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Identify Characteristics of Similar Chinese Patent Medicine for Stroke Based on Comparative Effectiveness Research (CER): Study Protocol of a Randomized Controlled Trial

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Abstract

Introduction: The main symptoms in stroke convalescent period include hemiplegia, dysphasia and facial paralysis. In China, a great number of patients in stroke convalescent period prefer to take Chinese patent medicines (CPM) to relieve the above symptoms, among which Naoxuekang capsule (NXG), Xinnaoshutong capsule (XNST) and Xuesetong capsule (XST) are frequently used. However, as the instructions of these three CPMs indicate similar functions based on the syndrome theory, it is hard to decide which one is the best choice for certain symptoms mentioned above. This study aims to find a new method to distinguish which CPM is the best choice for certain symptoms mentioned above, and finally establishes a effective method to differentiate the CPMs with similar effects from the perspective of relieving patients' symptoms.

Methods/ Design: The study is based on the theory of comparative effectiveness research (CER). Three patients groups with 120 people for each one will be recruited according to one of their urgent symptoms from hemiplegia, dysphasia and facial paralysis. Each group will be randomly and equally divided into 4 small groups, which respectively have treatment with NXG, XNST, XST and no CPM. The treatment will last for 30 days, and follow up 30 days. The outcome measurement is based on the patient-centered evaluation theory. The Delphi techniques will be used to assign weight to the index value of NIHSS scale and WHOQOL-BREF scale. The weighted index value will be computed as the final measurement index of the outcome, which is named Comprehensive recovery index of stroke rehabilitation (CRST) in this study.

Discussion: This study distinguishes the orientation of different CPMs from the aspect of symptoms and establishes an effective evaluation method which fits Chinese patent medicines' effectiveness in synthetic regulation. This study will differentiate the effectiveness of NXG, XNST and XST from the perspective of relieving patients' symptoms. This study provides a methodological foundation for the effective evaluation of other CPMs or treatment plans. Meanwhile, it also explores the usage of CER in TCM.

Trial registration: This trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-17010397). The date of registration was 11st Jan, 2017.

Keywords: Stroke, Chinese Patent Medicine, Comparative Effectiveness Research

Strengths and limitations of this study

- A multi centric, prospective and randomized controlled trial.
- This study explores the usage of CER in TCM.
- This study distinguishes the orientation of different CPMs from the aspect of symptoms.
- The evaluation of a patient's recovery involves both quality of life and clinical indexes.
- Using Delphi techniques to assign weight to the scale indexes.
- The sample size is not large enough due to funding constraints (n=360, each group=30).

Background

The annual incident of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have shown that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke. Naoxuekang capsule (NXG) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. Xinnaoshutong capsule (XNST) [7] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd, and Xuesetong capsule (XST) [8] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd.

NXG, XNST and XST are three CPMs that have similar instructions and are frequently utilized in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure.

Besides, owing to CPM interpreting illness from syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

The application feasibility of comparative effectiveness research in the evaluation of CPM

The concept of comparative effectiveness research (CER) was initiated in the 1990s by Mark Boutin, the deputy executive president and chief operating officer of the US National Health Council [9]. The Agency for Healthcare Research and Quality (AHRQ) defined comparative effectiveness research as: "Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options" [10]. The evidence was generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care [11].

In the following years, CER was introduced into the field of clinical research in a number of countries [12]. CER was introduced into TCM research at the sixth annual meeting of the International Society of Complementary Medicine Research by Claudia M Witt (Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany) in May 2011 [13]. The outcome of comparative effectiveness research focuses on the problems that patients care and want to solve mostly [14]. It is more patient-oriented, which means it respects the patients' will, cares about both the quality of lives and psychological function, as well as fitting the TCM clinical practice and showing the validity of the results.

CER is concerned with answering questions regarding effectiveness rather than efficacy of interventions, which has implications for the usefulness of various study designs. Non-randomized or observational studies, rather than randomized controlled trials (RCTs), may answer effectiveness questions better, even though well-known threats to validity exist for the former [15].

Effectiveness evaluation based on patient-oriented

Patients in stroke convalescent period suffer not only from various clinical symptoms but also the decline of the ability of daily activities and the quality of life. According to the study, the evaluation of a patient's recovery should involve both quality of life, including mental state, physical condition, psychological condition and social environment, and clinical indexes.

Quality of life: According to WHOQOL-BREF, quality of life is evaluated by one's mental state, psychological state and physical state, etc. [16-17]. **Clinical indexes:** The physiological indexes which show the degree of nervous functional defects can be evaluated by National Institutes of Health Stroke Scale (NIHSS).

In this research, WHOQOL and NIHSS are used to assess the curative effect and get their weight with Delphi. The comprehensive score is taken as the final curative effect. It avoid the randomness of the PRO (Patient Report Outcome) [18] coming from the patients' reports to some degree.

Delphi technique is a method to quantify a qualitative description, which means it can synthesize the opinions from many experts in a scientific way and therefore give a reasonable prediction about things. Delphi technique asks for, collects and counts individual opinions and judgments by distributing questionnaires, so as to get comparatively unanimous opinions on certain issues.

Objectives

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat certain symptoms above and there are no relevant instructions. This study

is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine shows the best effect.

Methods/Design

A multicenter randomized clinical trial is conducted. A flowchart of the study protocol is shown in Fig.1.

Inclusion criteria

1. Patients ages 30 to 65 years old.

2. The stroke should be the first incidence.

3. Diagnosis of unilateral, non-recurring, subacute stroke of ischemic and lacunar type, as defined by the International Classification of Diseases (ICD-10) through computed omography or magnetic resonance imaging conducted by neurologists.

4. TCM pattern diagnosis of stroke in meridian syndrome.

5. Patients should have a score between 6 and12 of National Institutes of Health Stroke Scale (NIHSS).

6. After injury from four weeks to eight weeks.

7. Provision of signed informed consent.

8. The above inclusion criteria will be applied to the experimental group and the control group.

Exclusion criteria

1. Patients have a history of stroke.

2. Known history of allergy or suspected allergy to the medicines used in the study.

3. Patients suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders.

4. Patients with other complications should not be selected in the trial as adjudged by the recruiting personnel.

5. Uncontrolled NYHA class III hypertension (systolic blood pressure ⩾180 mmHg and/or diastolic blood pressure ⩾110 mmHg).

6. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene, or peripheral neuropathy).

7. Liver function impairment with the value of ALT or AST over 1.5-fold the upper limit of normal range.

8. Renal dysfunction with the value of serum creatinine over 1.5-fold the upper limit of normal range.

9. Patients with active peptic ulcers or other hemorrhagic diseases.

10. Participation in other clinical trials, either currently or within the past 90 days.

Treatment allocation and Patient grouping

This study will be carried out in real conditions under the guideline of CER theory. The patients will be voluntarily chosen and well informed about their therapy. The patients of Group D will be well informed and voluntarily agree that they will only have basic treatments without using CPMs.

Treatment plan

(1)Basic treatment

The intervention program mainly takes China's Guidelines of Cerebrovascular Disease Prevention and Control and the consensus of foreign experts for reference. It considers all the risk factors of apoplexy into strict control. The program involves:

(a) Antiplatelet drug: aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines are chosen according to the cause and the order of severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(2) The final treatment plans:

The treatment plan for group A(TPGA): ①basic treatment +②Naoxuekang capsule (NXG).

The treatment plan for group B(TPGB): ①basic treatment +②Xinnaoshutong capsule (XNST).

The treatment plan for group C(TPGC): ①basic treatment +②Xuesetong capsule(XST).

The treatment plan for group D(TPGD): ①basic treatment.

The dosage and method of CPMs will follow the doctor's advice.

(3) Participant timeline

A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (30 days). A total of three follow-up points will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±1, and the third visit is on day 60±1.

Patient grouping

Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 360 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be in balance, and will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level.

(1) Patients will be divided into different groups according to their therapeutic needs and willingness (urgent symptom). Each group will have 120 patients. The patients whose urgent symptom is hemiplegia will be assigned to group H. The patients whose urgent symptom is dysphasia will be assigned to group D. The patients whose urgent symptom is facial paralysis will be assigned to group F.

(2) Patients with the same urgent symptom will be equally divided into group A, B, C and D. In each of the 4 groups they will be treated with a different treatment plans and the curative effects will be recorded. For

example, patients with hemiplegia as their urgent symptom will be treated with plan A in Group HA, while patients with hemiplegia as their urgent symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD, and each group contains 30 patients. The Table 1 shows the details as following:

Table 1: Groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure the same observation mode is kept between the experimental group and the control group. This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor is able to ensure an accurate assessment of the patient's symptoms, who is an expert in this field with doctor's experience over ten years. The questionnaire of WHOQOL-BREF and NIHSS of all the patients will be recorded by this doctor at the beginning of experiment, on the 30th and the 60th day.

(2) Evaluation Criteria

In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that the outcomes can represent the wills of the patients and clinicians, which meets the characteristic of comparative effectiveness research. The each index is designed as a questionnaire with four answers including “very important”, “important”, “average/ not very important” and “not important”. Each expert

judges the index system according to the four answers.

The formula is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N \quad \ldots\ldots(1)$$

DWi – the average value of the importance of the index i (i = w, n)

aij—the grade value of the index i;

j — the grade ordinal;

N— the number of the experts;

DW_W in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DW_N in eq. 2 and eq. 3indicates the weight of NIHSS.

(3)The final curative effects

The effectiveness of each index is evaluated by comparing it before and after the treatment. In this study, W_0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, W_1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W_2 in eq. 3 is the value of WHOQOL-BREF after follow up. N_0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N_1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N_2 in eq. 3 is the value of NIHSS after follow up.

The final curative effects can be figured out as

$$W_1 * DW_W + N_1 * DW_N - (W_0 * DW_W + N_0 * DW_N) \quad \ldots\ldots (2)$$

The curative effects after follow up can be figured out as

$$W_2 * DW_W + N_2 * DW_N - (W_0 * DW_W + N_0 * DW_N) \quad \ldots\ldots (3)$$

Sample size

Sample size in this study is based on the results of a trial and the recommendation of acupuncture specialists in previous reports [19].The method is under the hypothesis that the NIHSS score difference between the

NXG group and Placebo group before and after therapy is 4.5, with standard deviation of 4. Considering a 20% drop-out rate with type 1 error of 0.05 and a power of 90%, the total sample size needs 360 patients in total and 90 patients in each of the four groups.

Statistical analysis

General information, including patient's name, gender, age, weight, height, based diseases, type of symptom, accompanying symptom, education level and other basic information are firstly recorded and assessed after eligibility screening to ensure balanced baseline values. In addition, baseline data will be analyzed through an independent-test, analysis of variance and the $\chi 2$ test to check whether the randomization has resulted in equal distributions of the known confounding factors, such as age, sex, BMI, based diseases, type of symptom, accompanying symptom and education level. In case of incomparability, baseline-adjusted methods will be used. If the evaluation results indicate that the baseline data of two or more groups are not consistent, which means there probably are some confounding factors that may affect the results. According to the confounding factors types, any of the following analysis method can be chosen. The data will be analyzed by two-ways ANOVA using SAS9.1software package when the confounding factors type is classification or counting type. A logistic regression test or Cox proportional hazards regression model will be used when there are many confounding factors. The above method can be adopted to well observe the real effect of the intervention on the premise of balancing multiple confounding factors.

The evaluation result will be analyzed with the method of intention-to-treat analysis (ITT). The ITT analysis method makes the conclusions more reliable, which prevents the cases with poor effect in the final analysis from being excluded and therefore increases the comparability between the two groups. The loss of data will be conducted according to the last observation carried forward principle.

In this study, data analysis will be finished by researchers who do not participate into the experiment and clinical decision making, which make sure that the bias caused by the subjective factors from the researchers

can be eliminated.

The incidence of adverse events/safety analysis

Adverse events (AEs) and adverse drug reactions (ADRs) will be conducted and reported throughout this study. Furthermore, serious AEs or ADRs appearing during of the trial need to be informed to the person-in-charge of the project and the ethics committee. The incidence of AEs and ADRs is compared between various groups using the $\chi 2$ test with the level of significance set at $P < 0.05$.

Randomization, blinding and allocation concealment

Randomization of the trial patients will be finished using an independent data center using an interactive voice response system. The test medicine will be coded firstly, and then put in indistinguishable containers by specially assigned personnel. And this person will not participate in this trial. In addition, medicine assignments will be located in opaque envelopes, which were kept confidential by the trial management board. Thus, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.

Discussion

The critical task of translational medicine in TCM is to translate the achievements of medical research into clinical practice, so as to establish a series of clinical diagnosis and treatment technical standards, guidelines and/or pathway which is scientific, generalizable and acceptable to both TCM and western medicine practitioners [20]. A clear identification of the curative effect on symptoms is easier to understand by people who don't know much about TCM, which makes it easier for CPMs to be accepted by the whole world.

One of the advantages of CPM is to improve patients' health condition completely. This study gives a comprehensive evaluation on CPMs from the aspects of both clinical index and patients' quality of life. Index weighting ensures that the choice of the medicine is patient-oriented. As the scale used in the study is an international standardized one and the indexes of the scale are fixed, the result avoids the randomness that

exists in the PRO directly coming from the patient's report. Using Delphi techniques to weights the scales ensures the credibility, the validity and the structure of the international standardized scales.

In this study, the following measures will be taken to prevent bias. To avoid evaluator or rater bias, doctors who are assigned to assess the symptoms and record evaluation results will not take part in clinical decision making, and the researchers who analyze data do not participate into the experiment and clinical decision making either. To avoid performance bias, a long enough observation period will be maintained to make sure that the curative effect appears. Doctor A will be assigned to assess the symptoms and record evaluation results of all volunteers to make sure the same observation mode is kept both in the experimental group and the control group. The scales of WHOQOL-BREF and NIHSS of all the patients will be recorded by Doctor A at the beginning of experiment, on the 30th and the 60th day. To avoid attrition bias, the evaluation result will be analyzed by the method of intention to treat analysis (ITT). The loss of data will be conducted according to the last observation carried forward principle. To avoid selection bias, the number of the volunteers recruited in each hospital should be in balance, and the volunteers will be divided into the experiment group and control group. Strict inclusion criteria and exclusion criteria will be applied to both the experiment and the control group. To avoid unpredictable bias, baseline date will be analyzed and adjusted. Two-ways ANOVA, logistic regression test or Cox proportional hazards regression model will be adopted to well observe the true effect of the intervention on the premise of balancing multiple confounding factors.

Trial status

Currently patients are being recruited for the trial.

Ethical Approval and Consent to participate

This study has been approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20170007).

All participating patients need to sign informed consent, and the researcher explains the procedures and the objectives to be used in research, which includes detailed methods to be used, the risks and benefits, and stating the possibility of inclusion in a control or experimental group.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that no conflict of interest exists.

Funding

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Authors' contributions

Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN is in charge of all statistical works of the trial. XIA Q and Chen B helped conduct the survey. All authors have carefully read and approved the final manuscript.

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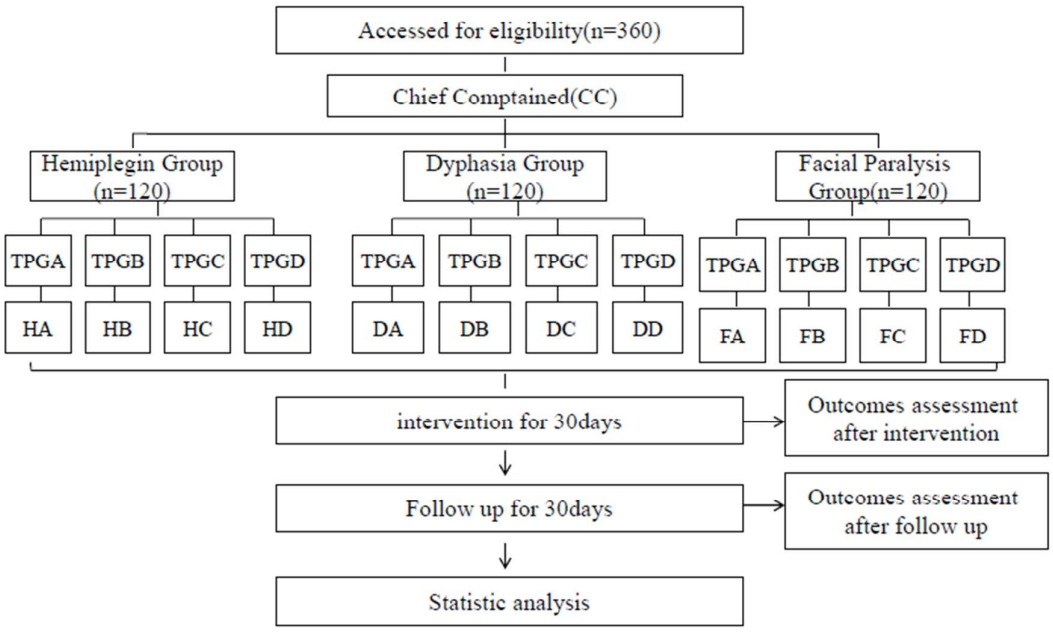
Figure/ Table Captions

Fig.1 A flowchart of the study protocol

Table 1 Groups divided according to main symptoms and treatment plans



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

Section/item	Item No	Description
Administrative information		
Title(P1L1)	1	Identify Characteristics of Similar Chinese Patent Medicine for Post-Stroke Based on Comparative Effectiveness Research (CER): Study Protocol for a randomized Controlled Trial
Trial registration (P3L1)	2a	Chinese clinical trials register ChiCTR-IOR-17010397.
	2b	Please retrieve the trial registration data of this study at this site http://www.chictr.org.cn/searchproj.aspx
Protocol version	3	Version: 81202849-2.1
Funding(P14L19)	4	The study is funded by the National Natural Science Foundation of China (No.81202849) and Tianjin 131 Talent of second levels （ZX160123）.
Roles and responsibilities (P14L14)	5a	Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN in charge of all statistical works of trial. XIA Q and Chen B helped conduct the survey. All authors carefully read and approved the final manuscript.
(P14L22)	5b	Huiling Chen: chen.huiling@163.com 1 School of Pharmaceutical Science and Technology, Tianjin University, 72 Weijin Road, Nankai District, Tianjin 300072, China; 2 TianJin University of Traditional Chinese Medicine；312 Anshanxi Road, Nankai District, Tianjin 300193, China.
	5c	Sponsor designed this protocol, prepared the draft and is responsible for the selection of research units, researchers and drug resources. The costs of publishing article, buying drugs and so on are provided by the funders.

(not appear in the article)	5d	Coordinating Center: Four sub-centers are responsible for collecting cases and assuring quality. Steering Committee: be responsible for the top-level design, guarantee the test goes smoothly. End Point Adjudication Committee: to assess the outcome event, to judge fall off and withdrawal cases. Data Management Team: be responsible for the data management, including data entry, verification, lock library and exporting.

Introduction

Background and rationale (P2L2)	6a	The main symptoms in stroke convalescent period include hemiplegia, dysphasia and facial paralysis. In China, a great number of patients in stroke convalescent period prefer to take Chinese patent medicines (CPM) to relieve the above symptoms, among which Naoxuekang capsule (NXG), Xinnaoshutong capsule (XNST) and Xuesetong capsule (XST) are frequently used. However, as the instructions of these three CPMs indicate similar functions based on the syndrome theory, it is hard to decide which one is the best choice for certain symptoms mentioned above. This study aims to find a new method to distinguish which CPM is the best choice for certain symptoms mentioned above, and finally establishes a most effective method to differentiate the CPMs with similar effects from the perspective of relieving patients' symptoms.
(P3L21)	6b	Naoxuekang capsule (NXG), Xinnaoshutong capsule (XNST) and Xuesetong capsule(XST) are three Chinese patent medicines that have similar curative effects and are used a lot in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure.
Objectives (P5L22)	7	The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat certain symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine shows the best effect.
Trial design (P6L5)	8	In this study, a multicenter randomized clinical trial is conducted.

Methods: Participants, interventions, and outcomes

Study setting (P8L12)	9	We will prepare to collect cases from the First Affiliated hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang hospital of TCM in China.

Eligibility criteria (P6L7)	10	● Inclusion criteria 1. Patients ages 30 to 65 years old; 2. The stroke should be the first incidence; 3. Diagnosis of unilateral, non-recurring, subacute stroke of ischemic and lacunar type, as defined by the International Classification of Diseases (ICD-10) through computed omography or magnetic resonance imaging conducted by neurologists; 4. TCM pattern diagnosis of stroke in meridian syndrome; 5. Patients should have a National Institutes of Health Stroke Scale (NIHSS) score between 6and12; 6. After injury from four weeks to eight weeks; 7. Provision of signed informed consent; 8. The above inclusion criteria will be applied to the experimental group and the control group. ● Exclusion criteria 1. Patients have a history of stroke; 2. Known history of allergy or suspected allergy to the study drug. 3. Patients suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders; 4. Uncontrolled NYHA class III hypertension (systolic blood pressure >=180 mmHg and/or diastolic blood pressure >=110 mmHg); 5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., peripheral neuropathy, or diabetic gangrene); 6. Liver function impairment with the value of alanine aminotransferase (ALT) or aspartate aminotransaminase (AST) over 1.5-fold the upper limit of normal range; 7. Renal dysfunction with the value of serum creatinine over 1.5-fold the upper limit of normal range; 8. Participation in another clinical trial, either currently or within the past 3 months; 9. Presence of active peptic ulcers and other hemorrhagic diseases; 10. Patients with other complications who should not be included in the trial as adjudged by the recruiting personnel.

Interventions (P7L14) 11a

Treatment plan

(1)Basic treatment

The intervention program mainly takes China's Guidelines of Cerebrovascular Disease Prevention and Control and the consensus of foreign experts for reference. It puts all the risk factors of apoplexy into strict control. The program involves:

(a) Antiplatelet drug: aspirin, taken as prescribed.

(b)Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines chosen according to the cause and the order of severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d)Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(2)The final treatment plans:

The treatment plan for group A(TPGA): ①basic treatment +②Naoxuekang capsule (NXG).

The treatment plan for group B(TPGB): ①basic treatment +②Xinnaoshutong capsule (XNST).

The treatment plan for group C(TPGC): ①basic treatment +②Xuesetong capsule(XST).

The treatment plan for group D(TPGD): ①basic treatment.

The dosage and method of CPM follow the doctor's advice.

Patient grouping

360 cases are going to be collected according to the plan. (1) Patients will be divided into different groups according to their Chief Complaied (CC) symptoms. Each group will have 120 cases. The patients whose CC is hemiplegia go to group H. The patients whose CC is dysphasia go to group D. The patients whose CC is facial paralysis go to group F.

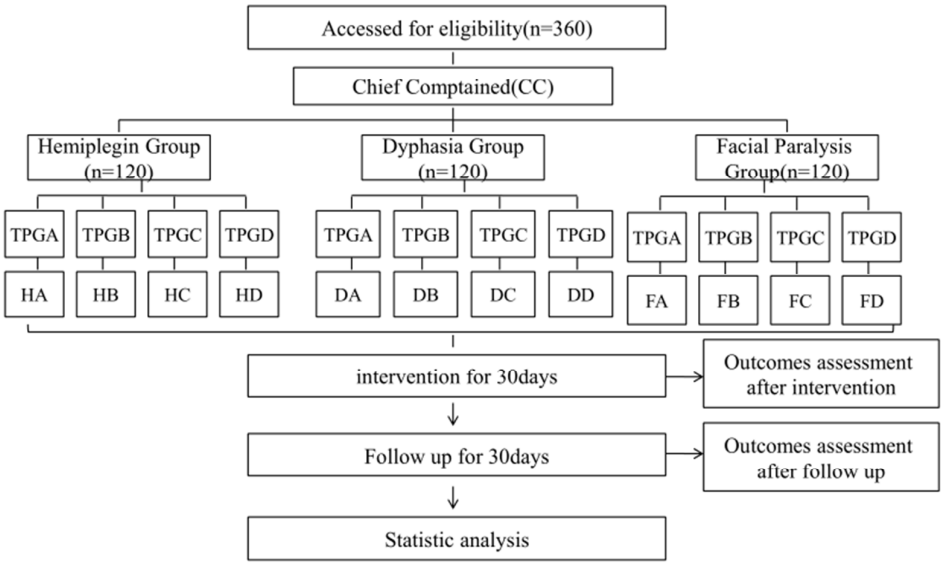
(2) Patients with the same main symptom will be equally divided into group A, B, C and D. In each of the 4 groups they will be treated with a different treatment plans and the curative effects will be observed. For example, patients who have hemiplegia as their main symptom and will be treated with plan A is in Group HA, while patients who have hemiplegia as their chief complained and will be treated with plan B is in Group HB. So in the end there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD. In each group there are 20 patients. The table is as follows:

Table 1: groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

(not appear in the article)	11b	Interventions for a given trial participant will be discontinued if the following situations occurred: ● Patients withdraw of their own accord for any reason; ● Serious adverse event occurred during trial; ● Major mistakes or serious deviations are identified in clinical trial protocol in the process of execution (though the plan is good), making it difficult to evaluate the efficacy of the drug; Trial is canceled by the authority.
(not appear in the article)	11c	**Compliance of investigators** Before the trial, all investigators must be trained as required by the trial information and technical requirements. Prime investigator is responsible for examining the case inclusion criteria of their units, deciding the end point and adverse events, handling SAE, controlling the trial quality of their own units, and confirming the completion of trial. **Compliance of subjects** Independent Data Monitor Committee (IDMC) made up of clinical experts, statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial; subject will receive trial drugs, transportation fee and necessary healthcare instructions(diet, mental adjustment)for free; subjects are required to maintain appropriate physical activities, control daily exercises; the dosage and remnant amount of drug shall be recorded authentically, drug counting method is used to monitor the compliance of subjects. **Monitoring** Clinical research associates are required to monitor various units on a regular and incessant basis; CRA shall give rigid examination of CRF to ensure consistency with the original data, and can trace to the source or directly visit the subjects when necessary; the CRA shall identify and feed back problems found in monitoring timely and transmit the guiding opinions of experts to the investigators within the shortest time. Relevant concomitant care and interventions that are permitted or prohibited during the trial
	11d	During the test, Chinese patent medicine for activating blood circulation and removing stasis and compounded Chinese medicine prescription will be banned from using.
Outcomes (P10L10)	12	In this research, we use WHOQOL and NIHSS and get their weight with DELPHI. The comprehensive score is taken as the final curative effects, which is named Comprehensive recovery index of stroke rehabilitation（CRST）in this study. The final curative effects can be figured out as W_1* DW_W+N_1* DW_N- (W_0* DW_W+ N_0* DW_N). The curative effects after follow up can be figured out as W_2* DW_W+N_2* DW_N- (W_0* DW_W+ N_0* DW_N).

Participant timeline (P8L7) (P6L5)	13	This study comprises two stages: the first treatment (30 days) and follow up (30 days). A total of three follow-up points are arranged in this trial: the first visit is day 0 after enrollment; the second visit is day 30±1, and the third visit is day 60±1.(Figure 1)



Sample size (P10L12)	14	Sample size in this study has been based on the results of a trial and the recommendation of acupuncture specialists in previous reports. The method is under the hypothesis that the HHISS score difference between the NXG group and Placebo group before and after therapy is 4.5, with standard deviation of 4. Considering a 20% dropout rate with type 1 error of 0.05 and a power of 90%, the total sample size needs 360 patients and 90 patients per four groups.
Recruitment (P8L18)	15	Six months prior to the trial, 360 cases qualified for inclusion are gathered from 4 hospitals of Tianjin City; basic data of the patients, including name, sex, age, type of symptom, contact, is registered. Patients will be divided into different groups according to their therapeutic needs and willingness (urgent symptom). Each group will have 120 patients. The patients whose urgent symptom is hemiplegia will be assigned to group H. The patients whose urgent symptom is dysphasia will be assigned to group D. The patients whose urgent symptom is facial paralysis will be assigned to group F.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation(P 12L13)	16a	Randomization of the trial patients will be finished using an independent data center using an interactive voice response system. In this study, Randomized block design is adopted, and urgent symptom is the group factors.

Allocation concealment (P12L14) mechanism	16b	A specially assigned drug administrator is responsible for the distribution of random numbers and drugs who will not participate in other procedures in the trial. A computer program is performed to obtain the random number table. When eligible patients were recruited, the doctor applied to the drug administrator for a patient's random number. The drug administrator informs the clinician patient random number, and give out the corresponding drug to the patient. Thus, the patients, doctors, trial coordinators, outcome assessors and statisticians will be blinded to against the risks of bias.
Implementation(not appear in the article)	16c	Third-party statisticians will product the allocation sequence. Physicians will enroll participants, and clinical research assistants will assign participants to interventions.
Blinding (masking) (P12L15)	17a	The volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.
(not appear in the article)	17b	If what patients received must be known in case of emergencies or rescue necessary for patients, persons-in-charge of the participating units shall immediately report to CRA and major investigators, and unblinding can be performed only upon their approval. Once the allocation is unblinded, the operation and record-taking must observe the trial requirements.

Methods: Data collection, management, and analysis

Data collection methods (not appear in the article) 18a

Items	Visit 1 0 day	2 30±1 days	3 60±1 days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical, treatment and allergies	√		
Taking drugs on current	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF		√	√
NIHSS		√	√
CRST		√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

18b Clinical research associates are required to monitor various units on a regular and incessant basis.

Data management (not appear in the article) 19

- Management Software

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

- Data recording

All data of the trial are subject to remote recording. Investigators will enter relevant data by logging on the internet, such a pattern contributes to upgrading quality and efficiency of clinical study.

- Data examination

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

- Data exporting

After the trial, data administrator will export the data confirmed correct from OC system as demanded by the statistician, and will be provided to the statistical analysts in the form of data interexchange code, statistical analysts will extract relevant data from the database according to the code and program for statistical analysis.

Statistical methods (P11L4)	20a	General information, including patient's gender, age are firstly recorded and assessed after eligibility screening to ensure balanced baseline values. In addition, baseline data will be analyzed through an independent *t*-test, analysis of variance and the χ^2 test to check if the randomization has resulted in equal distributions of known confounding factors, such as age, sex, age, BMI, based diseases, type of symptom, accompanying symptom, education level. In case of incomparability, baseline-adjusted methods will be used. If the evaluation results indicate that the baseline data of the two or more groups are not consistent, that is, there probably exist some confounding factors that may affect the results. According to the confounding factors types, we can choose the following analysis method . (1) The data will be analyzed by two-ways ANOVA using SAS9.1software package when the confounding factors type is Classification or counting type. (2)A logistic regression test or Cox proportional hazards regression model can be use when there are many confounding factors. The evaluation result will adopt the method of intention to treat analysis（ITT）. The ITT analysis method makes the conclusions more reliable, which prevent the cases with poor effect in the final analysis to be excluded, thus increasing the comparability between the two groups. The loss of data will be conducted according to the last observation carried forward principle.
	20b	Not Applicable
(not appear in the article)	20c	Good compliance indicates the drug actually taken equals 80 to 120 percent of the required dosage. Missing data or the data of non-adherence patients will be not included in the statistical analysis.

Methods: Monitoring

Data monitoring (not appear in the article)	21a	Independent Data Monitor Committee (IDMC) made up of clinical experts, statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial.
(P11L5)	21b	General information, including patient's gender, age are firstly recorded and assessed after eligibility screening to ensure balanced baseline values. In addition, baseline data will be analyzed through an independent *t*-test, analysis of variance and the χ^2 test to check if the randomization has resulted in equal distributions of known confounding factors, such as age, sex, age, BMI, based diseases, type of symptom, accompanying symptom, education level. In case of incomparability, baseline-adjusted methods will be used. Patients accord with termination standards will be terminated.

Harms (P12L2) 22 Standard operating procedures (SOP) for the management of adverse events must be worked out in order to guarantee adverse events under control. Clinical research associates are required to be involved in AE management and SOP drafting, so that they can manage adverse events during clinical test in a scientific and standardized manner.

Recording of AE

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

Rating of AE Severity

Table3: Severity grading and definition

Severity Grading	Definition
Mild	Short-lasting and mild symptoms, no pain caused to patients, bearable, daily activities not affected
Moderate	Overt symptoms but bearable, daily activities affected
Severe	Severe symptoms, daily activities seriously affected

Deciding the correlation between AE and drug

The correlation between AE and drug is estimated according to 5-grade criteria:

Table4: Determination of correlation between AE and Drug

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

(Note: “＋” means YES;“－”means NO; “？”means unclear situation)

Analysis of AE

X^2 test is used to compare the incidence of adverse events of drug A and B and the correlation between AE and drug is analyzed.

Auditing (not appear in the article) 23 Auditors are required to audit trial conduct by visiting or by documents in a mid-stage and the end of the study, and the process will be independent from investigators and the sponsor.

Ethics and dissemination

Research ethics approval (P13L21) 24 This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20160007).

Protocol amendments (not appear in the article)	25	If the protocol needs to be modified, we will apply for ethical review again.
Consent or assent (P14L1)	26a	Patients, immediate family member or supervisors will obtain informed consent.
	26b	Not Applicable
Confidentiality (not appear in the article)	27	The study established the principle that all information related to patient is confidential, and their name will not appear on the records.
Declaration of interests (P14L8)	28	The authors declare that they have no competing interests.
Access to data(not appear in the article)	29	Data administrators and statisticians have the access to the final trial data set.
Ancillary and post-trial care(not appear in the article)	30	Patients who suffer harm from trial participation will been treated and cared.
Dissemination policy (not appear in the article)	31a	The results will be submitted to a international journal. When the trial has been completed, we will tell participants the conclusion and give some advice for rational drug use. 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
	31b	When published, the use of any content in the article must be through the magazine and the authors' permission.
	31c	The protocol is to be published in open access journal and the researchers can download it through the network.
Appendices		
Informed consent materials(not appear in the article)	32	Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens (not appear in the article)	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

*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.

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Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial

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Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial

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Abstract

Introduction: Hemiplegia, dysphasia and facial paralysis are the three main symptoms in stroke convalescent period. In China, a great number of patients in stroke convalescent period prefer to take Chinese patent medicines (CPM) to relieve the symptoms above, among which Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST) are frequently used. However, as the instructions of these three CPMs indicate similar functions based on the syndrome theory, it is hard to decide which one is the best choice for each of the symptoms mentioned above. This study aims to find a new method to distinguish which CPM is the best choice for each of the symptoms mentioned above, and finally establishes an effective method to differentiate the CPMs with similar effects from the perspective of the remission of patients' symptoms.

Methods/ Design: The study is based on the theory of comparative effectiveness research (CER). Three patients groups, each with 120 people, will be recruited. The most main symptom of each group is respectively hemiplegia, dysphasia and facial paralysis. Each group will be randomly and equally divided into 4 smaller groups and they will respectively have treatment with NXK, XNST, XST and no CPM. The treatment will last for 30 days, and follow up 180 days. The outcome measurement is based on the patient-centered evaluation theory. The Delphi techniques will be used to assign weight to the index value of NIHSS scale and WHOQOL-BREF scale. The weighted index value will be computed as the final measurement index of the outcome, which is named Comprehensive recovery index of stroke rehabilitation (CRST) in this study.

Discussion: This study distinguishes the orientation of different CPMs from the aspect of symptoms and establishes an effective evaluation method which fits Chinese patent medicines' effectiveness in synthetic regulation. This study will differentiate the effectiveness of NXK, XNST and XST from the perspective of the remission of patients' symptoms. This study provides a methodological foundation for the effective evaluation of other CPMs or treatment plans. Meanwhile, it also explores the usage of CER in TCM.

Trial registration: This trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-17010397). The date of registration was 11st Jan, 2017.

Keywords: Stroke, Chinese Patent Medicine, Comparative Effectiveness Research

Strengths and limitations of this study

- A multicentric, prospective and randomized controlled trial.
- This study explores the usage of CER in TCM.
- This study distinguishes the orientation of different CPMs from the aspect of symptoms.
- The evaluation of a patient's recovery involves both the quality of life and clinical indexes.
- Using Delphi techniques to assign weight to the scale indexes.
- The sample size is not large enough due to funding constraints (n=360, each group=30).

Background

The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have shown that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three CPMs have come onto the market for many years and have got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, the main ingredient

of which is leech, is proved to be safe, effective and with less adverse reactions by clinical observation [7]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and people who are bleeding [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, the main ingredient of which is Steroidal saponins of Tribulus terrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of Peoples Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously [11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, the main ingredient of which is Panax Notoginseng Saponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14].

Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

The application feasibility of comparative effectiveness research in the evaluation of CPM

The concept of comparative effectiveness research (CER) was initiated in the 1990s by Mark Boutin, the deputy executive president and chief operating officer of the US National Health Council [15]. The Agency for Healthcare Research and Quality (AHRQ) defined comparative effectiveness research as: "Comparative

effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options" [16]. The evidence was generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care [17].

In the following years, CER was introduced into the field of clinical research in a number of countries [18]. CER was introduced into TCM research at the sixth annual meeting of the International Society of Complementary Medicine Research by Claudia M Witt (Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany) in May 2011 [19]. The outcome of comparative effectiveness research focuses on the problems that patients care and want to solve mostly [20]. It is more patient-oriented, which means it respects the patients' will, cares about both the quality of their lives and psychological functions, while fitting the TCM clinical practice and showing the validity of the results.

CER is concerned with answering questions about effectiveness rather than efficacy of interventions, which implies the usefulness of various study designs. Non-randomized or observational studies, rather than randomized controlled trials (RCTs), may answer effectiveness questions better, even though well-known threats to validity exist for the former [21].

Effectiveness evaluation based on patient-oriented theory

Patients in stroke convalescent period suffer not only from various clinical symptoms but also the decline of the ability for daily activities and the lower quality of life. According to the study, the evaluation of a patient's recovery should involve both the quality of life, including mental state, physical condition, psychological condition and social environment, and clinical indexes.

Quality of life: According to WHOQOL-BREF, quality of life is evaluated by one's mental state, psychological state and physical state, etc. [22-23]. **Clinical indexes:** The physiological indexes which show the degree of nervous functional defects can be evaluated by National Institutes of Health Stroke Scale

(NIHSS).

In this research, WHOQOL-BREF and NIHSS are used to assess the curative effect and get their weight with Delphi. The comprehensive score is taken as the final curative effect. In this way, it avoids the randomness of the PRO (Patient Report Outcome) [24] coming from the patients' reports to some degree.

Delphi technique is a method to quantify a qualitative description, which means it can synthesize the opinions from many experts in a scientific way and therefore give a reasonable prediction about things. Delphi technique asks for, collects and counts individual opinions and judgments by distributing questionnaires, so as to get comparatively unanimous opinions on certain issues.

Objectives

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.

Methods/Design

In this multi-centered and double-blind clinical trial, stratified randomization is used for the grouping of the patients, which is according to their most main symptoms (Hemiplegia, Dysphasia, Facial Paralysis). A flowchart of the study protocol is shown in Fig.1.

Inclusion criteria

1. Patients ages from 30 to 65 years old.

2. It is the first time that the patient has a stroke.

3. Diagnosis of unilateral, non-recurring, subacute stroke of ischemic and lacunar type, as defined by the International Classification of Diseases (ICD-10) through computed omography or magnetic resonance

imaging conducted by neurologists.

4. TCM pattern diagnosis of stroke in meridian syndrome.

5. Patients should have a score between 6 and12 according to National Institutes of Health Stroke Scale (NIHSS).

6. After injury from four weeks to eight weeks.

7. Provision of signed informed consent.

8. The above inclusion criteria will be applied to the experimental group and the control group.

Exclusion criteria

1. Patients who have a history of stroke.

2. Patients with a known history of allergy or suspected allergy to the medicines used in the study.

3. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders.

4. Patients with other complications.

5. Uncontrolled NYHA class III hypertension (systolic blood pressure ⩾180 mmHg and/or diastolic blood pressure ⩾110 mmHg).

6. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene, or peripheral neuropathy).

7. Liver function impairment with the value of ALT or AST over 1.5-fold the upper limit of normal range.

8. Renal dysfunction with the value of serum creatinine over 1.5-fold the upper limit of normal range.

9. Patients with active peptic ulcers or other hemorrhagic diseases.

10. Patients who participate in other clinical trials, either currently or within the past 90 days.

Treatment plan

(1)Basic treatment

The intervention program mainly takes China's Guidelines of Cerebrovascular Disease Prevention and Control and the consensus of foreign experts for reference. It considers all the risk factors of apoplexy into strict control. The program involves:

(a) Antiplatelet drug: Aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(2) The final treatment plans:

The treatment plan for group A(TPGA): ①basic treatment +②Naoxuekang capsule (NXK).

The treatment plan for group B(TPGB): ①basic treatment +②Xinnaoshutong capsule (XNST).

The treatment plan for group C(TPGC): ①basic treatment +②Xuesaitong capsule(XST).

The treatment plan for group D(TPGD): ①basic treatment.

The dosage and method of CPMs will follow the doctor's advice.

(3) Participant timeline

A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (180 days). A total of three follow-up points will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±1, and the third visit is on day 240±1.

Patient grouping

Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 360 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients

recruited in each hospital should be in balance, and the patients will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level.

(1) Patients will be divided into different groups according to their main symptoms. Each group will have 120 patients. The patients whose main symptom is hemiplegia will be assigned to group H. The patients whose main symptom is dysphasia will be assigned to group D. The patients whose main symptom is facial paralysis will be assigned to group F.

(2) Patients with the same main symptom will be divided into group A, B, C and D both randomly and equally. Each of the 4 groups will be treated with a different treatment plans and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD, and each group contains 30 patients. The Table 1 shows the details as following:

Table 1: Groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure that the same observation mode is kept between the experimental group and the control group.

This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor, who is an expert in this field with clinical experience over ten years, is able to ensure an accurate assessment of the patient's symptoms. The questionnaire of WHOQOL-BREF and NIHSS of all the patients will be recorded by this doctor at the beginning of experiment, on the 30th and the 240th day.

(2) Evaluation Criteria

In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that the outcomes can represent the wills of the patients and clinicians, in which way it can meet the characteristic of comparative effectiveness research. Each index is designed as a questionnaire with four answers including “very important”, “important”, “average/ not very important” and “not important”. Each expert judges the index system according to the four answers.

The formula is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N \quad \cdots\cdots(1)$$

DWi – the average value of the importance of the index i (i = w, n)

aij—the grade value of the index i;

j — the grade ordinal;

N— the number of the experts;

DW_W in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DW_N in eq. 2 and eq. 3indicates the weight of NIHSS.

(3)The final curative effects

The effectiveness of each index is evaluated by comparing its value before and after the treatment. In this study, W_0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, W_1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W_2 in eq. 3 is the value of WHOQOL-BREF

after follow up. N_0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N_1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N_2 in eq. 3 is the value of NIHSS after follow up.

The final curative effects can be figured out as

$W_1* DW_W+N_1* DW_N-(W_0*DW_W+ N_0* DW_N)$…… (2)

The curative effects after follow up can be figured out as

$W_2* DW_W+N_2* DW_N-(W_0* DW_W+ N_0* DW_N)$……(3)

Sample size

The sample size in this study is based on the trial results in previous reports [25,26] and the recommendation of specialists. The σ_i of WHOQOL-BREF scale of the experimental groups before and after treatment are 1.1, 0.86 and 1.27, while the σ_i of WHOQOL-BREF scale of the placebo group is 0.79. The μ_i of WHOQOL-BREF scale of the experimental groups before and after treatment are 18.47, 18.6 and 18.74, while the μ_i of WHOQOL-BREF scale of the placebo group before and after treatment is19.36. According to the calculation, μ is 18.79, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 296 patients are needed in the trial, 74 patients for each group. The σ_i of NIHSS scale of the experimental groups before and after treatment are 1.27, 1.23 and 1.21, while the σ_i of NIHSS scale of the placebo group is 1.5. The μ_i of NIHSS scale of the experimental groups before and after treatment are 2.45, 1.85 and 1.75, while the μ_i of NIHSS scale of the placebo group before and after treatment is 2.95. According to the calculation, μ is 2.25, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 240 patients are needed in the trial, 60 patients for each group.

According to the calculation above and the recommendation of the specialists, 360 patients are collected in the trial, 90 patients for each group.

Statistical analysis

General information, including patient's name, gender, age, weight, height, based diseases, type of symptom, accompanying symptom, education level and other basic information are firstly recorded and assessed after the patient has passed eligibility screening to ensure balanced baseline values. In addition, baseline data will be analyzed through an independent-test, analysis of variance and the $\chi 2$ test to check whether the randomization has resulted in equal distributions of the known confounding factors, such as age, sex, BMI, based diseases, type of symptom, accompanying symptom and education level. In case of incomparability, baseline-adjusted methods will be used. If the evaluation results indicate that the baseline data of two or more groups are not consistent, it means there probably are some confounding factors that may affect the results. According to the confounding factors types, any of the following analysis methods can be chosen. The data will be analyzed by two-ways ANOVA using SAS9.1 software package when the confounding factors type is classification or counting type. A logistic regression test or Cox proportional hazards regression model will be used when there are many confounding factors. The above method(s) can be adopted to well observe the real effect of the intervention on the premise of balancing multiple confounding factors.

Mean and deviation are used for the statistical description of the measurement data. Analysis variance will be used, if the data are normally distributed, while rank test will be used in case that the data are not normally distributed or there is heterogeneity of variance. The comparison between the three experimental groups and the control group is based on the analysis variance of the repeated measurement data. If $P<0.05$, then it is confirmed that there is a statistical difference.

The evaluation result will be analyzed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.

In this study, data analysis will be finished by researchers who do not participate into the experiment and clinical decision making, which makes sure that the bias caused by the subjective factors from the researchers can be eliminated.

The incidence of adverse events/safety analysis

Adverse events (AEs) and adverse drug reactions (ADRs) will be conducted and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be informed to the person-in-charge of the project and the ethics committee. The incidence of AEs and ADRs is compared between various groups using the $\chi 2$ test with the level of significance set at $P < 0.05$.

Randomization, blinding and allocation concealment

Cases are assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the trial patients will be finished using an independent data center with an interactive voice response system, and the random number will be generated by this data center. Original copies of the blind codes are sealed in the lightproof envelope, one kept by major research unit and the other by the applicant of the trial and are not allowed to be opened before formal statistical analysis. If a patient was eligible, a patient number will be allocated by doctors. The patient numbers is just the serial numbers for labeling patients. The test medicine will be coded firstly, and then put in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be located in opaque envelopes and are kept confidential by the trial management board. Thus, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.

Discussion

The critical task of translational medicine in TCM is to translate the achievements of medical research into clinical practice, so as to establish a series of clinical diagnosis and treatment technical standards, guidelines

and/or pathway which is scientific, generalizable and acceptable to both TCM and western medicine practitioners [27]. A clear identification of the curative effect on symptoms is easier to understand by people who don't know much about TCM, which makes it easier for CPMs to be accepted by the whole world.

One of the advantages of CPM is to improve patients' health condition as a whole. This study gives a comprehensive evaluation on CPMs from the aspects of both clinical index and the quality of patient's life. Index weighting ensures that the choice of the medicine is patient-oriented. As the scale used in the study is an international standardized one and the indexes of the scale are fixed, the result avoids the randomness that exists in the PRO directly coming from the patient's report. Using Delphi techniques to weights the scales ensures the credibility, the validity and the structure of the international standardized scales.

In this study, the following measures will be taken to prevent bias. To avoid evaluator or rater bias, doctors who are assigned to assess the symptoms and record evaluation results will not take part in clinical decision making, nor do the researchers who analyze data. The latter ones don't participate into the experiment either. To avoid performance bias, a long enough observation period will be maintained to make sure that the curative effect appears. Doctor A will be assigned to assess the symptoms and record evaluation results of all volunteers to make sure the same observation mode is kept both in the experimental group and the control group. The scales of WHOQOL-BREF and NIHSS of all the patients will be recorded by Doctor A at the beginning of experiment, on the 30th and the 240th day. To avoid attrition bias, the evaluation result will be analyzed by the method of intention to treat analysis (ITT). The loss of data will be conducted according to the last observation carried forward principle. To avoid selection bias, the number of the volunteers recruited in each hospital should be in balance, and the volunteers will be divided into the experiment group and the control group. Strict inclusion criteria and exclusion criteria will be applied to both the experiment and the control group. To avoid unpredictable bias, baseline date will be analyzed and adjusted. Two-ways ANOVA, logistic regression test or Cox proportional hazards regression model will be adopted to well observe the true

effect of the intervention on the premise of balancing multiple confounding factors.

Trial status

Currently patients are being recruited for the trial.

Ethical Approval and Consent to participate

This study has been approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007).

All participating patients need to sign informed consent, and the researcher explains the procedures and the objectives to be used in research, which includes detailed methods to be used, the risks and benefits, and stating the possibility of inclusion in a control or experimental group.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that no conflict of interest exists.

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Authors' contributions

Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN is in charge of all statistical works of the trial. XIA Q and Chen B helped conduct the survey. All authors have carefully read and approved the final manuscript.

Acknowledgments

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Figure/ Table Captions

Fig.1 A flowchart of the study protocol

Table 1 Groups divided according to main symptoms and treatment plans

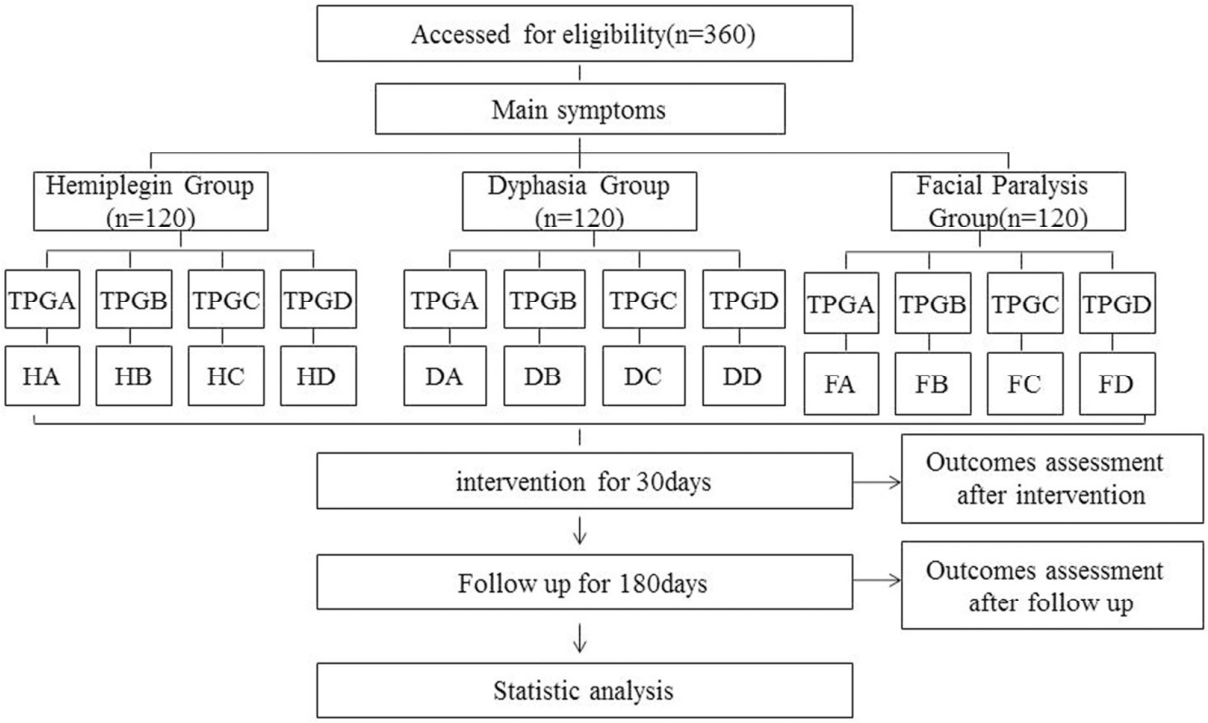
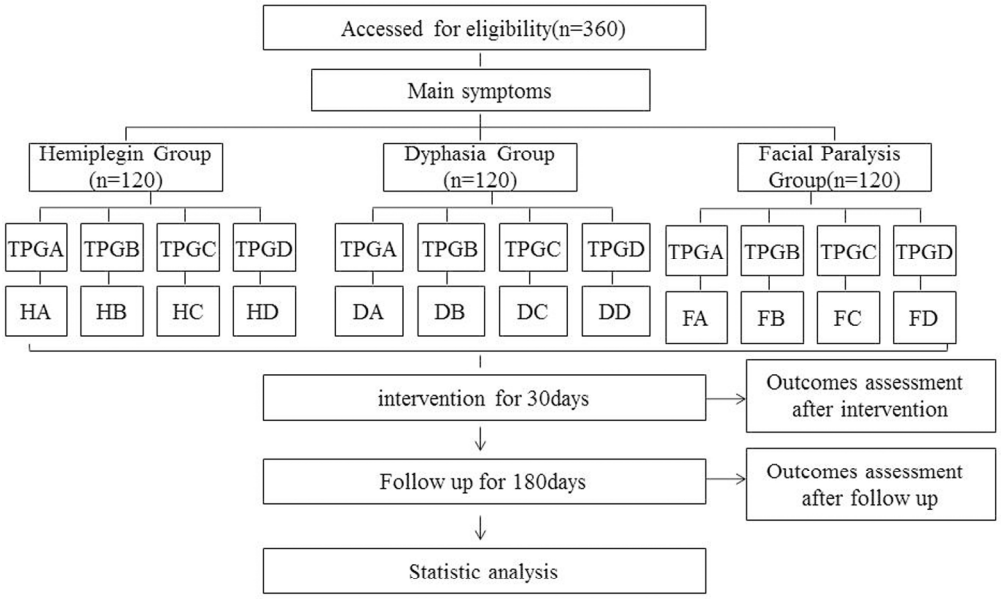


Fig.1 A flowchart of the study protocol

Table 1 Groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD



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

Section/item	Page and line Num-ber	Item No.	Description
Administrative information			
Title	P1L1	1	Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial
Trial registration	P3L2	2a	Chinese clinical trials register ChiCTR-IOR-17010397
		2b	Please retrieve the trial registration data of this study at this site http://www.chictr.org.cn/searchproj.aspx
Protocol version		3	Version: 81202849-2.1
Funding	P15L40	4	The study is funded by the National Natural Science Foundation of China (No.81202849) and Tianjin 131 Talent of second levels(ZX160123).
Roles and responsibilities	P15L45	5a	Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN in charge of all statistical works of trial. XIA Q and Chen B helped conduct the survey. All authors carefully read and approved the final manuscript.
	P1L8	5b	Huiling Chen: chen.huiling@163.com 1 School of Pharmaceutical Science and Technology, Tianjin University, 72 Weijin Road, Nankai District, Tianjin 300072, China; 2 TianJin University of Traditional Chinese Medicine；312 Anshanxi Road, Nankai District, Tianjin 300193, China.
	not appear in the article	5c	Sponsor designed this protocol, prepared the draft and is responsible for the selection of research units, researchers and drug resources. The costs of publishing article, buying drugs and so on are provided by the funders.

	not appear in the article	5d	Coordinating Center: Four sub-centers are responsible for collecting cases and assuring quality. Steering Committee: be responsible for the top-level design, guarantee the test goes smoothly. End Point Adjudication Committee: to assess the outcome event, to judge fall off and withdrawal cases. Data Management Team: be responsible for the data management, including data entry, verification, lock library and exporting.

Introduction

Background and rationale	P2L1	6a	Hemiplegia, dysphasia and facial paralysis are the three main symptoms in stroke convalescent period. In China, a great number of patients in stroke convalescent period prefer to take Chinese patent medicines (CPM) to relieve the symptoms above, among which Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesetong capsule (XST) are frequently used. However, as the instructions of these three CPMs indicate similar functions based on the syndrome theory, it is hard to decide which one is the best choice for each of the symptoms mentioned above. This study aims to find a new method to distinguish which CPM is the best choice for each of the symptoms mentioned above, and finally establishes an effective method to differentiate the CPMs with similar effects from the perspective of the remission of patients' symptoms.
	P4L28	6b	Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule(XST) are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure.
Objectives	P6L20	7	The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.
Trial design	P6L35	8	In this multi-centered clinical trial, stratified randomization is used for the grouping of the patients, which is according to their most urgent symptoms (Hemiplegia, Dysphasia, Facial Paralysis).

Methods: Participants, interventions, and outcomes

Study setting	P8L52	9	Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China.

Eligibility criteria	P6L45	10	● Inclusion criteria 1. Patients ages from 30 to 65 years old. 2. It is the first time that the patient has a stroke. 3. Diagnosis of unilateral, non-recurring, subacute stroke of ischemic and lacunar type, as defined by the International Classification of Diseases (ICD-10) through computed omography or magnetic resonance imaging conducted by neurologists. 4. TCM pattern diagnosis of stroke in meridian syndrome. 5. Patients should have a score between 6 and12 according to National Institutes of Health Stroke Scale (NIHSS). 6. After injury from four weeks to eight weeks. 7. Provision of signed informed consent. 8. The above inclusion criteria will be applied to the experimental group and the control group. ● Exclusion criteria 1. Patients who have a history of stroke. 2. Patients with an known history of allergy or suspected allergy to the medicines used in the study. 3. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders. 4. Patients with other complications. 5. Uncontrolled NYHA class III hypertension (systolic blood pressure ⩾ 180 mmHg and/or diastolic blood pressure ⩾110 mmHg). 6. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene, or peripheral neuropathy). 7. Liver function impairment with the value of ALT or AST over 1.5-fold the upper limit of normal range. 8. Renal dysfunction with the value of serum creatinine over 1.5-fold the upper limit of normal range. 9. Patients with active peptic ulcers or other hemorrhagic diseases. 10. Patients who participate in other clinical trials, either currently or within the past 90 days.

Interventions	P8L1	11a	**Treatment plan** **(1)Basic treatment** The intervention program mainly takes China's Guidelines of Cerebrovascular Disease Prevention and Control and the consensus of foreign experts for reference. It considers all the risk factors of apoplexy into strict control. The program involves: (a) Antiplatelet drug: Aspirin, taken as prescribed. (b) Blood fat control: Simvastatin, taken as prescribed. (c) Blood pressure control: medicines chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers. (d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control. (2) The final treatment plans: The treatment plan for group A(TPGA): ①basic treatment +②Naoxuekang capsule (NXK). The treatment plan for group B(TPGB): ①basic treatment +② Xinnaoshutong capsule (XNST). The treatment plan for group C(TPGC): ①basic treatment +②Xuesetong capsule(XST). The treatment plan for group D(TPGD): ①basic treatment. The dosage and method of CPMs will follow the doctor's advice. (3) Participant timeline A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (180 days). A total of three follow-up points will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±1, and the third visit is on day 240±1. Patient grouping Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 360 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be in balance, and the patients will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level. (1) Patients will be divided into different groups according to their main symptoms. Each group will have 120 patients. The patients whose main symptom is hemiplegia will be assigned to group H. The patients whose main symptom is dysphasia will be assigned to group D. The patients whose main symptom is facial paralysis will be assigned to group F. (2) Patients with the same main symptom will be divided into group A, B, C and D both randomly and equally. Each of the 4 groups will be treated with a different treatment plans and the curative effects will be

recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB.
Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD, and each group contains 30 patients. The Table 1 shows the details as following:

Table 1: groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

not appear in the article 11b

Interventions for a given trial participant will be discontinued if the following situations occurred:

- Patients withdraw of their own accord for any reason;
- Serious adverse event occurred during trial;
- Major mistakes or serious deviations are identified in clinical trial protocol in the process of execution (though the plan is good), making it difficult to evaluate the efficacy of the drug;
- Trial is canceled by the authority.

not appear in the article 11c

Compliance of investigators

Before the trial, all investigators must be trained as required by the trial information and technical requirements. Prime investigator is responsible for examining the case inclusion criteria of their units, deciding the end point and adverse events, handling SAE, controlling the trial quality of their own units, and confirming the completion of trial.

Compliance of subjects

Independent Data Monitor Committee (IDMC) made up of clinical experts statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial; subject will receive trial drugs, transportation fee and necessary healthcare instructions(diet, mental adjustment)for free; subjects are required to maintain appropriate physical activities, control daily exercises; the dosage and remnant amount of drug shall be recorded authentically, drug counting method is used to monitor the compliance of subjects.

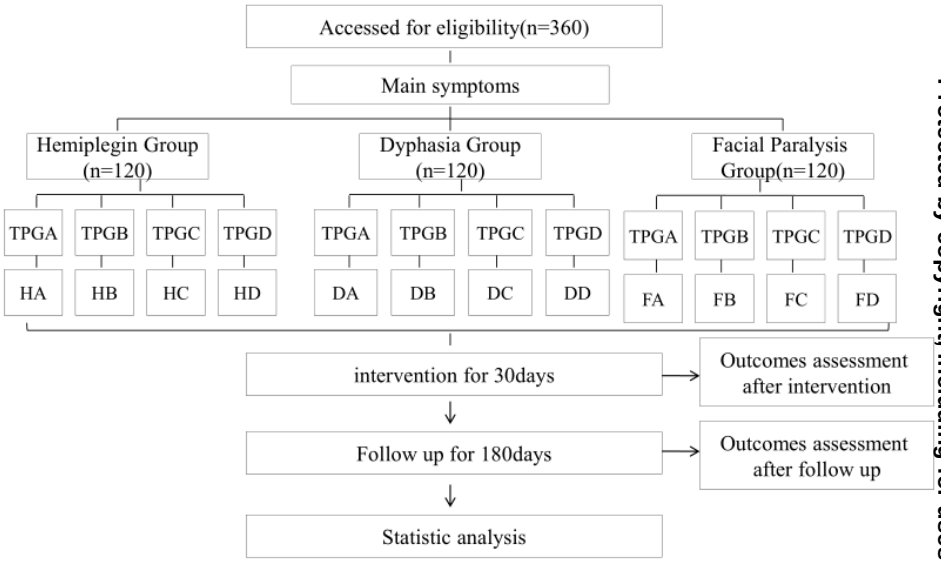
Monitoring

Clinical research associates are required to monitor various units on a regular and incessant basis; CRA shall give rigid examination of CRF to ensure consistency with the original data, and can trace to the source or directly visit the subjects when necessary; the CRA shall identify and feed back problems found in monitoring timely and transmit the guiding opinions of experts to the investigators within the shortest time.

Relevant concomitant care and interventions that are permitted or prohibited during the trial

	not appear in the article	11d	During the test, Chinese patent medicine for activating blood circulation and removing stasis and compounded Chinese medicine prescription will be banned from using.
Outcomes	P9L48	12	Effectiveness assessment (1) Assessment Expert One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure that the same observation mode is kept between the experimental group and the control group. This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor, who is an expert in this field with clinical experience over ten years, is able to ensure an accurate assessment of the patient's symptoms. The questionnaire of WHOQOL-BREF and NIHSS of all the patients will be recorded by this doctor at the beginning of experiment, on the 30th and the 240th day. (2) Evaluation Criteria In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that the outcomes can represent the wills of the patients and clinicians, in which way it can meet the characteristic of comparative effectiveness research. Each index is designed as a questionnaire with four answers including “very important”, “important”, “average/ not very important” and “not important”. Each expert judges the index system according to the four answers. The formula is as follows: ……(1) DWi – the average value of the importance of the index i (i = w, n) aij—the grade value of the index i; j — the grade ordinal; N— the number of the experts; DWW in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DWN in eq. 2 and eq. 3indicates the weight of NIHSS. (3)The final curative effects The effectiveness of each index is evaluated by comparing its value before and after the treatment. In this study, W0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, W1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W2 in eq. 3 is the value of WHOQOL-BREF after follow up. N0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N2 in eq. 3 is the value of NIHSS after follow up. The final curative effects can be figured out as W1* DWW+N1* DWN-(W0*DWW+ N0* DWN)…… (2) The curative effects after follow up can be figured out as W2* DWW+N2* DWN-(W0* DWW+ N0* DWN)……(3)

Participant timeline	P8L37 P21L1	13	A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (180 days). A total of three follow-up points will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±1, and the third visit is on day 240±1.(Figure 1)



Sample size	P11L18	14	The sample size in this study is based on the trial results in previous reports [25,26] and the recommendation of specialists. The σi of WHOQOL-BREF scale of the experimental groups before and after treatment are 1.1, 0.86 and 1.27, while the σi of WHOQOL-BREF scale of the placebo group is 0.79. The μi of WHOQOL-BREF scale of the experimental groups before and after treatment are 18.47, 18.6 and 18.74, while the μi of WHOQOL-BREF scale of the placebo group before and after treatment is19.36. According to the calculation, μ is 18.79, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 296 patients are needed in the trial, 74 patients for each group. The σi of NIHSS scale of the experimental groups before and after treatment are 1.27, 1.23 and 1.21, while the σi of NIHSS scale of the placebo group is 1.5. The μi of NIHSS scale of the experimental groups before and after treatment are 2.45, 1.85 and 1.75, while the μi of NIHSS scale of the placebo group before and after treatment is 2.95. According to the calculation, μ is 2.25, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 240 patients are needed in the trial, 60 patients for each group. According to the calculation above and the recommendation of the specialists, 360 patients are collected in the trial, 90 patients for each group.

Recruitment	P8L52	15	Six months prior to the trial, Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 360 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be in balance, and the patients will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level. (1) Patients will be divided into different groups according to their main symptoms. Each group will have 120 patients. The patients whose main symptom is hemiplegia will be assigned to group H. The patients whose main symptom is dysphasia will be assigned to group D. The patients whose main symptom is facial paralysis will be assigned to group F. (2) Patients with the same main symptom will be divided into group A, B, C and D both randomly and equally. Each of the 4 groups will be treated with a different treatment plans and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD, and each group contains 30 patients.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	P13L22	16a	Cases are assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the trial patients will be finished using an independent data center with an interactive voice response system, and the random number will be generated by this data center.
Allocation concealment mechanism	P13L30	16b	Original copies of the blind codes are sealed in the lightproof envelope, one kept by major research unit and the other by the applicant of the trial and are not allowed to be opened before formal statistical analysis. If a patient was eligible, a patient number will be allocated by doctors. The patient numbers is just the serial numbers for labeling patients.
Implementation	P13L28	16c	The random number will be generated by an independent data center. Physicians will enroll participants, and clinical research assistants will assign participants to interventions.

Blinding (masking)	P13L35	17a	If a patient was eligible, a patient number will be allocated by doctors. The patient numbers is just the serial numbers for labeling patients. The test medicine will be coded firstly, and then put in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be located in opaque envelopes and are kept confidential by the trial management board. Thus, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.
	not appear in the article	17b	If what patients received must be known in case of emergencies or rescue necessary for patients, persons-in-charge of the participating units shall immediately report to CRA and major investigators, and unblinding can be performed only upon their approval. Once the allocation is unblinded, the operation and record-taking must observe the trial requirements.

Methods: Data collection, management, and analysis

Data collection methods	not appear in the article	18a

Items	Visit 1 0 day	Visit 2 30±1 days	Visit 3 240±1 days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical, treatment and allergies	√		
Taking drugs on current	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF		√	√
NIHSS		√	√
CRST		√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

	not appear in the article	18b	Clinical research associates are required to monitor various units on a regular and incessant basis.

Data management	not appear in the article	19	• Management Software This trial plans to use Oracle Clinical (OC) software for unified data management, online data updating and tracing, and exercise dynamic and efficient management of clinical trial data at the same time with the support of the check function of the software. • Data recording All data of the trial are subject to remote recording. Investigators will enter relevant data by logging on the internet, such a pattern contributes to upgrading quality and efficiency of clinical study. • Data examination Data administrator performs logic check and automatic comparison of data information using the check function of OC software, check the result values inconsistent with the case report forms, and check one-by-one with the original case report form and make corrections, so as to ensure the data in the database consistent with the results of the case report form. This way enables traceability, accuracy, completeness and timeliness of data. • Data exporting After the trial, data administrator will export the data confirmed correct from OC system as demanded by the statistician, and will be provided to the statistical analysts in the form of data interexchange code, statistical analysts will extract relevant data from the database according to the code and program for statistical analysis.
Statistical methods	P12L35	20a	Mean and deviation are used for the statistical description of the measurement data. Analysis variance will be used, if the data are normally distributed, while rank test will be used in case that the data are not normally distributed or there is heterogeneity of variance. The comparison between the three experimental groups and the control group is based on the analysis variance of the repeated measurement data. If $P<0.05$, then it is confirmed that there is a statistical difference.

	P12L1	20b	General information, including patient's name, gender, age, weight, height, based diseases, type of symptom, accompanying symptom, education level and other basic information are firstly recorded and assessed after the patient has passed eligibility screening to ensure balanced baseline values. In addition, baseline data will be analyzed through an independent-test, analysis of variance and the χ2 test to check whether the randomization has resulted in equal distributions of the known confounding factors, such as age, sex, BMI, based diseases, type of symptom, accompanying symptom and education level. In case of incomparability, baseline-adjusted methods will be used. If the evaluation results indicate that the baseline data of two or more groups are not consistent, it means there probably are some confounding factors that may affect the results. According to the confounding factors types, any of the following analysis methods can be chosen. The data will be analyzed by two-ways ANOVA using SAS9.1software package when the confounding factors type is classification or counting type. A logistic regression test or Cox proportional hazards regression model will be used when there are many confounding factors. The above method(s) can be adopted to well observe the real effect of the intervention on the premise of balancing multiple confounding factors.
	P12L47	20c	The evaluation result will be analyzed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions which prevents the cases with poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.
Methods: Monitoring			
Data monitoring	not appear in the article	21a	Independent Data Monitor Committee (IDMC) made up of clinical experts, statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial.
	not appear in the article	21b	When significant abnormal data or data on serious adverse reactions are monitored, it depends on the joint decision of both the data monitoring center and the trial committee whether the trial should be stopped. Patients accord with termination standards will be terminated.

Harms	not appear in the article	22	Standard operating procedures (SOP) for the management of adverse events must be worked out in order to guarantee adverse events under control. Clinical research associates are required to be involved in AE management and SOP drafting, so that they can manage adverse events during clinical test in a scientific and standardized manner. Recording of AE When observing the efficacy, pay attention to the occurrence of AE and adverse reactions and record them in detail; serious adverse events arising out of the trial must be reported in good time to person-in-charge of the project and Ethics Committee. **Rating of AE Severity** Table3: Severity grading and definition

Severity Grading	Definition
Mild	Short-lasting and mild symptoms, no pain caused to patie bearable, daily activities not affected
Moderate	Overt symptoms but bearable, daily activities affected
Severe	Severe symptoms, daily activities seriously affected

Deciding the correlation between AE and drug

The correlation between AE and drug is estimated according to 5-grade criteria:

Table4: Determination of correlation between AE and Drug

Criteria	Definitely relevant	probably relevant	probably irrelevant	definitely irrelevant	unable to judge
Within the reasonable post-dosage time sequence	+	+	-	-	-
Within known types of reaction of suspected drug	+	+	-	-	?
Symptoms improved after withdrawal of drug	+	?	?	-	?
Reactions recur after repeated administration	+	?	?	-	?
Related to other treatment	-	+	+	+	?

(Note: “＋” means YES;“—”means NO; “？”means unclear situation)

Analysis of AE

X^2 test is used to compare the incidence of adverse events of drug A and B and the correlation between AE and drug is analyzed.

Auditing	not appear in the article	23	Auditors are required to audit trial conduct by visiting or by documents in a mid-stage and the end of the study, and the process will be independent from investigators and the sponsor.

Ethics and dissemination

Research ethics approval	P15L10	24	This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20160007).
Protocol amendments	not appear in the article	25	If the protocol needs to be modified, we will apply for ethical review again.
Consent or assent	P15L15	26a	Patients, immediate family member or supervisors will obtain informed consent.
		26b	Not Applicable
Confidentiality	not appear in the article	27	The study established the principle that all information related to patient is confidential, and their name will not appear on the records.
Declaration of interests	P15L38	28	The authors declare that they have no competing interests.
Access to data	not appear in the article	29	Data administrators and statisticians have the access to the final trial data set.
Ancillary and post-trial care	not appear in the article	30	Patients who suffer harm from trial participation will been treated and cared.
Dissemination policy	not appear in the article	31a	The results will be submitted to a international journal. When the trial has been completed, we will tell participants the conclusion and give some advice for rational drug use. 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
	not appear in the article	31b	When published, the use of any content in the article must be through the magazine and the authors' permission.
	not appear in the article	31c	The protocol is to be published in open access journal and the researchers can download it through the network.

Appendices

Informed consent materials	not appear in the article	32	Model consent form and other related documentation given to participants and authorised surrogates will be the last part of the checklist.
Biological specimens		33	Not appliable

*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.

Notes for Subjects

Dear Mr. / Ms:

You are invited to take part in the program"Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial", which is implemented by Tianjin University of Traditional Chinese Medicine. Before you make the final decision, please read the following parts carefully. It can help you learn the meaning of the trial, as well as the benefits and risks it may bring to you.

The background and objective of this study

1. Background

The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have shown that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three

CPMs have come onto the market for many years and have got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, the main ingredient of which is leech, is proved to be safe, effective and with less adverse reactions by clinical observation [7]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and people who are bleeding [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, the main ingredient of which is Steroidal saponins of Tribulus terrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of Peoples Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously[11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, the main ingredient of which is Panax Notoginseng Saponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14].

Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

2. Objective

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.

Trial procedure

This is a randomized controlled, double-blind design. 360 patients are assigned randomly using stratified blocked randomization method (1:1:1:1). If you agree to participate in the trial and meet the conditions, you will take part in the 30-day clinical trial and 180 follow up after signing the consent form voluntarily. This study comprises two stages:

1. Screening

Doctors are going to take your medical history and ask you to do certain medical and chemical examinations. If the results don't meet the conditions, then you will not participate in the second phase.

2. Treatment

After being chosen in the first phase, you will come into a 30 days treatment with medicines and a 180 days follow up. In this trial, you can be randomly distributed to group 1, group 2, group 3 or group 4, which has no influence on your conventional treatment.

The medicines used in this trial may modify your condition in various degrees according to your physical state. If you participate in the trial , we need you to obey the following rules:

- Do not medicate yourself with medicines that are not allowed for joint application.
- Strictly follow the doctors' orders about medicine taking and examinations.

Volunteers' Rights and Interests

Medicines given to you during the trial are free.

All the other conventional treatments and examinations that are not involved in the trial will be charged as usual.

The Security of the Volunteers' Privacy

The study established the principle that all information related to patient is confidential, and their name will not appear on the records. The results of the trial may be published in medical journals, but all your personal information will be classified. Only when it is necessary can ethics committee members of the hospital and the research member have access to your medical materials with approval. Others will not have access to your materials.

You are voluntarily participate in every phase of the trial. You can refuse to take part in it at the beginning, or quit without any reason at any time. All the decisions you make will not affect your conventional treatment. If you agree to participate, you or your agent need to sign the consent form.

The Risks and Discomfort that may occur in the trial and the countermeasures that will be taken

If there are foreseeable adverse reactions, such as itch, or the ones not yet discovered or unforeseeable, doctors will take treatment measures in time according to your condition, in order to reduce the possible risks. If you have serious adverse reactions, you will get active treatment.

Consent Form

Title of the research: “Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial”.

This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20170005). contact the ethics committee:022-27493265

The leader of the doctor have explained the content of the clinical research to me. I have chances to ask questions and have got answers to all of them. I have totally understood these answers.

I participate in the trial voluntarily. I can quit at any time, which will not affect the treatments I should have in the hospital. I have right to get a copy of the consent form.
I have carefully read the Notes for Volunteers and totally understood it. I agree to participate in the trial.

signature of the subject： Tel： Date：

signature of the agent： Tel： Date：

signature of the researcher： Tel： Date：

BMJ Open

Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial

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Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial

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Abstract

Introduction: Hemiplegia, dysphasia and facial paralysis are the three main symptoms in stroke convalescent period. In China, a great number of patients in stroke convalescent period prefer to take Chinese patent medicines (CPM) to relieve the symptoms above, among which Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST) are frequently used. However, as the instructions of these three CPMs indicate similar functions based on the syndrome theory, it is hard to decide which one is the best choice for each of the symptoms mentioned above. This study aims to unveil a new method to distinguish which CPM is the best choice for each symptom, and finally establishes an effective method to differentiate the CPMs with similar effects from the perspective of the remission of patients' symptoms.

Methods/ Design: The study is based on the theory of comparative effectiveness research (CER). Three strata, each with 80 eligible participants, will be enrolled. The main symptom for each strata is hemiplegia, dysphasia and facial paralysis respectively. Each strata will be randomly and equally divided into 4 groups and they will respectively have treatment with NXK, XNST, XST and placebo. The treatment will last for 30 days, and follow up 180 days. The outcome measurement is based on the patient-centered evaluation theory. The Delphi techniques will be used to assign weight to the index value of NIHSS scale and WHOQOL-BREF scale. The weighted index value will be computed as the final measurement index of the outcome, which is named Comprehensive recovery index of stroke rehabilitation (CRST) in this study.

Discussion: This study distinguishes the orientation of different CPMs from the aspect of symptoms and establishes an effective evaluation method which fits Chinese patent medicines' effectiveness in synthetic regulation. This study will differentiate the effectiveness of NXK, XNST and XST from the perspective of the remission for patients' symptoms. This study provides a methodological foundation for the effective evaluation of other CPMs or treatment plans. Meanwhile, it also explores the usage of CER in TCM.

Trial registration: This trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-17010397). The date of registration was 11st Jan, 2017.

Keywords: Stroke, Chinese Patent Medicine, Comparative Effectiveness Research

Strengths and limitations of this study

- A multicentric, prospective and randomized controlled trial.
- This study explores the usage of CER in TCM.
- This study distinguishes the orientation of different CPMs from the aspect of symptoms.
- The evaluation of a patient's recovery involves both the quality of life and clinical indexes.
- Using Delphi techniques to assign weight to the scale indexes.
- The sample size is not large enough due to funding constraints (n=240, each group=20).

Background

The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than that in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in the daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have showed that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three CPMs have appeared on the market for many years and got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, and the main ingredient of

which is leech, is proved to be safe, effective and with less adverse reactions by clinical observation [7]. According to Pharmacopoeia of the People's Republic of China, it is forbidden to be given to pregnant women and bleeding persons [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, and the main ingredient of which is Steroidal saponins of Tribulus terrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of the People's Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously [11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, and the main ingredient of which is Panax Notoginseng Saponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia of the People's Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14].

Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

The application feasibility of comparative effectiveness research in the evaluation of CPM

The concept of comparative effectiveness research (CER) was initiated in the 1990s by Mark Boutin, the deputy executive president and chief operating officer of the US National Health Council [15]. The Agency for Healthcare Research and Quality (AHRQ) defined comparative effectiveness research as: "Comparative

effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options" [16]. The evidence was generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care [17].

In the following years, CER was introduced into the field of clinical research in a number of countries [18]. CER was introduced into TCM research at the sixth annual meeting of the International Society of Complementary Medicine Research by Claudia M Witt (Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany) in May 2011 [19]. The outcome of comparative effectiveness research focuses on the problems that patients care and want to solve mostly [20]. It is more patient-oriented, which means it respects the patients' will, cares about both the quality of their lives and psychological functions, while fitting the TCM clinical practice and showing the validity of the results.

CER is concerned with answering questions about effectiveness rather than efficacy of interventions, which implies the usefulness of various study designs. Non-randomized or observational studies, rather than randomized controlled trials (RCTs), may answer effectiveness questions better, even though well-known threats to validity exist for the former [21].

Effectiveness evaluation based on patient-oriented theory

Patients in stroke convalescent period suffer not only from various clinical symptoms but also the decline of the ability for daily activities and the lower quality of life. According to the study, the evaluation of a patient's recovery should involve both the quality of life, including mental state, physical condition, psychological condition and social environment, and clinical indexes.

Quality of life: According to WHOQOL-BREF, quality of life is evaluated by one's mental state, psychological state and physical state, etc. [22-23]. **Clinical indexes:** The physiological indexes which show the degree of nervous functional defects can be evaluated by National Institutes of Health Stroke Scale

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(NIHSS).

In this research, WHOQOL-BREF and NIHSS are used to assess the curative effect and get their weight with Delphi. The comprehensive score is taken as the final curative effect. In this way, it avoids the randomness of the PRO (Patient Report Outcome) [24] coming from the patients' reports to some degree.

Delphi technique is a method to quantify a qualitative description, which means it can synthesize the opinions from many experts in a scientific way and therefore give a reasonable prediction about things. Delphi technique asks for, collects and counts individual opinions and judgments by distributing questionnaires, so as to get comparatively unanimous opinions on certain issues.

Objectives

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present, no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.

Methods/Design

In this multi-centered and double-blind clinical trial, stratified randomization is used for the grouping of the patients, which is according to their most main symptoms (Hemiplegia, Dysphasia, Facial Paralysis). A flowchart of the study protocol is shown in Fig.1.

Inclusion criteria

1. Patients ages from 30 to 65 years old.

2. It is the first time that the patient has a stroke.

3. Diagnosis of unilateral, non-recurring, subacute stroke of ischemic and lacunar type, as defined by the International Classification of Diseases (ICD-10) through computed omography or magnetic resonance

imaging conducted by neurologists.

4. TCM pattern diagnosis of stroke in meridian syndrome.

5. Patients should have a score between 6 and 20 according to National Institutes of Health Stroke Scale (NIHSS).

6. After injury from four weeks to eight weeks.

7. Provision of signed informed consent.

8. The above inclusion criteria will be applied to the experimental group and the control group.

Exclusion criteria

1. Patients with a known history of allergy or suspected allergy to the medicines used in the study.

2. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders.

3. Patients with other complications.

4. Uncontrolled NYHA class III hypertension (systolic blood pressure ⩾180 mmHg and/or diastolic blood pressure ⩾110 mmHg).

5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene, or peripheral neuropathy).

6. Liver function impairment with the value of ALT or AST over 1.5-fold the upper limit of normal range.

7. Renal dysfunction with the value of serum creatinine over 1.5-fold the upper limit of normal range.

8. Patients with active peptic ulcers or other hemorrhagic diseases.

9. Patients who participate in other clinical trials, either currently or within the past 90 days.

Treatment plan

(1) Basic treatment

The intervention program mainly takes China's Guidelines of Cerebrovascular Disease Prevention and

controls and the consensus of foreign experts for reference. It considers all the risk factors of apoplexy into strict control. The program involves:

(a) Antiplatelet drug: Aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(e) During the test, Chinese patent medicine for activating blood circulation and removing stasis and compounded Chinese medicine prescription will be banned from using.

(2) The final treatment plans:

The treatment plan for group A(TPGA): ①basic treatment +②Naoxuekang capsule (NXK).

The treatment plan for group B(TPGB): ①basic treatment +②Xinnaoshutong capsule (XNST).

The treatment plan for group C(TPGC): ①basic treatment +②Xuesaitong capsule(XST).

The treatment plan for group D(TPGD): ①basic treatment+ placebo.

The dosage and method of CPMs will follow the doctor's advice.

(3) Participant timeline

A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (180 days). The points of three times data collection will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±2, and the third visit is on day 210±5.

(4) Termination criteria

Interventions for the trial participants will be discontinued if the following situations occur: (a) patients quit of their own free will; (b) major mistakes or serious deviations are identified in clinical trial protocol in the

process of execution (though the plan is good), making it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur over the trial; (d) the trial is canceled by the authority.

(5) The adherence of patients to the instructions

Patients will receive trial drugs and necessary healthcare instructions (diet, mental adjustment) for free; patients are required to maintain appropriate physical activities and control daily exercises; the dosage of the medicine and its remnant shall be recorded authentically, drug counting method is used to monitor the adherence of patients. Patients who suffer from the trial will be treated and cared.

Patient grouping

Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 240 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be in balance, and the patients will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level.

(1) Patients will be divided into three strata according to their main symptoms. Each strata will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to strata H. The patients whose main symptom is dysphasia will be assigned to strata D. The patients whose main symptom is facial paralysis will be assigned to strata F.

(2) Patients with the same main symptom will be divided into group A, B, C and D both randomly and equally. Each of the 4 groups will be treated with a different treatment plans and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group

FA, Group FB, Group FC, Group FD, and each group contains 20 patients. The Table 1 shows the details as following:

Table 1: Groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure that the same observation mode is kept between the experimental group and the control group. This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor, who is an expert in this field with clinical experience over ten years, is able to ensure an accurate assessment of the patient's symptoms. The questionnaire of WHOQOL-BREF and NIHSS of all the patients will be recorded by this doctor at the beginning of experiment, the second visit is on day 30±2 and the third visit is on day 210±5.

(2) Evaluation Criteria

In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that the outcomes can represent the wills of the patients and clinicians, in which way it can meet the characteristic of comparative effectiveness research. Each index is designed as a questionnaire with four answers including “very important”, “important”, “average/ not very important” and “not important”. Each expert judges the index system according to the four answers.

The formula is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N \quad \ldots\ldots(1)$$

DWi – the average value of the importance of the index i (i = w, n)

aij—the grade value of the index i;

j — the grade ordinal;

N— the number of the experts;

DW_W in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DW_N in eq. 2 and eq. 3 indicates the weight of NIHSS.

(3)The final curative effects

The effectiveness of each index is evaluated by comparing its value before and after the treatment. In this study, W_0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, W_1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W_2 in eq. 3 is the value of WHOQOL-BREF after follow up. N_0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N_1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N_2 in eq. 3 is the value of NIHSS after follow up.

The final curative effects can be figured out as:

$W_1 * DW_W + N_1 * DW_N - (W_0 * DW_W + N_0 * DW_N)$…… (2)

The curative effects after follow up can be figured out as:

$W_2 * DW_W + N_2 * DW_N - (W_0 * DW_W + N_0 * DW_N)$……(3)

(4) Data collection methods

For each patient, measurement will be carried out at the following time points: 0, 30±2 and 210±5 days after treatment (Table 2). The clinical research associates are required to monitor various units on a regular and incessant basis. The data management of the trial follows Good Clinical Data Management Practice

(GCDMP) [25].

Table 2: Data are captured based on the CRF

Items	Visit		
	1 0 day	2 30±2days	3 210±5days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical, treatment and allergies	√		
Taking drugs on current	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF		√	√
NIHSS		√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

Sample size

The sample size in this study is based on the trial results in previous reports [26-32] and the recommendation of specialists. The values of σ_i for WHOQOL-BREF scale of the experimental groups before and after treatment are 12.12, 19.51 and 12.24 respectively; while the value of σ_i for WHOQOL-BREF scale of the placebo group is 11.2. The values of μ_i for WHOQOL-BREF scale of experimental groups before and after treatment are 17.13, 18 and 23.83 respectively, while the value of μ_i for WHOQOL-BREF scale of the placebo group before and after treatment is 10.83. According to the calculation, μ is 17.45, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 172 patients are needed in the trial (43 patients for each group). The values of σ_i for NIHSS scale of the experimental groups before and after treatment are 2.6, 7.31 and 3.11 respectively, while the values of σ_i for NIHSS scale of the placebo group is 12.5. The values

of μ_i for NIHSS scale of the experimental groups before and after treatment are 6.85, 4.95 and 6.1 respectively, while the values of μ_i for NIHSS scale of the placebo group before and after treatment is 1.39. According to the calculation, μ is 4.82, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 232 patients are needed in the trial (58 patients for each group).

According to the calculation above and the recommendation of the specialists, 240 patients are collected in the trial, 60 patients for each group.

Statistical analysis

General information, including patient's name, gender, age, weight, height, based diseases, type of symptom, accompanying symptom, education level and other basic information are firstly recorded and assessed after the patient has passed eligibility screening to ensure balanced baseline values.

Mean and deviation are used for the statistical description of the measurement data. Analysis variance will be used, if the data are normally distributed, while rank test will be used in case that the data are not normally distributed or there is heterogeneity of variance. The comparison between the three experimental groups and the control group is based on the analysis variance of the repeated measurement data. If $P<0.05$, then it is confirmed that there is a statistical difference.

The evaluation result will be analyzed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.

In this study, data analysis will be finished by researchers who do not participate into the experiment and clinical decision making, which makes sure that the bias caused by the subjective factors from the researchers can be eliminated.

Safety

Adverse events (AEs) and adverse drug reactions (ADRs) will be conducted and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be informed to the person-in-charge of the project and the ethics committee. Every AE will be recorded in detail and closely monitored before stabilization or resolution. HLC will cooperate with the physician in charge to evaluate the severity and determine the causality of the events. All relevant AEs will be reported to the institutional review board of the First Affiliated Hospital of Tianjin University of TCM within the relevant time frames. HLC will be responsible for reporting all adverse events. The coordinators will be responsible for establishing the standard procedures and the training of relevant staff before trial initiation. Regular monitoring will be used to ensure that all AEs are identified and addressed appropriately.

The incidence of AEs and ADRs is compared between various groups using the $\chi 2$ test with the level of significance set at $P < 0.05$.

Auditors are required to audit trial conducts by checking documents in the middle of and at the end of the study, and the process will be independent from the investigators and the sponsor.

Randomization, blinding and allocation concealment

Cases are assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the trial patients will be finished using an independent data center with an interactive voice response system, and the random number will be generated by this data center. Original copies of the blind codes are sealed in the lightproof envelope, and one kept by major research unit and the other by the applicant of the trial and are not allowed to be opened before formal statistical analysis. If a patient was eligible, a patient number will be allocated by doctors. The patient numbers is just the serial numbers for labeling patients. The test medicine will be coded firstly, and then put in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be located in opaque envelopes and are kept confidential

by the trial management board. The original capsule shells of NXK, XNST and XST were exchanged for the new uniform capsule shells, which was conducted by the Pharmaceutical Factory of Tianjin University of TCM. The placebo was put into the same capsule shells, the content of which was amylum. Thus, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.

If there are emergencies or necessary treatment for the patients, persons-in-charge of the participating units will immediately report to CRA and major investigators, and unblinding can only be performed upon their approval. Once the allocation is unblinded, the investigators must comply with the trial requirements when operating and recording.

Trial oversight

Steering Committee: responsible for the top-level design and guarantee that the test goes smoothly.

Coordinating Center: four sub-centers are responsible for collecting cases and assuring quality.

End Point Adjudication Committee: to assess the outcome event and judge fall off and withdrawal cases.

Data Management Team: responsible for the data management, including data entry, verification and exporting.

Discussion

The critical task of translational medicine in TCM is to translate the achievements of medical research into clinical practice, so as to establish a series of clinical diagnosis and treatment technical standards, guidelines and/or pathway which is scientific, generalizable and acceptable to both TCM and western medicine practitioners [33]. A clear identification of the curative effect on symptoms is easier to understand by people who don't know much about TCM, which makes it easier for CPMs to be accepted by the whole world.

One of the advantages of CPM is to improve patients' health condition as a whole. This study gives a comprehensive evaluation on CPMs from the aspects of both clinical index and the quality of patient's life.

Index weighting ensures that the choice of the medicine is patient-oriented. As the scale used in the study is an international standardized one and the indexes of the scale are fixed, the result avoids the randomness that exists in the PRO directly coming from the patient's report. Using Delphi techniques to weights the scales ensures the credibility, the validity and the structure of the international standardized scales.

In this study, the following measures will be taken to prevent bias. To avoid evaluator or rater bias, doctors who are assigned to assess the symptoms and record evaluation results will not take part in clinical decision making, nor do the researchers who analyze data. The latter ones don't participate into the experiment either. To avoid performance bias, a long enough observation period will be maintained to make sure that the curative effect appears. Doctor A will be assigned to assess the symptoms and record evaluation results of all volunteers to make sure the same observation mode is kept both in the experimental group and the control group. The scales of WHOQOL-BREF and NIHSS of all the patients will be recorded by Doctor A at the beginning of experiment, on the 30±2 and the 210±5 day after treatment. To avoid attrition bias, the evaluation result will be analyzed by the method of intention to treat analysis (ITT). The loss of data will be conducted according to the last observation carried forward principle. To avoid selection bias, the number of the volunteers recruited in each hospital should be in balance, and the volunteers will be divided into the experiment group and the control group. Strict inclusion criteria and exclusion criteria will be applied to both the experiment and the control group. To avoid unpredictable bias, baseline date will be analyzed and adjusted. Two-ways ANOVA, logistic regression test or Cox proportional hazards regression model will be adopted to well observe the true effect of the intervention on the premise of balancing multiple confounding factors.

Trial status

Currently patients are being recruited for the trial.

Ethical Approval and Consent to participate

This study has been approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007). If the protocol needs to be modified, we will apply for the ethical review again. All participating patients need to sign informed consent, and the researcher explains the procedures and the objectives to be used in research, which includes detailed methods to be used, the risks and benefits, and stating the possibility of inclusion in a control or experimental group. The study follows the principle that all information related to patients is confidential, and their names will not appear in the records.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that no conflict of interest exists.

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Authors' contributions

Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN is in charge of all statistical works of the trial. XIA Q and Chen B helped conduct the survey. All authors have carefully read and approved the final manuscript. Sponsor designed this protocol, prepared the draft and is responsible for the selection of research units, researchers and drug resources. The costs of publishing article, buying drugs and so on are provided by the funders.

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Data sharing statement The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All of the data are available.

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Table Captions

Table 1 Groups divided according to main symptoms and treatment plans

Table 2 Data are captured based on the CRF

Table 1 Groups divided according to main symptoms and treatment plans

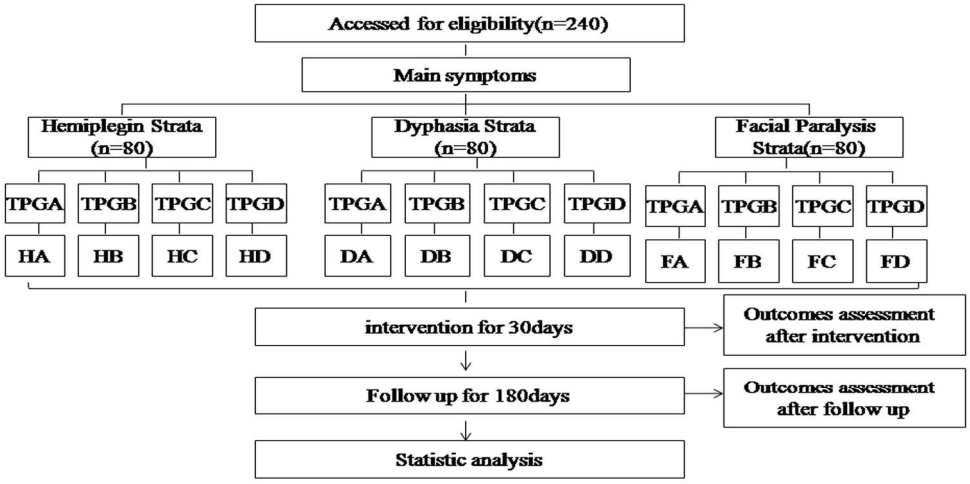
	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

Table 2 Data are captured based on the CRF

Items	Visit 1 0 day	2 30±2days	3 210±5days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical, treatment and allergies	√		
Taking drugs on current	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF		√	√
NIHSS		√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

Figure Captions

Fig.1 Flow chart of the protocol



233x113mm (300 x 300 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	Page and line Number	Item No.	Description
Administrative information			
Title	P1L1	1	Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial
Trial registration	P3L3	2a	Chinese clinical trials register ChiCTR-IOR-17010397
		2b	Please retrieve the trial registration data of this study at this site http://www.chictr.org.cn/searchproj.aspx
Protocol version		3	Version: 81202849-2.1
Funding	P17L36	4	The study is funded by the National Natural Science Foundation of China (No.81202849) and Tianjin 131 Talent of second levels(ZX160123).
Roles and responsibilities	P17L43	5a	Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN in charge of all statistical works of trial. XIA Q and Chen B helped conduct the survey. All authors carefully read and approved the final manuscript.
	P1L44	5b	Huiling Chen: chen.huiling@163.com 1 School of Pharmaceutical Science and Technology, Tianjin University, 72 Weijin Road, Nankai District, Tianjin 300072, China; 2 TianJin University of Traditional Chinese Medicine；312 Anshanxi Road, Nankai District, Tianjin 300193, China.
	P17L51	5c	Sponsor designed this protocol, prepared the draft and is responsible for the selection of research units, researchers and drug resources. The costs of publishing article, buying drugs and so on are provided by the funders.

P15L26 5d Steering Committee: responsible for the top-level design and guarantee that the test goes smoothly.
Coordinating Center: four sub-centers are responsible for collecting cases and assuring quality.
End Point Adjudication Committee: to assess the outcome event and judge fall off and withdrawal cases.
Data Management Team: responsible for the data management, including data entry, verification and exporting.

Introduction

Background and rationale	P3L28	6a	The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than that in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in the daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2]. For the current treatment in the convalescence of stroke, clinical trials have showed that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three CPMs have appeared on the market for many years and got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, and the main ingredient of which is leech, is proved to be safe, effective and with less adverse reactions by clinical observation [7]. According to Pharmacopoeia of the People's Republic of China, it is forbidden to be given to pregnant women and bleeding persons [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, and the main ingredient of which is Steroidal saponins of Tribulus terrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of the People's Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously [11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, the main ingredient of which is Panax Notoginseng Saponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia of the People's Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14]. Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

	P4L28	6b	Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule(XST) are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure.
Objectives	P6L23	7	The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present, no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.
Trial design	P6L38	8	In this multi-centered clinical trial, stratified randomization is used for the grouping of the patients, which is according to their most urgent symptoms (Hemiplegia, Dysphasia, Facial Paralysis).

Methods: Participants, interventions, and outcomes

Study setting	P9L21	9	Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China.

Eligibility criteria	P6L48	10	● Inclusion criteria 1. Patients ages from 30 to 65 years old. 2. It is the first time that the patient has a stroke. 3. Diagnosis of unilateral, non-recurring, subacute stroke of ischemic and lacunar type, as defined by the International Classification of Diseases (ICD-10) through computed omography or magnetic resonance imaging conducted by neurologists. 4. TCM pattern diagnosis of stroke in meridian syndrome. 5. Patients should have a score between 6 and 20 according to National Institutes of Health Stroke Scale (NIHSS). 6. After injury from four weeks to eight weeks. 7. Provision of signed informed consent. 8. The above inclusion criteria will be applied to the experimental group and the control group. ● Exclusion criteria 1. Patients with a known history of allergy or suspected allergy to the medicines used in the study. 2. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders. 3. Patients with other complications. 4. Uncontrolled NYHA class III hypertension (systolic blood pressure ⩾ 180 mmHg and/or diastolic blood pressure ⩾110 mmHg). 5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene, or peripheral neuropathy). 6. Liver function impairment with the value of ALT or AST over 1.5-fold the upper limit of normal range. 7. Renal dysfunction with the value of serum creatinine over 1.5-fold the upper limit of normal range. 8. Patients with active peptic ulcers or other hemorrhagic diseases. 9. Patients who participate in other clinical trials, either currently or within the past 90 days.

Interventions P7L54 11a

Treatment plan

(1)Basic treatment

The intervention program mainly takes China's Guidelines of Cerebrovascular Disease Prevention and Control and the consensus of foreign experts for reference. It considers all the risk factors of apoplexy into strict control. The program involves:

(a) Antiplatelet drug: Aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(e) During the test, Chinese patent medicine for activating blood circulation and removing stasis and compounded Chinese medicine prescription will be banned from using.

(2) The final treatment plans:

The treatment plan for group A(TPGA): ① basic treatment + ② Naoxuekang capsule (NXK).

The treatment plan for group B(TPGB): ① basic treatment + ② Xinnaoshutong capsule (XNST).

The treatment plan for group C(TPGC): ① basic treatment + ② Xuesaitong capsule(XST).

The treatment plan for group D(TPGD): ①basic treatment+placebo.

The dosage and method of CPMs will follow the doctor's advice.

(3) Participant timeline

A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (180 days). The points of three times data collection will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±2, and the third visit is on day 210±5.

(4) Termination criteria

Interventions for the trial participants will be discontinued if the following situations occur: (a) patients quit of their own free will; (b) major mistakes or serious deviations are identified in clinical trial protocol in the process of execution (though the plan is good), making it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur over the trial; (d) the trial is canceled by the authority.

(5) The adherence of patients to the instructions

Patients will receive trial drugs and necessary healthcare instructions (diet, mental adjustment) for free; patients are required to maintain appropriate physical activities and control daily exercises; the dosage of the medicine and its remnant shall be recorded authentically, drug counting method is used to monitor the adherence of patients. Patients who suffer from the trial will be treated and cared.

Patient grouping

Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 240 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid

selective bias, the number of the patients recruited in each hospital should be in balance, and the patients will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level.

(1) Patients will be divided into three strata according to their main symptoms. Each strata will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to strata H. The patients whose main symptom is dysphasia will be assigned to strata D. The patients whose main symptom is facial paralysis will be assigned to strata F.

(2) Patients with the same main symptom will be divided into group A, B, C and D both randomly and equally. Each of the 4 groups will be treated with a different treatment plans and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD, and each group contains 20 patients. The Table 1 shows the details as following:

Table 1: groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis （F）	FA	FB	FC	FD

P8L53 11b Interventions for the trial participants will be discontinued if the following situations occur: (a) patients quit of their own free will; (b) major mistakes or serious deviations are identified in clinical trial protocol in the process of execution (though the plan is good), making it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur over the trial; (d) the trial is canceled by the authority.

P8L8 11c **adherence of patients**

Patients will receive trial drugs and necessary healthcare instructions (diet, mental adjustment) for free; patients are required to maintain appropriate physical activities and control daily exercises; the dosage of the medicine and its remnant shall be recorded authentically, drug counting method is used to monitor the adherence of patients. Patients who suffer from the trial will be treated and cared.

P8L19 11d During the test, Chinese patent medicine for activating blood circulation and removing stasis and compounded Chinese medicine prescription will be banned from using.

Outcomes P10L17 12

Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure that the same observation mode is kept between the experimental group and the control group. This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor, who is an expert in this field with clinical experience over ten years, is able to ensure an accurate assessment of the patient's symptoms. The questionnaire of WHOQOL-BREF and NIHSS of all the patients will be recorded by this doctor at the beginning of experiment, the second visit is on day 30±2 and the third visit is on day 210±5.

(2) Evaluation Criteria

In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that the outcomes can represent the wills of the patients and clinicians, in which way it can meet the characteristic of comparative effectiveness research. Each index is designed as a questionnaire with four answers including “very important”, “important”, “average/ not very important” and “not important”. Each expert judges the index system according to the four answers.

The formula is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N$$

……(1)

DW_i – the average value of the importance of the index i (i = w, n)

aij—the grade value of the index i;

j — the grade ordinal;

N— the number of the experts;

DWW in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DWN in eq. 2 and eq. 3indicates the weight of NIHSS.

(3)The final curative effects

The effectiveness of each index is evaluated by comparing its value before and after the treatment. In this study, W0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, W1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W2 in eq. 3 is the value of WHOQOL-BREF after follow up. N0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N2 in eq. 3 is the value of NIHSS after follow up.

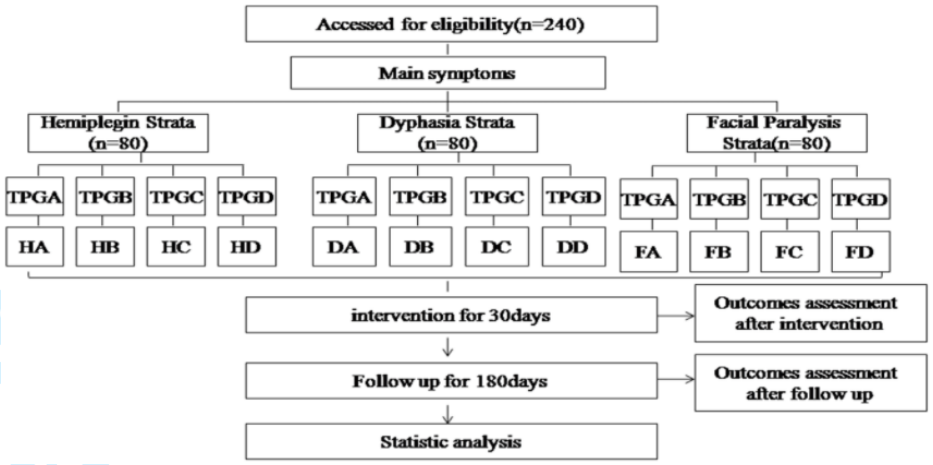
The final curative effects can be figured out as

$W_1 * DW_W + N_1 * DW_N - (W_0 * DW_W + N_0 * DW_N)$…… (2)

The curative effects after follow up can be figured out as

$W_2 * DW_W + N_2 * DW_N - (W_0 * DW_W + N_0 * DW_N)$……(3)

Participant timeline	P8L41 P6L44	13	A long enough observation period will be lasted to make sure that the curative effect appears. This study will comprise two stages: the first treatment (30 days) and follow up (180 days). The points of three times data collection will be arranged in this trial: the first visit is on day 0 after enrollment; the second visit is on day 30±2, and the third visit is on day 210±5.(Figure 1)



Sample size	P12L37	14	The sample size in this study is based on the trial results in previous reports [26-32] and the recommendation of specialists. The values of σ_i for WHOQOL-BREF scale of the experimental groups before and after treatment are 12.12, 19.51 and 12.24 respectively; while the value of σ_i for WHOQOL-BREF scale of the placebo group is 11.2. The values of μ_i for WHOQOL-BREF scale of experimental groups before and after treatment are 17.13, 18 and 23.83 respectively, while the value of μ_i for WHOQOL-BREF scale of the placebo group before and after treatment is 10.83. According to the calculation, μ is 17.45, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 172 patients are needed in the trial (43 patients for each group). The values of σ_i for NIHSS scale of the experimental groups before and after treatment are 2.6, 7.31 and 3.11 respectively, while the values of σ_i for NIHSS scale of the placebo group is 12.5. The values of μ_i for NIHSS scale of the experimental groups before and after treatment are 6.85, 4.95 and 6.1 respectively, while the values of μ_i for NIHSS scale of the placebo group before and after treatment is 1.39. According to the calculation, μ is 4.82, type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 232 patients are needed in the trial (58 patients for each group). According to the calculation above and the recommendation of the specialists, 240 patients are collected in the trial, 60 patients for each group.

Recruitment	P9L19	15	Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. 240 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be in balance, and the patients will be divided into experiment group and control group. Basic data of the patients will be registered, including name, sex, age, BMI, based diseases, type of symptom, accompanying symptom and education level. (1) Patients will be divided into three strata according to their main symptoms. Each strata will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to strata H. The patients whose main symptom is dysphasia will be assigned to strata D. The patients whose main symptom is facial paralysis will be assigned to strata F. (2) Patients with the same main symptom will be divided into group A, B, C and D both randomly and equally. Each of the 4 groups will be treated with a different treatment plans and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, Group FD, and each group contains 20 patients.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	P14L36	16a	Cases are assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the trial patients will be finished using an independent data center with an interactive voice response system, and the random number will be generated by this data center.
Allocation concealment mechanism	P14L44	16b	Original copies of the blind codes are sealed in the lightproof envelope, and one kept by major research unit and the other by the applicant of the trial and are not allowed to be opened before formal statistical analysis. If a patient was eligible, a patient number will be allocated by doctors. The patient numbers is just the serial numbers for labeling patients.
Implementation	P14L39	16c	Randomization of the trial patients will be finished using an independent data center with an interactive voice response system, and the random number will be generated by this data center.

Blinding (masking)	P14L49	17a	If a patient was eligible, a patient number will be allocated by doctors. The patient numbers is just the serial numbers for labeling patients. The test medicine will be coded firstly, and then put in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be located in opaque envelopes and are kept confidential by the trial management board. The original capsule shells of NXK, XNST and XST were exchanged for the new uniform capsule shells, which was conducted by the Pharmaceutical Factory of Tianjin University of TCM. The placebo was put into the same capsule shells, the content of which was amylum. Thus, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.
	P15L13	17b	If there are emergencies or necessary treatment for the patients, persons-in-charge of the participating units will immediately report to CRA and major investigators, and unblinding can only be performed upon their approval. Once the allocation is unblinded, the investigators must comply with the trial requirements when operating and recording..

Methods: Data collection, management, and analysis

Data collection methods — P11L51 P22L3 — 18a

Items	Visit 1 0 day	Visit 2 30±2days	Visit 3 210±5days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical, treatment and allergies	√		
Taking drugs on current	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF		√	√
NIHSS		√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

	P11L53	18b	Clinical research associates are required to monitor various units on a regular and incessant basis.
Data management	P11L56	19	The data management of the trial follows Good Clinical Data Management Practice (GCDMP) [25]. ● Management Software This trial plans to use Oracle Clinical (OC) software for unified data management, online data updating and tracing, and exercise dynamic and efficient management of clinical trial data at the same time with the support of the check function of the software. ● Data recording All data of the trial are subject to remote recording. Investigators will enter relevant data by logging on the internet, such a pattern contributes to upgrading quality and efficiency of clinical study. ● Data examination Data administrator performs logic check and automatic comparison of data information using the check function of OC software, check the result values inconsistent with the case report forms, and check one-by-one with the original case report form and make corrections, so as to ensure the data in the database consistent with the results of the case report form. This way enables traceability, accuracy, completeness and timeliness of data. ● Data exporting After the trial, data administrator will export the data confirmed correct from OC system as demanded by the statistician, and will be provided to the statistical analysts in the form of data interexchange code, statistical analysts will extract relevant data from the database according to the code and program for statistical analysis.
Statistical methods	P13L26	20a	Mean and deviation are used for the statistical description of the measurement data. Analysis variance will be used, if the data are normally distributed, while rank test will be used in case that the data are not normally distributed or there is heterogeneity of variance. The comparison between the three experimental groups and the control group is based on the analysis variance of the repeated measurement data. If $P<0.05$, then it is confirmed that there is a statistical difference.
	P16L41	20b	To avoid unpredictable bias, baseline date will be analyzed and adjusted. Two-ways ANOVA, logistic regression test or Cox proportional hazards regression model will be adopted to well observe the true effect of the intervention on the premise of balancing multiple confounding factors.
	P13L38	20c	The evaluation result will be analyzed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.

Methods: Monitoring

Data monitoring	P11L56	21a	The data management of the trial follows Good Clinical Data Management Practice (GCDMP) [25]. Independent Data Monitor Committee (IDMC) made up of clinical experts, statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial.
	P11L56	21b	The data management of the trial follows Good Clinical Data Management Practice (GCDMP) [25]. When significant abnormal data or data on serious adverse reactions are monitored, it depends on the joint decision of both the data monitoring center and the trial committee whether the trial should be stopped. Patients accord with termination standards will be terminated.
Harms	P14L1	22	Adverse events (AEs) and adverse drug reactions (ADRs) will be conducted and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be informed to the person-in-charge of the project and the ethics committee. Every AE will be recorded in detail and closely monitored before stabilization or resolution. HLC will cooperate with the physician in charge to evaluate the severity and determine the causality of the events. All relevant AEs will be reported to the institutional review board of the First Affiliated Hospital of Tianjin University of TCM within the relevant time frames. HLC will be responsible for reporting all adverse events. The coordinators will be responsible for establishing the standard procedures and the training of relevant staff before trial initiation. Regular monitoring will be used to ensure that all AEs are identified and addressed appropriately. The incidence of AEs and ADRs is compared between various groups using the $\chi 2$ test with the level of significance set at $P < 0.05$.
Auditing	P14L29	23	Auditors are required to audit trial conduct by checking documents in the middle of and at the end of the study, and the process will be independent from investigators and the sponsor.

Ethics and dissemination

Research ethics approval	P17L1	24	This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20160007).
Protocol amendments	P17L2	25	If the protocol needs to be modified, we will apply for the ethical review again.
Consent or assent	P17L6	26a	Patients, immediate family member or supervisors will obtain informed consent.

		26b	Not Applicable
Confidentiality	P17L13	27	The study established the principle that all information related to patients is confidential, and their names will not appear in the records.
Declaration of interests	P17L31	28	The authors declare that they have no competing interests.
Access to data	P15L33	29	Data Management Team: responsible for the data management, including data entry, verification and exporting. Data administrators and statisticians have the access to the final trial data set.
Ancillary and post-trial care	P9L16	30	Patients who suffer from the trial will been treated and cared.
Disseminati on policy	P18L28	31a	The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All of the data are available. 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
		31b	When published, the use of any content in the article must be through the magazine and the authors' permission.
		31c	The protocol is to be published in open access journal and the researchers can download it through the network.
Appendices			
Informed consent materials		32	Model consent form and other related documentation given to participants and authorised surrogates will be the last part of the checklist.
Biological specimens		33	Not appliable

*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.

Notes for Subjects

Dear Mr. / Ms:

You are invited to take part in the program"Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial",

which is implemented by Tianjin University of Traditional Chinese Medicine. Before you make the final decision, please read the following parts carefully. It can help you learn the meaning of the trial, as well as the benefits and risks it may bring to you.

The background and objective of this study

1. Background

The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have shown that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three CPMs have come onto the market for many years and have got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, the main ingredient of which is leech, is proved to be safe, effective and with less adverse reactions by clinical observation [7]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and people who are bleeding [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, the main ingredient of which is Steroidal saponins of Tribulus terrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of Peoples Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously[11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, the main ingredient of which is Panax Notoginseng Saponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia

of Peoples Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14].

Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

2. Objective

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.

Trial procedure

This is a randomized controlled, double-blind design. 360 patients are assigned randomly using stratified blocked randomization method (1:1:1:1). If you agree to participate in the trial and meet the conditions, you will take part in the 30-day clinical trial and 180 follow up after signing the consent form voluntarily. This study comprises two stages:

1. Screening

Doctors are going to take your medical history and ask you to do certain medical and chemical examinations. If the results don’ t meet the conditions, then you will not participate in the second phase.

2. Treatment

After being chosen in the first phase, you will come into a 30 days treatment with medicines and a 180 days follow up. In this trial, you can be randomly distributed to group 1, group 2, group 3 or group 4, which has no influence on your conventional treatment.

The medicines used in this trial may modify your condition in various degrees according to your physical state. If you participate in the trial , we need you to obey the following rules:

- Do not medicate yourself with medicines that are not allowed for joint application.
- Strictly follow the doctors’ orders about medicine taking and examinations.

Volunteers' Rights and Interests

Medicines given to you during the trial are free.

All the other conventional treatments and examinations that are not involved in the trial will be charged as usual.

The Security of the Volunteers' Privacy

The study established the principle that all information related to patient is confidential, and their name will not appear on the records. The results of the trial may be published in medical journals, but all your personal information will be classified. Only when it is necessary can ethics committee members of the hospital and the research member have access to your medical materials with approval. Others will not have access to your materials. You are voluntarily participate in every phase of the trial. You can refuse to take part in it at the beginning, or quit without any reason at any time. All the decisions you make will not affect your conventional treatment. If you agree to participate, you or your agent need to sign the consent form.

The Risks and Discomfort that may occur in the trial and the countermeasures that will be taken

If there are foreseeable adverse reactions, such as itch, or the ones not yet discovered or unforeseeable, doctors will take treatment measures in time according to your condition, in order to reduce the possible risks. If you have serious adverse reactions, you will get active treatment.

Consent Form

Title of the research: "Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial".

This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20170005). contact the ethics committee:022-27493265

The leader of the doctor have explained the content of the clinical research to me. I have chances to ask questions and have got answers to all of them. I have totally understood these answers.

I participate in the trial voluntarily. I can quit at any time, which will not affect the treatments I should have in the hospital. I have right to get a copy of the consent form.
I have carefully read the Notes for Volunteers and totally understood it. I agree to participate in the trial.

signature of the subject: Tel: Date:

signature of the agent: Tel: Date:

signature of the researcher: Tel: Date:

BMJ Open

Identify Characteristics of Chinese Patent Medicines (Naoxuekang, Xinnaoshutong and Xuesaitong capsules) based on Symptoms: a Protocol for a Randomized Controlled Trial

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Identify Characteristics of Chinese Patent Medicines (Naoxuekang, Xinnaoshutong and Xuesaitong capsules) based on Symptoms: a Protocol for a Randomized Controlled Trial

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Abstract

Introduction: The main symptoms of a stroke convalescent period include hemiplegia, dysphasia and facial paralysis. Currently, no CPM is primarily used to treat each of these symptoms, and there are no relevant instructions. This study is an attempt to set up a new approach based on CER, which distinguishes the curative effects of three CPMs that are often used in stroke convalescence, to determine which medicine has the best effect for certain symptom(s).

Methods and analysis: In this multi-centre and double-blind clinical trial, stratified randomization is used for grouping the patients according to their primary symptoms (Hemiplegia, Dysphasia, Facial Paralysis). Three strata, each with 80 eligible participants, will be enrolled. Each stratum will be randomly and equally divided into 4 groups and they will receive treatment with NXK, XNST, XST and placebo, respectively. This study will include two stages: the first treatment (30 days) and follow-up (180 days). Three replicates for each data point will be arranged in this trial. The first visit is on day 0 after enrolment, and the second visit is on day 30±2, and the third visit is on day 210±5. Delphi technique is adopted to achieve index weighting, which ensures that the outcome of the evaluation is patient-oriented. The weighted index value will be computed as the final measurement index of the outcome.

Ethics and dissemination:

This study has been approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007). The results will be offered for publication in peer-reviewed journals.

Registration details: This trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-17010397). The date of registration was 11st Jan, 2017.

Keywords: Stroke, Chinese Patent Medicine, Comparative Effectiveness Research (CER)

Strengths and limitations of this study

- A multicentre, prospective and randomized controlled trial.
- This study explores the usage of CER in TCM.
- This study distinguishes the orientation of different CPMs using symptoms.
- The evaluation of a patient's recovery involves both the quality of life and clinical indexes.
- Using Delphi technique to assign weight to the scale indexes.
- The sample size is not large enough due to funding constraints (n=240, each group=20).

Background

The overall annual age-standardized incidence and death rates from stroke in the general population of the PRC were 115.61 and 81.88 per 100 000, respectively, in 1986. [1]Among these patients, approximately 75% of them suffer from cerebral ischaemic stroke. Because 70% to 80% of the patients who survive stroke suffer from various degrees of disabilities and cognitive handicaps, they need assistance in daily life, which seriously affects the quality of their lives and puts a heavy burden on their families and society. [2]

For the current treatment in the convalescence of stroke, clinical trials have showed that CPM has a significant curative effect. [3 4] Many patients in the convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence (many CPMs for patients with stroke are OTCs). [5] There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang (NXK), Xinnaoshutong (XNST) and Xuesaitong capsules (XST). These three CPMs have been on the market for many years and have received good clinical feedback. The Naoxuekang capsules (NXK) [6] are manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, and the main ingredient is leech, which has been proven to be safe, effective and has fewer adverse reactions according to clinical observation.[7] According to the Pharmacopoeia of the People's Republic of China, it is forbidden to give a NXK capsule to pregnant women and bleeding people. [8] Xinnaoshutong capsules (XNST) [9] are manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, and the main ingredient is Steroidal

saponins of Tribulus terrestris, which had no obvious adverse reactions in clinical trials. [10] According to the Pharmacopoeia of the People's Republic of China, XNST occasionally leads to adverse reactions, such as dry mouth and upset stomach. It is forbidden to give the medicine to patients who have intracranial haemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine with caution. [11] Xuesaitong capsules (XST) [12] are manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST and the main ingredient is Panax Notoginseng Saponins, which has minor adverse reactions and can be given to patients normally. [13] According to the Pharmacopoeia of the People's Republic of China, XST cannot be given to pregnant women and people with allergies. [14] These three CPMs are frequently used for the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, cephalophyma or cerebral thrombosis with symptoms caused by encephalorrhagia with high blood pressure. [8 11 14]

In addition, because CPM interprets an illness based on syndrome theories, medical practitioners who are not well educated in TCM theories or do not have enough clinical experience, are generally not able to provide reasonable prescriptions for CPM. Therefore, it is more easily understood and accepted by doctors and patients to provide instructions on how to use CPMs based on symptoms.

The feasibility of comparative effectiveness research in the evaluation of a CPM

The concept of comparative effectiveness research (CER) was initiated in the 1990s by Mark Boutin, the deputy executive president and chief operating officer of the US National Health Council. [15] The Agency for Healthcare Research and Quality (AHRQ) defined comparative effectiveness research as: "Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options".[16] The evidence was generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care. [17]

In the following years, CER was introduced into the field of clinical research in a number of countries. [18]

CER was introduced into TCM research at the sixth annual meeting of the International Society of Complementary Medicine Research by Claudia M Witt (Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany) in May 2011. [19] The outcome of comparative effectiveness research focuses on the problems that patients care about and want to solve mostly. [20] CER is concerned with answering questions about effectiveness rather than efficacy of interventions. [21] It is more patient-oriented, which means it respects the patients' will, cares about both the quality of their lives and psychological functions, as well as fits the TCM clinical practice and shows the validity of the results.

Effectiveness evaluation based on a patient-oriented theory

During a stroke convalescent period, patients suffer not only from various clinical symptoms but also the decline of their ability to perform daily activities and lower quality of life. Therefore, evaluation of a patient's recovery should involve both quality of life, including mental state, physical condition, psychological condition and social environment as well as clinical indexes.

Quality of life: According to WHOQOL-BREF, quality of life is evaluated by one's mental state, psychological state and physical state, among other factors. [22 23] **Clinical indexes:** The physiological indexes that show the degree of nervous functional defects can be evaluated using the National Institutes of Health Stroke Scale (NIHSS).

In this research study, WHOQOL-BREF and NIHSS are used to assess curative effects and determine their weight with Delphi. A comprehensive score is considered as the final curative effect. This approach avoids the randomness of the PRO (Patient Report Outcome) coming directly from patient reports to some degree.[24]

The Delphi technique is a method to quantify a qualitative description, which means it can synthesize the opinions from many experts in a scientific manner and provide a reasonable prediction about certain things. The Delphi technique asks for, collects and counts individual opinions and judgements by distributing questionnaires to obtain comparatively unanimous opinions on certain issues.

Methods/Design

A flowchart of the study protocol is shown in Fig. 1.

Inclusion criteria

1. Patients with ages from 30 to 65 years-old.

2. It is the first time that the patient has a stroke.

3. Diagnosis of unilateral, non-recurring, subacute stroke that is an ischaemic and lacunar type as defined by the International Classification of Diseases (ICD-10) through computed tomography or magnetic resonance imaging conducted by neurologists.

4. TCM pattern diagnosis of stroke in meridian syndrome.

5. Patients should have a score between 6 and 20 for the National Institutes of Health Stroke Scale (NIHSS).

6. It will have been four to eight weeks since the original stroke.

7. The patient will provide signed informed consent.

8. The above inclusion criteria will be applied to the experimental group and the control group.

Exclusion criteria

1. Patients with a known history of allergies or suspected allergies to the medicines used in the study.

2. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders.

3. Patients with other complications.

4. Uncontrolled NYHA class III hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg).

5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene or peripheral neuropathy).

6. Liver function impairment with values of ALT or AST over 1.5-fold the upper limit of the normal range.

7. Renal dysfunction with values of serum creatinine over 1.5-fold the upper limit of the normal range.

8. Patients with active peptic ulcers or other haemorrhagic diseases.

9. Patients who participate in other clinical trials, either currently or within the past 90 days.

Treatment plan

(1) Basic treatment

The intervention programme mainly uses China's Guidelines of Cerebrovascular Disease Prevention and controls as well as the consensus of foreign experts for a reference. This approach considers all the risk factors of apoplexy under strict control. The programme involves:

(a) An antiplatelet drug: Aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines are chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(e) During the test, Chinese patent medicine for activating blood circulation and removing stasis as well as compound Chinese medicines prescription will be banned from.

(2) The final treatment plans:

The treatment plan for group A (TPGA): □basic treatment +□Naoxuekang capsule (NXK).

The treatment plan for group B (TPGB): □basic treatment +□Xinnaoshutong capsule (XNST).

The treatment plan for group C (TPGC): □basic treatment +□Xuesaitong capsule(XST).

The treatment plan for group D (TPGD): □basic treatment+ placebo.

The dosage and method of CPMs will follow the doctor's advice.

(3) Participant timeline

A substantial observation period will last long enough to make sure that the curative effect appears. This

study will include two stages: the first treatment (30 days) and follow-up (180 days). Three replicates for each data point will be arranged in this trial. The first visit is on day 0 after enrolment, and the second visit is on day 30±2, and the third visit is on day 210±5.

(4) Termination criteria

Interventions for the trial participants will be discontinued if the following situations occur: (a) patients quit the study of their own free will; (b) major mistakes or serious deviations are identified in the clinical trial protocol in the process of execution (although the plan is good), which makes it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur over the trial; and (d) if the trial is cancelled by the authorities.

(5) The adherence of patients to the instructions

Patients will receive trial drugs and necessary healthcare instructions (diet, mental adjustment) for free. Patients are required to maintain appropriate physical activities and daily exercises. The dosage of the medicine and its remnant shall be recorded in real-time, and a drug counting method is used to monitor the adherence of patients. Patients get worse from the trial will be treated and cared for.

Patient grouping

Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. Overall, 240 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be balances, and the patients will be divided into three experimental groups and a control group.

(1) Patients will be divided into three strata according to their main symptoms. Each stratum will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to strata H. The patients whose main symptom is dysphasia will be assigned to strata D. The patients whose main symptom is facial

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paralysis will be assigned to strata F.

(2) Patients with the same main symptom will be divided into groups A, B, C and D both randomly and equally. Each of the 4 groups will be treated with different treatment plans, and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, including Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, and Group FD. Each group contains 20 patients. Table 1 shows the details as follows:

Table 1: Groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure that the same observation mode is maintained among the experimental groups and the control group. This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor, who is an expert in this field with clinical experience over ten years, is able to ensure an accurate assessment of the patient's symptoms. The WHOQOL-BREF and NIHSS questionnaires of all the patients will be recorded by this doctor at the beginning of experiment. The second visit is on day 30±2 and the third visit is on day 210±5.

(2) Evaluation Criteria

In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that

the outcomes can represent the wills of the patients and clinicians in a way that can meet the characteristic of comparative effectiveness research. Each index is designed as a questionnaire with four answers, including “very important”, “important”, “average/ not very important” and “not important”. Each expert judges the index system according to the four answers.

The formula for calculation is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N$$

…………………………………………………………………(1)

DW_i – the average value of the importance of the index i (i = w, n)

a_{ij} — the grade value of the index i;

j — the grade ordinal;

N — the number of the experts;

(3) The final curative effects

The effectiveness of each index is evaluated by comparing its value before and after the treatment. In this study, W_0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, including W_1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W_2 in eq. 3 is the value of WHOQOL-BREF after follow-up. N_0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N_1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N_2 in eq. 3 is the value of NIHSS after follow-up.

The formula for final curative effects calculation is as follows:

$W_1 * DW_W + N_1 * DW_N - (W_0 * DW_W + N_0 * DW_N)$………………… (2)

The formula for curative effects after follow-up is as follows:

$W_2 * DW_W + N_2 * DW_N - (W_0 * DW_W + N_0 * DW_N)$…………………(3)

DW_W in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DW_N in eq. 2 and eq. 3 indicates the

weight of NIHSS.

(4) Data collection methods

For each patient, measurement will be carried out at the following time points: 0, 30±2 and 210±5 days after treatment (Table 2). The clinical research associates are required to monitor various units on a regular and incessant basis. The data management of the trial follows Good Clinical Data Management Practice (GCDMP). [25]

Table 2 Data are captured based on the CRF

Items	Visit		
	1	2	3
	0 day	30±2days	210±5days
Medical History			
Inclusion/exclusion criteria	√		
Informed consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical treatments and allergies	√		
Current medications	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgement		√	√
Evaluation index			
WHOQOL-BREF	√	√	√
NIHSS	√	√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

Sample size

The sample size in this study is based on the trial results from previous reports and the recommendation of specialists. [26-32] The values of σ_i for WHOQOL-BREF scale of the experimental groups are 12.12, 19.51 and 12.24, respectively, while the value of σ_i for WHOQOL-BREF scale of the placebo group is 11.2. The values

of μ_i for the WHOQOL-BREF scale of experimental groups are 17.13, 18 and 23.83, respectively, while the value of μ_i for the WHOQOL-BREF scale of the placebo group is 10.83. According to the calculation, μ is 17.45, a type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 172 patients are needed in the trial (43 patients for each group). The values of σ_i for NIHSS scale of the experimental groups are 2.6, 7.31 and 3.11, respectively, while the values of σ_i for NIHSS scale of the placebo group is 12.5. The values of μ_i for the NIHSS scale of the experimental groups are 6.85, 4.95 and 6.1, respectively, while the values of μ_i for the NIHSS scale of the placebo group is 1.39. According to the calculation, μ is 4.82, a type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 232 patients are needed in the trial (58 patients for each group).

According to the calculations above and the recommendation of the specialists, 240 patients are collected in the trial with 60 patients for each group.

Statistical analysis

General information about the patients will be registered, including patient's number, sex, age, BMI, based diseases, type of symptom, accompanying symptom, education level and other basic information.

Mean and deviation will be used for the statistical description of the measurement data. Analysis variance will be used, if the data are normally distributed, while a rank test will be used in case the data are not normally distributed or there is heterogeneity of variance. The comparison between the three experimental groups and the control group is based on the analysis variance of the repeated measurement data. If $P<0.05$, then it is confirmed that there is a significant difference.

The evaluation result will be analysed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with a poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.

In this study, data analysis will be completed by researchers who do not participate into the experiment and clinical decision making, which makes sure that the bias caused by subjective factors from the researchers can be avioded.

Safety

Adverse events (AEs) and adverse drug reactions (ADRs) will be conducted and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be reported to the person in charge of the project and the ethics committee. Every AE will be recorded in detail and closely monitored before stabilization or resolution.

HLC will cooperate with the physician in charge to evaluate the severity and determine the cause of the events. All relevant AEs will be reported to the institutional review board of the First Affiliated Hospital of Tianjin University of TCM within the relevant time frames. HLC will be responsible for reporting all adverse events. The coordinators will be responsible for establishing the standard procedures and the training of relevant staff before trial initiation. Regular monitoring will be used to ensure that all AEs are identified and addressed appropriately.

The incidence of AEs and ADRs is compared between various groups using the χ^2 test with the level of significance set at $P < 0.05$.

Auditors are required to audit trials by checking documents in the middle of and at the end of the study, and the process will be independent of the investigators and the study sponsor.

Randomization, blinding and allocation concealment

Cases will be assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the trial patients will be finished using an independent data centre with an interactive voice response system, and the random number will be generated by these data centre. Original copies of the blind codes will be sealed in the lightproof

envelope, and one will be kept by the major research unit and the other by the applicant of the trial. The envelopes are not allowed to be opened before formal statistical analysis. If a patient is eligible, a patient number will be allocated by the doctors. The patient numbers are just the serial numbers for labelling patients. The test medicine will be coded first, and then it will be put in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be in opaque envelopes and are kept confidential by the trial management board. The original capsule shells of NXK, XNST and XST are exchanged for the new uniform capsule shells, which are conducted by the Pharmaceutical Factory of Tianjin University of TCM. Placebos are put into the same capsule shells, the content of which is amylum. Therefore, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.

If there are emergencies or necessary treatments for the patients, the person in charge of the participating units will immediately report to CRA and major investigators, and unblinding can only be performed with their approval. Once the allocation is unblinded, the investigators must comply with the trial requirements when operating and recording data.

Trial oversight

Steering Committee: responsible for the top-level design and guarantee that the test goes smoothly.

Coordinating Centre: four sub-centres are responsible for collecting cases and assuring quality.

End Point Adjudication Committee: to assess the outcome events and judge fall off and withdrawal cases.

Data Management Team: responsible for the data management, including data entry, verification and exporting.

CONCLUSIONS

The critical task of translational medicine in TCM is to translate the achievements of medical research into clinical practice, to establish a series of clinical diagnosis and treatment technical standards, guidelines

and/or pathways that are scientific, generalizable and acceptable to both TCM and western medicine practitioners. [33] A clear identification of the curative effect on symptoms is easier to understand by people who do not know much about TCM, which makes it easier for CPMs to be accepted by the whole world.

One of the advantages of CPM is to improve overall patient health. This study provides a comprehensive evaluation on CPMs from aspects of both clinical index and quality of life. Delphi technique is adopted to achieve index weighting, which ensures that the outcome of the evaluation is patient-oriented. Because the scale used in the study is an internationally standardized one, and the indexes of the scale are fixed, the result avoids the randomness that exists in the PRO directly coming from the patient's report.

ETHICS AND DISSEMINATION

This study has been approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007). If the protocol needs to be modified, we will apply for a new ethical review. All participating patients need to sign informed consent, and the researcher is required to explain the procedures and the objectives to be used in research, which includes detailed methods to be used, the risks and benefits, and stating the possibility of inclusion in a control or experimental group. The study follows the principle that all information related to patients is confidential, and their names will not appear in the records.

Trial status

Currently patients are being recruited for the trial.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

All authors declare no competing interests.

Funding

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Authors' contributions

Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN was in charge of all statistical works of the trial. XIA Q and Chen B helped conduct the survey. All authors have carefully read and approved the final manuscript. Sponsor designed this protocol, prepared the draft and was responsible for the selection of research units, researchers and drug resources. The costs of publishing article, buying drugs and so on are provided by the funders.

Acknowledgments

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Data sharing statement

The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All of the data are available.

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Table Captions

Table 1 Groups divided according to main symptoms and treatment plans

Table 2 Data are captured based on the CRF

Table 1 Groups divided according to main symptoms and treatment plans

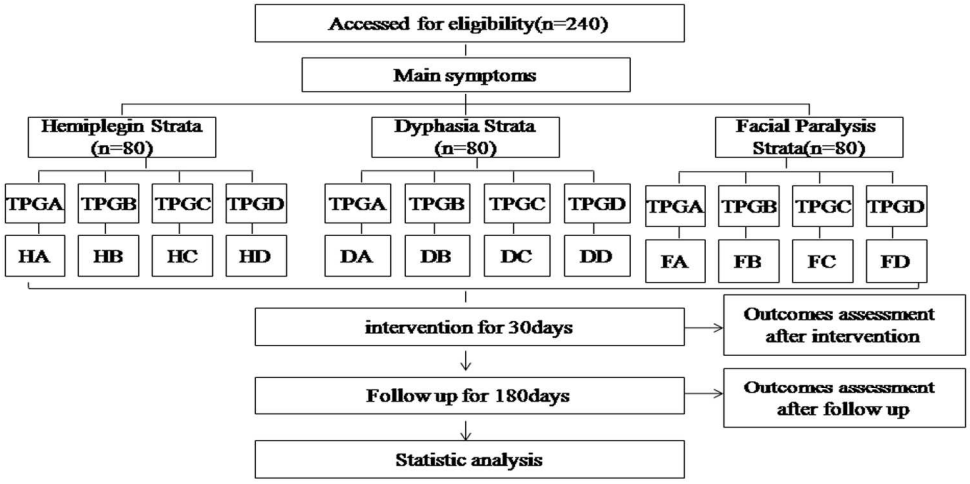
	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis（F）	FA	FB	FC	FD

Table 2 Data are captured based on the CRF

Items	Visit		
	1 0 day	2 30±2days	3 210±5days
Medical History			
Inclusion/exclusion criteria	√		
Informed consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical treatments and allergies	√		
Current medications	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgement		√	√
Evaluation index			
WHOQOL-BREF	√	√	√
NIHSS	√	√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

Figure Captions

Fig. 1 Flow chart of the protocol



233x113mm (300 x 300 DPI)

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

Section/item	Page and line Number	Item No.	Description
Administrative information			
Title	P1L1	1	Identify Characteristics of Chinese Patent Medicines (Naoxuekang, Xinnaoshutong and Xuesaitong capsules) based on Symptoms: a Protocol for a Randomized Controlled Trial
Trial registration	P2L48	2a	Chinese clinical trials register ChiCTR-IOR-17010397
		2b	Please retrieve the trial registration data of this study at this site http://www.chictr.org.cn/searchproj.aspx
Protocol version		3	Version: 81202849-2.1
Funding	P16L6	4	The study is funded by the National Natural Science Foundation of China (No. 81202849, No. 30600834, No. 81603659).
Roles and responsibilities	P16L11	5a	Chen HL designed the protocol and wrote the draft. GAO WY developed the idea and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited and contributed to the final report. ZHAO TN in charge of all statistical works of trial. XIA Q and Chen B helped conduct the survey. All authors carefully read and approved the final manuscript.
	P1L44	5b	Huiling Chen: chen.huiling@163.com 1 School of Pharmaceutical Science and Technology, Tianjin University, 72 Weijin Road, Nankai District, Tianjin 300072, China; 2 TianJin University of Traditional Chinese Medicine；312 Anshanxi Road, Nankai District, Tianjin 300193, China.

P16L19	5c	Sponsor designed this protocol, prepared the draft and is responsible for the selection of research units, researchers and drug resources. The costs of publishing article, buying drugs and so on are provided by the funders.
P14L39	5d	Steering Committee: responsible for the top-level design and guarantee that the test goes smoothly. Coordinating Centre: four sub-centres are responsible for collecting cases and assuring quality. End Point Adjudication Committee: to assess the outcome events and judge fall off and withdrawal cases. Data Management Team: responsible for the data management, including data entry, verification and exporting.

Introduction

Background and rationale	P3L16 6a	The overall annual age-standardized incidence and death rates from stroke in the general population of the PRC were 115.61 and 81.88 per 100 000, respectively, in 1986. 1Among these patients, approximately 75% of them suffer from cerebral ischaemic stroke. Because 70% to 80% of the patients who survive stroke suffer from various degrees of disabilities and cognitive handicaps, they need assistance in daily life, which seriously affects the quality of their lives and puts a heavy burden on their families and society. [2] For the current treatment in the convalescence of stroke, clinical trials have showed that CPM has a significant curative effect. [3 4] Many the patients in the convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence (many CPMs for patients with stroke are OTCs). [5]There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang (NXK), Xinnaoshutong (XNST) and Xuesaitong capsules (XST). These three CPMs have been on the market for many years and have received good clinical feedback. The Naoxuekang capsules (NXK) [6] are manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, and the main ingredient is leech, which has been proven to be safe, effective and has fewer adverse reactions according to clinical observation.[7]According to the Pharmacopoeia of the People's Republic of China, it is forbidden to give a NXK capsule to pregnant women and bleeding people. [8] Xinnaoshutong capsules (XNST) [9] are manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, and the main ingredient is Steroidal saponins of Tribulus terrestris, which had no obvious adverse reactions in clinical trials. [10]According to the Pharmacopoeia of the People's Republic of China, XNST occasionally leads to adverse reactions, such as dry mouth and upset stomach. It is forbidden to give the medicine to patients who have intracranial haemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine with caution. [11] Xuesaitong capsules (XST) [12] are manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST and the main ingredient is Panax Notoginseng Saponins, which has minor adverse reactions and can be given to patients normally. [13] According to the Pharmacopoeia of the People's Republic of China, XST cannot be given to pregnant women and people with allergies. [14] These three CPMs are frequently used for the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, cephalophyma or cerebral thrombosis with symptoms caused by encephalorrhagia with high blood pressure. [8 11 14] In addition, because CPM interprets an illness based on syndrome theories, medical practitioners who are not well educated in TCM theories or do not have enough clinical experience, are generally not able to provide reasonable prescriptions for CPM. Therefore, it is more easily understood and accepted by doctors and patients to provide instructions on how to use CPMs based on symptoms.

	P4L21	6b	Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule(XST) are frequently used for the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, cephalophyma or cerebral thrombosis with symptoms caused by encephalorrhagia with high blood pressure.
Objectives	P2L3	7	The main symptoms of a stroke convalescent period include hemiplegia, dysphasia and facial paralysis. Currently, no CPM is primarily used to treat each of these symptoms, and there are no relevant instructions. This study is an attempt to set up a new approach based on CER, which distinguishes the curative effects of three CPMs that are often used in stroke convalescence, to determine which medicine has the best effect for certain symptom(s).
Trial design	P2L16	8	In this multi-centre and double-blind clinical trial, stratified randomization is used for grouping the patients according to their primary symptoms (Hemiplegia, Dysphasia, Facial Paralysis). Three strata, each with 80 eligible participants, will be enrolled. Each stratum will be randomly and equally divided into 4 groups and they will respectively have treatment with NXK, XNST, XST and placebo. This study will include two stages: the first treatment (30 days) and follow-up (180 days).

Methods: Participants, interventions, and outcomes

Study setting	P8L38	9	Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China.

Eligibility criteria	P6L8	10	● Inclusion criteria 1. Patients with ages from 30 to 65 years-old. 2. It is the first time that the patient had a stroke. 3. Diagnosis of unilateral, non-recurring, subacute stroke that is an ischaemic and lacunar type as defined by the International Classification of Diseases (ICD-10) through computed tomography or magnetic resonance imaging conducted by neurologists. 4. TCM pattern diagnosis of stroke in meridian syndrome. 5. Patients should have a score between 6 and 20 for the National Institutes of Health Stroke Scale (NIHSS). 6. It has been four to eight weeks since the original stroke. 7. The patient provided signed informed consent. 8. The above inclusion criteria were applied to the experimental group and the control group. ● Exclusion criteria 1. Patients with a known history of allergies or suspected allergies to the medicines used in the study. 2. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders. 3. Patients with other complications. 4. Uncontrolled NYHA class III hypertension (systolic blood pressure ⩾ 180 mmHg and/or diastolic blood pressure ⩾110 mmHg). 5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene or peripheral neuropathy). 6. Liver function impairment with values of ALT or AST over 1.5-fold the upper limit of the normal range. 7. Renal dysfunction with values of serum creatinine over 1.5-fold the upper limit of the normal range. 8. Patients with active peptic ulcers or other haemorrhagic diseases. 9. Patients who participate in other clinical trials, either currently or within the past 90 days.

Interventions P7L8 11a **Treatment plan**

(1)Basic treatment

The intervention programme mainly uses China's Guidelines of Cerebrovascular Disease Prevention and controls as well as the consensus of foreign experts for a reference. This approach considers all the risk factors of apoplexy under strict control. The programme involves:

(a) An antiplatelet drug: Aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines are chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(e) During the test, Chinese patent medicine for activating blood circulation and removing stasis as well as compound Chinese medicines prescription were banned from.

(2) The final treatment plans:

The treatment plan for group A(TPGA): ① basic treatment + ② Naoxuekang capsule (NXK).

The treatment plan for group B(TPGB): ① basic treatment + ② Xinnaoshutong capsule (XNST).

The treatment plan for group C(TPGC): ① basic treatment + ② Xuesaitong capsule(XST).

The treatment plan for group D(TPGD): ①basic treatment+ placebo.

The dosage and method of CPMs will follow the doctor's advice.

(3) Participant timeline

A substantial observation period will last long enough to make sure that the curative effect appears. This study will include two stages: the first treatment (30 days) and follow-up (180 days). Three replicates for each data point will be arranged in this trial. The first visit is on day 0 after enrolment, and the second visit is on day 30±2, and the third visit is on day 210±5.

(4) Termination criteria

Interventions for the trial participants will be discontinued if the following situations occur: (a) patients quit the study of their own free will; (b) major mistakes or serious deviations are identified in the clinical trial protocol in the process of execution (although the plan is good), which makes it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur over the trial; and (d) if the trial is cancelled by the authorities.

(5) The adherence of patients to the instructions

Patients will receive trial drugs and necessary healthcare instructions (diet, mental adjustment) for free. Patients are required to maintain appropriate physical activities and daily exercises. The dosage of the medicine and its remnant shall be recorded in real-time, and a drug counting method is used to monitor the adherence of patients. Patients get worse from the trial will be treated and cared for.

Patient grouping

Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. Overall, 240 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be balances, and the patients will be divided into three experimental groups and a control group.

(1) Patients will be divided into three strata according to their main symptoms. Each stratum will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to strata H. The patients whose main symptom is dysphasia will be assigned to strata D. The patients whose main symptom is facial paralysis will be assigned to strata F.

(2) Patients with the same main symptom will be divided into groups A, B, C and D both randomly and equally. Each of the 4 groups will be treated with different treatment plans, and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, including Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, and Group FD. Each group contains 20 patients. Table 1 shows the details as follows:

Table 1: groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis （F）	FA	FB	FC	FD

P8L10 11b Interventions for the trial participants will be discontinued if the following situations occur: (a) patients quit the study of their own free will; (b) major mistakes or serious deviations are identified in the clinical trial protocol in the process of execution (although the plan is good), which makes it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur over the trial; and (d) if the trial is cancelled by the authorities.

P8L24 11c **The adherence of patients to the instructions**

Patients will receive trial drugs and necessary healthcare instructions (diet, mental adjustment) for free. Patients are required to maintain appropriate physical activities and daily exercises. The dosage of the medicine and its remnant shall be recorded in real-time, and a drug counting method is used to monitor the adherence of patients. Patients get worse from the trial will be treated and cared for.

P7L34 11d During the test, Chinese patent medicine for activating blood circulation and removing stasis as well as compounded Chinese medicine prescription were banned from.

Outcomes P9L30 12 Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to make sure that the same observation mode is maintained among the experimental groups and the control group. This doctor will not take part in clinical decisions to avoid evaluator bias. The doctor, who is an expert in this field with clinical experience over ten years, is able to ensure an accurate assessment of the patient's symptoms. The WHOQOL-BREF and NIHSS questionnaires of all the patients will be recorded by this doctor at the beginning of experiment. The second visit is on day 30±2 and the third visit is on day 210±5.

(2) Evaluation Criteria

In this study, the weight table of the indexes above will be given to both the doctors and the patients, so that the outcomes can represent the wills of the patients and clinicians in a way that can meet the characteristic of comparative effectiveness research. Each index is designed as a questionnaire with four answers, including “very important”, “important”, “average/ not very important” and “not important”. Each expert judges the index system according to the four answers.

The formula for calculation is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N$$

……(1)

DW_i – the average value of the importance of the index i (i = w, n)

aij—the grade value of the index i;

j — the grade ordinal;

N— the number of the experts;

DW_W in eq. 2 and eq. 3 indicates the weight of WHOQOL-BREF, and DW_N in eq. 2 and eq. 3indicates the weight of NIHSS.

(3)The final curative effects

The effectiveness of each index is evaluated by comparing its value before and after the treatment. In this study, W0 in eq. 2 and eq. 3 represents the value of WHOQOL-BREF before treatment, including W1 in eq. 2 and eq. 3 indicates the value of WHOQOL-BREF after treatment, and W2 in eq. 3 is the value of WHOQOL-BREF after follow-up. N0 in eq. 2 and eq. 3 represents the value of NIHSS before treatment, and N1 in eq. 2 and eq. 3 indicates the value of NIHSS after treatment in this study, and N2 in eq. 3 is the value of NIHSS after follow-up.

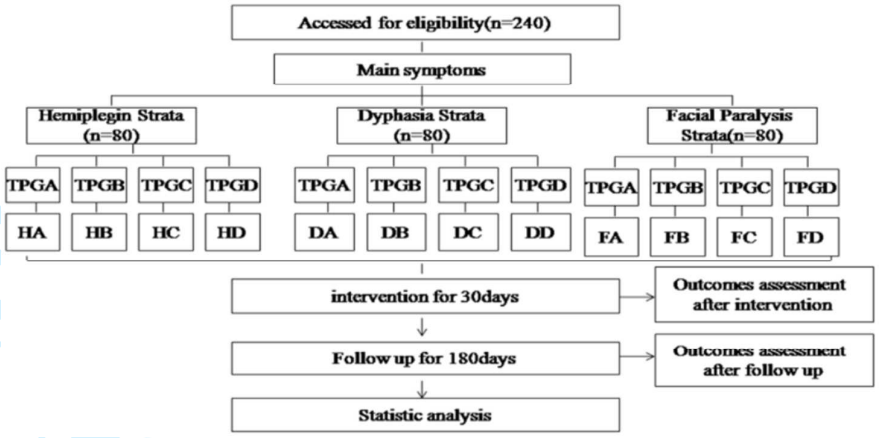
The formula for final curative effects calculation is as follows:

$W_1 * DW_W + N_1 * DW_N - (W_0 * DW_W + N_0 * DW_N)$…… (2)

The formula for curative effects after follow-up is as follows:

$W_2 * DW_W + N_2 * DW_N - (W_0 * DW_W + N_0 * DW_N)$……(3)

Participant timeline	P7L55 P6L3	13	A substantial observation period will last long enough to make sure that the curative effect appears. This study will include two stages: the first treatment (30 days) and follow-up (180 days). Three replicates for each data point will be arranged in this trial. The first visit is on day 0 after enrolment, and the second visit is on day 30±2, and the third visit is on day 210±5. (Figure 1)



Sample size	P11L48	14	The sample size in this study is based on the trial results from previous reports and the recommendation of specialists. 26-32 The values of σi for WHOQOL-BREF scale of the experimental groups before and after treatment are 12.12, 19.51 and 12.24, respectively, while the value of σi for WHOQOL-BREF scale of the placebo group is 11.2. The values of μi for the WHOQOL-BREF scale of experimental groups before and after treatment are 17.13, 18 and 23.83, respectively, while the value of μi for the WHOQOL-BREF scale of the placebo group before and after treatment is 10.83. According to the calculation, μ is 17.45, a type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 172 patients are needed in the trial (43 patients for each group). The values of σi for NIHSS scale of the experimental groups before and after treatment are 2.6, 7.31 and 3.11, respectively, while the values of σi for NIHSS scale of the placebo group is 12.5. The values of μi for the NIHSS scale of the experimental groups before and after treatment are 6.85, 4.95 and 6.1, respectively, while the values of μi for the NIHSS scale of the placebo group before and after treatment is 1.39. According to the calculation, μ is 4.82, a type I error is 0.05 and the power is 90%. If the drop-out rate is 20%, 232 patients are needed in the trial (58 patients for each group). According to the calculations above and the recommendation of the specialists, 240 patients are collected in the trial with 60 patients for each group.

Recruitment	P8L38	15	Cases will be collected in the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. Overall, 240 cases qualified for inclusion will be gathered from 4 hospitals at the same time. To avoid selective bias, the number of the patients recruited in each hospital should be balances, and the patients will be divided into three experimental groups and a control group. (1) Patients will be divided into three strata according to their main symptoms. Each stratum will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to strata H. The patients whose main symptom is dysphasia will be assigned to strata D. The patients whose main symptom is facial paralysis will be assigned to strata F. (2) Patients with the same main symptom will be divided into groups A, B, C and D both randomly and equally. Each of the 4 groups will be treated with different treatment plans, and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, there are 12 groups, including Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, and Group FD. Each group contains 20 patients.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	P13L48	16a	Cases are assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the trial patients will be finished using an independent data centre with an interactive voice response system, and the random number will be generated by these data centre.
Allocation concealment mechanism	P13L56	16b	Original copies of the blind codes are sealed in the lightproof envelope, and one was kept by the major research unit and the other by the applicant of the trial and the envelopes are not allowed to be opened before formal statistical analysis. If a patient was eligible, a patient number will be allocated by the doctors. The patient numbers are just the serial numbers for labelling patients.
Implementation	P13L51	16c	Randomization of the trial patients will be finished using an independent data centre with an interactive voice response system, and the random number will be generated by these data centre.

Blinding (masking) P14L3 17a If a patient was eligible, a patient number will be allocated by the doctors. The patient numbers are just the serial numbers for labelling patients. The test medicine will be coded first, and then it will be put in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be in opaque envelopes and are kept confidential by the trial management board. The original capsule shells of NXK, XNST and XST were exchanged for the new uniform capsule shells, which was conducted by the Pharmaceutical Factory of Tianjin University of TCM. The placebo was put into the same capsule shells, the content of which was amylum. Therefore, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to treatment assignment.

P14L26 17b If there are emergencies or necessary treatments for the patients, the person in charge of the participating units will immediately report to CRA and major investigators, and unblinding can only be performed with their approval. Once the allocation is unblinded, the investigators must comply with the trial requirements when operating and recording data.

Methods: Data collection, management, and analysis

Data collection methods P11L17 18a

Items	Visit 1 0 day	2 30±2days	3 210±5days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical treatment and allergies	√		
Current medications	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF	√	√	√
NIHSS	√	√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

	P11L8	18b	Clinical research associates are required to monitor various units on a regular and incessant basis.
Data management	P11L11	19	The data management of the trial follows Good Clinical Data Management Practice (GCDMP). [25] ● Management Software This trial plans to use Oracle Clinical (OC) software for unified data management, online data updating and tracing, and exercise dynamic and efficient management of clinical trial data at the same time with the support of the check function of the software. ● Data recording All data of the trial are subject to remote recording. Investigators will enter relevant data by logging on the internet, such a pattern contributes to upgrading quality and efficiency of clinical study. ● Data examination Data administrator performs logic check and automatic comparison of data information using the check function of OC software, check the result values inconsistent with the case report forms, and check one-by-one with the original case report form and make corrections, so as to ensure the data in the database consistent with the results of the case report form. This way enables traceability, accuracy, completeness and timeliness of data. ● Data exporting After the trial, data administrator will export the data confirmed correct from OC system as demanded by the statistician, and will be provided to the statistical analysts in the form of data interexchange code, statistical analysts will extract relevant data from the database according to the code and program for statistical analysis.
Statistical methods	P12L38	20a	Mean and deviation are used for the statistical description of the measurement data. Analysis variance will be used, if the data are normally distributed, while a rank test will be used in case the data are not normally distributed or there is heterogeneity of variance. The comparison between the three experimental groups and the control group is based on the analysis variance of the repeated measurement data. If $P<0.05$, then it is confirmed that there is a significant difference.
	P13L3	20b	In this study, data analysis will be completed by researchers who do not participate into the experiment and clinical decision making, which makes sure that the bias caused by subjective factors from the researchers can be eliminated.
	P12L51	20c	The evaluation result will be analysed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with a poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.

Methods: Monitoring

Data monitoring	P11L11	21 a	The data management of the trial follows Good Clinical Data Management Practice (GCDMP). [25] Independent Data Monitor Committee (IDMC) made up of clinical experts, statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial.
	P11L11	21 b	The data management of the trial follows Good Clinical Data Management Practice (GCDMP) . [25] When significant abnormal data or data on serious adverse reactions are monitored, it depends on the joint decision of both the data monitoring center and the trial committee whether the trial should be stopped. Patients accord with termination standards will be terminated.
Harms	P13L13	22	Adverse events (AEs) and adverse drug reactions (ADRs) will be conducted and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be reported to the person in charge of the project and the ethics committee. Every AE will be recorded in detail and closely monitored before stabilization or resolution. HLC will cooperate with the physician in charge to evaluate the severity and determine the cause of the events. All relevant AEs will be reported to the institutional review board of the First Affiliated Hospital of Tianjin University of TCM within the relevant time frames. HLC will be responsible for reporting all adverse events. The coordinators will be responsible for establishing the standard procedures and the training of relevant staff before trial initiation. Regular monitoring will be used to ensure that all AEs are identified and addressed appropriately. The incidence of AEs and ADRs is compared between various groups using the $\chi 2$ test with the level of significance set at $P < 0.05$.
Auditing	P13L41	23	Auditors are required to audit trials by checking documents in the middle of and at the end of the study, and the process will be independent of the investigators and the study sponsor.

Ethics and dissemination

Research ethics approval	P15L23	24	This study has been approved by the medical ethics committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007).
Protocol amendments	P15L26	25	If the protocol needs to be modified, we will apply for a new ethical review.
Consent or assent	P15L28	26a	Patients, immediate family member or supervisors will obtain informed consent.

		26b	Not Applicable
Confidentiality	P15L36	27	The study follows the principle that all information related to patients is confidential, and their names will not appear in the records.
Declaration of interests	P16L1	28	All authors declare no competing interests.
Access to data	P14L46	29	Data Management Team: responsible for the data management, including data entry, verification and exporting.
Ancillary and post-trial care	P8L33	30	Patients get worse from the trial will been treated and cared for.
Disseminati on policy	P17L1	31a	The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All of the data are available. 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
		31b	When published, the use of any content in the article must be through the magazine and the authors' permission.
		31c	The protocol is to be published in open access journal and the researchers can download it through the network.
Appendices			
Informed consent materials		32	Model consent form and other related documentation given to participants and authorised surrogates will be the last part of the checklist.
Biological specimens		33	Not appliable

*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.

Notes for Subjects

Dear Mr. / Ms:

You are invited to take part in the program"Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial",

which is implemented by Tianjin University of Traditional Chinese Medicine. Before you make the final decision, please read the following parts carefully. It can help you learn the meaning of the trial, as well as the benefits and risks it may bring to you.

The background and objective of this study

1. Background

The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have shown that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three CPMs have come onto the market for many years and have got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, the main ingredient of which is leech, is proved to be safe, effective and with less adverse reactions by clinical observation [7]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and people who are bleeding [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. XNST, the main ingredient of which is Steroidal saponins of Tribulus terrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of Peoples Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously[11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, the main ingredient of which is Panax Notoginseng Saponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia

of Peoples Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14].

Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

2. Objective

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.

Trial procedure

This is a randomized controlled, double-blind design. 360 patients are assigned randomly using stratified blocked randomization method (1:1:1:1). If you agree to participate in the trial and meet the conditions, you will take part in the 30-day clinical trial and 180 follow up after signing the consent form voluntarily. This study comprises two stages:

1. Screening

Doctors are going to take your medical history and ask you to do certain medical and chemical examinations. If the results don't meet the conditions, then you will not participate in the second phase.

2. Treatment

After being chosen in the first phase, you will come into a 30 days treatment with medicines and a 180 days follow up. In this trial, you can be randomly distributed to group 1, group 2, group 3 or group 4, which has no influence on your conventional treatment.

The medicines used in this trial may modify your condition in various degrees according to your physical state. If you participate in the trial , we need you to obey the following rules:

- Do not medicate yourself with medicines that are not allowed for joint application.
- Strictly follow the doctors' orders about medicine taking and examinations.

Volunteers' Rights and Interests

Medicines given to you during the trial are free.

All the other conventional treatments and examinations that are not involved in the trial will be charged as usual.

The Security of the Volunteers' Privacy

The study established the principle that all information related to patient is confidential, and their name will not appear on the records. The results of the trial may be published in medical journals, but all your personal information will be classified. Only when it is necessary can ethics committee members of the hospital and the research member have access to your medical materials with approval. Others will not have access to your materials. You are voluntarily participate in every phase of the trial. You can refuse to take part in it at the beginning, or quit without any reason at any time. All the decisions you make will not affect your conventional treatment. If you agree to participate, you or your agent need to sign the consent form.

The Risks and Discomfort that may occur in the trial and the countermeasures that will be taken

If there are foreseeable adverse reactions, such as itch, or the ones not yet discovered or unforeseeable, doctors will take treatment measures in time according to your condition, in order to reduce the possible risks. If you have serious adverse reactions, you will get active treatment.

Consent Form

Title of the research: "Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial".

This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20170005). contact the ethics committee:022-27493265

The leader of the doctor have explained the content of the clinical research to me. I have chances to ask questions and have got answers to all of them. I have totally understood these answers.

I participate in the trial voluntarily. I can quit at any time, which will not affect the treatments I should have in the hospital. I have right to get a copy of the consent form.
I have carefully read the Notes for Volunteers and totally understood it. I agree to participate in the trial.

signature of the subject： Tel： Date：

signature of the agent： Tel： Date：

signature of the researcher： Tel： Date：

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Naoxuekang, Xinnaoshutong and Xuesaitong capsules for treating stroke: A protocol for a randomized controlled trial

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Naoxuekang, Xinnaoshutong and Xuesaitong capsules for treating stroke: A protocol for a randomized controlled trial

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Abstract

Introduction: After stroke, hemiplegia, dysphasia and facial paralysis can manifest during the convalescent period. Currently, no Chinese patent medicine (CPM) is previously reported to cure each of these symptoms primarily, and thus, there are no relevant instructions for the use of CPM. This study presents a new approach based on comparative effectiveness research (CER) to distinguish the curative effects of three CPMs that are often used in stroke convalescence in order to determine the ideal medicine for the treatment of each symptom.

Methods and analysis: In this multi-centre and double-blind clinical trial, stratified randomization is used to group the patients according to their primary symptoms (hemiplegia, dysphasia, and facial paralysis). Three strata will be enrolled, with 80 eligible participants included in each stratum. Each stratum will be randomly and equally divided into 4 groups, and each group will receive one of the following treatments: Naoxuekang (NXK), Xinnaoshutong (XNST), Xuesaitong (XST) or placebo. This study will include two stages: the initial treatment period (30 days) and a follow-up period (180 days). Three replicates for each data point will be completed during this trial. The first visit will occur on day 0 after enrolment, the second visit on day 30±2, and the third visit on day 210±5. The Delphi technique is adopted to achieve index weighting, which ensures that the evaluation outcome is patient oriented. The weighted index value will be computed as the final measurement index of the outcome.

Ethical approval and data dissemination:

This study has been approved by the Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007). The results will be offered for publication in peer-reviewed journals.

Registration details: This trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-17010397). The date of registration was 11 Jan 2017.

Keywords: Stroke, Chinese Patent Medicine, Comparative Effectiveness Research (CER)

Strengths and limitations of this study

- A multi-centre, prospective and randomized controlled trial design is utilized.
- The evaluation of patient recovery will include both quality of life and clinical indexes.
- The Delphi technique will be used to assign weight to the scale indexes.
- The sample size is small due to funding constraints.

Background

The overall annual age-standardized incidence and death rate from stroke in the general population of the PRC were 115.61 and 81.88 per 100 000 people, respectively, in 1986.[1] Among these patients, approximately 75% of them suffered from cerebral ischaemic stroke. Because 70% to 80% of the patients who survive stroke experience various degrees of disability and suffer from cognitive handicaps, they require assistance in performing activities of daily life, which severely affects their quality of life and places a heavy burden on their families as well as society.[2]

For the current treatment in the convalescence of stroke, clinical trials have shown that Chinese patent medicine (CPM) has a significant curative effect.[3 4] Many patients in the convalescent or sequelae stage voluntarily take CPMs to treat this disease and prevent recurrence (many CPMs for patients with stroke are OTCs).[5] There are various kinds of CPMs with similar instructions for the treatment of stroke, such as Naoxuekang (NXK), Xinnaoshutong (XNST) and Xuesaitong (XST) capsules. These three CPMs have been on the market for many years and have received positive clinical feedback. NXK capsules[6] are manufactured by Shandong HaoFu Pharmaceutical Co., Ltd. The main ingredient of NXK is leech, and NXK has been proven to be effective and to cause minor adverse reactions according to clinical observation.[7] According to the Pharmacopoeia of the People's Republic of China, pregnant women and individuals with bleeding disorders should never be treated with NXK.[8] Xinnaoshutong (XNST)[9] capsules are manufactured by Jilin

Aodong Taonan Pharmaceutical Co., Ltd. The main ingredient of XNST is steroidal saponins of Tribulus terrestris, and XNST has not elicited obvious adverse reactions in clinical trials.[10] According to the Pharmacopoeia of the People's Republic of China, XNST occasionally leads to mild adverse reactions, such as dry mouth and upset stomach. Patients who have intracranial haemorrhage should not be treated with XNST, while patients with a history of bleeding or blood-low-viscosity-syndrome should be treated with XNST, albeit with caution.[11] Xuesaitong (XST) capsules[12] are manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. The main ingredient of XST is Panax notoginseng saponins, and according to the results of clinical trials, only minor adverse reactions have been reported; thus, it can be given to all patients without restriction.[13] However, according to the Pharmacopoeia of the People's Republic of China, XST should not be given to pregnant women or people with allergies.[14] These three CPMs are frequently used for the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, cephalophyma or cerebral thrombosis with symptoms caused by encephalorrhagia with high blood pressure.[8 11 14]

In addition, because CPM interprets an illness based on syndrome theories, medical practitioners who are not well educated in Traditional Chinese Medicine (TCM) theories or those with little clinical experience are often unable to prescribe appropriate CPMs. Therefore, providing instructions on how to use CPMs based on symptoms is more easily understood and accepted by both doctors and patients.

The feasibility of comparative effectiveness research in the evaluation of a CPM

The concept of comparative effectiveness research (CER) was introduced in the 1990s by Mark Boutin, the deputy executive president and chief operating officer of the US National Health Council.[15] The Agency for Healthcare Research and Quality (AHRQ) defined CER as follows: "Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options".[16] The evidence was generated from research studies that compare drugs,

medical devices, tests, surgeries, or healthcare delivery methods.[17]

In the following years, CER was introduced into the field of clinical research in numerous countries.[18] In May 2011, CER was introduced into TCM research at the Sixth Annual Meeting of the International Society of Complementary Medicine Research by Claudia M Witt (Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany).[19] The outcome of CER focuses on solving the most important problems facing patients.[20] Thus, CER is concerned with answering questions about the overall effectiveness of interventions rather than efficacy of interventions.[21] It is more patient oriented, which means it respects the patients' will, focuses on both the quality of life and psychological wellbeing of patients, aligns with TCM clinical practice.

Effectiveness evaluation based on a patient-oriented theory

During the convalescent period after stroke, patients suffer not only from various clinical symptoms but also from an inability to perform certain activities of daily living and a lower quality of life. Therefore, evaluation of a patient's recovery should involve both their quality of life, including their mental state, physical condition, psychological condition and social environment, and their clinical indexes.

In this study, the WHOQOL-BREF and National Institutes of Health Stroke Scale (NIHSS) are used to assess curative effects and determine their weight with the Delphi technique. A comprehensive score is considered the final curative effect. This approach avoids the randomness of the patient report outcome (PRO) to some degree, which originates directly from patient reports.[22]

The Delphi technique is used to quantify a qualitative description; thus, it can synthesize the opinions of many experts in a scientific manner to provide reasonable predictions. The Delphi technique asks for, collects and counts individual opinions and judgements by distributing questionnaires to obtain comparatively unanimous opinions on certain issues.

Methods/Design

A flowchart of the study protocol is shown in Fig.1.

Inclusion criteria

1. Patients aged 30 to 65 years.

2. Patients experiencing their first stroke event.

3. Diagnosis of unilateral, non-recurring, subacute stroke that is anischaemic and lacunar type as defined by the International Classification of Diseases (ICD-10) through computed tomography or magnetic resonance imaging conducted by neurologists.

4. TCM pattern diagnosis of stroke in meridian syndrome.

5. Patients with a score between 6 and 20 for the NIHSS.

6. Duration of four to eight weeks since the original stroke event.

7. Signed informed consent provided by the patient.

The above inclusion criteria will be applied to the experimental group and the control group.

Exclusion criteria

1. Patients with a known history of allergies or suspected allergies to the medicines used in the study.

2. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders.

3. Patients with other complications.

4. Uncontrolled NYHA class III hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg).

5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene or peripheral neuropathy).

6. Liver function impairment with values of ALT or AST over 1.5-fold the upper limit of the normal range.

7. Renal dysfunction with values of serum creatinine over 1.5-fold the upper limit of the normal range.

8. Patients with active peptic ulcers or other haemorrhagic diseases.

9. Patients who are actively participating in other clinical trials or who participated in another clinical trial within the past 90 days.

Treatment plan

(1)Basic treatment

The intervention programme mainly uses China's Guidelines of Cerebrovascular Disease Prevention and controls as well as the consensus of foreign experts for a reference. This approach considers all the risk factors of apoplexy under strict control. The programme involves the following:

(a) An antiplatelet drug: Aspirin, taken as prescribed.

(b) Blood fat control: Simvastatin, taken as prescribed.

(c) Blood pressure control: medicines are chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers.

(d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control.

(e) During the test, all CPMs for activating blood circulation and removing stasis as well as combined Chinese medicine prescriptions will be banned.

(2) The final treatment plans

The treatment plan for group A (TPGA): basic treatment +Naoxuekang capsule (NXK)

The treatment plan for group B (TPGB): basic treatment +Xinnaoshutong capsule (XNST)

The treatment plan for group C (TPGC): basic treatment +Xuesaitong capsule(XST)

The treatment plan for group D (TPGD): basic treatment+ placebo

The CPM dosage and administration method will follow the doctor's recommendation.

(3) Participant timeline

An extended observation period will occur to ensure that the curative effect will be accurately determined.

This study will include two stages: the initial treatment period (30 days) and a follow-up period (180 days). Three replicates for each data point will be arranged in this trial. The first visit will occur on day 0 after enrolment, the second visit on day 30±2, and the third visit on day 210±5.

(4) Termination criteria

Interventions for the trial participants will be discontinued if (a) patients leave the study of their own free will; (b) major errors or serious deviations in study execution (although the plan is good) are identified during the clinical trial protocol that would make it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur during the trial; and (d) the trial is discontinued by the authorities.

(5) Patient adherence to the instructions

Patients will receive trial drugs and all necessary healthcare instructions (diet, mental adjustment) for free. Patients are required to maintain appropriate physical activity levels and perform daily exercises. The dosage of the medicine and any remnant shall be recorded in realtime, and a drug counting method will be used to monitor the adherence of patients. Patients whose conditions worsen during the trial will be treated appropriately.

Patient grouping

Patients will be recruited from the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. Overall, 240 patients who qualify for inclusion will be recruited from all 4 hospitals during the same time period. To avoid selective bias, the number of patients receiving treatment at each hospital should be balanced, and the patients will be divided into three experimental groups and a control group.

(1) Patients will be stratified according to their main symptoms. Each stratum will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to stratum H. The patients whose main symptom is dysphasia will be assigned to stratum D. The patients whose main symptom is facial paralysis

will be assigned to stratum F.

(2) Patients with the same main symptom will be divided into Groups A, B, C and D both randomly and equally. Each of the 4 groups will be treated with different treatment plans, and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, 12 groups will be generated: Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, and Group FD. Each group will contain 20 patients. Table 1 presents the details according to patient groups.

Table 1: Groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia (H)	HA	HB	HC	HD
Dysphasia (D)	DA	DB	DC	DD
Facial Paralysis (F)	FA	FB	FC	FD

Effectiveness assessment

(1) Assessment expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to ensure that observation mode is consistent across the experimental groups and the control group. This doctor will not participate in clinical decisions to avoid evaluator bias. With over ten years of clinical experience, this physician is an expert in this field and is able provide an accurate assessment of patient symptoms. The WHOQOL-BREF and NIHSS questionnaires of all the patients will be recorded by this doctor on day 0, at the beginning of the experiment; the second visit will occur on day 30±2, and the third visit on day 210±5.

(2) Evaluation criteria

Quality of life: According to the WHOQOL-BREF, quality of life is evaluated by one's mental state, psychological state and physical state, among other factors. [23 24] **Clinical indexes:** The physiological indexes

that show the degree of nervous functional defects can be evaluated using the NIHSS.

In this study, the weight table of the indexes will be provided to both the doctors and the patients so that the outcomes can represent the will of each patient and their clinician in a way that aligns with comparative effectiveness research. Each index is designed as a questionnaire with four answers, including “very important”, “important”, “average/not very important” and “not important”. Each expert will evaluate the index system according to these four answers.

The formula is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N \qquad \text{(1)}$$

DW_i – the average value of the importance of the index i (i=w, n);

a_{ij} — the grade value of the index i;

j — the grade ordinal; and

N — the number of the experts.

(3) Final curative effects

Treatment effectiveness is evaluated by comparing the value of each index before treatment with that after treatment. In this study, W_0 in eqs. 2 and 3 represents the value of the WHOQOL-BREF before treatment, W_1 in eqs. 2 and 3 indicates the value of the WHOQOL-BREF after treatment, and W_2 in eq. 3 is the value of the WHOQOL-BREF after follow-up. N_0 in eqs. 2 and 3 represents the value of the NIHSS before treatment, N_1 in eqs. 2 and 3 indicates the value of the NIHSS after treatment, and N_2 in eq. 3 is the value of the NIHSS after follow-up.

The formula for final curative effects calculation is as follows:

$$W_1 \times DW_W + N_1 \times DW_N - (W_0 \times DW_W + N_0 \times DW_N) \qquad \text{(2)}$$

The formula for curative effects after follow-up is as follows:

$W_2 \times DW_W + N_2 \times DW_N - (W_0 \times DW_W + N_0 \times DW_N)$……(3)

DW_W in eqs. 2 and 3 indicates the weight of the WHOQOL-BREF, and DW_N in eqs. 2 and 3 indicates the weight of the NIHSS.

(4) Data collection methods

For each patient, measurements will be taken at 0, 30±2 and 210±5 days after treatment (Table2). The clinical research associates are required to monitor various units on a regular and continuous basis. The data management of the trial follows Good Clinical Data Management Practice (GCDMP).[25]

Table 2 Data based on the CRF

Items	Visit		
	1 0 day	2 30±2days	3 210±5days
Medical history			
Inclusion/exclusion criteria	√		
Informed consent form(ICF)	√		
Symptom differentiation	√		
General information	√		
History of medical treatments and allergies	√		
Current medications	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgement		√	√
Evaluation index			
WHOQOL-BREF	√	√	√
NIHSS	√	√	√
Safety observation			
Vital signs	√	√	√
Adverse events(AEs)		√	√

Sample size

The sample size in this study is based on the trial results from previous reports and the recommendation of specialists.[26-32] The values of σ_i for the WHOQOL-BREF scale of the experimental groups are 12.12, 19.51

and 12.24, while the value of σ_i for the WHOQOL-BREF scale of the placebo group is 11.2. The values of μ_i for the WHOQOL-BREF scale of experimental groups are 17.13, 18 and 23.83, while the value of μ_i for the WHOQOL-BREF scale of the placebo group is 10.83. According to the calculation, μ is 17.45, the type I error is 0.05, and the power is 90%. If the drop-out rate is 20%, then 172 patients are needed in the trial (43 patients per group). The values of σ_i for the NIHSS scale of the experimental groups are 2.6, 7.31 and 3.11,while the values of σ_i for the NIHSS scale of the placebo group is 12.5. The values of μ_i for the NIHSS scale of the experimental groups are 6.85, 4.95 and 6.1, while the values of μ_i for the NIHSS scale of the placebo group is 1.39. According to the calculation, μ is 4.82, the type I error is 0.05, and the power is 90%. If the drop-out rate is 20%, then 232 patients are needed in the trial (58 patients per group).

According to the calculations above and recommendations from the specialists, 240 patients will be used for the trial, with 60 patients per group.

Statistical analysis

General information about the patients will be registered, including the patient number, sex, age, BMI, comorbid diseases, type of symptoms, accompanying symptoms, education level and other basic information.

The mean±standard deviation will be used for the statistical description of the measurement data. An analysis of variance will be used if the data are normally distributed, while a sum-rank test will be used if the data are not normally distributed or if heterogeneity is found. A comparison among the three experimental groups and the control group will be based on analysis of variance of the repeated measurement data. $P<0.05$ will be considered as a significant difference.

The evaluation result will be analysed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with a poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be

conducted according to the last observation carried forward principle.

Data analysis will be conducted by researchers who are not involved in experimental or clinical decision-making processes to ensure that bias caused by subjective factors from the researchers is avoided.

Safety

Adverse events (AEs) and adverse drug reactions (ADRs) will be assessed and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be reported to the principal investigator and the ethics committee. Every AE will be recorded in detail and closely monitored before stabilization or resolution.

HLC will cooperate with the physician in charge to evaluate the severity and determine the cause of the events. All relevant AEs will be reported to the Institutional Review Board of the First Affiliated Hospital of Tianjin University of TCM within the relevant time frames. HLC will be responsible for reporting all AEs. The coordinators will be responsible for establishing standard procedures and for training the relevant staff before trial initiation. Regular monitoring will be used to ensure that all AEs are identified and addressed appropriately.

The incidence of AEs and ADRs is compared among various groups using the χ^2 test with the level of significance set at $P<0.05$.

Auditors are required to audit trials by checking documents at the midpoint and endpoint of the study, and the process will occur independently of the investigators and the study sponsor.

Randomization, blinding and allocation concealment

Patients will be assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the patients will be completed using an independent data centre with an interactive voice response system, and a random number will be generated by this data centre for each patient. Original copies of the blind codes will be

sealed in a light-proof envelope; one copy will be retained by the major research unit, and another copy will be kept by the applicant of the trial. The envelopes will not be opened prior to formal statistical analysis. If a patient is eligible, that patient number will be allocated by the doctors. These patient numbers are merely serial numbers for labelling patients. The test medicine will be coded first, and then it will be placed in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be in opaque envelopes and kept confidential by the trial management board. The original capsule shells of NXK, XNST and XST will exchanged for new uniform capsule shells provided by the Pharmaceutical Factory of Tianjin University of TCM. The placebo amylum will be placed into capsule shells that are identical to the shells of the experimental drugs. Therefore, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to the treatment assignments.

If emergencies occur or treatments are needed, the person responsible for the participating units will immediately report to CRA and the major investigators, and patient unblinding will be performed only with their approval. Once the allocation is unblinded, the investigators must comply with the trial requirements when analysing and recording data.

Trial oversight

Steering Committee: responsible for creating the superior trial design and for ensuring that the trial runs smoothly.

Coordinating Centre: all four sub-centres are responsible for patient recruitment and quality assurance.

End Point Adjudication Committee: responsible for assessing the trial outcomes and identifying patient attrition and withdrawal.

Data Management Team: responsible for data management, including data entry, verification and exporting.

Ethical approval and data dissemination

This study has been approved by the Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007). If the protocol needs to be modified, we will re-apply for ethical approval. All patients are required to sign informed consent prior to participation, and the researcher is required to explain the procedures and the objectives of the research, including details regarding the methods to be used, the risks and benefits, and the possibility of inclusion in a control or experimental group. The study follows the principle that all information related to patients is confidential; their names will not appear in any records.

Trial status

Patients are being actively recruited for this trial.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

All authors declare that they have no competing interests to disclose.

Funding

The study is funded by the National Natural Science Foundation of China (No.81202849, No. 30600834, and No. 81603659).

Author contributions

Chen HL designed the protocol and wrote the draft. GAO WY conceived the study, and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited the manuscript and contributed to the final draft. ZHAO TN was responsible for all statistical analysis in this trial. XIA Q and Chen B helped conduct the trial. All authors have carefully read and approved the final manuscript. The trial

sponsor designed this protocol, prepared the draft and was responsible for the selection of research units, researchers and drug resources. The costs, such as those for publishing the article and purchasing CPMs, are supported by the funders.

Acknowledgements

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Data sharing statement

The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All the data will be available upon request.

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Table Captions

Table 1 Groups divided according to main symptoms and treatment plans

Table 2 Data are captured based on the CRF

Table 1 Groups divided according to main symptoms and treatment plans

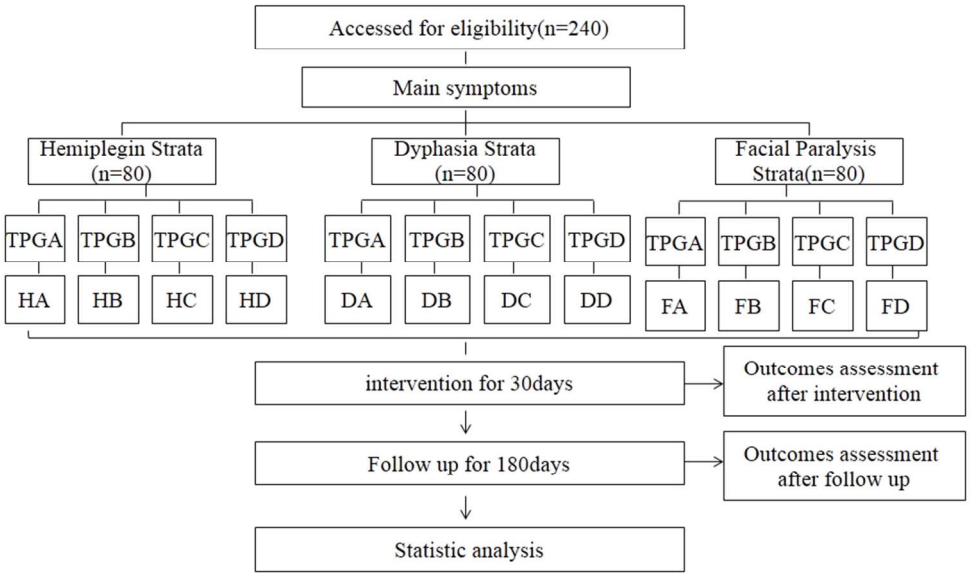
	TPGA	TPGB	TPGC	TPGD
Hemiplegia (H)	HA	HB	HC	HD
Dysphasia (D)	DA	DB	DC	DD
Facial Paralysis (F)	FA	FB	FC	FD

Table 2 Data based on the CRF

Items	Visit		
	1 0 day	2 30±2days	3 210±5days
Medical history			
Inclusion/exclusion criteria	√		
Informed consent form (ICF)	√		
Symptom differentiation	√		
General information	√		
History of medical treatments and allergies	√		
Current medications	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgement		√	√
Evaluation index			
WHOQOL-BREF	√	√	√
NIHSS	√	√	√
Safety observation			
Vital signs	√	√	√
Adverse events (AEs)		√	√

Figure Captions

Fig.1 Flow chart of the protocol



Flow chart of the protocol

233x173mm (300 x 300 DPI)

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

Section/ item	Page and line Num-ber	Item No.	Description
Administrative information			
Title	P1,L1	1	Naoxuekang, Xinnaoshutong and Xuesaitong capsules for treating stroke: A protocol for a randomized controlled trial
Trial registration	P2L53	2a	Chinese clinical trials register ChiCTR-IOR-17010397
		2b	Please retrieve the trial registration data of thisstudy at this site http://www.chictr.org.cn/searchproj.aspx
Protocol version		3	Version: 81202849-2.1
Funding	P15L41	4	The study is funded by the National Natural Science Foundation of China (No. 81202849, No. 30600834 and No. 81603659).
Roles and responsibilities	P15L46	5a	Chen HL designed the protocol and wrote the draft. GAO WY conceived the study, and Cao HB revised the manuscript critically for important intellectual content. GUO X and ZHAO MD edited the manuscript and contributed to the final draft. ZHAO TN was responsible for all statistical analysis in this trial. XIA Q and Chen B helped conduct the trial. All authors have carefully read and approved the final manuscript. The trial sponsor designed this protocol, prepared the draft and was responsible for the selection of research units, researchers and drug resources. The costs, such as those for publishing the article and purchasing CPMs, are supported by the funders.
	P1L43	5b	Huiling Chen: chen.huiling@163.com 1 School of Pharmaceutical Science and Technology, Tianjin University, 72 Weijin Road, Nankai District, Tianjin 300072, China; 2 TianJin University of Traditional Chinese Medicine； 312 Anshanxi Road, Nankai District, Tianjin 300193, China.

	P16L1	5c	The trial sponsor designed this protocol, prepared the draft and was responsible for the selection of research units, researchers and drug resources. The costs, such as those for publishing the article and purchasing CPMs, are supported by the funders.
	P14L39	5d	Steering Committee: responsible for creating the superior trial design and for ensuring that the trial runs smoothly. Coordinating Centre: all four sub-centres are responsible for patient recruitment and quality assurance. End Point Adjudication Committee: responsible for assessing the trial outcomes and identifying patient attrition and withdrawal. Data Management Team: responsible for data management, including data entry, verification and exporting.
Introduction			

Background and rationale P3L16 6a

The overall annual age-standardized incidence and death rate from stroke in the general population of the PRC were 115.61 and 81.88 per 100 000 people, respectively, in 1986.1 Among these patients, approximately 75% of them suffered from cerebral ischaemic stroke. Because 70% to 80% of the patients who survive stroke experience various degrees of disability and suffer from cognitive handicaps, they require assistance in performing activities of daily life, which severely affects their quality of life and places a heavy burden on their families as well as society.[2]

For the current treatment in the convalescence of stroke, clinical trials have shown that Chinese patent medicine (CPM) has a significant curative effect.[3 4] Many patients in the convalescent or sequelae stage voluntarily take CPMs to treat this disease and prevent recurrence (many CPMs for patients with stroke are OTCs).[5] There are various kinds of CPMs with similar instructions for the treatment of stroke, such as Naoxuekang (NXK), Xinnaoshutong (XNST) and Xuesaitong (XST) capsules. These three CPMs have been on the market for many years and have received positive clinical feedback. NXK capsules[6] are manufactured by Shandong HaoFu Pharmaceutical Co., Ltd. The main ingredient of NXK is leech, and NXK has been proven to be effective and to cause minor adverse reactions according to clinical observation.[7] According to the Pharmacopoeia of the People's Republic of China, pregnant women and individuals with bleeding disorders should never be treated with NXK.[8] Xinnaoshutong (XNST) [9] capsules are manufactured by Jilin Aodong Taonan Pharmaceutical Co., Ltd. The main ingredient of XNST is steroidal saponins of Tribulus terrestris, and XNST has not elicited obvious adverse reactions in clinical trials.[10] According to the Pharmacopoeia of the People's Republic of China, XNST occasionally leads to mild adverse reactions, such as dry mouth and upset stomach. Patients who have intracranial haemorrhage should not be treated with XNST, while patients with a history of bleeding or blood-low-viscosity-syndrome should be treated with XNST, albeit with caution.[11] Xuesaitong (XST) capsules[12] are manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. The main ingredient of XST is Panax notoginseng saponins, and according to the results of clinical trials, only minor adverse reactions have been reported; thus, it can be given to all patients without restriction.[13] However, according to the Pharmacopoeia of the People's Republic of China, XST should not be given to pregnant women or people with allergies.14 These three CPMs are frequently used for the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, cephalophyma or cerebral thrombosis with symptoms caused by encephalorrhagia with high blood pressure.[8 11 14]

In addition, because CPM interprets an illness based on syndrome theories, medical practitioners who are not well educated in Traditional Chinese Medicine (TCM) theories or those with little clinical experience are often unable to prescribe appropriate CPMs. Therefore, providing instructions on how to use CPMs based on symptoms is more easily understood and accepted by both doctors and patients.

	P4L24	6b	Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule(XST) are frequently used for the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, cephalophyma or cerebral thrombosis with symptoms caused by encephalorrhagia with high blood pressure.
Objectives	P2L3	7	After stroke, hemiplegia, dysphasia and facial paralysis can manifest during the convalescent period. Currently, no Chinese patent medicine (CPM) is previously reported to cure each of these symptoms primarily, and thus, there are no relevant instructions for the use of CPM. This study presents a new approach based on comparative effectiveness research (CER) to distinguish the curative effects of three CPMs that are often used in stroke convalescence in order to determine the ideal medicine for the treatment of each symptom.
Trial design	P2L16	8	In this multi-centre and double-blind clinical trial, stratified randomization is used to group the patients according to their primary symptoms (hemiplegia, dysphasia, and facial paralysis). Three strata will be enrolled, with 80 eligible participants included in each stratum. Each stratum will be randomly and equally divided into 4 groups, and each group will receive one of the following treatments: Naoxuekang (NXK), Xinnaoshutong (XNST), Xuesaitong (XST) or placebo. This study will include two stages: the initial treatment period (30 days) and a follow-up period (180 days).

Methods: Participants, interventions, and outcomes

Study setting	P8L38	9	Patients will be recruited from the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China.

Eligibility criteria	P6L4	10	● Inclusion criteria 1. Patients aged 30 to 65 years. 2. Patients experiencing their first stroke event. 3. Diagnosis of unilateral, non-recurring, subacute stroke that is anischaemic and lacunar type as defined by the International Classification of Diseases (ICD-10) through computed tomography or magnetic resonance imaging conducted by neurologists. 4. TCM pattern diagnosis of stroke in meridian syndrome. 5. Patients with a score between 6 and 20 for the NIHSS. 6. Duration of four to eight weeks since the original stroke event. 7. Signed informed consent provided by the patient. The above inclusion criteria will be applied to the experimental group and the control group. ● Exclusion criteria 1. Patients with a known history of allergies or suspected allergies to the medicines used in the study. 2. Patients who suffered from serious heart, liver or kidney-related diseases, blood coagulation dysfunction or severe mental disorders. 3. Patients with other complications. 4. Uncontrolled NYHA class III hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg). 5. Fasting blood glucose <2.8 or >16.8 mmol/l or with severe complications due to diabetes (e.g., diabetic gangrene or peripheral neuropathy). 6. Liver function impairment with values of ALT or AST over 1.5-fold the upper limit of the normal range. 7. Renal dysfunction with values of serum creatinine over 1.5-fold the upper limit of the normal range. 8. Patients with active peptic ulcers or other haemorrhagic diseases. 9. Patients who are actively participating in other clinical trials or who participated in another clinical trial within the past 90 days.

Interventions	P7L8	11a	**Treatment plan** **(1)Basic treatment** The intervention programme mainly uses China's Guidelines of Cerebrovascular Disease Prevention and controls as well as the consensus of foreign experts for a reference. This approach considers all the risk factors of apoplexy under strict control. The programme involves the following: (a) An antiplatelet drug: Aspirin, taken as prescribed. (b) Blood fat control: Simvastatin, taken as prescribed. (c) Blood pressure control: medicines are chosen according to the cause and the severity of high blood pressure. The level of blood pressure is controlled by the researchers. (d) Blood sugar control: according to China's Guidelines of Diabetes Prevention and Control. (e) During the test, all CPMs for activating blood circulation and removing stasis as well as combined Chinese medicine prescriptions will be banned. **(2) The final treatment plans** The treatment plan for group A (TPGA): basic treatment +Naoxuekang capsule (NXK) The treatment plan for group B (TPGB): basic treatment +Xinnaoshutong capsule (XNST) The treatment plan for group C (TPGC): basic treatment +Xuesaitong capsule(XST) The treatment plan for group D (TPGD): basic treatment+ placebo The CPM dosage and administration method will follow the doctor's recommendation. **(3) Participant timeline** An extended observation period will occur to ensure that the curative effect will be accurately determined. This study will include two stages: the initial treatment period (30 days) and a follow-up period (180 days). Three replicates for each data point will be arranged in this trial. The first visit will occur on day 0 after enrolment, the second visit on day 30±2, and the third visit on day 210±5. **(4) Termination criteria** Interventions for the trial participants will be discontinued if (a) patients leave the study of their own free will; (b) major errors or serious deviations in study execution (although the plan is good) are identified during the clinical trial protocol that would make it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur during the trial; and (d) the trial is discontinued by the authorities. **(5) Patient adherence to the instructions** Patients will receive trial drugs and all necessary healthcare instructions (diet, mental adjustment) for free. Patients are required to maintain appropriate physical activity levels and perform daily exercises. The dosage of the medicine and any remnant shall be recorded in realtime, and a drug counting method will be used to monitor the adherence of patients. Patients whose conditions worsen during the trial will be treated appropriately. **Patient grouping**

Patients will be recruited from the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. Overall, 240 patients who qualify for inclusion will be recruited from all 4 hospitals during the same time period. To avoid selective bias, the number of patients receiving treatment at each hospital should be balanced, and the patients will be divided into three experimental groups and a control group.

(1) Patients will be stratified according to their main symptoms. Each stratum will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to stratum H. The patients whose main symptom is dysphasia will be assigned to stratum D. The patients whose main symptom is facial paralysis will be assigned to stratum F.

(2) Patients with the same main symptom will be divided into Groups A, B, C and D both randomly and equally. Each of the 4 groups will be treated with different treatment plans, and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, 12 groups will be generated: Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, and Group FD. Each group will contain 20 patients. Table 1 presents the details according to patient groups.

Table 1: groups divided according to main symptoms and treatment plans

	TPGA	TPGB	TPGC	TPGD
Hemiplegia（H）	HA	HB	HC	HD
Dysphasia （D）	DA	DB	DC	DD
Facial Paralysis （F）	FA	FB	FC	FD

P8L11 11b

Interventions for the trial participants will be discontinued if (a) patients leave the study of their own free will; (b) major errors or serious deviations in study execution (although the plan is good) are identified during the clinical trial protocol that would make it difficult to evaluate the efficacy of the drug; (c) serious adverse events occur during the trial; and (d) the trial is discontinued by the authorities.

P8L24 11c

Patient adherence to the instructions

Patients will receive trial drugs and all necessary healthcare instructions (diet, mental adjustment) for free. Patients are required to maintain appropriate physical activity levels and perform daily exercises. The dosage of the medicine and any remnant shall be recorded in realtime, and a drug counting method will be used to monitor the adherence of patients. Patients whose conditions worsen during the trial will be treated appropriately.

P7L34 11d During the test, Chinese patent medicine for activating blood circulation and removing stasis as well as compounded Chinese medicine prescription were banned from.

Outcomes P9L30 12

Effectiveness assessment

(1) Assessment Expert

One doctor will be assigned to assess the curative effect and record the evaluation results of all volunteers to ensure that observation mode is consistent across the experimental groups and the control group. This doctor will not participate in clinical decisions to avoid evaluator bias. With over ten years of clinical experience, this physician is an expert in this field and is able provide an accurate assessment of patient symptoms. The WHOQOL-BREF and NIHSS questionnaires of all the patients will be recorded by this doctor on day 0, at the beginning of the experiment; the second visit will occur on day 30±2, and the third visit on day 210±5.

(2) Evaluation Criteria

Quality of life: According to the WHOQOL-BREF, quality of life is evaluated by one's mental state, psychological state and physical state, among other factors. [23 24] **Clinical indexes:** The physiological indexes that show the degree of nervous functional defects can be evaluated using the NIHSS.

In this study, the weight table of the indexes will be provided to both the doctors and the patients so that the outcomes can represent the will of each patient and their clinician in a way that aligns with comparative effectiveness research. Each index is designed as a questionnaire with four answers, including "very important", "important", "average/not very important" and "not important". Each expert will evaluate the index system according to these four answers.

The formula is as follows:

$$DW_i = \sum_{j=1}^{m} a_{ij}\, n_{ij}/N$$

……(1)

DW_i – the average value of the importance of the index i (i=w, n);

a_{ij}—the grade value of the index i;

j — the grade ordinal; and

N— the number of the experts.

(3)The final curative effects

Treatment effectiveness is evaluated by comparing the value of each index before treatment with that after treatment. In this study, W_0 in eqs. 2 and 3 represents the value of the WHOQOL-BREF before treatment, W_1 in eqs. 2 and 3 indicates the value of the WHOQOL-BREF after treatment, and W_2 in eq. 3 is the value of the WHOQOL-BREF after follow-up. N_0 in eqs. 2 and 3 represents the value of the NIHSS before treatment, N_1 in eqs. 2 and 3 indicates the value of the NIHSS after treatment, and N_2 in eq. 3 is the value of the NIHSS after follow-up.

The formula for final curative effects calculation is as follows:

$W_1 \times DW_W + N_1 \times DW_N - (W_0 \times DW_W + N_0 \times DW_N)$…… (2)

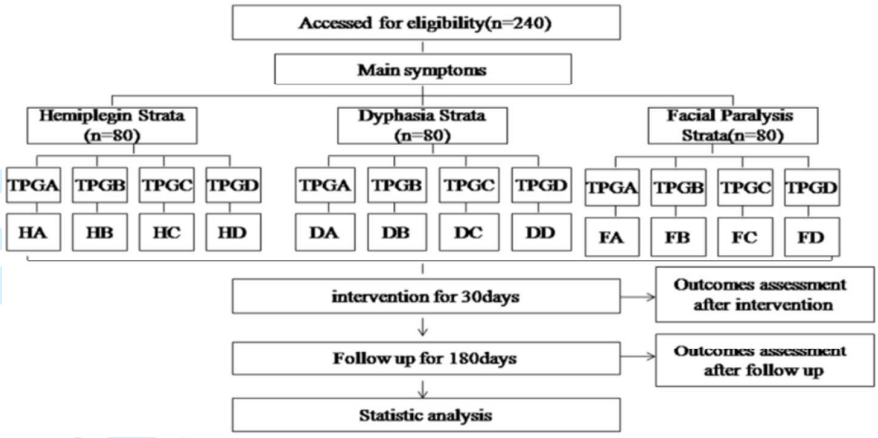
The formula for curative effects after follow-up is as follows:

$W_2 \times DW_W + N_2 \times DW_N - (W_0 \times DW_W + N_0 \times DW_N)$……(3)

DW_W in eqs. 2 and 3 indicates the weight of the WHOQOL-BREF, and

DW_N in eqs. 2 and 3 indicates the weight of the NIHSS.

Participant timeline	P7L55 P6L1	13	An extended observation period will occur to ensure that the curative effect will be accurately determined. This study will include two stages: the initial treatment period (30 days) and a follow-up period (180 days). Three replicates for each data point will be arranged in this trial. The first visit will occur on day 0 after enrolment, the second visit on day 30±2, and the third visit on day 210±5. (Figure 1)



Sample size	P11L50	14	The sample size in this study is based on the trial results from previous reports and the recommendation of specialists.[26-32] The values of σ_i for the WHOQOL-BREF scale of the experimental groups are 12.12, 19.51 and 12.24, while the value of σ_i for the WHOQOL-BREF scale of the placebo group is 11.2. The values of μ_i for the WHOQOL-BREF scale of experimental groups are 17.13, 18 and 23.83, while the value of μ_i for the WHOQOL-BREF scale of the placebo group is 10.83. According to the calculation, μ is 17.45, the type I error is 0.05, and the power is 90%. If the drop-out rate is 20%, then 172 patients are needed in the trial (43 patients per group). The values of σ_i for the NIHSS scale of the experimental groups are 2.6, 7.31 and 3.11,while the values of σ_i for the NIHSS scale of the placebo group is 12.5. The values of μ_i for the NIHSS scale of the experimental groups are 6.85, 4.95 and 6.1, while the values of μ_i for the NIHSS scale of the placebo group is 1.39. According to the calculation, μ is 4.82, the type I error is 0.05, and the power is 90%. If the drop-out rate is 20%, then 232 patients are needed in the trial (58 patients per group). According to the calculations above and recommendations from the specialists, 240 patients will be used for the trial, with 60 patients per group.

Recruitment	P8L38	15	Patients will be recruited from the First Affiliated Hospital and Second Affiliated Hospital of Tianjin University of TCM, Tianjin Nankai Hospital and Baokang Hospital of TCM in China. Overall, 240 patients who qualify for inclusion will be recruited from all 4 hospitals during the same time period. To avoid selective bias, the number of patients receiving treatment at each hospital should be balanced, and the patients will be divided into three experimental groups and a control group. (1) Patients will be stratified according to their main symptoms. Each stratum will have 80 patients. The patients whose main symptom is hemiplegia will be assigned to stratum H. The patients whose main symptom is dysphasia will be assigned to stratum D. The patients whose main symptom is facial paralysis will be assigned to stratum F. (2) Patients with the same main symptom will be divided into Groups A, B, C and D both randomly and equally. Each of the 4 groups will be treated with different treatment plans, and the curative effects will be recorded. For example, patients whose main symptom is hemiplegia will be treated with plan A in Group HA, while patients with the same symptom will be treated with plan B in Group HB. Therefore, 12 groups will be generated: Group HA, Group HB, Group HC, Group HD, Group DA, Group DB, Group DC, Group DD, Group FA, Group FB, Group FC, and Group FD. Each group will contain 20 patients.

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	P13L48	16a	Patients will be assigned randomly by the stratified randomization method (1:1:1:1); the stratification factor is the main symptom (hemiplegia, dysphasia and facial paralysis). Randomization of the patients will be completed using an independent data centre with an interactive voice response system, and a random number will be generated by this data centre for each patient.
Allocation concealment mechanism	P13L56	16b	Original copies of the blind codes will be sealed in a light-proof envelope; one copy will be retained by the major research unit, and another copy will be kept by the applicant of the trial. The envelopes will not be opened prior to formal statistical analysis. If a patient is eligible, that patient number will be allocated by the doctors. These patient numbers are merely serial numbers for labelling patients.
Implementation	P13L51	16c	Randomization of the patients will be completed using an independent data centre with an interactive voice response system, and a random number will be generated by this data centre for each patient.

Open access: first published as 10.1136/bmjopen-2017-015983 on 8 November 2017.

Blinding (masking)	P14L3	17a	If a patient is eligible, that patient number will be allocated by the doctors. These patient numbers are merely serial numbers for labelling patients. The test medicine will be coded first, and then it will be placed in indistinguishable containers by specially assigned personnel who will not participate in this trial. In addition, medicine assignments will be in opaque envelopes and kept confidential by the trial management board. The original capsule shells of NXK, XNST and XST will exchanged for new uniform capsule shells provided by the Pharmaceutical Factory of Tianjin University of TCM. The placebo amylum will be placed into capsule shells that are identical to the shells of the experimental drugs. Therefore, the volunteers, doctors, participating nurses, trial coordinators, statisticians and outcome assessors will be blinded to the treatment assignments.
	P14L28	17b	If emergencies occur or treatments are needed, the person responsible for the participating units will immediately report to CRA and the major investigators, and patient unblinding will be performed only with their approval. Once the allocation is unblinded, the investigators must comply with the trial requirements when analysing and recording data.

Methods: Data collection, management, and analysis

Data collection methods — P11L18 — 18a

Items	Visit 1 0 day	Visit 2 30±2days	Visit 3 210±5days
Medical History			
Inclusion/exclusion criteria	√		
Inform consent form（ICF）	√		
Symptom differentiation	√		
General information	√		
History of medical treatment and allergies	√		
Current medications	√		
Drug distribution	√		
Drug recovery		√	√
Compliance judgment		√	√
Evaluation index			
WHOQOL-BREF	√	√	√
NIHSS	√	√	√
Safety observation			
Vital signs	√	√	√
Adverse Event（AE）		√	√

	P11L11	18b	The clinical research associates are required to monitor various units on a regular and continuous basis.
Data management	P11L13	19	The data management of the trial follows Good Clinical Data Management Practice (GCDMP).[25] ● Management Software This trial plans to use Oracle Clinical (OC) software for unified data management, online data updating and tracing, and exercise dynamic and efficient management of clinical trial data at the same time with the support of the check function of the software. ● Data recording All data of the trial are subject to remote recording. Investigators will enter relevant data by logging on the internet, such a pattern contributes to upgrading quality and efficiency of clinical study. ● Data examination Data administrator performs logic check and automatic comparison of data information using the check function of OC software, check the result values inconsistent with the case report forms, and check one-by-one with the original case report form and make corrections, so as to ensure the data in the database consistent with the results of the case report form. This way enables traceability, accuracy, completeness and timeliness of data. ● Data exporting After the trial, data administrator will export the data confirmed correct from OC system as demanded by the statistician, and will be provided to the statistical analysts in the form of data interexchange code, statistical analysts will extract relevant data from the database according to the code and program for statistical analysis.
Statistical methods	P12L38	20a	The mean±standard deviation will be used for the statistical description of the measurement data. An analysis of variance will be used if the data are normally distributed, while a sum-rank test will be used if the data are not normally distributed or if heterogeneity is found. A comparison among the three experimental groups and the control group will be based on analysis of variance of the repeated measurement data. P<0.05 will be considered as a significant difference.
	P13L3	20b	Data analysis will be conducted by researchers who are not involved in experimental or clinical decision-making processes to ensure that bias caused by subjective factors from the researchers is avoided.
	P12L51	20c	The evaluation result will be analysed with the method of intention-to-treat analysis (ITT). The ITT analysis method leads to more reliable conclusions, which prevents the cases with a poor effect in the final analysis from being excluded and therefore increases the comparability among the groups. The loss of data will be conducted according to the last observation carried forward principle.

Methods: Monitoring

Data monitoring	P11L13	21a	The data management of the trial follows Good Clinical Data Management Practice (GCDMP).[25] Independent Data Monitor Committee (IDMC) made up of clinical experts, statisticians and relevant workers will provide regular monitoring of the periodic data of the trial to ensure the fairness of the trial.
	P11L13	21b	The data management of the trial follows Good Clinical Data Management Practice (GCDMP) .[25] When significant abnormal data or data on serious adverse reactions are monitored, it depends on the joint decision of both the data monitoring center and the trial committee whether the trial should be stopped. Patients accord with termination standards will be terminated.
Harms	P13L11	22	Adverse events (AEs) and adverse drug reactions (ADRs) will be assessed and reported throughout this study. Furthermore, serious AEs or ADRs appearing during the trial need to be reported to the principal investigator and the ethics committee. Every AE will be recorded in detail and closely monitored before stabilization or resolution. HLC will cooperate with the physician in charge to evaluate the severity and determine the cause of the events. All relevant AEs will be reported to the Institutional Review Board of the First Affiliated Hospital of Tianjin University of TCM within the relevant time frames. HLC will be responsible for reporting all AEs. The coordinators will be responsible for establishing standard procedures and for training the relevant staff before trial initiation. Regular monitoring will be used to ensure that all AEs are identified and addressed appropriately. The incidence of AEs and ADRs is compared among various groups using the χ^2 test with the level of significance set at $P<0.05$.
Auditing	P13L41	23	Auditors are required to audit trials by checking documents at the midpoint and endpoint of the study, and the process will occur independently of the investigators and the study sponsor.

Ethics and dissemination

Research ethics approval	P15L1	24	This study has been approved by the Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (registration number TJUTCM-EC20160007).

Protocol amendments	P15L3	25	If the protocol needs to be modified, we will re-apply for ethical approval.
Consent or assent	P15L5	26a	Patients, immediate family member or supervisors will obtain informed consent.
		26b	Not Applicable
Confidentiality	P15L14	27	The study follows the principle that all information related to patients is confidential; their names will not appear in any records.
Declaration of interests	P15L35	28	All authors declare that they have no competing interests to disclose.
Access to data	P14L54	29	Data Management Team: responsible for data management, including data entry, verification and exporting.
Ancillary and post-trial care	P8L31	30	Patients whose conditions worsen during the trial will be treated appropriately.
Dissemination policy	P16L44	31a	The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All the data will be available upon request. 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
		31b	When published, the use of any content in the article must be through the magazine and the authors' permission.
		31c	The protocol is to be published in open access journal and the researchers can download it through the network.
Appendices			
Informed consent materials		32	Model consent form and other related documentation given to participants and authorised surrogates will be the last part of the checklist.

Biological specimens	33	Not appliable

*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.

Notes for Subjects

Dear Mr. / Ms:

You are invited to take part in the program"Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial", which is implemented by Tianjin University of Traditional Chinese Medicine. Before you make the final decision, please read the following parts carefully. It can help you learn the meaning of the trial, as well as the benefits and risks it may bring to you.

The background and objective of this study

1. Background

The annual incidence of stroke in China is 2.16%. Each year the number of patients who suffer from stroke increases by 1.5 to 1.8 million, which is more than in the west [1]. Among these patients, about 75% of them suffer from cerebral ischemic stroke. As 70% to 80% of the patients who survive from stroke suffer from various degrees of disabilities and cognitive handicaps, they need attendance in daily life, which seriously affects the quality of their lives and brings heavy burden to their families and society [2].

For the current treatment in the convalescence of stroke, clinical trials have shown that CPM has a significant curative effect [3-4]. A lot of the patients in convalescence or sequelae stage voluntarily purchase and take CPMs to treat this disease and prevent it from recurrence [5] (Many CPMs for patients with stroke are OTCs). There are various kinds of CPMs with similar instructions used for the treatment of stroke, such as Naoxuekang capsule (NXK), Xinnaoshutong capsule (XNST) and Xuesaitong capsule (XST). These three CPMs have come onto the market for many years and have got good clinical feedbacks. Naoxuekang capsule (NXK) [6] is manufactured by Shandong HaoFu pharmaceutical co., Ltd. NXK, the main ingredient of which is leech, is proved to be safe, effective and with less

adverse reactions by clinical observation [7]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and people who are bleeding [8]. Xinnaoshutong capsule (XNST) [9] is manufactured by Jilin AodongTaonan Pharmaceutical Co., Ltd. XNST, the main ingredient of which is Steroidal saponins of Tribulusterrestris, leads to no obvious adverse reactions in clinical trials [10]. According to Pharmacopoeia of Peoples Republic of China, it occasionally leads to adverse reactions such as dry mouth and stomach upset. It is forbidden to give the medicine to patients who have intracranial hemorrhage, while patients with a history of bleeding or blood-low-viscosity-syndrome should be given the medicine cautiously[11]. Xuesaitong capsule (XST) [12] is manufactured by Kunming Shenghuo Pharmaceutical (Group) Co., Ltd. According to clinical trials, XST, the main ingredient of which is PanaxNotoginsengSaponins, leads to minor adverse reactions and can be given to patients normally [13]. According to Pharmacopoeia of Peoples Republic of China, it is forbidden to be given to pregnant women and allergic people [14]. These three CPMs are frequently used in the treatment of stroke, hemiplegia, facial distortion, dysphasia, dark purplish tongue with ecchymosis, as well as cephalophyma or cerebral thrombosis with the symptoms above that are caused by encephalorrhagia with high blood pressure [8,11,14].

Besides, as CPM interprets illness on the basis of syndrome theories, medical practitioners, who are not well educated in TCM theories or without enough clinical experience, are generally not able to give out reasonable prescriptions for CPM. So, it is more easily understood and accepted by doctors and patients to give instruction on how to use CPMs from the aspect of symptoms.

2. Objective

The main symptoms of stoke convalescent include hemiplegia, dysphasia and facial paralysis. At present no CPM is particularly used to treat each of the symptoms above and there are no relevant instructions. This study is trying to set up a new approach based on CER, which distinguishes the curative effects of the three CPMs that are often used in stroke convalescence and to point out the symptom(s) on which each medicine has the best effect.

Trial procedure

This is a randomized controlled, double-blind design.360 patientsare assigned randomly using stratified blocked randomization method (1:1:1:1).If you agree to participate in the trial and meet the conditions, you will take part in the 30-day clinical trial and 180 follow up after signing the consent form voluntarily. This study comprises two stages:

1. Screening

Doctors are going to take your medical history and ask you to do certain medical and chemical examinations. If the results don't meet the conditions, then you will not participate in the second phase.

2. Treatment

After being chosen in the first phase, you will come into a 30 days treatment with medicines anda 180 daysfollow up. In this trial, you can be randomly distributed to group 1, group 2, group 3 or group 4, which has no influence on your conventional treatment.

The medicines used in this trial may modify your condition in various degrees according to your physical state. If you participate in the trial , we need you to obey the following rules:

- Do not medicate yourself with medicines that are not allowed for joint application.
- Strictly follow the doctors' orders about medicine taking and examinations.

Volunteers' Rights and Interests

Medicines given to you during the trial are free.

All the other conventional treatments and examinations that are not involved in the trial will be charged as usual.

The Security of the Volunteers' Privacy

The study established the principle that all information related to patient is confidential, and their name will not appear on the records.The results of the trial may be published in medical journals, but all your personal information will be classified. Only when it is necessary can ethics committee members of the hospital and the research member have access to your medical materials with approval. Others will not have access to your materials. You are voluntarily participate in every phase of the trial. You can refuse to take part in it at the beginning, or quit without any reason at any time. All the decisions you make will not affect your conventional treatment. If you agree to participate, you or your agent need to sign the consent form.

The Risks and Discomfort that may occur in the trial and the countermeasures that will be taken

If there are foreseeable adverse reactions, such as itch, or the ones not yet discovered or unforeseeable, doctors will take treatment measures in time according to your condition, in

order to reduce the possible risks. If you have serious adverse reactions, you will get active treatment.

Consent Form

Title of the research: “Identify Characteristics of Similar Chinese Patent Medicine for Stroke based on Symptoms: Study Protocol of a Randomized Controlled Trial”.

This protocol has been approved by the medical ethics committee of Tianjin University of TCM (registration number is TJUTCM-EC20170005).contact the ethics committee:022-27493265

The leader of the doctor have explained the content of the clinical research to me. I have chances to ask questions and have got answers to all of them. I have totally understood these answers.

I participate in the trial voluntarily. I can quit at any time, which will not affect the treatments I should have in the hospital. I have right to get a copy of the consent form.
I have carefully read the Notes for Volunteers and totally understood it. I agree to participate in the trial.

signature of the subject：Tel：Date：

signature of the agent：Tel：Date：

signature of the researcher：Tel：Date：