0.05; power = 0.9).

2.9 Interventions

All participants will receive dual antiplatelet therapy (aspirin 100 mg/d + clopidogrel 75 mg/d) and anticoagulation therapy (unfractionated heparin) according to the 2014 American College of Cardiology/American Heart Association Guidelines for the Diagnosis and Treatment of Non-ST-Segment Acute Coronary Syndrome, and in accordance with the guidelines to accept statins, angiotensin-converting enzyme inhibitors, beta-blockers, and nitrates. Patients with mild UA will undergo a standardized baseline assessment before the treatment, including detailed medical history, physical examination, and laboratory testing. Meanwhile, the following treatments will be given to different groups:

(1) XST treatment group: The patients will be treated via an intravenous drip with 500mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days.

(2) Control group: The patients will be treated via an intravenous drip with 25mg XST (lyophilized) diluted with 250–500 mL of 5% glucose injection or sodium chloride injection, once per day for 7–14 days.

The experimental drugs will be distributed by a drug administrator and injected by trained nurses.

Patients will be admitted to the hospital on the day of registration for the first intervention, and patients who discharge will move directly to the follow-up period. The efficacy and safety of XST will be assessed after treatment for 7–14 days and follow-up for 1, 3, and 6 months (Figs. 1 and Table 2).

2.10 Outcome measurements

2.10.1 Primary outcomes

The primary endpoints will include the incidence of the composite endpoints for MACE, which is a commonly used indicator to evaluate the prognosis of patients with coronary heart disease or UA [13],including cardiovascular death, nonfatal myocardial

infarction, and revascularization.

The primary endpoint is the time of enrollment to the end of the study (including the medication observation period and follow-up period) when any of the MACE events occur for the first time. The researchers will record through telephone interviews, in-patient and outpatient medical records of patients, and information provided by their family members. Patients without MACE during the study will be defined as censored at the end of the study. For patients who quit the trial early due to reasons other than MACE, the time of occurrence is defined as censoring at the time of early termination. Death not due to cardiovascular diseases or that occurs after the MACE will not be evaluated.

2.10.2 Secondary outcomes

The efficacy of angina pectorals will be observed at the time of enrollment and by the end of treatment, including the frequency of angina attack, the clinical manifestations, ECG, and laboratory examination.

Myocardial injury markers [serum creatine kinase MB; cardiac troponin T/cardiac troponin I (cTnI)/high-sensitivity troponin I] will be monitored, to observe changes in myocardial injury during treatment and to assess the efficacy and safety during treatment.

2.10.3Safety assessment

An adverse event(AE) is any adverse medical event that occurs during the trial. The researchers will record the observation of vital signs, testing of blood and urine samples, renal and liver function at the start and end of the run-in period, and recorded abnormal changes and AEs at any time.

In view of the particularity of the disease, the condition of the participants may

change significantly during the observation, including the need for hospitalization for the deterioration of the disease, or even life-threatening. Since cardiovascular death, non-fatal myocardial infarction, and revascularization were the endpoints of this study, the above events would not be reported as serious adverse events (and described in the study history). Known adverse reaction of the XST: systemic injury: fever, chills, anaphylactic reaction, anaphylactic shock, etc.; respiratory system damage: chest tightness, breathing difficulties, shortness of breath, asthma, laryngeal edema, etc.; skin and its appendages damage: rash, pruritus, dermatitis exfoliating;heart rate and arrhythmia: palpitations, tachycardia, etc.; central and peripheral nervous system damage: dizziness, headache, convulsions, tremor, etc.; gastrointestinal system damage: nausea, vomiting, etc.; cardiovascular system damage: cyanosis, flushing, decreased blood pressure, elevated blood pressure, etc.; other damage: blood in the urine, abnormal liver function, etc.

Patients will be required to report all AEs at each visit. All AEs will be recorded, regardless of the severity, to assess the safety of XST.

If an AE occurs, the researchers will have to determine whether to stop the observation and proceed with the diagnosis and corresponding treatment. If any severe AE occurs, the researchers must take immediate action to ensure the safety of the participants. They must also report to the ethics committee within 24 h. The responsible staff from The First Affiliated Hospital of Guangzhou University of Chinese Medicine must promptly notify other participating centers and initiate any necessary legal procedures.

2.11 Follow-up

All included participants will be evaluated for the occurrence of MACE after 1, 3, and 6 months through phone calls after the end of the medication. The trial will be ended if the following endpoints occur: death, nonfatal myocardial infarction, or

revascularization (including PCI and CABG). The academic research on hemorrhage in Europe and the United States proposed a unified definition of hemorrhage type 3–5.

The occurrence of the MACE must be recorded in an original supporting document, including but not limited to a copy of the discharge summary, a copy of the medical record, or other documents that can be used to verify the occurrence of the MACE and the date of its occurrence.

2.12 Statistical analysis

2.12.1 Enrollment and case completion

The completion of the trial at each center must be recorded and described. All cases of shedding must be listed.

2.12.2 Baseline comparability analysis

The baseline characteristics of patients will be summarized and compared using the *t* test or nonparametric statistical test. Qualitative data will be analyzed using the chi-square or Fisher exact tests, Cochran–Mantel–Hasenszel (CMH) test, and Wilcoxon test.

2.12.3 Analysis of efficacy

(1) Baseline comparability analysis: This includes the description of demographic data, symptoms, and general conditions. The *t* test or nonparametric statistical method will be used for quantitative data. Qualitative data will be determined using the chi-square test, Fisher's exact probability method, CMH test, and Wilcoxon rank-sum test.

(2) Primary and secondary outcomes: The incidence of the composite endpoints for MACE and the efficacy of angina pectorals will be compared between the two

groups and analyzed using the chi-square or Fisher exact tests and two-sample *t* tests or Wilcoxon rank-sum test. The laboratory data on myocardial injury markers will be analyzed for the changes before and after the intervention. The average value of each laboratory data after the treatment will be compared.

(3) For cases of rejection and shedding, statistical descriptions will be performed one by one. Adverse reactions will be statistically described. The incidence of adverse reactions will be compared using the chi-square or Fisher exact tests.

3. Discussion

XST is a traditional Chinese herbal injection consisting of a series of saponins extracted from *Panax notoginseng*. It has been approved by the China Food and Drug Administration (China drug approval number: Z 20025652) and collected according to the "2012 national essential drugs list" and the People's Republic of China Pharmacopoeia, respectively.*T*otalsaponins, isolated from the root and rhizome of *P. notoginseng,* are the main components of XST.

P. notoginseng is known for promoting blood circulation, preventing thrombosis, and dilating blood vessels. It is widely applied to treat acute cerebral infarction, stroke, and coronary heart disease in clinical practice[14, 15].Wang et al.[16]found that in a rat model of middle cerebral arteryocclusion-reperfusion, administration of XST combined with salvianolate lyophilized(SLI) injection not only significantly decreased neurological deficit scores and infarct volumes,and increased regional cerebral blood flow. Gan et al.[17]evaluated the efficacy and safety of the *P. notoginseng* extract via intracoronary injection for treating the post-PCI slow-reflow phenomenon in patients with ST-segment elevation myocardial infarction and its impact on patients' prognosis. They found that coronary injection with tirofiban and XST was more effective in improving coronary blood flow and showed no increase in the incidence of hemorrhagic complications compared with the injection with

tirofiban only. *P. notoginseng* has been found to be beneficial in patients with UA. The use of the extract has been recommended for patients with UA in clinical practice as a complementary and alternative therapy[18]. However, more randomized controlled trials with reliable designs, large samples, and long-term observations are needed for further evaluations.

The meta-analysis of XST injection combined with routine basic treatment was superior to routine basic treatment alone in alleviating clinical symptoms, with statistically significant differences between the groups. XST injection combined with routine basic treatment could alleviate UA pectorals. However, due to the low quality of the included studies, further well-designed, multicenter, and large-scale RCTs are still needed to evaluate the efficacy of XST injection[19]. Moreover, the total revenue from XST in the Chinese market in 2013 was over $700 million [20]. Therefore, enormous consumption requires stricter and accurate evidence on its safety. However, many reports of XST were case reports, and hence large-sample and high-level evidence for the efficacy and safety of XST is still lacking. Therefore, this study will be conducted to investigate the efficacy and safety of XST in reducing the incidence of MACE in patients with UA. The findings of this study will provide clinical evidence for the use of XST in reducing the incidence of MACE in patients with UA.

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Contributors

ZY and WL wrote the study protocol. SX, HL, TY and YT developed the original

study design. XH, JL, YH, JD, YL and WL were all involved in the revision of the study design and contributed to the review process of the protocol manuscript. YT and QL are jointly responsible for the collection of data and administration of study participants. LL provides methodological guidance on research statistics. ZY is the principal investigator and responsible for the funding and overall management of the trial.

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Disclaimer

The funders have no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Trial status

Currently the participants are being enrolled for the trial.

Conflicts of interest

All authors declare no conflicts of interest.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
● Patients who meet all the following requirements ● Patients diagnosed with coronary heart disease who met at least one of the following diagnostic criteria[1]: (1) a clear history of myocardial	◆ Patients with cardiac function class IV (New York Heart Association cardiac function grading); or patients at a high risk of UA short-term risk stratification ◆ Patients with uncontrolled grade III hypertension having systolic blood

infarction (MI); (2) prior coronary revascularization; (3) coronary angiography or coronary angiography suggesting at least one coronary artery stenosis with catheter stenosis ⩾50%; (4) cardiac magnetic resonance imaging or radionuclide myocardial perfusion imaging to confirm myocardial ischemia in the patient having coronary heart disease ● Patients complying with the diagnosis of UA and having at least one of the following conditions[21]: (1) electrocardiograph with a transient or persistent ST-segment depression of 0.1 mV and even more on one or more leads[22]; (2) Thrombolysis In Myocardial Infarction (TIMI) risk score[23]⩾3 ● Patients receiving dual antiplatelet therapy (aspirin + clopidogrel) ● Patients aged 40–75 years, irrespective of sex ● Patients willing to accept the drug treatment and provide written	pressure⩾180 mm Hg and/or diastolic blood pressure⩾110 mm Hg; severe cardiopulmonary insufficiency; severe arrhythmia; severe primary diseases of the liver, kidney, and hematopoietic system; or serious diseases (such as tumors) and mental diseases ◆ Patients also having other clinical conditions that might increase the risk of bleeding, such as a history of important organ bleeding in the last 6 months (such as intracerebral hemorrhage and upper gastrointestinal bleeding), decreased platelet count, abnormal coagulation function, and recent active bleeding ◆ Patients with abnormal function indexes of the liver and kidney [blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level more than two times the upper normal reference range; glomerular filtration rate (GFR) <60 mL/(min × 1.73 m²)]. Simplified Modification of Diet in Renal Disease formula: GFR [mL/(min × 1.73 m²)] = 186.3 × serum creatinine (Scr)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 female); Scr in mg/dL and age in years

informed consent, conforming to the relevant regulations of Good Clinical Practice	◆ Patients who planned to undergo revascularization [PCI or coronary artery bypass grafting (CABG)] recently ◆ Patients allergic to a variety of foods, or with known allergy to study drugs, including their components ◆ Patients pregnant, preparing for pregnancy, or lactating ◆ Patients participating in other clinical trials during the same period ◆ Patients considered inappropriate to participate in this study

Table 2. Study schedule of assessments

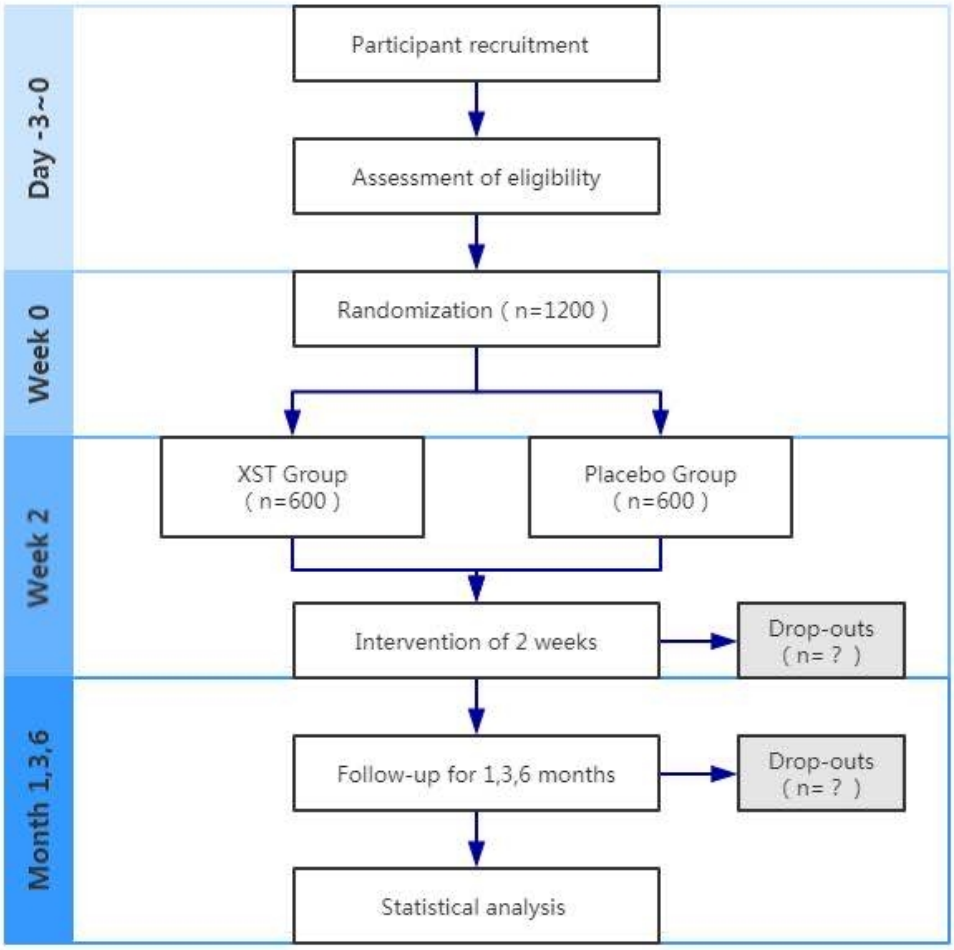
Abbreviations: CK-MB, creatine kinase MB; MACE, major adverse cardiac events; cTn, cardiac troponin; hsTn, high-sensitivity Troponin; UA, unstable angina.

	Study period			
	Enrollment	**Allocation**	**Intervention**	**Follow-up**
Time point	**-3~0 days**	**0**	**7 ~ 14 days**	**1, 3 and 6 months**
ENROLLMENT:	**X**			
Eligibility screen	**X**			
Informed consent	**X**			

Allocation		X		
INTERVENTIONS:				
SXT treatment			X	
Placebo treatment			X	
ASSESSMENTS:				
MACE			X	X
CK-MB		X	X	
cTnT		X	X	
cTnI		X	X	
hsTnI		X	X	
Adverse events			X	X

Figure legends

Figure 1. Flowchart of the study procedure.



Flowchart of the study procedure.

159x155mm (96 x 96 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17-18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	5,6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8 21-22
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	23-24
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	23-24
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13,15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8,17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.