

## **Author's response to reviews**

**Title:** Chinese Acute Ischemic Stroke Treatment Outcome Registry (CASTOR): protocol for a prospective registry study on patterns of real-world treatment of acute ischemic stroke in China

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**Version: 1 Date:** 28 Feb 2017

### **Author's response to reviews:**

March, 2017

BMC Complementary and Alternative Medicine

BCAM-D-16-01240

Dear Tom Rowles PhD,

We thank you and the reviewers of our manuscript entitled “Chinese Acute Ischemic Stroke Treatment Outcome Registry (CASTOR): protocol for a prospective registry study on patterns of real-world treatment of acute ischemic stroke in China” for your time and helpful feedback. Based on your advice and suggestions, we have extensively revised our manuscript, added some literature and restructured the results and discussion sections. We are pleased to submit our revised manuscript to BMC Complementary and Alternative Medicine. The major revisions have been highlighted in red in the revised version of the manuscript. We include below a detailed response to the questions raised by the reviewers. The questions and our responses are as follows.

Thank you again for your time and assistance.

Sincerely,

Yining Huang

Reviewer reports:

Reviewer 1: Review of "Chinese Acute Ischemic Stroke Treatment Outcome Registry (CASTOR): protocol for a prospective registry study on patterns of real-world treatment of acute ischemic stroke in China". The authors provided a study protocol with clear structure and detailed study design information. The whole manuscript is well written and easy to understand.

Author's response: We thanks for reviewer's comments. The protocol we provide aims to evaluate the patterns and pharmacoeconomics of current treatments for AIS (acute ischemic stroke) in real-world settings in China.

1. The use of QALY (Quality Adjusted Life Years) should be re-considered since the total follow-up of maximum for 1 year.

Author's response: Thanks for reviewer's suggestion on the use of QALY (Quality Adjusted Life Years). In our study, we calculated QALY to conduct the cost-utility analysis. We understand the follow-up period of maximum for 1 year is shorter for the evaluation of QALY. However, a longer follow-up would be associated with a higher loss rate. So we used QALY in this study for the exploratory cost-utility analysis. And we would be caution to explain the results.

2. What is the rationale of defining 5 visits in 12 months? There are clear cut international standards for visits such as the Helsingborg Declaration released in 1998 and 2006. Is there any evidence-based agreed guidance for this?

Author's response: In our study, we have 5 visits in the follow-up period. Baseline characteristics will be obtained at the first visit. The second visit at 1 week is aimed mainly to capture the early change of neurological function and safety measures. Many trials on AIS have set a visit at the similar time point, such as SYNTHESIS Expansion (Ciccione A, et al. NEJM, 2013, 368, 904-913) and MR CLEAN (Berkhemer O A, et al. NEJM, 372, 11-20). The third visit at discharge is aimed to collect the diagnostic and treatment detail in hospital and stroke outcome at discharge.

The similar design is in China QUEST (Quality Evaluation of Stroke Care and Treatment) registry (Wei J W, et al. Stroke, 41, 1877-1883). The fourth visit at 90 days is aimed to measure the primary outcome. This time point is often used in stroke research. The fifth visit at 1 year is mainly for the exploratory cost-utility analysis. The Helsingborg Declaration suggests the stroke outcome measured at 1 month and 3 month after stroke. The measurement is aimed to evaluate the quality of stroke management. To be different, our study was aimed to explore the potential effective treatment. We focused on the individual outcome after stroke.

Ciccone A, Valvassori L, Nichelatti M, et al. SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke[J]. New England Journal of Medicine, 2013, 368, 904-913

Berkhemer O A, Fransen P S, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke[J]. New England Journal of Medicine, 2015, 372(1):11-20.

Wei J W, Heeley ELWang J G, Huang Y, et al. Comparison of recovery patterns and prognostic indicators for ischemic and hemorrhagic stroke in China: the ChinaQUEST (Quality Evaluation of Stroke Care and Treatment) Registry study.[J]. Stroke, 2010, 41(9):1877-1883.

3. In addition, I strongly suggest that the authors give this paper to an English native speaker to do the grammar checking.

Author's response: We thanks reviewer for pointing out this. As suggested, we have extensively revised our paper, which hopes to your requirement. And the changes can be seen in revised manuscript.

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#16 what is patterns?

Author's response: The pattern of current treatments indicates the usage proportion, dosage and duration of each kind of medication.

#25 acute phase of AIS = AIS?

Author's response: Yes. We have deleted "acute phase of" in the manuscript, which can be seen in our revised paper.

#27 "The patients are treated for AIS as how they would really be treated in the hospitals." is not clear for me.

Author's response: CASTOR is a registry study. The study does not interfere with the treatment choice of the patients included. There is no specific therapy required or prohibit in this study. The management of the patients with AIS included in our study follows the stroke guidelines and local practice.

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#1 increased---increasing

Author's response: We thanks reviewer for pointing out this. As suggested, we have corrected "increased" to "increasing".

#9 help to find

Author's response: As suggested, we have corrected "find to "to find".

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#12 cerebral stroke is stroke?

Author's response: We thanks reviewer for pointing out this. It should be "stroke". We have modified the sentence.

#29 please unify the terminology of stroke, the authors can use the name from "American Heart Association"

[http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/Types-of-Stroke\\_UCM\\_308531\\_SubHomePage.jsp](http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/Types-of-Stroke_UCM_308531_SubHomePage.jsp)

Author's response: Thanks for reviewer's suggestion. We have unified the terminology of stroke in our manuscript.

#30 has thrombectomy device put into practice in China?

Author's response: Yes. In China, the thrombectomy device has been used in the endovascular treatment of AIS. But the endovascular treatment is not very popular because it is restricted by equipment, cost and experienced physicians. We have inserted a description in the second paragraph of "Background" section.

#45 the second 'is' is not necessary"

Author's response: As suggested, we have modified the sentence, and delated the second "is".

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#49 prospective, not perspective

Author's response: As suggested, we have modified the sentence, and corrected the "perspective" to "prospective". We are very appreciated the reviewers' careful work and rigorous attitude.

#55 do you mean that the reason you define the sample size of 10,000 patients because there is a Chinese Guideline?

Author's response: We understand a larger sample size may increase the statistical power in a registry study. However, the sample size is also restricted by the availability of research center and patients and the resource to support the study. In our study, the choice of the sample size was based on the resource available. We have inserted an explanation in the section of sample size.

#60 you mean you have a follow-up totally one year or after 5 visits, is there an extra 1 year follow up?

Author's response: The total follow-up period is 1 year. There are 5 visits within the 1-year follow-up. We have modified our sentences to make it clear.

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#38 does it make sense to do CUA? Whose perspective is key in the economic evaluation (payer? societal?) You enrolled the patients within 1 week after onset, and collect data until visit 4, all the data is prospective, is there big difference?

Author's response: We thanks reviewer for pointing out this. The economic evaluation is based on the payer's perspective. In our study, we collect data from the enrollment to visit 5. The total follow-up period is 1 year. We admit the follow-up period is short and there may be no significant difference in the quality-adjusted life year (QALY) among different treatments. So the cost-utility analysis in our study is an exploratory analysis. We will explain the results with caution.

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#8 you have a SOP to guide the data collection procedure?

Author's response: Yes, we have. We also have the data collection training program.

#11 could you please specify, how often do you plan to conduct 'periodic analysis'? or until how many number of patients being enrolled?

Author's response: We thanks reviewer for pointing out this. We have revised related sentences. We have cleared the issue in the section of "Interim analysis". As we described in our revised manuscript, we plan to conduct an interim analysis after 5000 patients enrolled in our study.

#28 could you please explain again about how you define the sample size?

Author's response: A larger sample size may increase the statistical power in a registry study. However, the sample size is also restricted by the availability of research center and patients and the resource to support the study. In our study, the choice of the sample size was based on the resource available. We have inserted an explanation in the section of sample size.

Major consideration:

The whole manuscript as well as the references are not reflecting the current international state-of-the-art on population-based stroke registries. The study protocol reflects the authors' previous publication track rather than methodological scientific standards and international good-practice experiences in the field of stroke registries. From 20 references, 16 references are from mainland China. Most important publications in this field are ignored.

Author's response: We thanks reviewers for pointing out this and we agree with reviewers' points. As suggested, we have added the related information and references, which hopes to meet with your requirement.

In the last two decades 'real-world' population-based stroke registries in US, European Union, Australia/ NZ defined global standards (Wahlgren 2007 (SITS-MOST); Heuschmann PU et al. 2004 (in-hospital mortality of AIS); Kolominsky-Rabas et al. 2001 (TOAST classification in stroke registry) as well as 5 RCTs in 2015 on thrombectomy in AIS patients. These basic publications should be part of every registry protocol reflecting good scientific standards in the 21st century.

Author's response: As suggested, we have carefully revised our manuscript and added the references above in our revised manuscript accordingly.