PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatments and Outcomes of Untreated cerebral Cavernous malformations in CHINA (TOUCH): Study protocol of a nationwide multicenter prospective cohort study.
AUTHORS	Lin, Fuxin; He, Qiu; Gao, Zhuyu; Yu, Lianghong; Wang, Dengliang; Zheng, Shufa; Lin, Yuanxiang; Kang, Dezhi

VERSION 1 – REVIEW

REVIEWER	Kelly Flemming Mayo Clinic USA
REVIEW RETURNED	19-Mar-2020

GENERAL COMMENTS	The authors lay out a well designed study using imaging, serum biomarkers, and clinical data to assess outcomes in a population of patients with cavernous malformations undergoing conservative vs. surgical therapy. Strengths * THe large population planned will be the largest of its kind * THe question asked is very important and the study will fill gaps in the literature * The methods and plan are very well laid out; the addition of the serum biomarkers is an excellent idea Weakness * There will remain limitations in interpretation due to the fact that deteriorating patients require surgery and deteriorating patients would often have lower MRS scores. * Minor suggestions - What is the plan for spinal cord CM. Inclusion suggests brain only. Is spinal CM an exclusion? - On which sequence (T2?) will you measure size of CM, do you include or exclude the hemosiderin ring? - Patients with CM fluctuate where within the same year, the MRS score after a bleed could be 3, but within 3 months, they could be a 2. Will you be looking at a single point MRS score or the persistence of an MRS score <2 for more than 6 months (or more than 1 year) as poor outcome? - If you are doing such a nice, large study, I would consider adding on PROMIS-29 or Euro-QOL quality of life data as a secondary endpoint (suggestion, not required for this manuscript).

REVIEWER	Rebecca Wilson Cardiff University, UK
REVIEW RETURNED	24-Mar-2020

GENERAL COMMENTS	This manuscript describes a protocol for a prospective cohort study. The authors present a strong rationale for the study, at the end of the introduction. The setting and population are appropriate to answer the research question. My main concern is the lack of clarity on how the primary outcome is measured and when, these just need a better and more clear description. Using the primary and secondary outcomes to give structure, the statistical analysis section needs to be more clear and will hopefully be easier to follow. This is, overall, a very comprehensive and considered protocol for an important study. Introduction The introduction gives a good overview and nicely sets up the purpose of the study. Just some very minor edits needed for ease of reading. Although you give some background information on CCMs, this is a general medicine journal and I think you need to give a basic definition to open the introduction. Page 2, line 44 – remove “the composite of” Page 2, line 45 – change “was” to “is” Page 2, line 50 – change “The conflicting” to “The conflicting evidence” or “The conflict in the evidence” Page 2, line 53 – spell out UCCM the first time you use the acronym Page 2, line 57 – change “resources” to “records” Page 3, line 32 – refer to the outcomes when describing the objective, at present it is slightly vague Methods The methods section is very thorough, again just some minor suggestions. Page 3, line 50 – change “This study has been started” to “This study started” Page 3, line 53 – not sure what is meant by “Consecutive patients”, suggest rewording Page 3, line 55 – Surely the “feasibility” of the study would have been assessed prior to the start of the study rather than during, I’m not sure this is what you mean. Similarly, what do you mean by “preciseness”? Fig 2 is helpful but I think it needs some re-working, it’s not entirely clear. There are two primary outcome boxes on the left, one at follow-up and one at five years. And where patients are in ‘re-bleeding or deterioration of FND, the two next boxes are primary outcome (one on the left and one on the white), why is this? I don’t understand why there is primary outcome under follow-up and again under 5 years. There should just be one primary outcome. Page 4, line 35 – change “electric” to “electronic” Page 4, lines 37-48 – there are a few acronyms that could do with spelling out here, ORC, mRS, PTC – this comment applies throughout Page 4, Data collection – some more information would be helpful here, are these data routinely collected or are they being collected for the purpose of the study? If so, who is responsible for entering the data, a clinician or other research personnel? Page 4, line 59 – should this be “or” rather than “and”? Page 6, line3 – change “centre” to “centres” Page 6, primary outcome – two important points, more information is needed about the mRS, this is poorly explained. At what time point is the primary outcome? 5 years?

	Page 6, sample size calculation – I don't think this section is relevant for an observational study. Certainly, what is written here doesn't constitute a sample size calculation. You would expect to see a sample size calculation for a trial or study where a number of participants are required to achieve adequate power. I would remove this section, or you could just say, under 'participants', "we expect to register xxx patients over xx years". Page 7-8, Statistical analysis – I think this section could do with some restructuring to aid coherence. You first describe descriptive analysis, I would then go on to describe how you are going to analyse the primary outcome and then, in turn, the secondary outcomes. Presently, I can't see any mention of analysis of the primary outcome.

VERSION 1 – AUTHOR RESPONSE

Responds to the reviewers' comments:

Reviewer :1

1. There will remain limitations in interpretation due to the fact that deteriorating patients require surgery and deteriorating patients would often have lower MRS scores.

Response: Thank you very much for the comment. There may be an imbalance baseline condition between the two cohorts. To resolve this problem, we will analyze the data in different subgroups and by Propensity Score Matching analysis. This limitation has been stated at the "Strengths and limitations" section.

2. What is the plan for spinal cord CM. Inclusion suggests brain only. Is spinal CM an exclusion?

Response: Thank you very much for the comment. In this study, we only focus on brain CCMs. The treatment strategy and prognosis are different between spinal and cerebral CCMs, we cannot evaluate their outcomes at the same criteria.

3. On which sequence (T2?) will you measure size of CM, do you include or exclude the hemosiderin ring?

Response: Thank you very much for the comment. As suggested, we have modified the section of Data collection as follows: CCM size (T2 sequence, excluding the hemosiderin ring), hematoma size (CT scans), associated developmental venous anomaly (DVA) and multiplicity are documented.

4. Patients with CM fluctuate where within the same year, the MRS score after a bleed could be 3, but within 3 months, they could be a 2. Will you be looking at a single point MRS score or

the persistence of an MRS score <2 for more than 6 months (or more than 1 year) as poor outcome?

Response: Thank you very much for the comment. We have modified the primary outcomes as "mRS>2 lasting at least 1year at the last follow up" according to the trial registry on www.clinicaltrials.gov.

5. If you are doing such a nice, large study, I would consider adding on PROMIS-29 or Euro-QOL quality of life data as a secondary endpoint (suggestion, not required for this manuscript).

Response: Thank you very much for the comment. Considering this study has been conducted in multiple centers, It is hard to retraining the assessors again in differ center. We will include PROMIS-29 or Euro-QOL scores in our next study.

Reviewer :2

1. The introduction gives a good overview and nicely sets up the purpose of the study. Just some very minor edits needed for ease of reading. Although you give some background information on CCMs, this is a general medicine journal and I think you need to give a basic definition to open the introduction.

Response: Thank you very much for the comment. As suggested, we have added the definition of CCMs, pathological changes and common presenting symptoms of CCMs in Introduction, such as: Cerebral cavernous malformations (CCM) is the second most common cerebral vascular malformation. CCM affect people at any age and occur throughout the central nervous system.[1] The prevalence is estimated at 0.16% to 0.5%, and an annual detection rate was estimated at 0.56 per 100 000 per year for adults.[2 3] Due to weakening of the vascular endothelial cell junctions or changes in lumen polarity, the typical histological presentations of CCM are multiple lumen malformations, vascular leakage at the brain capillary level, and disruption of the blood-brain barrier (BBB). These pathological changes could cause hemorrhage, headache, seizures and focal neurological deficits.

2.Page 2, line 44 – remove "the composite of"

Response: Thank you very much for the comment. As suggested, the "the composite of" were deleted.

3.Page 2, line 45 – change "was" to "is"

Response: Thank you very much for the comment. As suggested, we changed "was" to "is"

4. Page 2, line 50 – change "The conflicting" to "The conflicting evidence" or "The conflict in the evidence"

Response: Thank you very much for the comment. As suggested, we changed "The conflicting" to "The conflicting evidence"

5.Page 2, line 53 – spell out UCCM the first time you use the acronym

Response: Thank you very much for the comment. As suggested, we spelt the “Untreated cerebral Cavernous malformations (UCCM)” the first time in the article.

6.Page 2, line 57 – change “resources” to “records”

Response: Thank you very much for the comment. As suggested, we changed “resources” to “records”.

7.Page 3, line 32 – refer to the outcomes when describing the objective, at present it is slightly vague

Response: Thank you very much for the comment. As suggested, we added the details of the outcomes in this section as follows: The long-term outcomes include mRS score (Table 1), morbidity, and all-cause mortality. The nature history is studied by the incidence rate of symptomatic hemorrhage, drug refractory epilepsy, and focal neurological deficits.

8.Page 3, line 50 – change “This study has been started” to “This study started”

Response: Thank you very much for the comment. As suggested, we changed “This study has been started” to “This study started”

9.Page 3, line 53 – not sure what is meant by “Consecutive patients”, suggest rewording

Response: Thank you very much for the comment. We have revised the word “Consecutive patients” to “All eligible patients”.

10.Page 3, line 55 – Surely the “feasibility” of the study would have been assessed prior to the start of the study rather than during, I’m not sure this is what you mean. Similarly, what do you mean by “preciseness”?

Response: Thank you very much for the comment. Sorry for the wrong words we have chosen. Initially, we want to express that the compliance with the plan and the accuracy of data are supervised by the Clinical Research Data Security Committee in Fujian Medical University. We have revised accordingly in the revised manuscript.

11.Fig 2 is helpful but I think it needs some re-working, it’s not entirely clear. There are two primary outcome boxes on the left, one at follow-up and one at five years. And where patients are in ‘re-bleeding or deterioration of FND, the two next boxes are primary outcome (one on the left and one on the white), why is this? I don’t understand why there is primary outcome under follow-up and again under 5 years. There should just be one primary outcome.

Response: Thank you very much for your excellent comments. We modified the flow diagram in the new Fig. 2. to make it concise and clear.

12.Page 4, line 35 – change “electric” to “electronic”

Response: Thank you very much for the comment. As suggested, we changed “electric” to “electronic” .

13.Page 4, lines 37-48 – there are a few acronyms that could do with spelling out here, ORC, mRS, PTC – this comment applies throughout

Response: Thank you very much for the comment. As suggested, we spelt out some acronyms in section Participants and study settings, such as C-reactive protein (CRP), procalcitonin (PCT), and some other uncommon blood biomarkers, such as interleukin-6 (IL-6), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), vascular endothelial growth factor (VEGF), interleukin-2 (IL-2), immunoglobulins (IGs), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β).

14.Page 4, Data collection – some more information would be helpful here, are these data routinely collected or are they being collected for the purpose of the study? If so, who is responsible for entering the data, a clinician or other research personnel?

Response: Thank you very much for the comment. Actually, not all biomarkers are routinely collected, such as MMP-2, MMP-9, VEGF and IL-2. A part of the blood biomarkers and clinical data are collected for the purpose of the study. The clinical coordinators (CRC) in each center are responsible for collecting all the data needed in eCRF. The CRCs were trained before the start of this study. We have declared this information at the "Data collection" section as following: The clinical coordinators (CRC) in each center are responsible for collecting all the data needed in eCRF. The CRCs are trained before the start of this study.

15.Page 4, line 59 – should this be "or" rather than "and"?

Response: Thank you very much for the comment. As suggested, we changed "and" to "or" .

16.Page 6, line3 – change "centre" to "centres"

Response: Thank you very much for the comment. As suggested, we changed "centre" to "centres".

17.Page 6, primary outcome – two important points, more information is needed about the mRS, this is poorly explained. At what time point is the primary outcome? 5 years?

Response: Thank you very much for the comment. As suggested, we added the details of mRS in table 1. This is a cohort follow-up study across a 5-year period with a 2 years interval of enrollment and 3 years follow up for each patient. we defined the primary outcomes as "mRS>2 lasting at least 1year at the last follow up". Thus, the time point of the primary outcome is the last visit of the patients at least 3 years after enrollment.

18.Page 6, sample size calculation – I don't think this section is relevant for an observational study. Certainly, what is written here doesn't constitute a sample size calculation. You would expect to see a sample size calculation for a trial or study where a number of participants are required to achieve adequate power. I would remove this section, or you could just say, under 'participants', "we expect to register xxx patients over xx years".

Response: Thank you very much for the comment. Before the starting of this study, we have done a questionnaire about the number of the CCM patients treated or consulted in each participating center. We speculated that at least of 1200 patients will be registered within a 2-year enrollment. According to your suggestion, we revised the title "Sample size calculation" into "Expected sample size", and declared that "With a 2-year-interval of enrollment, under participants, we expect to register 1200 patients and follow up at least 3 years."

19.Page 7-8, Statistical analysis – I think this section could do with some restructuring to aid coherence. You first describe descriptive analysis, I would then go on to describe how you are going to analyse the primary outcome and then, in turn, the secondary outcomes. Presently, I can't see any mention of analysis of the primary outcome.

Response: Thank you very much for the comment. The objectives of this study are to determine whether surgical treatment improves the long-term outcomes of patients diagnosed as U-CCM or not, and to determine the nature history of U-CCM in Chinese people based on conservative treatment arm. Accordingly, we divided the "Statistical analysis" into two parts, which are "Nature history" and "Effect of surgical treatment". The surgical outcomes are rated by mRS score. The nature history is studied by the incidence rate of symptomatic hemorrhage, drug refractory epilepsy, and focal neurological deficits. Thus, we described the statistical method of each parameter in corresponding parts may be more reasonable.

20. Please remove table 1 that is uploaded as it is already embedded in main document.

Response: Thank you very much for the comment. As suggested, we removed table 1.

21. 'Strengths and limitations of this study' should consist of 3-5 bullet points. Please ensure that you have met the required number of bullets.

Response: Thank you very much for the reminder. We have added more points in the section of Strengths and limitations: 3 This cohort study is an observational study and the evidence level is lower than Randomized Controlled Trial. 4 The follow-up is relatively short for incident CCM patients (less than 5 years). 5 This cohort study focuses on cerebral cavernous malformations but not includes spinal cavernous malformations.

22. Patient and Public Involvement: Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions: How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences? How did you involve patients in the design of this study? Were patients involved in the recruitment to and conduct of the study? How will the results be disseminated to study participants? For randomised controlled trials, was the burden of the intervention assessed by patients themselves? Patient advisers should also be thanked in the contributorship statement/acknowledgements.

Response: Thank you very much for the comment. As suggested, we added the section of "Patient and Public Involvement" as follows: The research questions were designed by the multidisciplinary team of CCM in our center based on clinical practice and literature review, and audited by the Clinical Research Center of The First Affiliated Hospital of Fujian Medical University. Neither patients nor the public were directly involved in the selection of outcome measures, design and implementation of the study. Patients will be informed the study flow and provide feedback on reducing burden. The main results of the study will be disseminated to participants if interested with respect to their results from baseline and end-of-study assessments.

In all, we found the reviewer's comments are quite helpful, and I revised my paper point-by-point. Thank

you and the review again for your help!