

## 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

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| <b>TITLE (PROVISIONAL)</b> | The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms   |
| <b>AUTHORS</b>             | Chen, Yunchang; Fan, Haiyan; He, Xuying; Guo, Shenquan; Li, Xifeng; He, Min; Qu, Yan; Yang, Xinjian; Zhang, Hongqi; Sun, Xiaochuan; Wang, Liqun; wang, Zhong; Tong, Xiaoguang; Zhong, Ming; Maimaitili, Aisha; Tong, Zhiyong; Duan, Chuanzhi |

### VERSION 1 – REVIEW

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| <b>REVIEWER</b>        | Ning Lin MD<br>Weill Cornell Medicine, Department of Neurological Surgery, New York, USA |
| <b>REVIEW RETURNED</b> | 22-Nov-2017  |

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| <b>GENERAL COMMENTS</b> | <p>This manuscript describes an ambitious, multi-center, prospective, observational trial that evaluates the treatment patterns of intracranial aneurysms in China, as well as the safety, effectiveness, and economic benefits of the clipping vs. coiling. There are a number of well-respected neurosurgery centers among the participants (Tiantan hospital, Xuanwu hospital, etc). The strength of the study includes high volume recruitments, coverage of wide geographic locations, and international collaboration with UCLA. There are also a number of areas that can be improved.</p> <ol style="list-style-type: none"><li>1. It is unclear how the study can evaluate the rate of aneurysm rupture or the risks of aneurysm rupture. As far as I can tell the study recruits patients with UIA's and separate them into two treatment arms based upon practitioner's recommendation. Is there a 3rd arm of "observation"?</li><li>2. The authors stated that the prevalence of aneurysms in China can be as high as 7% which is significantly more than the widely accepted 2-3% prevalence rate in other studies. Is this an isolated phenomenon in China or UIA's are also prevalent in higher rate in other eastern Asian countries (Japan, Korean, etc)?</li><li>3. The endpoints for evaluating safety and effectiveness of treatment were given in the tabulated format at <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>, but should also be clearly stated in the manuscript itself. In addition, ipsilateral stroke and neurological deficits within 30 days should be considered as a safety measure.</li><li>4. How do the authors plan to evaluate economic benefits of treatment?</li><li>5. As flow diversion becomes a standard of care for many large, wide-necked aneurysms, how would authors evaluate the safety and effectiveness of patients treated with flow diversion? The follow-up period of 6 months is likely too short and this treatment likely carries a different kind of risk profile than aneurysm coiling.</li></ol> |
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|  | <p>Grouping them together may be confusing.</p> <p>6. The author list is probably too long and includes 10 authors from the same institution. This should be shortened.</p> <p>Overall this is a worthwhile effort and a large collaborative study to evaluate the landscape of aneurysm treatment in China. The manuscript is adequately written and with proper modification should be published. Will be happy to review it again.</p> |
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| <b>REVIEWER</b>        | Mark Harrigan<br>UAB, USA |
| <b>REVIEW RETURNED</b> | 24-Nov-2017               |

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| <b>GENERAL COMMENTS</b> | <p>The authors describe a multicenter, prospective observational study of the management of unruptured intracranial aneurysms that is already in progress. This project is large, and, if done well, will provide information that is complementary to ISUIA and UCAS. The Chinese population may turn out to have significant differences compared to the populations studied in ISUIA and UCAS. The principal strength of Chinese studies like this is the ability to recruit vast numbers of subjects in a relatively short period of time. The investigators plan to assess the risk of antithrombotic therapy in patients with unruptured intracranial aneurysms, which is much needed. However, the manuscript needs a lot of work.</p> <ol style="list-style-type: none"> <li>1. The title should be changed to something like, "Rationale and design of China Intracranial Aneurysm Project..." Furthermore, the authors are encouraged to look at similar publications about major studies for examples of how this kind of a "design and rationale" paper looks.</li> <li>2. The primary endpoint and secondary endpoints need to be clearly stated.</li> <li>3. The sample size calculation (or justification) should be explained in a separate section.</li> <li>4. Text throughout the whole manuscript needs to be tightened up. The statement in the abstract, "...incidence of IA is very dangerous..." is grammatically incorrect and also an over simplification. Many small anterior circulation aneurysms seem to have a low annual rate of rupture, whereas larger and posterior circulation aneurysms are relatively more "dangerous." The term "dangerous" should be avoided in a scientific paper. Another example: "Previous research has also shown that the risk of IA rupture is 1% to 2%..." They mean annual risk, and this applies to many aneurysms but not all. There are other examples.</li> </ol> |
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| <b>REVIEWER</b>        | Igor Nikolic<br>Clinical Center of Serbia,<br>Serbia |
| <b>REVIEW RETURNED</b> | 29-Nov-2017  |

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| <b>GENERAL COMMENTS</b> | Nice designed study of one important problem in neurosurgery |
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### VERSION 1 – AUTHOR RESPONSE

Editorial Requests:

- Please amend the title to clarify this is a protocol. We suggest: "The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms."

Answer: The title of the manuscript was amended to "The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms".

- Please include a brief summary of your dissemination plans in the abstract >> ethics and dissemination section.

Answer: Dissemination plans have been added.

- Please clarify the ethics statement. You say: "The research protocol and the informed consent form (ICF) for participants in this study are supported by the ethics committee.." Do you mean "..are approved by the ethics committee.."?

Answer: The author made a corresponding change in the manuscript.

- Please go through the STROBE reporting checklist and make sure that all applicable items are reported in the manuscript. See: [https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE\\_checklist\\_v4\\_cohort.pdf](https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_cohort.pdf)

Answer: The manuscript all applicable items are reported in the manuscript.

Point-by-point response to the comments:

1. Reviewer 1 Comments

①Comments: It is unclear how the study can evaluate the rate of aneurysm rupture or the risks of aneurysm rupture. As far as I can tell the study recruits patients with UIA's and separate them into two treatment arms based upon practitioner's recommendation. Is there a 3rd arm of "observation"?

Answer: The China intracranial aneurysm project (CIAP) consisted of five sub-studies, and mainly study the aneurysms in the following aspects: 1) Risks of antithrombotic therapy in patients with un-ruptured intracranial aneurysms complicated with ischemic cardiovascular diseases; 2) The rupture rate; 3) Rupture risk and prediction model of rupture; 4) Treatment options for UIAs; 5) The study of standardized treatment of UIA bleeding in early stage. The study evaluates the treatment options for UIAs, the other two studies evaluate the rate of aneurysm rupture, the risks of aneurysm rupture, respectively. There is a 3rd arm of "observation". For patients with UIA who are not treated, we have a regular follow-up schedule, specifically, sub-studies 1, 2 and 3 will be included in this part of the patient.

②Comments: The authors stated that the prevalence of aneurysms in China can be as high as 7% which is significantly more than the widely accepted 2-3% prevalence rate in other studies. Is this an isolated phenomenon in China or UIA's are also prevalent in higher rate in other eastern Asian countries (Japan, Korean, etc)?

Answer: "The prevalence of aneurysms in China can be as high as 7%", this result comes from the highest data reported by Chinese scholars (Li MH, Chen SW, Li YD, Chen YC, Cheng YS, Hu DJ, Tan HQ, Wu Q, Wang W, Sun ZK et al: Prevalence of unruptured cerebral aneurysms in Chinese adults aged 35 to 75 years: a cross-sectional study. ANN INTERN MED 2013; 159:514-521.). What is the prevalence of aneurysms in China? this is a goal of the CIAP, and I hope CIAP's findings will give an explanation of this issue: Is this an isolated phenomenon in China or UIA's are also prevalent in higher rate in other eastern Asian countries (Japan, Korean, etc)?

③Comments: The endpoints for evaluating safety and effectiveness of treatment were given in the tabulated format at [clinicaltrials.gov](http://clinicaltrials.gov), but should also be clearly stated in the manuscript itself. In addition, ipsilateral stroke and neurological deficits within 30 days should be considered as a safety measure.

Answer: The primary and secondary endpoints have been added to the manuscript by the author (Table 3). Ipsilateral stroke and neurological deficits within 30 days supplemented the safety evaluation of our study and will play a positive role in our findings.

④Comments: How do the authors plan to evaluate economic benefits of treatment?

Answer: The authors plan to combine the following three aspects of patient evaluation of the economic benefits of treatment: admission (GCS、WFNS、mRS、MMSE) , the third day after surgery (GCS、WFNS、mRS、MMSE) , the total cost of hospitalization. Multivariate logistic regression analyses will adopted to adjust for GCS、WFNS、mRS、MMSE(admission and the third day after surgery) , then compare the total cost of hospitalization for both treatments. There are drawbacks to this approach, but the authors have not thought of a better approach to evaluating economic benefits of treatment.

⑤Comments: As flow diversion becomes a standard of care for many large, wide-necked aneurysms, how would authors evaluate the safety and effectiveness of patients treated with flow diversion? The follow-up period of 6 months is likely too short and this treatment likely carries a different kind of risk profile than aneurysm coiling. Grouping them together may be confusing.

Answer: This comment is very meaningful. In our study, the vast majority of flow-guiding devices were used only for aneurysms which located in the internal carotid artery, so there have a negative impact on the outcome if it is included in the study with other interventional treatment devices(① LVIS ; ② Solitare ; ③ Enterprise ; ④ Neuroform) . We plan to evaluate the safety and effectiveness of patients treated with flow diversion in another study.

⑥Comments: The author list is probably too long and includes 10 authors from the same institution. This should be shortened.

Answer: The list of authors has been shortened

## 2. Reviewer 2 Comments

①Comments: The title should be changed to something like, “Rationale and design of China Intracranial Aneurysm Project...” Furthermore, the authors are encouraged to look at similar publications about major studies for examples of how this kind of a “design and rationale” paper looks.

Answer: According to the editor's request, the title of the manuscript was amend to “The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms”.

②Comments: The primary endpoint and secondary endpoints need to be clearly stated

Answer: The primary and secondary endpoints have been added to the manuscript by the author (Table3).

③Comments: The sample size calculation (or justification) should be explained in a separate section.

Answer: The sample size calculation is explained in a separate section.

④Comments: Text throughout the whole manuscript needs to be tightened up. The statement in the abstract, “...incidence of IA is very dangerous....” is grammatically incorrect and also an over simplification. Many small anterior circulation aneurysms seem to have a low annual rate of rupture, whereas larger and posterior circulation aneurysms are relatively more “dangerous.” The term “dangerous” should be avoided in a scientific paper. Another example: “Previous research has also shown that the risk of IA rupture is 1% to 2%...” They mean annual risk, and this applies to many aneurysms but not all. There are other examples.

Answer: The manuscript have been corrected in many non-rigorous terms and some grammatically incorrect.

### VERSION 2 – REVIEW

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| <b>REVIEWER</b>        | Ning Lin MD<br>Department of Neurological Surgery<br>Weill Cornell Medicine<br>New York, NY, USA |
| <b>REVIEW RETURNED</b> | 31-Dec-2017  |

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| <b>GENERAL COMMENTS</b> | <p>The authors addressed a number of our concerns adequately but some questions remain:</p> <ol style="list-style-type: none"> <li>1. It is still unclear how the study can evaluate the rate of aneurysm rupture or the risks of aneurysm rupture. Authors' explanation made it actually more confusion. I understand there are 5 sub studies. But the design described in the manuscript cannot address the two sub-studies regarding the rate of aneurysm rupture and risks of aneurysm rupture. It is good there is an "observation" arm. How large will this arm be? I assume this is in addition to the 1500 subjects who will be treated either surgically or endovascularly. How long would the follow-up be for the observation arm? Clearly 6 month would be too short if the authors would like to intend to study the natural history of a cohort of aneurysm patients and evaluate the annual rate of aneurysm rupture and risk factors of rupture. These areas need to be addressed specifically in the manuscript.</li> <li>2. The methods of how economic benefits of surgery vs. coiling should be stated in the manuscript. The idea of comparing total hospitalization cost based on treatment methods (clipping vs. coiling) with control of other clinical factors is fine. Other economics related variable include length of ICU stay, length of hospital stay, readmission rate, etc.</li> <li>3. If the authors plan not to include any patients who receive flow diversion as aneurysm treatment, then this should be clearly stated in the including/exclusion criteria and in the manuscript. Will be happy to review it again.</li> </ol> |
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| <b>REVIEWER</b>        | Mark Harrigan<br>University of Alabama, Birmingham, USA |
| <b>REVIEW RETURNED</b> | 10-Jan-2018   |

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| <b>GENERAL COMMENTS</b> | My comments have been adequately addressed. |
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### VERSION 2 – AUTHOR RESPONSE

**Editorial Requests:**

- The quality of English is still not at the requisite standard for publication. Some examples are included below (please note this is not an exhaustive list):

1. Abstract: "There are two approaches for the treatment of IA: interventional therapy and craniotomy, both have their advantages and disadvantages in terms of treatment efficacy."
2. Abstract: "subjects will recorded objectively" should be "subjects will be recorded objectively"
3. Page 8: "During the study, 20% of the patients would be missed follow-up, so, the study requires 1,400 subjects. The study finally decided to include 1,500 subjects."
4. The quality of English in the "Endpoints of the study" section (page 8 of the word document) also needs improving.

Please thoroughly copy-edit the manuscript. We recommend consulting a native English speaker/ professional copy-editing service if possible.

Answer: We re-edited the manuscript in detail with the help of professional copy-editing service: <http://www.charlesworthauthorservices.com> , hoping to meet the requisite standard for publication.

- Please use the term "participants" instead of "subjects" throughout the manuscript.

Answer: It has been amended throughout the manuscript.

- Can you please add the specific primary and secondary outcomes to the abstract?

Answer: It has been amended, please see “Abstract” section, page 3.

- Please make the following limitation clearer: “The limitation of the proposed study is that it may include multiple forms of clinical data, which may differ from the intended purpose due to human subjectivity.” How are the multiple forms of clinical data ‘subjective’?

Answer: It has been amended, please see “Strengths and limitations of this study” section, page 4.

- Why did you include 1500 participants when the sample size calculation indicated that you required 1185 participants? Was the sample size calculation a priori i.e. carried out before the collection and analysis of data?

Answer: I am so sorry, in the manuscript, 1422 was written as 1400. During the study, The author considers that 20% of the participants would be missed follow-up, so there are  $1185 \times (1+0.2) = 1422$ , the study finally decided to include 1500 participants to ensure that the sample size is absolutely sufficient. We calculated the sample size during the design phase of the study and carefully considered the size of the sample, considering that inclusion of 1,500 participants was reasonable.

- Please also discuss the study’s limitations in the discussion section.

Answer: It has been amended, please see “Discussion” section, page9.

Point-by-point response to the comments:

Reviewer 1 Comments

1. It is still unclear how the study can evaluate the rate of aneurysm rupture or the risks of aneurysm rupture. Authors’ explanation made it actually more confusion. I understand there are 5 sub studies. But the design described in the manuscript cannot address the two sub-studies regarding the rate of aneurysm rupture and risks of aneurysm rupture. It is good there is an “observation” arm. How large will this arm be? I assume this is in addition to the 1500 subjects who will be treated either surgically or endovascularly. How long would the follow-up be for the observation arm? Clearly 6 month would be too short if the authors would like to intend to study the natural history of a cohort of aneurysm patients and evaluate the annual rate of aneurysm rupture and risk factors of rupture. These areas need to be addressed specifically in the manuscript.

Answer : The author is really sorry to that the reviewers have confused over this manuscript for reasons of expression and I hope the explanation below will solve the problem.

The China intracranial aneurysm project (CIAP) consisted by five sub-studies, the following are study protocol titles:

- ①The China intracranial aneurysm project (CIAP): prospective cohort study of ruptured intracranial un-ruptured aneurysm ;
- ②The China intracranial aneurysm project (CIAP):a registry study on a multidimensional prediction model for rupture risk of un-ruptured intracranial aneurysms in China;
- ③The China intracranial aneurysm project (CIAP):the prospective cohort study on the benefit-risk of antithrombotic or anticoagulant therapy in patients with un-ruptured intracranial aneurysms associated with ischemic heart disease or ischemic cerebrovascular disease;
- ④The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms;
- ⑤The China intracranial aneurysm project (CIAP): a Registry Study for Emergency Medical Service of Aneurismal Subarachnoid Hemorrhage With Different Economic Development Levels Areas in China

The sub- studies ① and ② are used to evaluate the rate of aneurysm rupture and the risk aneurysm of rupture, respectively, so the manuscript of sub- studies ④ does not specifically describe how to evaluate the rate of aneurysm rupture and the risk of aneurysm rupture.

The follow-up time of CIAP is 5 years for patients with intracranial aneurysms. The study follow-up plan is given in Figure 2, and when the study is finished, participants are followed at least once a year for a total of 5 years, at least two DSA data should be included(6 and 18 months) . The manuscript supplements this part, please see “Data collection” section , page7.

2. The methods of how economic benefits of surgery vs. coiling should be stated in the manuscript. The idea of comparing total hospitalization cost based on treatment methods (clipping vs. coiling) with control of other clinical factors is fine. Other economics related variable include length of ICU stay, length of hospital stay, readmission rate, etc.

Answer : It has been amended, please see “The methods of evaluate economic benefits of treatment” section . This comment is very meaningful , make this manuscript more comprehensive about the content of this study. In the study CRF-A, there have a record of length of ICU stay, length of hospital stay, readmission rate etc., as they directly reflect the cost of hospitalization. The methods stated in the manuscript(page8 ).

3. If the authors plan not to include any patients who receive flow diversion as aneurysm treatment, then this should be clearly stated in the including/exclusion criteria and in the manuscript.

Answer : It has been amended, please see “Participants selection and screening” and “Table 2” section, page 6 and page 13.

### VERSION 3 – REVIEW

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| <b>REVIEWER</b>         | Ning Lin MD<br>Department of Neurological Surgery<br>Weill Cornell Medicine<br>New York, USA |
| <b>REVIEW RETURNED</b>  | 19-Feb-2018  |
| <b>GENERAL COMMENTS</b> | The authors adequately addressed our concerns.   |

### VERSION 3 – AUTHOR RESPONSE

Editorial Requests:

- While you say this paper has been professionally copy-edited it is not clear whether this is the case. There are still numerous typographical/ grammatical errors throughout the manuscript. Some examples are included below but please note this is not an exhaustive list.

Can you please consult a professional copy-editing service again? We would recommend Edanz or American Journal Experts (AJE).

Examples:

“As IA is extremely harmful if it is ruptured.” (abstract)

“which incorporates an adequate sample size to but ensures that the study can be completed on time.” (page 4)

“To the best of our knowledge, CIAP is the project to explore the characteristics...” (do you mean “..the first project..”?)

Answer: With the help of the American Journal Experts (AJE), we revised the manuscript again and hopefully it can meet the publication requirements.

- Please do not include "Primary and secondary endpoints" as a separate sub-heading in the abstract. Please include information about the endpoints in the 'Methods and analysis' section.

Answer: We have modified this part(page3).

- Re the following sentence in the abstract: "The results of this study are expected to be disseminated in the professional printed media in 2021." Can you please be clearer about what you mean by "professional printed media" e.g. peer reviewed journals?

Answer: We have modified it(page3).

- Can you please improve the final bullet point of the 'strengths and limitations' section on page 5? Your description of the study's limitations is currently quite vague. Please note that each bullet point should be a separate strength or limitation of the study. There should be up to 5 bullet points each in total, no longer than one sentence each.

We also feel that your description of the study's limitations in the discussion section lacks clarity and needs improving.

Answer: We have modified it(page4, page10).

- Please include an 'ethics and dissemination' section after the methods and analysis section (and before the discussion section), as per journal requirements for study protocols (see: <http://bmjopen.bmj.com/site/about/guidelines.xhtml#studyprotocols>)

Answer: We include the "ethics and dissemination" section before the discussion section (page9).