**ARTICLE DETAILS**

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Naoxuekang, Xinnaoshutong and Xuesaitong capsules for treating stroke: A protocol for a randomized controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>CHEN, Huiling; Cao, Hongbo; Guo, Xu; ZHAO, Meidan; Xia, Qing; Bo, Chen; Zhao, Tieniu; Gao, Wenyuan</td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

This study aims to distinguish which Chinese Patent Medicine (CPM) has the best effectiveness for post-stroke patients. The authors designed the protocol 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. Overall, the study design applied the patient-centered evaluation and the CER theory. This report has its novelty in study design. Such protocol should be able to inspire the future clinical research in Chinese medicine and other clinical researches.

**REVIEWER**

Hung-Rong Yen  
China Medical University, Taichung, Taiwan

**REVIEW RETURNED**  
29-Jan-2017

**GENERAL COMMENTS**

- needs more background on the traditional medications (safety profiles, ingredients)  
- follow up time is inadequate to answer question. Patients should be followed for 6-12 months in my view  
- does not account for stroke mechanism (subcortical strokes more likely to cause spasticity)
This is an unreasonable designed RCT based on the following considerations.  
(1) It is not comply with the SPIRIT 2013 checklist in many items.  
(2) In this multicenter trial, considering the objectives of this study, the randomisation procedure should be stratified by center and symptoms (hemiplegia, dysphasia and facial paralysis).  
(3) The the randomisation and blinding procedure was described unclearly. The three sections ‘Treatment allocation and patient grouping’ (Page 7), ‘patient grouping’ (page 8) and ‘Randomization, blinding and allocation concealment’ (Page 12) can not be one-to-one correspondence.  
(4) Sample size was calculated based on the NIHSS score difference, however, this trial’s primary outcome was based on a comprehensive score which will be needed to be investigated future and combine WHOQOL and NIHSS in the study.  
(5) In statistical analysis section, this study did not mention how to do comparative effectiveness analysis for the four groups to fit its objectives.
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].

Comment: follow up time is inadequate to answer question. Patients should be followed for 6-12 months in my view

Response: Thanks for your suggestion. The follow-up period has been extended to 180 days.

Comment: does not account for stroke mechanism (subcortical strokes more likely to cause spasticity)

Response: Thanks for your suggestion. TCM regulates human body functions as a whole, so as to treat diseases and relieve symptoms. It has its own theories and diagnostic pattern which are completely different from those of western medicine. As defined in the inclusion criteria No. 4(4. TCM pattern diagnosis of stroke in meridian syndrome.) of this trial, only patients who are diagnosed with stroke in meridian syndrome according to TCM pattern diagnosis can be chosen.

All your suggestions are important to us. They help a lot to our paper writing and research work.

Reviewer: 3
Reviewer Name
Zehuai Wen
Institution and Country
Key Unit of Methodology in Clinical Research
Guangdong Provincial Hospital of Chinese Medicine
Guangzhou University of Chinese Medicine
Guangzhou, China

Comment: It is not comply with the SPIRIT 2013 checklist in many items.

Response: Thanks for your advice. We have rechecked SPIRIT 2013 checklist and revised it. The revised version will be submitted as a checklist document. In this version, a line of page number and line number has been added to mark its position in the paper.

Comment: In this multicenter trial, considering the objectives of this study, the randomisation procedure should be stratified by center and symptoms (hemiplegia, dysphasia and facial paralysis).

Response: Thank you for your valuable advice. Actually we do take stratified randomization according to major symptoms, but we didn’t describe it clearly in the previous version. We have made it more explicit of the revised version as follows :

“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 (P13L22).”

“(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:

Comment:

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

<table>
<thead>
<tr>
<th>TPGB</th>
<th>TPGC</th>
<th>TPGD</th>
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</table>

The randomisation and blinding procedure was described unclearly. The three sections ‘Treatment allocation and patient grouping’ (Page 7), ‘patient grouping’ (page 8) and ‘Randomization, blinding and allocation concealment’ (Page 12) can not be one-to-one correspondence.

Response: Thank you for your careful work. According to your advice, we have focused on ‘Randomization, blinding and allocation concealment’ and made a detailed description of the implementation of randomization blind method.

“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.”(P13L22-P13L47)

Comment: Sample size was calculated based on the NIHSS score difference, however, this trial’s primary outcome was based on a comprehensive score which will be needed to be investigated future and combine WHOQOL and NIHSS in the study.

Response: Thank you for your reminding. We are sorry for imprecise interpretation. In the new manuscript, we have corrected it as following:

“The sample size in this study is based on the trial results in previous reports [25,26] and the recommendation of specialists. The \( \sigma \) of WHOQOL-BREF scale of the experimental groups before and after treatment are 1.1, 0.86 and 1.27, while the \( \sigma \) of WHOQOL-BREF scale of the placebo group is 0.79. The \( \mu \) of WHOQOL-BREF scale of the experimental groups before and after treatment are 18.47, 18.6 and 18.74, while the \( \mu \) of WHOQOL-BREF scale of the placebo group before and after treatment is 19.36. According to the calculation, \( \mu \) 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 \( \sigma \) of NIHSS scale of the experimental groups before and after treatment are 1.27, 1.23 and 1.21, while the \( \sigma \) of NIHSS scale of the placebo group is 1.5. The \( \mu \) of NIHSS scale of the experimental groups before and after treatment are 2.45, 1.85 and 1.75, while the \( \mu \) of NIHSS scale of the placebo group before and after treatment is 2.95. According to the calculation, \( \mu \) 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.”(P11L20-P11L52)
Comment: In statistical analysis section, this study did not mention how to do comparative effectiveness analysis for the four groups to fit its objectives.

Response: We are grateful for this suggestion. To be more clear interpretation, we have added a brief description as follows: "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. “

(P12L35-P12L45)

Thanks again for your advice. We hope to learn more from you.

VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Zehuai Wen</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Guangdong Provincial Hospital of Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>14-May-2017</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
<th>The methodological reports in the revised manuscript have improved reasonably, but there are still a lot of issues to report more clearly and accurately.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. P2L23-P2L34:</td>
<td>Author mentioned “Three patients groups, each with 120 people, will be recruited. The most main symptom of each group is respectively hemiplegia, dysphasia and facial paralysis”. There may be misunderstanding of stratified randomization. Here, I urgently suggest the word “group” revise as “strata” (same suggestion for the main text, see P9L9). The sentence may be modified as “Three strata, each with 120 eligible participants, will be enrolled”. Please check the inconsistencies between the registration ChiCTR-IOR-17010397, the Abstract and main text: “follow up 180 days”(P2L34), “the third visit is on day 240 +/- 1”(P8L46), “the 240th day”(P10L8) and mentioned in P21L22 and P22L24. In addition, the visit time window was roughly out as +/- 1 day may not be flexible in this trial.</td>
</tr>
<tr>
<td>2. P4L3, P4L11,</td>
<td>To correct the book name as “Pharmacopoeia of the People’s Republic of China” and check the reference 8, 11 and 14.</td>
</tr>
<tr>
<td>and P4L26:</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>3. P6L38:</td>
<td>Authors declare this a double-blind trial. However, in the Treatment Plan section (P8L21-P8L31) the treatment plan was mentioned that the three groups A, B, and C received basic treatment plus NXK, XNST and XST respectively, and the group D treated with basic treatment alone. Meanwhile, in the section “Randomization, blinding and allocation concealment” (P13L21) authors did not describe any relevant issues about placebo or how to ensure the three capsules of NXK, XNST and XST be blinded to investigators and participants. So I guess this is a open-label trial. If authors state double-blind trial, it’s needed more details to support this declare.</td>
</tr>
</tbody>
</table>
4. P7L16 and P7L21: No. 8 “The above inclusion criteria will be applied to the experimental group and the control group” in the inclusion criteria and No. 1 “patients who have a history of stroke” in the exclusion criteria seem to be unnecessary because of duplication.

5. P11L18 -P11L48: The description of sample size calculation is still unclear. I guessed the Greek letter μ(mu) refers to the mean of differences of scores between before and after treatment. Please check it. If my guess is right, the differences of means between groups are small and difficult to determine the changes of WHOQOL-BREF (from 18.47 to 19.36) and NIHSS (from 1.75 to 2.95), because it is not enough to reveal the clinical importance of changes from baseline.

6. P12L6 -P12L19: Hypothesis tests on baseline characteristics might be unnecessary (see: Schulz KF, Grimes DA. Lancet 2002; 359: 614-618, and CONSORT 2010 statement), and it only need to report a table showing baseline characteristics for each group. Considering adjusted analysis for confounding factors, prognostic factors or strata should be pre-planned.

7. P24 -P37: As for the SPIRIT 2013 Checklist, it is designed only to guide authors to report their protocol of trial how to describe the contents of the listed items. Most of the descriptions in this table should be moved to the main text in this paper.

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**VERSION 2 – AUTHOR RESPONSE**

**Reviewer: 3**

**Reviewer Name**
Zehuai Wen

**Institution and Country**
Key Unit of Methodology in Clinical Research
Guangdong Provincial Hospital of Chinese Medicine
Guangzhou University of Chinese Medicine
Guangzhou, China

**Comment:** 1. P2L23-P2L34: Author mentioned “Three patients groups, each with 120 people, will be recruited. The most main symptom of each group is respectively hemiplegia, dysphasia and facial paralysis”. There may be misunderstanding of stratified randomization. Here, I urgently suggest the word “group” revise as “strata” (same suggestion for the main text, see P9L9). The sentence may be modified as “Three strata, each with 120 eligible participants, will be enrolled”. Please check the inconsistencies between the registration ChiCTR-IOR-17010397, the Abstract and main text: “follow up 180 days”(P2L34), “the third visit is on day 240 +/- 1”(P8L46), “the 240th day”(P10L8) and mentioned in P21L22 and P22L24. In addition, the visit time window was roughed out as +/- 1 day may not be flexible in this trial.

**Response:** Thanks for your detailed advice. We have revised “group” to “strata” on P2L28 and P9L36, and the sentence has been modified to “Three strata, each with 80 eligible participants, will be enrolled”. In addition, we have checked the inconsistencies between registration ChiCTR-IOR-17010397, the Abstract and main text. The related sentences have been uniformed as “the third visit is on day 210±5”.(P10L35,P11L55,P16L29)
Comment: P4L3, P4L11, and P4L26: To correct the book name as “Pharmacopoeia of the People's Republic of China” and check the reference 8, 11 and 14.
Response: Thank you for your careful work. The book name has been corrected as “Pharmacopoeia of the People's Republic of China”. (P4L3, P4L11, and P4L26) In addition, we have checked and confirmed the reference 8, 11 and 14 as the reviewer advised.

Comment: P6L38: Authors declare this a double-blind trial. However, in the Treatment Plan section (P8L21–P8L31) the treatment plan was mentioned that the three groups A, B, and C received basic treatment plus NXK, XNST and XST respectively, and the group D treated with basic treatment alone. Meanwhile, in the section “Randomization, blinding and allocation concealment” (P13L21) authors did not describe any relevant issues about placebo or how to ensure the three capsules of NXK, XNST and XST be blinded to investigators and participants. So I guess this is a open-label trial. If authors state double-blind trial, it’s needed more details to support this declare.
Response: Thank you for your valuable advice. Actually, this is a double-blind trial. The treatment plan for group D has been modified as basic treatment+ placebo. (P8L33) To make it clearer, a brief description has been added in the section of “Randomization, blinding and allocation concealment” as follows: “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.” (P15L1)

Comment: P7L16 and P7L21: No. 8 “The above inclusion criteria will be applied to the experimental group and the control group” in the inclusion criteria and No. 1 “patients who have a history of stroke” in the exclusion criteria seem to be unnecessary because of duplication.
Response: Thank you for your reminding. The No. 1 “patients who have a history of stroke” in the exclusion criteria has been deleted. (P7L21)

Comment: P11L18 -P11L48: The description of sample size calculation is still unclear. I guessed the Greek letter μ(mu) refers to the mean of differences of scores between before and after treatment. Please check it. If my guess is right, the differences of means between groups are small and difficult to determine the changes of WHOQOL-BREF (from 18.47 to 19.36 ) and NIHSS (from 1.75 to 2.95), because it is not enough to reveal the clinical importance of changes from baseline.
Response: We are sorry for the imprecise interpretation. We have retrieved the literatures again. In the new manuscript, it has been corrected as follows:” 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 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 WHOQOL-BREF scale of experimental groups before and after treatment are 17.13, 18 and 23.83 respectively, while the value of μi 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 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 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 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.” (P12L37-P13L13)
Comment: P12L6-P12L19: Hypothesis tests on baseline characteristics might be unnecessary (see: Schulz KF, Grimes DA. Lancet 2002; 359: 614-618, and CONSORT 2010 statement), and it only need to report a table showing baseline characteristics for each group. Considering adjusted analysis for confounding factors, prognostic factors or strata should be pre-planned.

Response: Thanks again for your advice. We have learned much from you. We have deleted the part of baseline characteristics for each group and the part of confounding factors. The deleted contents are as follows: “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 SAS9.1 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.” (P13L16)

Comment: P24-P37: As for the SPIRIT 2013 Checklist, it is designed only to guide authors to preport their protocol of trial how to describe the contents of the listed items. Most of the descriptions in this table should be moved to the main text in this paper.

Response: Thank you for your valuable advice. The contents in the SPIRIT 2013 Checklist have been moved to the main text. We have complemented the details in the manuscript to complete the contents.

VERSION 3 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Zehuai Wen</th>
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<tbody>
<tr>
<td></td>
<td>Key Unit of Methodology in Clinical Research, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China</td>
</tr>
</tbody>
</table>

| REVIEW RETURNED | 08-Jul-2017 |

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
<th>The manuscript was revised carefully to response all comments, but there were still some issues to be described exactly.</th>
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</thead>
<tbody>
<tr>
<td>1. In the Background (P3L28), author mentioned “the annual incidence of stroke in China is 2.16%”. This is very high incidence rate of stroke in my knowledge, please check the original paper of the reference No 1.</td>
<td></td>
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<tr>
<td>2. In Table 2, the WHOQOL-BREF and NIHSS should be measured at baseline (day 0).</td>
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<tr>
<td>3. In the Statistical Analysis section (P13L16), patient’s name should not be recorded in the CRF because of privacy protection. To the best of my knowledge, assessing patients’ baseline characteristics after screening can not balance their baseline characteristics.</td>
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<tr>
<td>4. Delphi technique is used to made a consensus among a group of experts. It certainly is not employed to ensure the credibility, validity and structure of a scale or questionnaire. (P16L9)</td>
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</table>
Comment: In the Background (P3L28), author mentioned “the annual incidence of stroke in China is 2.16%”. This is very high incidence rate of stroke in my knowledge, please check the original paper of the reference No 1.

Response: Thanks for your detailed advice. We have checked the reference No 1, and updated the manuscript as follows. “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.”(P3L18)

Comment: In Table 2, the WHOQOL-BREF and NIHSS should be measured at baseline (day 0).
Response: Thank you for your careful work. Table 2 has been corrected as you suggested, and WHOQOL-BREF and NIHSS will be measured at baseline (day 0). (P11L16) (P21L28)

Comment: In the Statistical Analysis section (P13L16), patient’s name should not be recorded in the CRF because of privacy protection. To the best of my knowledge, assessing patients’ baseline characteristics after screening can not balance their baseline characteristics.

Response: Thank you for your valuable advice. Patient’s name has been replaced as their number. The manuscript has been modified as follows: “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.” (P12L33)

Comment: Delphi technique is used to made a consensus among a group of experts. It certainly is not employed to ensure the credibility, validity and structure of a scale or questionnaire. (P16L9).

Response: Thank you for your reminding. The sentence has been modified as “Delphi techniques were adopted to achieve index weighting, which ensures that the outcome of the evaluation is patient-oriented.” (P15L11)

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**VERSION 4 – REVIEW**

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Zehuai Wen</th>
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<tbody>
<tr>
<td>Key Unit of Methodology in Clinical Research, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>14-Aug-2017</td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

Author has responded appropriately to all my comments point by point.
Naoxuekang, Xinnaoshutong and Xuesaitong capsules for treating stroke: a protocol for a randomised controlled trial
Huiling Chen, Hongbo Cao, Xu Guo, Meidan Zhao, Qing Xia, Bo Chen, Tieniu Zhao and Wenyuan Gao

BMJ Open 2017 7:
doi: 10.1136/bmjopen-2017-015983

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