Author's response to reviews

Title: Rationale and Design of a Double-blind, Placebo-controlled, Randomized Trial to Evaluate the Safety and Efficacy of Nimodipine in Preventing Cognitive Impairment in Ischemic Cerebrovascular Events (NICE)

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Author's response to reviews: see over
Dear Deesha,

Thank you very much for your letter about revising our manuscript: Rationale and Design of a Double-blind, Placebo-controlled, Randomized Trial to Evaluate the Safety and Efficacy of Nimodipine in Preventing Cognitive Impairment in Ischemic Cerebrovascular Events (NICE).

First, we were not able to make the suggested changes within the general framework of the original protocol for the reason that the study has been approved by our ethic committee and conducted already. We could not make any amendment for protocol when the multi-center study going well. But we still highly appreciate all comments from your team and reviewers. Please see the attached file of the statement.

Second, additional files 3, 4, 5 and 6 had been removed, and added the Abbreviations, Competing Interests, Authors' Contributions and Acknowledgements sections to the text of the manuscript. The whole manuscript had been checked and revised by Liwen Bianji (Edanz Group China), according to BMC guidelines for manuscript format.

Finally, we try our best to address the editorial and referees' comments in a revised manuscript, and make a point-by-point response to the concerns as the following attachments.

Should you have any questions please do not hesitate to contact us.

With all best wishes,

Penglian
On behalf of The NICE trial Group

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Response to Daniele Tomassoni

Title: Rationale and Design of a Double-blind, Placebo-controlled, Randomized Trial to Evaluate the Safety and Efficacy of Nimodipine in Preventing Cognitive Impairment in Ischemic Cerebrovascular Events (NICE)

Dear Professor Tomassoni,

First, we would like to thank you for reviewing our protocol and give some good suggestion. Please could you see the following answers to your comments.

1. Regarding of information about the progress of the trails, we already recruited 555 patients who all conform to the screening criteria up to 25 July 2012. You may find the details in http://www.cssnt.org/webhome/index/topic.top.html.

2. Unfortunately, we could not provide information about the demographic date, sex, age, et al, because collected data are managed by Giant Med-Pharma Service Group, and the Steering Committee only reviews the status of the trial and limited available blinded data. We are looking forward to seeing the results of this trial. As you suggested\(^1\), larger trials are needed to confirm the effect of nimodipine on stroke patients with vascular dementia. When getting the final data, we are pleasure to let you know.

Thank you again. Hope you could agree with us. If having any questions, please do not hesitate to let us know.

Kind regards,

Penglian Wang
On behalf of The NICE trial Group

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Reference:
Response to Roberto Federico Villa

Title: Rationale and Design of a Double-blind, Placebo-controlled, Randomized Trial to Evaluate the Safety and Efficacy of Nimodipine in Preventing Cognitive Impairment in Ischemic Cerebrovascular Events (NICE)

Dear Professor Villa,

Thank you very much for reviewing our protocol and give some very useful comments. Please could you find our explanations to your comments.

1. Your suggestion of adding a battery of neuropsychological tests (language, attention, executive functions) and tests of activities of daily living (for example ADDTC) is very useful for verify the efficacy of treatment. Unfortunately, we were not able to make changes within the general framework of original protocol. However, we may carry on another trial using different neuropsychological tests and tests of activities of daily living if the NICE results were expectable.

2. We did not excluded acute ischemic patients with post-stroke hypertension and a history of type 2 diabetes mellitus that may affect the results in the NICE study. As you know, we could not make changes within the general framework of original protocol. If the results were affected by these two factors in the NICE study, we may use a multivariate analysis that adjusted for post-stroke hypertension and a history of type 2 diabetes mellitus to identify whether nimodipine could prevent cognitive impairment in ischemic cerebrovascular events.

3. The duration of NICE study was defined as 6 months in NICE general framework. As this situation, we also were not able to make change. However, we may continue to follow-up these patients to obtain information if this suggestion was approved by ethics committees.

4. The results should be affected by age, because old age was associated with enzymatic activities linked to Krebs' cycle, electron transfer chain et al\(^1\), and other studies showed that neuronal damaged severity was more in old age patients with stroke\(^2,3\). Thus we definitely will use a multivariate analysis to adjust for the effect of age factor.

Thank you again. Hope you could agree with us. Should you have any questions please do not hesitate to contact us.

Kind regards,

Penglian Wang
On behalf of The NICE trial Group
Reference:
Response to Svetlana Lorenzano

Title: Rationale and Design of a Double-blind, Placebo-controlled, Randomized Trial to Evaluate the Safety and Efficacy of Nimodipine in Preventing Cognitive Impairment in Ischemic Cerebrovascular Events (NICE)

Dear Professor Lorenzano,

All staff of the NICE study group appreciated you for reviewing our protocol and giving some very helpful comments. Please see the following point-to-point responses to your comments:

1. We have added some information about potential mechanisms of action\textsuperscript{1,2}, by which nimodipine could be effective specifically in preventing mild cognitive impairment in patients with acute ischemic stroke. Please see page 5 line 22 and page 6 line 1, 4-7.

2. In the paragraph “Rationale” (page 8), the sentence about the aim of the NICE study had been rephrased. Please see page 8 line 6-8.

3. Yes, patients with a history of stroke and disability may be included in the study. To be honest, we can not distinguish the mild cognitive impairment in patients with a stroke history before this index stroke, because we did not pay more attention to cognitive impairment on stroke patients in China though it could affect the outcomes of patients. That is the reason that the NICE study would like to investigate whether nimodipine could prevent mild cognitive impairment in patients with acute ischemic stroke. We do not know how much patients whose brain lesion may not be stable when they were enrolled up to now, but it will take 3-5 days to implement relative neuronal image and lab tests before enrolling in the study and recruited patients will discontinue taking nimodipine or placebo if the investigators consider patients suffering from second stroke according clinical symptoms and neuronal imaging. Under these situations, it is difficult to evaluate the real effects of nimodipine administered during acute phase on cognitive functions.

4. The patients are enrolled equal or fewer 7 days after the stroke onset (had been corrected in the abstract, the table and the figure).

5. In the paragraph “Ethics and informed consent”, “the written informed consent is obtained before being assigned into the study from surrogate family member if the patients are not able to sign the informed consent”. (Please see page 9 line 9).

6. In the paragraph “Treatment and Follow-up”:
   (1). We simply explain the randomization process in page 9 line 17-19.
   (2). As you know, either white matter hyperintensities or infarct size indeed had a
role on the development of cognitive impairment after stroke, so the NICE study would like to collect these data. However, it may not be included in this study outcome. It would be interested to analyze these data if we got another specific trial for these variables.

(3). For the moment, we are not planning to use an etiopathogenetic classification of the stroke.

(4). The assessments for disability scale were not included in this study.

7. In the paragraph “Statistical analysis”:
   (1). We had tried to rephrase the null hypothesis (please see page 12 line 8-11).
   (2). Missing values are still treated as missing. Patients are examined at the last follow-up (at the occurrence of clinical event, the end of study, or the last follow-up before drop-out) (please see page 12 line 15-17).

8. The whole manuscript had been checked and revised by Liwen Bianji (Edanz Group China) (Please see the attached file).

9. Yes, you are right. “Place-controlled” should be “placebo-controlled” in the “Abstract”.

10. In the paragraph “Background”, we rephrased the sentence according to your kindly comments in Page 5 line 5-7 and line 17-18.

11. In the paragraph “Rationale”:
   (1) We correct the sentence according to your suggestive comments (in page 6 line 2-4).
   (2) We correct the publication year of ref 31 by re-searching Pubmed database (instead by Ref 22).
   (3) Rephrase the term of “…retrogressive…dementia” according to original article’s description (in page 6 line 8-12).
   (4) WMD means Weighted Mean Difference (in page 6 line 18).

12. D180 means day 180 in the paragraph “Statistical analysis” (had been changed in the text in page12 line 19).

13. Yes, your purpose is right. The primary objective of the NICE is to is to prove the efficacy of nimodipine in the prevention/treatment of mild cognitive impairment in patients with acute ischemic stroke (had been changed in the paragraph “Conclusion” in page14 line 6).

14. The capital “N” in nimodipine had been changed in any place where it needs to be changed.

In addition, we know you and your group had done lots of work about intravenous
thrombolysis for acute ischemic stroke patients either aged older than 80 year\(^3\) or 18- to 50-year-old patients\(^4\). Your data further emphasized the concept of tailoring care to individual patients with acute ischemic stroke and using Neurovascular treatment unit\(^5\). It will provide helpful evidence and advice for therapy of ischemic stroke.

Thanks again.

Please don't hesitate to contact us if you have any comments and questions regarding our manuscript.

Kind regards,

Penglian Wang
On behalf of The NICE trial Group

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