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## The China intracranial aneurysm project (CIAP): A prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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Complete List of Authors:	<p>Chen, Yunchang; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Fan, Haiyan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Li, Gancheng; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Guo, Shenquan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Li, Ran; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Liu, wenchao; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>He, Min; West China Hospital, Sichuan University, Department of Neurosurgery</p> <p>Qu, Yan; Tangdu Hospital, Fourth Military Medical University, Department of Neurosurgery</p> <p>Yang, Xinjian; Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Department of Interventional Neuroradiology</p> <p>Zhang, Hongqi; Xuanwu Hospital, Capital Medical University, Department of Neurosurgery</p> <p>Sun, Xiaochuan; The 1st Affiliated Hospital of Chongqing Medical University, Department of Neurosurgery</p> <p>Wang, Liqun; The Second Hospital of Hebei Medical University, Department of Neurosurgery</p> <p>wang, Zhong; The First Affiliated Hospital of Soochow University, Department of Neurosurgery</p> <p>Tong, Xiaoguang; Tianjin Huanhu Hospital, Department of Neurosurgery</p> <p>Zhong, Ming; The First Affiliate of Wenzhou Medical University, Department of Neurosurgery</p> <p>Maimaitili, Aisha; The First Affiliated Hospital of Xinjiang Medical University, Department of Neurosurgery</p> <p>Tong, Zhiyong; The First Hospital of China Medical University, Department of Neurosurgery</p> <p>Zhang, Xin; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Li, Xifeng; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>He, Xuying; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery</p> <p>Duan, Chuanzhi; Southern Medical University, Zhujiang Hospital,</p>

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	Department of Neurosurgery
Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

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**The China intracranial aneurysm project (CIAP): A prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms**

**Yunchang Chen<sup>1</sup>, Haiyan Fan<sup>1</sup>, Gancheng Li<sup>1</sup>, Shenquan Guo<sup>1</sup>, Ran Li<sup>1</sup>, Wenchao Liu<sup>1</sup>, Min He<sup>2</sup>, Yan Qu<sup>3</sup>, Xinjian Yang<sup>4</sup>, Hongqi Zhang<sup>5</sup>, Xiaochuan Sun<sup>6</sup>, Liqun Wang<sup>7</sup>, Zhong Wang<sup>8</sup>, Xiaoguang Tong<sup>9</sup>, Ming Zhong<sup>10</sup>, Maimaitili Aisha<sup>11</sup>, Zhiyong Tong<sup>12</sup>, Xin Zhang<sup>1</sup>, Xifeng Li<sup>1</sup>, Xuying He<sup>1</sup>, Chuanzhi Duan<sup>1</sup>**

<sup>1</sup>Department of Neurosurgery, Southern Medical University, Zhujiang Hospital, 253# Industry road, Guangzhou, Guangdong, 510282, RP China.

<sup>2</sup>Department of Neurosurgery, West China Hospital, Sichuan University, Guoxue Street 37#, Chengdu, Sichuan, 610041, RP China.

<sup>3</sup>Department of Neurosurgery, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shaanxi, 710038, RP China.

<sup>4</sup>Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Beijing, 100050, RP China.

<sup>5</sup>Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, RP China

<sup>6</sup>Department of Neurosurgery, The 1st Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing, 400016, RP China

<sup>7</sup>Department of Neurosurgery, The Second Hospital of Hebei Medical University, No.215 Hepingxi Road Shijiazhuang City, Hebei Province, 050000, RP China

<sup>8</sup>Department of Neurosurgery, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou, Jiangsu Province, 215006, RP China

<sup>9</sup>Department of Neurosurgery, Tianjin Huanhu Hospital, No.6, JiZhao Road, Jinnan District, Tianjin, 300350, RP China

<sup>10</sup>Department of Neurosurgery, The First Affiliate of Wenzhou Medical University, The New Campus of First Affiliate of Wenzhou Medical University, Street of Nanbaixiang, Ouhai District, Wenzhou, Zhe Jiang Province, 325000, RP China

<sup>11</sup>Department of Neurosurgery, The First Affiliated Hospital of Xinjiang Medical University, No.137 Of Liyushannan Road Urumqi, Xinjiang Uyghur Autonomous

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Region, 830054, RP China

<sup>12</sup>Department of Neurosurgery, The First Hospital of China Medical University, No.155, Nanjingbei Road, Heping District, Shenyang, Liaoning Province, 110001, RP China

Corresponding Author: Director and Professor Chuan-Zhi Duan

Tel: +86-013539962233; Fax: +86-020-61643269; E-mail: [doctor\\_duanZJ@163.com](mailto:doctor_duanZJ@163.com)

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## ABSTRACT

**Introduction:** Intracranial aneurysm (IA) is a complex condition with serious side effects. There are two approaches for the treatment of IA: interventional therapy and craniotomy, each have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms (UIA), save valuable medical resources, and reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. However, making this clinical decision is difficult. Here, we propose a refined prospective, multicenter study for the Chinese population with strictly defined patient inclusion criteria, along with the selection of representative clinical participating centers.

**Methods and analysis:** This is a multicenter, prospective cohort study. Since the incidence of IA is very dangerous and ethical issues need to be taken into account, researchers are not able to use randomized controlled trials. The proposed study will be carried out by 12 clinical centers located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be complete in 2020. We expect 1500 subjects with UIA to be included. Clinical information relating to the subjects will be recorded objectively. The main endpoints are an evaluation of the safety, efficiency and economic benefits of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up.

**Ethics and dissemination:** The research protocol and the informed consent form (ICF) for participants in this study are supported by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001).

**Clinical Trials registration number:** NTC03133598

**Keywords:** Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

### Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus fully representing the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been combined with China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size but ensures that the study can be completed on time.
3. The research process will be coordinated by several departments to ensure the quality and reliability of research data.
4. The only 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.

## INTRODUCTION

IA is a common cause of subarachnoid hemorrhage (SAH) and is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across different countries.<sup>1</sup> According to recent research, the overall prevalence of UIA is 7.0% in Chinese adults aged 35 to 75 years, with women more affected than men (8.4% versus 5.5%, respectively).<sup>2</sup> In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.<sup>3</sup> Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we take into account information relating to pathological, radiological, and clinical studies, there is still no specific criteria that can be used select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help in selecting the most appropriate treatment for UIA.<sup>4</sup>

A large number of researchers have investigated the treatment options available for IA and many of these studies indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy. These previous studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.<sup>5-9</sup> Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.<sup>10</sup> The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in this study had small aneurysms. Consequently, this trial could not definitively conclude that coiling is safer than clipping for all cases of IA.<sup>11-14</sup> While controversial, the ISAT did provide us with some degree of understanding of IA.<sup>15 16</sup>

Previous research has also shown that the risk of IA rupture is 1% to 2%, and leads to intracranial hemorrhage, a dangerous condition which is associated with a high mortality and disability rate.<sup>17</sup> However, while UIAs do not generally rupture during long-term follow-up, some medical treatment can increase bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment versus craniotomy, and propose a scientific strategy for selecting the appropriate form of surgical treatment for UIA, which could be deployed across clinics worldwide.

## METHODS AND ANALYSIS

### Study design

CIAP is an ongoing, multicenter trial supported by the National Key Research

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3 Development Program, and predominantly studies aneurysms from 5 different aspects:  
4 1) The risk of antithrombotic therapy in patients with UIAs complicated by ischemic  
5 cardio cerebrovascular diseases; 2) The rate of rupture; 3) The risk of rupture and  
6 developing a model to predict rupture; 4) Treatment options for UIAs and 5) The  
7 development of standardized treatments for early stage UIA bleeding; this study is  
8 one of the sub-topics, is an observational study.  
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11 This study evaluates the treatment options for UIAs from the point of view of safety,  
12 efficacy and economic benefits, and compares these factors between interventional  
13 therapy and craniotomy. The incidence of aneurysms is relatively high among the  
14 population, and China is a large country with a wide population distribution. Thus, in  
15 order to fully reflect the population more objectively, the researchers using  
16 multicenter, prospective cohort study to complete this study, which will last for five  
17 continuous years continuously. Furthermore, refer to previous research studies and  
18 take into account the characteristics and hazards of UIA, the researchers does not  
19 involve random division of subjects into groups<sup>3</sup> and 1500 UIA subjects are expected  
20 to be included. Each subject will be followed up at fixed time points by researchers  
21 and the normal procedures of treatment would not be affected by subjects joining the  
22 CIAP study. All follow-up data, and other clinical information, relating to the subjects  
23 are recorded in detail, and data is analyzed statistically. A concise flow chart of the  
24 entire study is shown in Figure 1. The study protocol was approved by the Ethics  
25 Committee of Zhujiang Hospital of Southern Medical University (Reference Number:  
26 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has  
27 been registered at ClinicalTrials.gov with reference number NTC03133598.  
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### 33 **Participation center qualification**

34 In order to evaluate UIA treatment objectively, it is important to avoid subject bias  
35 and ensure that an adequate number of cases are included in the study. The  
36 researchers selected 12 clinical centers (each center covering more than 2 community  
37 or referral units) to conduct this study in collaboration which distributed across  
38 several regions of China (south east, southwest, northwest, northeast). According to  
39 an incomplete dataset; in 2015, a total of 6000 IA patients had been evaluated across  
40 the 12 clinical centers. Consequently, we believe that each center can adequately  
41 represent the real level of IA diagnosis and treatment at a regional and national level.  
42 The 12 clinical centers are therefore representative.  
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47 There are no specific guidelines for the treatment of UIA. As such, differences exist in  
48 the diagnosis and treatment of IA across different regions, different centers, and even  
49 between different neurosurgeons. in this study, the basic requirement of  
50 neurosurgeons who performs surgery on subjects is able to complete the aneurysm  
51 surgery more than 30 cases per year independently. The study also features an  
52 imaging interpretation center (Internationally Recognized Image Interpretation  
53 Laboratory, established by Xuanwu Hospital and Image Center of the University of  
54 California, Los Angeles, UCLA); this center is responsible for the unified standard  
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3 interpretation of imaging data arising from the 12 clinical centers.  
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### 5 **Subjects selection and screening**

6 The purpose of this study is to recruit patients who are suffering IA without rupture.  
7 First, subjects are diagnosed with UIA, either by computed tomography angiography  
8 (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography  
9 (DSA). Patients with fusiform, traumatic, bacterial or dissecting aneurysms, or with  
10 SAH of unknown origin, are excluded. These types of patients, involving other  
11 vascular diseases (arteriovenous malformation [AVM], arteriovenous fistula [AVF]),  
12 malignant tumors, or poor physical condition factors are expected to live for less than  
13 a year, therefore, all not suitable for study. In order not to disturb the objectivity of the  
14 study and provide good opportunities for follow-up, the researchers also emphasized  
15 the ability of subjects to live independently (using the modified Rankin scale (mRS)  
16 and included those with a score of  $\leq 3$ ). Patients were also excluded if they were  
17 unable to communicate normally due to serious mental illness; the size of the  
18 aneurysm was less than 3 mm; the diagnosis of aneurysms is unclear or difficult. The  
19 specific inclusion and exclusion criteria for the trial are provided in Table 1 and Table  
20 2, respectively.  
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26 The study involves twelve recruiting centers, each of which requiring IRB approval  
27 before recruiting cases. Patients diagnosed with UIA not only receive formal  
28 diagnosis and treatment for their aneurysms, but also, along with their families,  
29 receive full communication from the researchers, with regard to the aims of the study.  
30 Patients can then voluntarily join the study and sign the ICF. Once this is done, the  
31 subject's imaging data will be transmitted to the imaging interpretation center to  
32 re-confirm the diagnosis. If the two diagnoses are not consistent, then the subject is  
33 excluded. The subjects can withdraw from the study at any time, and the researchers  
34 can determine whether the subjects continue the study according to their physical  
35 status. When serious adverse events occur during the course of the trial, the  
36 researchers must terminate the study in advance and report to the ethics committee;  
37 adverse events are also entered into the case report form (CRF). This study is an  
38 observational study that does not interfere with the normal course of clinical diagnosis  
39 and treatment; even if subjects withdraw from the study, it would not affect their  
40 treatment.  
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### 46 **Data collection**

47 Once subjects are included in the study, all information about the course of diagnosis  
48 and treatment are recorded in the CRF. This study also uses an electronic data  
49 collection system (EDC) developed by the National Center for Cardiovascular  
50 Disease; information stored on CRFs are entered into the EDC by a designated person  
51 on each site, and each site shares data with the EDC. The objective of this study was  
52 to objectively compare the safety, efficacy and economic benefits of the two treatment  
53 methods for UIA, and each subject followed for at least one year (at 3, 6, and 12  
54 months), follow-up data were acquired by a neurosurgeon either by telephone or by  
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3 social tools as soon as possible. In most cases, DSA examination should be carried out  
4 six months after the operation to confirm the effect of treatment, which is the vital end  
5 point of this study, data acquired at three and twelve months after surgery are also an  
6 important aspect of the study. A detailed follow-up plan is given in Figure 2. During  
7 the study, the researchers were obliged to protect the personal privacy and medical  
8 information of each subject, and strictly adhere to ethical guidelines.  
9

### 10 11 **Data management**

12 As all data will be collected using CRFs and the EDC, the CIAP have established a  
13 data management committee (DMC, located in Xuanwu hospital) to supervise data  
14 quality, and hired a special data management company responsible for constructing  
15 the EDC and ensuring data security, integrity and accuracy. Before the subjects are  
16 formally enrolled, the DMC holding CRF and EDC data entry study classes for main  
17 researches in each collaboration clinical center; considers data entry, modification and  
18 retrieval, and sets permissions for the main researchers in the EDC. A clinical  
19 research operator (CRO) supervises project progress and quality of data  
20 implementation, and the researcher assigned, the clinical research associate (CRA)  
21 regularly visits each participating center to ensure that all contents of the research  
22 program are strictly adhered to; if not, the CRA promptly submits information to the  
23 investigators. Throughout the project, a research summary conference will be held  
24 every 6 months, to discuss progress and solve any problems that may arise.  
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### 30 **Data analysis**

31 The Department of Medical Statistics at the National Center for Cardiovascular  
32 Diseases is responsible for all data management and statistical analysis. SPSS V21.0  
33 statistical software (IBM Corp, Armonk, New York, USA) is used to analyze the  
34 results, with normally distributed data represented by  $\pm$ SD. Skewed distribution data  
35 is described by the median (M) and the four quartile range (P25; P75), using an  
36 independent t test or rank sum test. Categorical variables are described by frequency  
37 and percentage and grouped data, rate or percentages between the groups are  
38 compared with the Chi square test or Fisher exact test. Rank data is analyzed by the  
39 rank sum test.  $P < 0.05$  was considered to indicate statistical significance.  
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### 43 **DISCUSSION**

44 To our best knowledge, CIAP is the first project to explore the characteristics of  
45 Chinese intracranial aneurysms within the nation of Chinese people, and does so from  
46 a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of  
47 rupture; and the emergency treatment required for ruptured aneurysms; etc., in  
48 particular, the study compares two different treatment methods for UIA. IA is a  
49 common cause of SAH, but this does not mean that the SAH rate is high so that the  
50 incidence of IA is also high,<sup>18</sup> SAH can lead to an erroneous understanding of IA to a  
51 certain extent. Consequently, we should exclude the unknown causes of SAH.<sup>19</sup> DSA  
52 has traditionally been considered the gold standard for detecting aneurysms. However,  
53 combined with existing data, indicates that the incidence of UIA within the population  
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3 varies according to the method of examination, the main reason for this is that the  
4 accuracy of different diagnostic methods is affected by the size of aneurysms. Studies  
5 have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm),  
6 and that the efficacy of computed tomographic (CT) angiography for diagnosing  
7 intracranial aneurysms is increasingly being recognized,<sup>1 20-23</sup> this study excludes  
8 patients with small aneurysms, and in doing so, increases the accuracy of the study.  
9 This, however, means that the study can be considered as incomplete as it only targets  
10 aneurysms of a certain size.  
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14 The treatment of IA cannot be separated from interventional treatment and  
15 craniotomy. Interventional therapy is becoming more and more popular among  
16 neurosurgeons, but selecting which of the two approaches to use for treatment has  
17 been controversial.<sup>24-26</sup> Most scholars believe that interventional therapy is associated  
18 with lower mortality compared with craniotomy, that the recurrence and re-bleeding  
19 rate of interventional therapy is higher,<sup>12</sup> and combined with other techniques may  
20 achieve better results.<sup>5 27 28</sup> The recurrence rate of interventional therapy is higher  
21 because for certain types of aneurysms, such as wide neck aneurysms, the treatment  
22 effect is not satisfactory. However, as the intervention materials and technology  
23 improves, many scholars have adopted this approach for the treatment of aneurysms  
24 and have obtained good results.<sup>29-33</sup> Comparing the two methods in terms of safety  
25 and effectiveness, it is necessary to consider a range of factors, such as age, gender,  
26 subarachnoid hemorrhage and aneurysm size; this is because these are the principal  
27 factors which can influence the re-bleeding of aneurysms.<sup>34 35</sup> Surgery can cause  
28 hemodynamic changes of an aneurysm, but there is no conclusive evidence to show  
29 that this plays a positive role in the recurrence of aneurysms, the study does not take  
30 into account the effects of hemodynamics on the results,<sup>36 37</sup> rather, the researchers,  
31 with the help of a professional statistical team, can try to minimize the impact of  
32 baseline data differences upon the results.  
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39 With careful research design, it is possible to consider and exclude the factors which  
40 could potentially influence the results. In doing this, and by referring to foreign  
41 research programs, this study may provide helpful information for therapeutic  
42 strategies for UIA in clinical practice. Results from this study may provide us with a  
43 chance of using normative interventions for UIA before deploying interventional  
44 treatment and craniotomy and thus provide significant benefit for patients with  
45 aneurysms.  
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#### 48 **Contributors**

49 CD obtained the research funding and was the principal investigator of this study. YC,  
50 HF, GL, MH, YQ, XY and HZ developed the study protocol and YC was the main  
51 author of this article. HF, GL, SG and RL revised the manuscript. XS, LW, ZW, XT,  
52 MZ, MA and ZT were the main people responsible for the seven clinical centers and  
53 responsible for implementing this study. CD approved publication of the final  
54 manuscript.  
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**Conflict of interest**

None declared

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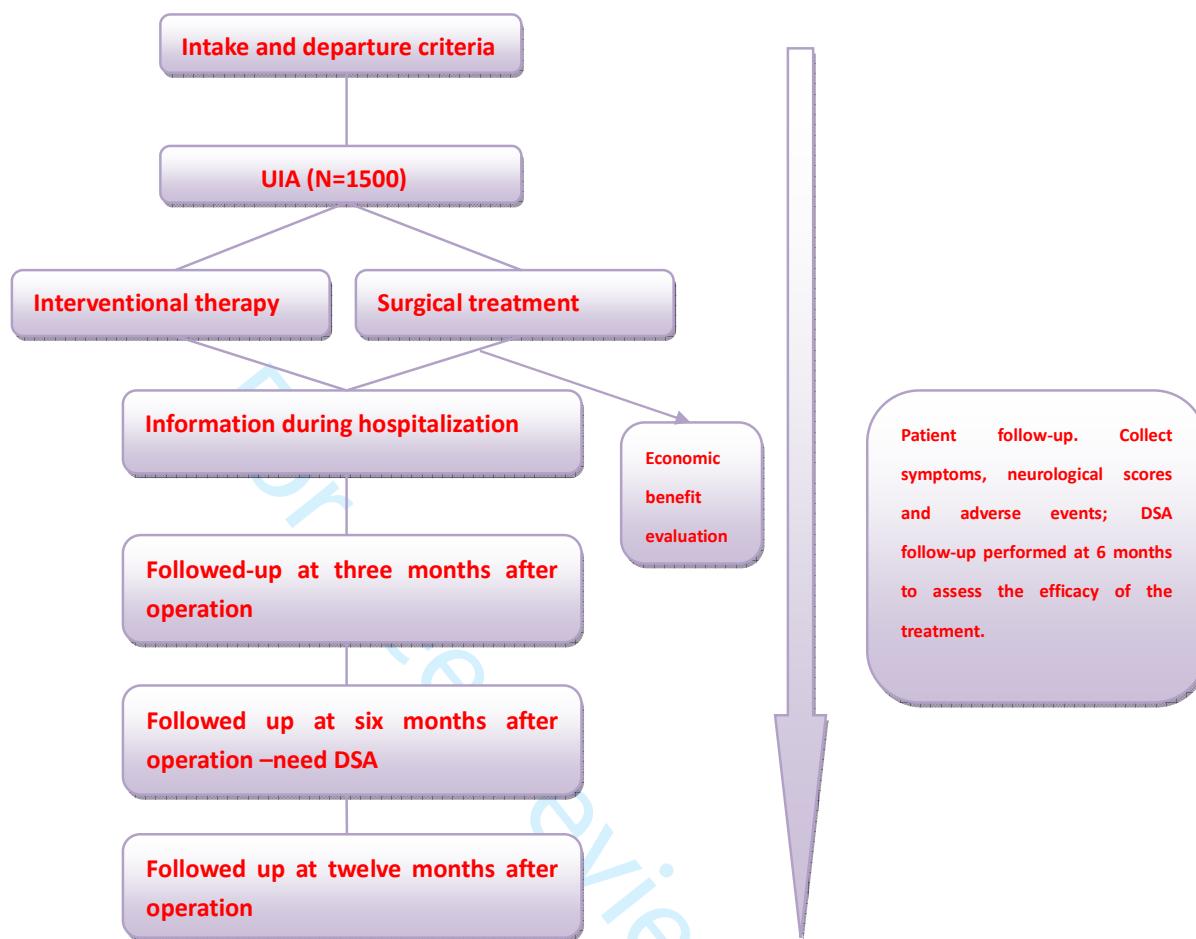
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Figure 1. Research flowchart:



UIA: un-ruptured aneurysms; DSA: digital subtraction angiography



Figure 2. Subject visit and evaluation schedule.

	Screening period	Treatment period		follow-up period		
Visit number	1	2	3	4	5	6
Study	Preoperative screening	In operation	Before discharge	3 months±14 days	6 months±30 days	12 months±30 days
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

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3 Table 1. Inclusion criteria.  
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- 5 1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging  
6 (CTA/MRA/DSA), whether or not there are clinical symptoms  
7  
8 2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless  
9 of whether they have been treated or not  
10  
11 3. Patients currently have the ability to live independently and have an mRS scale  
12 score of  $\leq 3$   
13  
14 4. Age is  $> 14$  years old  
15  
16 5. Patients or family members agree to provide informed written consent
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17 Table 2. Exclusion criteria.  
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- 19 1. Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for  
20 30 days  
21  
22 2. Patients with other intracranial vascular malformations, such as AVM or AVF  
23  
24 3. Patients with intracranial or other parts of the body suffering from malignancy  
25  
26 4. Fusiform, traumatic, bacterial, or dissecting aneurysms  
27  
28 5. Patients with severe mental illness who are unable to communicate when disease is  
29 diagnosed  
30  
31 6. Patients with poor overall state, expected survival time less than 1 year or poor  
32 physical status, cannot tolerate general anesthesia or aneurysm surgeries  
33  
34 7. Patients involved in other clinical studies of intracranial aneurysms  
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36 8. Patients undergoing surgical clipping or endovascular treatment simultaneously  
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38 9. Patients who refused to follow up  
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40 10. The size of the aneurysm  $\leq 3$  mm
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CTA: computed tomography angiography; MRA: magnetic resonance angiography;  
DSA: digital subtraction angiography; AVM: arteriovenous malformation; AVF:  
arteriovenous fistula; mRS: modified Rankin scale

# BMJ Open

## The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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Complete List of Authors:	Chen, Yunchang; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Fan, Haiyan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery He, Xuying; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Guo, Shenquan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Li, Xifeng; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery He, Min; West China Hospital, Sichuan University, Department of Neurosurgery Qu, Yan; Tangdu Hospital, Fourth Military Medical University, Department of Neurosurgery Yang, Xinjian; Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Department of Interventional Neuroradiology Zhang, Hongqi; Xuanwu Hospital, Capital Medical University, Department of Neurosurgery Sun, Xiaochuan; The 1st Affiliated Hospital of Chongqing Medical University, Department of Neurosurgery Wang, Liqun; The Second Hospital of Hebei Medical University, Department of Neurosurgery wang, Zhong; The First Affiliated Hospital of Soochow University, Department of Neurosurgery Tong, Xiaoguang; Tianjin Huanhu Hospital, Department of Neurosurgery Zhong, Ming; The First Affiliate of Wenzhou Medical University, Department of Neurosurgery Maimaitili, Aisha; The First Affiliated Hospital of Xinjiang Medical University, Department of Neurosurgery Tong, Zhiyong; The First Hospital of China Medical University, Department of Neurosurgery Duan, Chuanzhi; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Surgery
Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

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5 **prospective cohort study of interventional treatment and craniotomy**  
6 **for un-ruptured aneurysms**  
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13 Yunchang Chen<sup>1</sup>, Haiyan Fan<sup>1</sup>, Xuying He<sup>1</sup>, Shenquan Guo<sup>1</sup>, Xifeng Li<sup>1</sup>,  
14 Min He<sup>2</sup>, Yan Qu<sup>3</sup>, Xinjian Yang<sup>4</sup>, Hongqi Zhang<sup>5</sup>, Xiaochuan Sun<sup>6</sup>,  
15 Liqun Wang<sup>7</sup>, Zhong Wang<sup>8</sup>, Xiaoguang Tong<sup>9</sup>, Ming Zhong<sup>10</sup>, Maimaitili  
16 Aisha<sup>11</sup>, Zhiyong Tong<sup>12</sup>, Chuanzhi Duan<sup>1</sup>  
17  
18  
19  
20  
21  
22  
23  
24

25 <sup>1</sup>Department of Neurosurgery, Southern Medical University, Zhujiang Hospital, 253#  
26 Industry road, Guangzhou, Guangdong, 510282, RP China.

27 <sup>2</sup>Department of Neurosurgery, West China Hospital, Sichuan University, Guoxue  
28 Street 37#, Chengdu, Sichuan, 610041, RP China.

29 <sup>3</sup>Department of Neurosurgery, Tangdu Hospital, Fourth Military Medical University,  
30 Xi'an, Shaanxi, 710038, RP China.

31 <sup>4</sup>Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and  
32 Beijing Tiantan Hospital, Capital Medical University, Beijing, 100050, RP China.

33 <sup>5</sup>Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing  
34 100053, RP China

35 <sup>6</sup>Department of Neurosurgery, The 1st Affiliated Hospital of Chongqing Medical  
36 University, No.1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing, 400016, RP  
37 China

38 <sup>7</sup>Department of Neurosurgery, The Second Hospital of Hebei Medical University,  
39 No.215 Hepingxi Road Shijiazhuang City, Hebei Province, 050000, RP China

40 <sup>8</sup>Department of Neurosurgery, The First Affiliated Hospital of Soochow University,  
41 188 Shizi Street, Suzhou, Jiangsu Province, 215006, RP China

42 <sup>9</sup>Department of Neurosurgery, Tianjin Huanhu Hospital, No.6, JiZhao Road, Jinnan  
43 District, Tianjin, 300350, RP China

44 <sup>10</sup>Department of Neurosurgery, The First Affiliate of Wenzhou Medical University,  
45 The New Campus of First Affiliate of Wenzhou Medical University, Street of  
46 Nanbaixiang, Ouhai District, Wenzhou, Zhe Jiang Province, 325000, RP China

47 <sup>11</sup>Department of Neurosurgery, The First Affiliated Hospital of Xinjiang Medical  
48 University, No.137 Of Liyushannan Road Urumqi, Xinjiang Uyghur Autonomous  
49 Region, 830054, RP China

50 <sup>12</sup>Department of Neurosurgery, The First Hospital of China Medical University,  
51  
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1  
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3 No.155, Nanjingbei Road, Heping District, Shenyang, Liaoning Province, 110001, RP  
4 China  
5  
6  
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8  
9 *Corresponding Author: Director and Professor Chuan-Zhi Duan*

10  
11 *Tel: +86-013539962233; Fax: +86-020-61643269; E-mail:*

12  
13 *doctor\_duanZJ@163.com*  
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## ABSTRACT

**Introduction:** Intracranial aneurysm (IA) is a complex condition with serious side effects. There are two approaches for the treatment of IA: interventional therapy and craniotomy, both have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms (UIA), save valuable medical resources, and reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. However, making this clinical decision is difficult. Here, we propose a refined prospective, multicenter study for the Chinese population with strictly defined patient inclusion criteria, along with the selection of representative clinical participating centers.

**Methods and analysis:** This is a multicenter, prospective cohort study. As IA is extremely harmful if it is ruptured and ethical issues need to be taken into account, researchers are not able to use randomized controlled trials. The proposed study will be carried out by 12 clinical centers located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be complete in 2020. We expect 1500 subjects with UIA to be included. Clinical information relating to the subjects will be recorded objectively. The main endpoints are an evaluation of the safety, efficiency and economic benefits of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up.

**Ethics and dissemination:** The research protocol and the informed consent form (ICF) for participants in this study are approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001). The results of this study are expected to be disseminated in professional printed media in 2021.

**Clinical Trials registration number:** NTC03133598

**Keywords:** Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

### Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus, it can fully represent the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been combined with China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size to but ensures that the study can be completed on time.
3. The research process will be coordinated by several departments to ensure the quality and reliability of research data.
4. 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.

## INTRODUCTION

IA is a common cause of subarachnoid hemorrhage (SAH) and is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across different countries.<sup>1</sup> According to recent research, the overall prevalence of UIA is 7.0% in Chinese adults aged 35 to 75 years, with women more affected than men (8.4% *versus* 5.5%, respectively).<sup>2</sup> In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.<sup>3</sup> Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we take into account information relating to pathological, radiological, and clinical studies, there is still no specific criteria that can be used to select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help in selecting the most appropriate treatment for UIA.<sup>4</sup>

A large number of researchers have investigated the treatment options available for IA and many of these studies indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy.<sup>5-9</sup> These previous studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.<sup>5-9</sup> Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.<sup>10</sup> The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in this study had small aneurysms. Consequently, this trial could not definitively conclude that coiling is safer than clipping for all cases of IA.<sup>11-14</sup> While controversial, the ISAT did provide us with some degree of understanding of IA.<sup>15 16</sup>

Previous research has also shown that the risk of many IA rupture is 1% to 2%, and leads to intracranial hemorrhage, a dangerous condition which is associated with a high mortality and disability rate.<sup>17</sup> However, while UIAs do not generally rupture during long-term follow-up, some medical treatment can increase bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment *versus* craniotomy, and propose a scientific strategy for selecting the appropriate form of surgical treatment for UIA, which could be deployed across clinics worldwide.

## METHODS AND ANALYSIS

### Study design

CIAP is an ongoing, multicenter trial supported by the National Key Research Development Program, and predominantly studies aneurysms from 5 different aspects:



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3 1) The risk of antithrombotic therapy in patients with UIAs complicated by ischemic  
4 cardio cerebrovascular diseases; 2) The rate of rupture; 3) The risk of rupture and  
5 developing a model to predict rupture; 4) Treatment options for UIAs and 5) The  
6 development of standardized treatments for early stage UIA bleeding; this study is one  
7 of the sub-topics, is an observational study.  
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10 This study evaluates the treatment options for UIAs from the point of view of safety,  
11 efficacy and economic benefits, and compares these factors between interventional  
12 therapy and craniotomy. The incidence of aneurysms is relatively high among the  
13 population, and China is a large country with a wide population distribution. Thus, in  
14 order to fully reflect the population more objectively, the researchers using  
15 multicenter, prospective cohort study to complete this study, which will last for five  
16 continuous years continuously. Furthermore, refer to previous related research studies  
17 and take into account the characteristics and hazards of UIA, the researchers does not  
18 involve random division of subjects into groups<sup>3</sup> and 1500 UIA subjects are expected  
19 to be included. Each subject will be followed up at fixed time points by researchers  
20 and the normal procedures of treatment would not be affected by subjects joining the  
21 CIAP study. Follow-up data, and other clinical information, relating to the subjects are  
22 recorded in detail, and data is analyzed statistically. A concise flow chart of the entire  
23 study is shown in Figure 1. The study protocol was approved by the Ethics Committee  
24 of Zhujiang Hospital of Southern Medical University (Reference Number:  
25 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has  
26 been registered at ClinicalTrials.gov with reference number NTC03133598.  
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### 32 **Participation center qualification**

33 In order to evaluate UIA treatment objectively, it is important to avoid subject bias  
34 and ensure that an adequate number of cases are included in the study. The researchers  
35 selected 12 clinical centers (each center covering more than 2 community or referral  
36 units) to conduct this study in collaboration which distributed across several regions  
37 of China (south east, southwest, northwest, northeast). According to an incomplete  
38 dataset; in 2015, a total of 6000 IA patients had been evaluated across the 12 clinical  
39 centers. Consequently, the researchers believe that each center can adequately  
40 represent the real level of IA diagnosis and treatment at a regional and national level.  
41 The 12 clinical centers are therefore representative.  
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45 There are no specific guidelines for the treatment of UIA. As such, differences exist in  
46 the diagnosis and treatment of IA across different regions, different centers, and even  
47 between different neurosurgeons. In this study, the basic requirement of  
48 neurosurgeons who performs surgery on subjects is able to complete the aneurysm  
49 surgery more than 30 cases per year independently. The study also features an  
50 imaging interpretation center (Internationally Recognized Image Interpretation  
51 Laboratory, established by Xuanwu Hospital and Image Center of the University of  
52 California, Los Angeles, UCLA); this center is responsible for the unified standard  
53 interpretation of imaging data arising from the 12 clinical centers.  
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### Subjects selection and screening

The purpose of this study is to recruit patients who are suffering IA without rupture. First, subjects are diagnosed with UIA, either by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting aneurysms, or with SAH of unknown origin, are excluded. These types of patients, involving other vascular diseases (arteriovenous malformation [AVM], arteriovenous fistula [AVF]), malignant tumors, or poor physical condition factors are expected to live for less than a year, therefore, all not suitable for study. In order not to disturb the objectivity of the study and provide good opportunities for follow-up, the researchers also emphasized the ability of subjects to live independently (using the modified Rankin scale (mRS) and included those with a score of  $\leq 3$ ). Patients were also excluded if they were unable to communicate normally due to serious mental illness; the size of the aneurysm was less than 3 mm; the diagnosis of aneurysms is unclear or difficult. The specific inclusion and exclusion criteria for the trial are provided in Table 1 and Table 2, respectively.

The study involves twelve recruiting centers, each of which requiring IRB approval before recruiting cases. Patients diagnosed with UIA not only receive formal diagnosis and treatment for their aneurysms, but also, along with their families, receive full communication from the researchers, with regard to the aims of the study. Patients can then voluntarily join the study and sign the ICF. Once this is done, the subject's imaging data will be transmitted to the imaging interpretation center to re-confirm the diagnosis. If the two diagnoses are not consistent, then the subject is excluded. The subjects can withdraw from the study at any time, and the researchers can determine whether the subjects continue the study according to their physical status. When serious adverse events occur during the course of the trial, the researchers must terminate the study in advance and report to the ethics committee; adverse events are also entered into the case report form (CRF). This study is an observational study that does not interfere with the normal course of clinical diagnosis and treatment; even if subjects withdraw from the study, it would not affect their treatment.

### Sample size calculation

Calculating sample size based on formula:

$$n = \frac{(z_{\alpha} \sqrt{(1 + \frac{1}{R})pq} + z_{\beta} \sqrt{p_1q_1 + p_0q_0/R})^2}{(P_1 - P_0)^2}$$

( $\alpha = 0.05$ , two-sided test, 80% of the degree of control.)

According to the results of ISUA test, the mortality rate of the intervention group was

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3 8.7% in one year and that of the craniotomy group was 14.1%, and the intervention  
4 group was two times as much as subjects as those in the craniotomy group, we  
5 calculated that  $n=1185$  (intervention group:  $n = 395$ ; craniotomy group:  $n = 790$ ).  
6 During the study, 20% of the patients would be missed follow-up, so, the study  
7 requires 1,400 subjects. The study finally decided to include 1,500 subjects.  
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### 10 **Data collection**

11 Once subjects are included in the study, all information about the course of diagnosis  
12 and treatment are recorded in the CRF. This study also uses an electronic data  
13 collection system (EDC) developed by the National Center for Cardiovascular  
14 Disease; information stored on CRFs are entered into the EDC by a designated person  
15 on each site, and each site shares data with the EDC. The objective of this study was  
16 to objectively compare the safety, efficacy and economic benefits of the two treatment  
17 methods for UIA, and each subject followed for at least one year (at 3, 6, and 12  
18 months), follow-up data were acquired by a neurosurgeon either by telephone or by  
19 social tools as soon as possible. In most cases, DSA examination should be carried out  
20 six months after the operation to confirm the effect of treatment, which is the vital end  
21 point of this study. Besides, data acquired at three and twelve months after surgery are  
22 also an important aspect of the study. A detailed follow-up plan is given in Figure 2.  
23 During the study, the researchers were obliged to protect the personal privacy and  
24 medical information of each subject, and strictly adhere to ethical guidelines.  
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### 30 **Data management**

31 As all data will be collected using CRFs and the EDC, the CIAP have established a  
32 data management committee (DMC, located in Xuanwu hospital) to supervise data  
33 quality, and hired a special data management company responsible for constructing  
34 the EDC and ensuring data security, integrity and accuracy. Before the subjects are  
35 formally enrolled, the DMC holding CRF and EDC data entry study classes for main  
36 researches in each collaboration clinical center; considers data entry, modification and  
37 retrieval, and sets permissions for the main researchers in the EDC. A clinical research  
38 operator (CRO) supervises project progress and quality of data implementation, and  
39 the researcher assigned, the clinical research associate (CRA) regularly visits each  
40 participating center to ensure that all contents of the research program are strictly  
41 adhered to; if not, the CRA promptly submits information to the investigators.  
42 Throughout the project, a research summary conference will be held every 6 months,  
43 to discuss progress and solve any problems that may arise.  
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### 48 **Data analysis**

49 The Department of Medical Statistics at the National Center for Cardiovascular  
50 Diseases is responsible for all data management and statistical analysis. SPSS V21.0  
51 statistical software (IBM Corp, Armonk, New York, USA) is used to analyze the  
52 results, with normally distributed data represented by  $\bar{x} \pm SD$ . Skewed distribution data  
53 is described by the median ( $M$ ) and the four quartile range ( $P25$ ;  $P75$ ), using an  
54 independent t test or rank sum test. Categorical variables are described by frequency  
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3 and percentage and grouped data, rate or percentages between the groups are  
4 compared with the Chi square test or Fisher exact test. Rank data is analyzed by the  
5 rank sum test.  $P < 0.05$  was considered to indicate statistical significance.  
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### 8 **Endpoints of the study**

9 The endpoints of the study were also divided into primary and secondary endpoints.  
10 The safety and effectiveness of interventional and craniotomy are considered as the  
11 primary endpoint of the study, and they are the goals of investigator. Using the  
12 subjects' mortality and morbidity rate to evaluated the safety of interventional and  
13 craniotomy, in addition, ipsilateral stroke and neurological deficits within 30 days  
14 Ipsilateral stroke and neurological deficits within 30 days supplemented the safety  
15 evaluation of our study and will play a positive role in our findings. The effectiveness  
16 is evaluated with aneurysm recurrence rate, re-bleeding rate and complete occlusion  
17 rate. The secondary end point mainly considered the time of postoperative evaluation  
18 and the occurrence of adverse events. The primary endpoint and the secondary  
19 endpoint are detailed in Table 3.  
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### 24 **DISCUSSION**

25 To our best knowledge, CIAP is the project to explore the characteristics of Chinese  
26 intracranial aneurysms within the nation of Chinese people, and does so from a range  
27 of different aspects: the rate of spontaneous aneurysm rupture; risk factors of rupture;  
28 and the emergency treatment required for ruptured aneurysms; etc., in particular, the  
29 study compares two different treatment methods for UIA. IA is a common cause of  
30 SAH, but this does not mean that the SAH rate is high so that the incidence of IA is  
31 also high,<sup>18</sup> SAH can lead to an erroneous understanding of IA to a certain extent.  
32 Consequently, we should exclude the unknown causes of SAH.<sup>19</sup> DSA has  
33 traditionally been considered the gold standard for detecting aneurysms. However,  
34 combined with existing data, indicates that the incidence of UIA within the population  
35 varies according to the method of examination, the main reason for this is that the  
36 accuracy of different diagnostic methods is affected by the size of aneurysms. Studies  
37 have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm),  
38 and that the efficacy of computed tomographic (CT) angiography for diagnosing  
39 intracranial aneurysms is increasingly being recognized,<sup>1 20-23</sup> this study excludes  
40 patients with small aneurysms, and in doing so, increases the accuracy of the study.  
41 This, however, means that the study can be considered as incomplete as it only targets  
42 in aneurysms of a certain size.  
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48 The treatment of IA cannot be separated from interventional treatment and craniotomy.  
49 Interventional therapy is becoming more and more popular among neurosurgeons, but  
50 selecting which of the two approaches to use for treatment has been controversial.<sup>24-26</sup>  
51 Most scholars believe that interventional therapy is associated with lower mortality  
52 compared with craniotomy, which the recurrence and re-bleeding rate of  
53 interventional therapy is higher,<sup>12</sup> and combined with other techniques may achieve  
54 better results.<sup>5 27 28</sup> The recurrence rate of interventional therapy is higher because for  
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3 certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not  
4 satisfactory. However, as the intervention materials and technology improves, many  
5 scholars have adopted this approach for the treatment of aneurysms and have obtained  
6 good results.<sup>29-33</sup> Comparing the two methods in terms of safety and effectiveness, it  
7 is necessary to consider a range of factors, such as age, gender, subarachnoid  
8 hemorrhage and aneurysm size; because these are the principal factors which can  
9 influence the re-bleeding of aneurysms.<sup>34,35</sup> Surgery can cause hemodynamic changes  
10 of an aneurysm, but there is no conclusive evidence to show that this plays a positive  
11 role in the recurrence of aneurysms, the study does not take into account the effects of  
12 hemodynamics on the results,<sup>36, 37</sup> rather, the researchers, with the help of a  
13 professional statistical team, can try to minimize the impact of baseline data  
14 differences upon the results.  
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19 With careful research design, it is possible to consider and exclude the factors which  
20 could potentially influence the results, and by referring to foreign research programs,  
21 this study may provide helpful information for therapeutic strategies for UIA in  
22 clinical practice. Results from this study may provide us with a chance of using  
23 normative interventions for UIA before deploying interventional treatment and  
24 craniotomy and thus provide significant benefit for patients with aneurysms.  
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26

### 27 **Contributors**

28 CD obtained the research funding and was the principal investigator of this study. YC,  
29 HF, XL, MH, YQ, XY and HZ developed the study protocol and YC was the main  
30 author of this article. HF, XH, SG and XL revised the manuscript. XS, LW, ZW, XT,  
31 MZ, MA and ZT were the main people responsible for the seven clinical centers and  
32 responsible for implementing this study. CD approved publication of the final  
33 manuscript.  
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36

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### 44 **Conflict of interest**

45 None declared  
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4 Table 1. Inclusion criteria.

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- 5 1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging
  - 6 (CTA/MRA/DSA), whether or not there are clinical symptoms
  - 7
  - 8 2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless
  - 9 of whether they have been treated or not
  - 10
  - 11 3. Patients currently have the ability to live independently and have an mRS scale
  - 12 score of  $\leq 3$
  - 13
  - 14 4. Age is  $> 14$  years old
  - 15
  - 16 5. Patients or family members agree to provide informed written consent
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17 Table 2. Exclusion criteria.

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- 18 1. Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for
  - 19 30 days
  - 20
  - 21 2. Patients with other intracranial vascular malformations, such as AVM or AVF
  - 22
  - 23 3. Patients with intracranial or other parts of the body suffering from malignancy
  - 24
  - 25 4. Fusiform, traumatic, bacterial, or dissecting aneurysms
  - 26
  - 27 5. Patients with severe mental illness who are unable to communicate when disease is
  - 28 diagnosed
  - 29
  - 30 6. Patients with poor overall state, expected survival time less than 1 year or poor
  - 31 physical status, cannot tolerate general anesthesia or aneurysm surgeries
  - 32
  - 33 7. Patients involved in other clinical studies of intracranial aneurysms
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  - 35 8. Patients undergoing surgical clipping or endovascular treatment simultaneously
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  - 37 9. Patients who refused to follow up
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  - 39 10. The size of the aneurysm  $\leq 3$  mm
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CTA: computed tomography angiography; MRA: magnetic resonance angiography;  
DSA: digital subtraction angiography; AVM: arteriovenous malformation; AVF:  
arteriovenous fistula; mRS: modified Rankin scale

Table 3. endpoints of the study

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1. The primary endpoint

① The main security endpoint:

The safety evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 6 months: including subjects' mortality (mRS = 6), morbidity ( $3 \leq \text{mRS} \leq 5$  points); the emergency of ipsilateral stroke and neurological deficits within 30 days are also recognized as reliability measures to evaluate the security of interventional and craniotomy.

② The main effectiveness endpoint:

The effectiveness evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 6 months: including the recurrence (Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects.

2. The secondary endpoints

① The safety evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 12 months: including subjects' mortality (mRS = 6), morbidity ( $3 \leq \text{mRS} \leq 5$  points);

② The effectiveness evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 12 months: including the recurrence (Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects;

③ The success rate of treatment;

④ The success rate of 6 months after interventional therapy or craniotomy clipping (the DSA hint: aneurysm completely or nearly total occlusion, re-canalization or re-growth did not appear);

⑤ The incidence of major adverse events during hospitalization;

⑥ The incidence of major adverse events after 3 months of surgery;

⑦ The incidence of major adverse events in 3 months and 6 months later after operation;

⑧ The incidence of major adverse events in 6 months and 12 months later after operation.

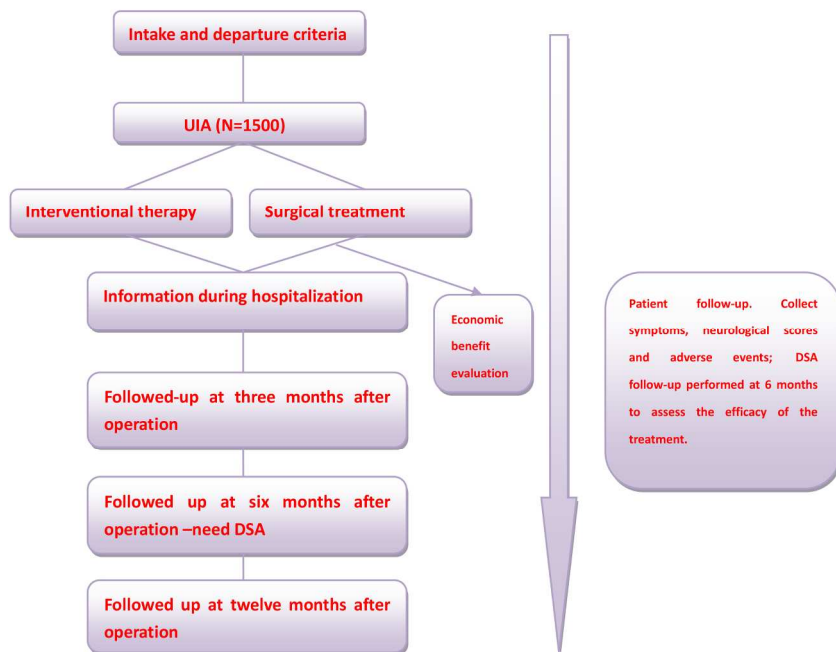
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Figure legends

Figure 1. Research flowchart

Figure 2. Subject visit and evaluation schedule

Figure 1. Research flowchart:



UJA: un-ruptured aneurysms; DSA: digital subtraction angiography

169x243mm (300 x 300 DPI)

Figure 2. Subject visit and evaluation schedule.

Visit number	Screening period	Treatment period		follow-up period		
	1	2	3	4	5	6
Study	Preoperative screening	In operation	Before discharge	3 months±14 days	6 months±30 days	12 months±30 days
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

154x231mm (300 x 300 DPI)

# BMJ Open

## The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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Complete List of Authors:	Chen, Yunchang; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Fan, Haiyan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery He, Xuying; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Guo, Shenquan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Li, Xifeng; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery He, Min; West China Hospital, Sichuan University, Department of Neurosurgery Qu, Yan; Tangdu Hospital, Fourth Military Medical University, Department of Neurosurgery Yang, Xinjian; Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Department of Interventional Neuroradiology Zhang, Hongqi; Xuanwu Hospital, Capital Medical University, Department of Neurosurgery Sun, Xiaochuan; The 1st Affiliated Hospital of Chongqing Medical University, Department of Neurosurgery Wang, Liqun; The Second Hospital of Hebei Medical University, Department of Neurosurgery wang, Zhong; The First Affiliated Hospital of Soochow University, Department of Neurosurgery Tong, Xiaoguang; Tianjin Huanhu Hospital, Department of Neurosurgery Zhong, Ming; The First Affiliate of Wenzhou Medical University, Department of Neurosurgery Maimaitili, Aisha; The First Affiliated Hospital of Xinjiang Medical University, Department of Neurosurgery Tong, Zhiyong; The First Hospital of China Medical University, Department of Neurosurgery Duan, Chuazhi; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Surgery
Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

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4 **The China intracranial aneurysm project (CIAP): protocol for a**  
5 **prospective cohort study of interventional treatment and craniotomy**  
6 **for un-ruptured aneurysms**  
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13 Yunchang Chen<sup>1</sup>, Haiyan Fan<sup>1</sup>, Xuying He<sup>1</sup>, Shenquan Guo<sup>1</sup>, Xifeng Li<sup>1</sup>,  
14 Min He<sup>2</sup>, Yan Qu<sup>3</sup>, Xinjian Yang<sup>4</sup>, Hongqi Zhang<sup>5</sup>, Xiaochuan Sun<sup>6</sup>,  
15 Liqun Wang<sup>7</sup>, Zhong Wang<sup>8</sup>, Xiaoguang Tong<sup>9</sup>, Ming Zhong<sup>10</sup>, Maimaitili  
16 Aisha<sup>11</sup>, Zhiyong Tong<sup>12</sup>, Chuanzhi Duan<sup>1</sup>  
17  
18  
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23  
24

25 <sup>1</sup>Department of Neurosurgery, Southern Medical University, Zhujiang Hospital, 253#  
26 Industry road, Guangzhou, Guangdong, 510282, RP China.

27 <sup>2</sup>Department of Neurosurgery, West China Hospital, Sichuan University, Guoxue  
28 Street 37#, Chengdu, Sichuan, 610041, RP China.

29 <sup>3</sup>Department of Neurosurgery, Tangdu Hospital, Fourth Military Medical University,  
30 Xi'an, Shaanxi, 710038, RP China.

31 <sup>4</sup>Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and  
32 Beijing Tiantan Hospital, Capital Medical University, Beijing, 100050, RP China.

33 <sup>5</sup>Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing  
34 100053, RP China

35 <sup>6</sup>Department of Neurosurgery, The 1st Affiliated Hospital of Chongqing Medical  
36 University, No.1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing, 400016, RP  
37 China

38 <sup>7</sup>Department of Neurosurgery, The Second Hospital of Hebei Medical University,  
39 No.215 Hepingxi Road Shijiazhuang City, Hebei Province, 050000, RP China

40 <sup>8</sup>Department of Neurosurgery, The First Affiliated Hospital of Soochow University,  
41 188 Shizi Street, Suzhou, Jiangsu Province, 215006, RP China

42 <sup>9</sup>Department of Neurosurgery, Tianjin Huanhu Hospital, No.6, JiZhao Road, Jinnan  
43 District, Tianjin, 300350, RP China

44 <sup>10</sup>Department of Neurosurgery, The First Affiliate of Wenzhou Medical University,  
45 The New Campus of First Affiliate of Wenzhou Medical University, Street of  
46 Nanbaixiang, Ouhai District, Wenzhou, Zhe Jiang Province, 325000, RP China

47 <sup>11</sup>Department of Neurosurgery, The First Affiliated Hospital of Xinjiang Medical  
48 University, No.137 Of Liyushannan Road Urumqi, Xinjiang Uyghur Autonomous  
49 Region, 830054, RP China

50 <sup>12</sup>Department of Neurosurgery, The First Hospital of China Medical University,  
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No.155, Nanjingbei Road, Heping District, Shenyang, Liaoning Province, 110001, RP  
China

*Corresponding Author: Director and Professor Chuan-Zhi Duan*

*Tel: +86-013539962233; Fax: +86-020-61643269; E-mail:*

*doctor\_duanZJ@163.com*

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## ABSTRACT

**Introduction:** Intracranial aneurysm (IA) is a complex condition with serious side effects. There are two approaches for the treatment of IA: interventional therapy and craniotomy, both of these approaches have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms (UIA), save valuable medical resources, and reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. However, making this clinical decision is difficult. Here, we propose a refined prospective, multicenter study for the Chinese population with strictly defined patient inclusion criteria, along with the selection of representative clinical participating centers.

**Methods and analysis:** This is a multicenter, prospective cohort study. As IA is extremely harmful if it is ruptured. Therefore, ethical issues need to be taken into account with regard to this study and researchers are not, therefore, able to use randomized controlled trials. The proposed study will be carried out by 12 clinical centers located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be completed in 2020. We expect 1500 participants with UIA to be included. Clinical information relating to the participants will be recorded objectively. The main endpoints are an evaluation of the safety, efficiency and economic benefits of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up.

**Primary and secondary endpoints:** The primary endpoint of this study is safety and efficacy when participants are treated for 6 months. The second endpoint is the evaluation of safety and the efficacy of interventional therapy and craniotomy clipping when participants are treated for 12 months. We also address the success of treatment and the incidence of adverse events.

**Ethics and dissemination:** The research protocol and the informed consent form (ICF) for participants in this study are approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001). The results of this study are expected to be disseminated in the professional printed media in 2021.

**Clinical Trials registration number:** NTC03133598

**Keywords:** Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

### Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus, it can fully represent the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been adopted in the light of China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size to but ensures that the study can be completed on time.

3. The research process will be coordinated by several departments to ensure the quality and reliability of the research data.
4. The proposed study features some limitations which need to be considered. For example, it includes multiple clinical data and multiple control clinical factors, and the treatment process involves human subjectivity. These factors may bias the conclusions arising from this study.

## INTRODUCTION

IA is a common cause of subarachnoid hemorrhage (SAH) and is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across different countries.<sup>1</sup> According to recent research, the overall prevalence of UIA is 7.0% in Chinese adults aged 35 to 75 years, with women more affected than men (8.4% *versus* 5.5%, respectively).<sup>2</sup> In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.<sup>3</sup> Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we take into account information relating to pathological, radiological, and clinical studies, there are still no specific criteria that can be used to select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help in selecting the most appropriate treatment for UIA.<sup>4</sup>

A large number of researchers have investigated the treatment options available for IA and many of these studies have indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy.<sup>5-9</sup> These previous studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.<sup>5-9</sup> Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.<sup>10</sup> The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in this study had small aneurysms. Consequently, this trial could not definitively conclude that coiling is safer than clipping for all cases of IA.<sup>11-14</sup> While controversial, the ISAT did provide us with some degree of understanding of IA.<sup>15 16</sup>

Previous research has also shown that the risk of many IA rupture is 1% to 2%, and leads to intracranial hemorrhage, a dangerous condition which is associated with a high mortality and disability rate.<sup>17</sup> However, while UIAs do not generally rupture during long-term follow-up, some medical treatment can increase bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment *versus* craniotomy, and to propose a scientific

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3 strategy for selecting the appropriate form of surgical treatment for UIA, which could  
4 be deployed across clinics worldwide.  
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## 6 **METHODS AND ANALYSIS**

### 7 **Study design**

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9 CIAP is an ongoing, multicenter trial supported by the National Key Research  
10 Development Program, and predominantly studies aneurysms from five different  
11 aspects: 1) The risk of antithrombotic therapy in patients with UIAs complicated by  
12 ischemic cardio cerebrovascular diseases; 2) The rate of rupture; 3) The risk of  
13 rupture and developing a model to predict rupture; 4) Treatment options for UIAs and  
14 5) The development of standardized treatments for early stage UIA bleeding; this  
15 study is one of the sub-topics, is an observational study.  
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19 This study evaluates the treatment options for UIAs from the point of view of safety,  
20 efficacy and economic benefits, and compares these factors between interventional  
21 therapy and craniotomy. The incidence of aneurysms is relatively high among the  
22 population, and China is a large country with a wide population distribution. Thus, in  
23 order to fully reflect the population more objectively, the researchers will carry out  
24 this multicenter, prospective cohort study, which will last for five continuous years.  
25 Furthermore, referring to previous related research studies and taking into account the  
26 characteristics and hazards of UIA, the researchers will not include the random  
27 division of participants into groups<sup>3</sup> and 1500 UIA participants are expected to be  
28 included. Each participant will be followed up at fixed time points by researchers and  
29 the normal procedures of treatment will not be affected by participants joining the  
30 CIAP study. Follow-up data, and other clinical information, relating to the participants  
31 are recorded in detail, and data is analyzed statistically. A concise flow chart of the  
32 entire study is shown in Figure 1. The study protocol was approved by the Ethics  
33 Committee of Zhujiang Hospital of Southern Medical University (Reference Number:  
34 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has  
35 been registered at ClinicalTrials.gov with reference number NTC03133598.  
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### 41 **Participation center qualification**

42 In order to evaluate UIA treatment objectively, it is important to avoid participant bias  
43 and to ensure that an adequate number of cases are included in the study. The  
44 researchers selected 12 clinical centers (each center covering more than 2 community  
45 or referral units) to conduct this study in collaboration which distributed across  
46 several regions of China (south east, southwest, northwest and northeast). According  
47 to an incomplete dataset, in 2015 a total of 6000 IA patients had been evaluated across  
48 the 12 clinical centers. Consequently, the researchers believe that each center can  
49 adequately represent the real level of IA diagnosis and treatment at a regional and  
50 national level. The 12 clinical centers used in this study are therefore representative.  
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54 There are no specific guidelines for the treatment of UIA. As such, differences exist in  
55 the diagnosis and treatment of IA across different regions, different centers, and even  
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3 between different neurosurgeons. In this study, the basic requirement of the  
4 neurosurgeons who perform surgery on participants is that they are able to complete  
5 the aneurysm surgery in more than 30 cases per year independently. The study also  
6 features an imaging interpretation center (Internationally Recognized Image  
7 Interpretation Laboratory, established by Xuanwu Hospital and the Image Center of  
8 the University of California, Los Angeles, UCLA); this center is responsible for the  
9 unified standard interpretation of imaging data arising from the 12 clinical centers.  
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### 12 **Participant selection and screening**

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14 The purpose of this study is to recruit patients who are suffering IA without rupture.  
15 First, participants are diagnosed with UIA, either by computed tomography  
16 angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction  
17 angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting  
18 aneurysms, or with SAH of unknown origin, are excluded. These types of patients,  
19 involving other vascular diseases (arteriovenous malformation [AVM], arteriovenous  
20 fistula [AVF]), malignant tumors, or poor physical condition factors are expected to  
21 live for less than a year, and are not suitable for study. In order not to disturb the  
22 objectivity of the study and provide good opportunities for follow-up, the researchers  
23 also emphasize the ability of participants to live independently (using the modified  
24 Rankin scale (mRS) and included those with a score of  $\leq 3$ ). Patients are also  
25 excluded if they are unable to communicate normally due to serious mental illness; if  
26 they receive flow diversion as part of their aneurysm treatment (as flow diversion  
27 becomes a standard of care for many large, wide-necked aneurysms, which are  
28 located in the internal carotid artery); if the size of the aneurysm was less than 3 mm;  
29 or if aneurysm diagnosis is unclear or difficult. The specific inclusion and exclusion  
30 criteria for the trial are provided in Tables 1 and 2, respectively.  
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36 The study involves twelve recruiting centers, each of which require IRB approval  
37 before recruiting cases. Patients diagnosed with UIA not only receive formal  
38 diagnosis and treatment for their aneurysms, but also, along with their families,  
39 receive full communication from the researchers, with regard to the aims of the study.  
40 Patients can then voluntarily join the study and sign the ICF. Once this is done, the  
41 participant's imaging data will be transmitted to the imaging interpretation center to  
42 re-confirm the diagnosis. If the two diagnoses are not consistent, then the participant  
43 is excluded. The participants can withdraw from the study at any time, and the  
44 researchers can determine whether the participants continue the study according to  
45 their physical status. When serious adverse events occur during the course of the trial,  
46 the researchers must terminate the study in advance and report to the ethics committee;  
47 adverse events are also entered into the case report form (CRF). This study is an  
48 observational study that does not interfere with the normal course of clinical diagnosis  
49 and treatment; even if participants withdraw from the study, it will not affect their  
50 treatment.  
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### 55 **Sample size calculation**

Calculating sample size based on the formula:

$$n = \frac{(z_{\alpha} \sqrt{(1 + 1/R)pq} + z_{\beta} \sqrt{p_1q_1 + p_0q_0/R})^2}{(P_1 - P_0)^2}$$

( $\alpha = 0.05$ , two-sided test, 80% of the degree of control.)

According to the results of ISUA test, the mortality rate of the intervention group was 8.7% in one year and that of the craniotomy group was 14.1%, and the intervention group was two times as much as in the participants as those in the craniotomy group, we calculated that  $n=1185$  (intervention group:  $n = 395$ ; craniotomy group:  $n = 790$ ). During the study, 20% of the patients would be lost during follow-up, thus, the study requires 1,422 participants. Ultimately, we decided to include 1,500 participants.

### Data collection

Once participants are included in the study, all information about the course of diagnosis and treatment are recorded in the CRF-A. This study also uses an electronic data collection system (EDC) developed by the National Center for Cardiovascular Disease; information stored on CRFs is entered into the EDC by a designated person on each site, and each site shares data with the EDC. The objective of this study is to objectively compare the safety, efficacy and economic benefits of the two treatment methods for UIA, and each participant is followed for at least one year (at 3, 6, and 12 months). Consequently, each participant will have at least one year of follow-up data, and when the study is finished, participants will be followed at least once a year until 5 years. All participants undergo DSA at 18 months. Follow-up data will be acquired by a neurosurgeon either by telephone or by social tools as soon as possible and recorded in the CRF-B. In most cases, DSA examination should be carried out six months after the operation to confirm the effect of treatment, which is the vital end point of this study. Furthermore, data acquired at three and twelve months after surgery are also an important aspect of the study. A detailed follow-up plan is given in Figure 2. During the study, the researchers will be obliged to protect the personal privacy and medical information of each participant, and strictly adhere to ethical guidelines.

### Data management

As all data will be collected using CRFs and the EDC, the CIAP have established a data management committee (DMC, located in Xuanwu hospital) to supervise data quality, and have hired a specialist data management company responsible for constructing the EDC and ensuring data security, integrity and accuracy. Before the participants are formally enrolled, the DMC holding CRF and EDC data entry study classes for the main researches in each collaboration clinical center; considers data entry, modification and retrieval, and sets permissions for the main researchers in the EDC. A clinical research operator (CRO) supervises project progress and quality of

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3 data implementation, and the researcher assigned, the clinical research associate  
4 (CRA) will regularly visit each participating center to ensure that all contents of the  
5 research program are strictly adhered to; if not, the CRA promptly submits  
6 information to the investigators. Throughout the project, a research summary  
7 conference will be held every 6 months, to discuss progress and solve any problems  
8 that may arise.  
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### 10 11 **Data analysis**

12 The Department of Medical Statistics at the National Center for Cardiovascular  
13 Diseases will be responsible for all data management and statistical analysis. SPSS  
14 V21.0 statistical software (IBM Corp, Armonk, New York, USA) will be used to  
15 analyze the results, with normally distributed data represented by  $\bar{x} \pm SD$ . Skewed  
16 distribution data will be described by the median ( $M$ ) and the four quartile range ( $P25$ ;  
17  $P75$ ), using an independent t test or rank sum test. Categorical variables will be  
18 described by frequency, percentage and grouped data, and rate or percentages between  
19 the groups will be compared with the Chi square test or by the Fisher exact test. Rank  
20 data will be analyzed by the rank sum test.  $P < 0.05$  will be considered to indicate  
21 statistical significance.  
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### 26 **Endpoints of the study**

27 The endpoints of the study have also been divided into primary and secondary  
28 endpoints. The safety and efficacy of interventional treatment and craniotomy are  
29 considered as the primary endpoint of the study, and represent the key goals of  
30 investigators. Using the participant mortality and morbidity rates to evaluate the  
31 safety of interventional and craniotomy, and by considering ipsilateral stroke and  
32 neurological deficits within 30 days, we shall enhance the safety evaluation of our  
33 study and these features will play a positive role in our findings. Efficacy will be  
34 evaluated by aneurysm recurrence rate, re-bleeding rate and complete occlusion rate.  
35 The secondary endpoint mainly considers the time of postoperative evaluation and the  
36 occurrence of adverse events. The primary endpoint and the secondary endpoint are  
37 described in Table 3.  
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### 42 **Methods of evaluating the economic benefits of treatment**

43 The study combines the following three aspects of patient evaluation in terms of the  
44 economic benefits of treatment: admission (GCS, WFNS, mRS, MMSE), the third day  
45 after surgery (GCS, WFNS, mRS, MMSE) and the total cost of hospitalization.  
46 Multivariate logistic regression analyses will be used to adjust for GCS, WFNS, mRS,  
47 MMSE (admission and the third day after surgery), and then to compare the total cost  
48 of hospitalization for both treatments with control of other economic factors, such as  
49 length of ICU stay, length of hospital stay, readmission rate, drug changes, adverse  
50 events, intraoperation complications and postoperative complications, etc..  
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### 54 **DISCUSSION**

55 To the best of our knowledge, CIAP is the project to explore the characteristics of  
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3 Chinese intracranial aneurysms within the nation of Chinese people, and does so from  
4 a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of  
5 rupture; and the emergency treatment required for ruptured aneurysms; etc., in  
6 particular, this study compares two different treatment methods for UIA. IA is a  
7 common cause of SAH, but this does not imply that the SAH rate is high the  
8 incidence of IA therefore also high,<sup>18</sup> to a certain extent, SAH can lead to an  
9 erroneous understanding of IA. Consequently, we should exclude the unknown causes  
10 of SAH.<sup>19</sup> DSA has traditionally been considered the gold standard for detecting  
11 aneurysms. However, combined with existing data, the present study indicates that the  
12 incidence of UIA within the population varies according to the method of examination;  
13 the main reason for this is that the accuracy of different diagnostic methods is affected  
14 by the size of aneurysms. Studies have shown that the sensitivity of DSA is only 85%  
15 for small aneurysms (<3 mm), and that the efficacy of computed tomographic (CT)  
16 angiography for diagnosing intracranial aneurysms is increasingly being recognized;<sup>1</sup>  
17 <sup>20-23</sup> this study excludes patients with small aneurysms and, in doing so, increases the  
18 accuracy of the study. This, however, means that the study can be considered as  
19 incomplete, as it only targets in aneurysms of a certain size.  
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25 The treatment of IA cannot be separated from interventional treatment and craniotomy.  
26 Interventional therapy is becoming more and more popular among neurosurgeons, but  
27 selecting which of the two approaches to use for treatment has been controversial.<sup>24-26</sup>  
28 Most scholars believe that interventional therapy is associated with lower mortality  
29 compared with craniotomy, in which the recurrence and re-bleeding rate of  
30 interventional therapy is higher,<sup>12</sup> and combined with other techniques it may achieve  
31 better results.<sup>5 27 28</sup> The recurrence rate of interventional therapy is higher because for  
32 certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not  
33 satisfactory. However, as the intervention materials and technology improve, many  
34 scholars have adopted this approach for the treatment of aneurysms and have obtained  
35 good results.<sup>29-33</sup> Comparing the two methods in terms of safety and efficacy, it is  
36 necessary to consider a range of factors, such as age, gender, subarachnoid  
37 hemorrhage and aneurysm size; because these are the principal factors which can  
38 influence the re-bleeding of aneurysms.<sup>34 35</sup> Surgery can cause hemodynamic changes  
39 in an aneurysm, but there is no conclusive evidence to show that this plays a positive  
40 role in the recurrence of aneurysms, the study does not take into account the effects of  
41 hemodynamics on the results,<sup>36 37</sup> but rather, the researchers, with the help of a  
42 professional statistical team, can try to minimize the impact of baseline data  
43 differences upon the results.  
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49 The authors believe that the most obvious limitations of this study lie in the following  
50 points. First of all, this study is a multicenter study involving 12 clinical centers that  
51 fully demonstrate the diagnosis and treatment of IA. However, each clinical center  
52 may not necessarily have the same view of treatment for IA, and there may be  
53 differences in the sources of the original data, but multicenter research is essential for  
54 this study. Secondly, in the study process, there are many factors affecting outcome,  
55 including treatment time, drug changes and adverse events, etc.. These are very  
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difficult to avoid in clinical studies, so the control of clinical factors is fine in our study design. In addition, our study includes 1,500 participants. Whether this sample accurately represents the Chinese patients with IA is unknown; there are no national studies to indicate the overall incidence of IA in China, and we can only refer to the existing literature. CIAP sub-project 1 aims to indicate the incidence of IA in China.

With careful research design, it is possible to consider and exclude the factors that could potentially influence the results, and by referring to foreign research programs, this study may provide helpful information for therapeutic strategies for UIA in clinical practice. Results from this study may provide us with a chance of using normative interventions for UIA before deploying interventional treatment and craniotomy and thus provide significant benefit for patients with aneurysms.

### Contributors

CD obtained the research funding and is the principal investigator of this study. YC, HF, XL, MH, YQ, XY and HZ have developed the study protocol and YC is the main author of this article. HF, XH, SG and XL have revised the manuscript. XS, LW, ZW, XT, MZ, MA and ZT are the main people responsible for the seven clinical centers and responsible for implementing this study. CD has approved publication of the final manuscript.

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### Conflict of interest

None declared

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1  
2  
3 Table 1. Inclusion criteria.

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- 4 1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging
  - 5 (CTA/MRA/DSA), whether or not there are clinical symptoms
  - 6 2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless
  - 7 of whether they have been treated or not
  - 8 3. Patients currently have the ability to live independently and have an mRS scale
  - 9 score of  $\leq 3$
  - 10 4. Age is  $> 14$  years old
  - 11 5. Patients or family members agree to provide informed written consent
- 

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15  
16 Table 2. Exclusion criteria.

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- 17 1. Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for
  - 18 30 days
  - 19 2. Patients with other intracranial vascular malformations, such as AVM or AVF
  - 20 3. Patients with intracranial or other parts of the body suffering from malignancy
  - 21 4. Fusiform, traumatic, bacterial, or dissecting aneurysms
  - 22 5. Patients with severe mental illness who are unable to communicate when disease is
  - 23 diagnosed
  - 24 6. Patients with poor overall state, expected survival time less than 1 year or poor
  - 25 physical status, cannot tolerate general anesthesia or aneurysm surgeries
  - 26 7. Patients involved in other clinical studies of intracranial aneurysms
  - 27 8. Patients undergoing surgical clipping or endovascular treatment simultaneously
  - 28 9. Patients who receive flow diversion as aneurysm treatment
  - 29 10. Patients who refused to follow up
  - 30 11. The size of the aneurysm  $\leq 3$  mm
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36 CTA: computed tomography angiography; MRA: magnetic resonance angiography;  
37 DSA: digital subtraction angiography; AVM: arteriovenous malformation; AVF:  
38 arteriovenous fistula; mRS: modified Rankin scale  
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Table 3. endpoints of the study

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1. The primary endpoint

① The main security endpoint:

The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including participants' mortality (mRS = 6), morbidity ( $3 \leq \text{mRS} \leq 5$  points); the emergency of ipsilateral stroke and neurological deficits within 30 days are also recognized as reliability measures to evaluate the security of interventional and craniotomy.

② The main effectiveness endpoint:

The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including the recurrence (Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects.

2. The secondary endpoints

① The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including participants' mortality (mRS = 6), morbidity ( $3 \leq \text{mRS} \leq 5$  points);

② The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including the recurrence (Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects;

③ The success rate of treatment;

④ The success rate of 6 months after interventional therapy or craniotomy clipping (the DSA hint: aneurysm completely or nearly total occlusion, re-canalization or re-growth did not appear);

⑤ The incidence of major adverse events during hospitalization;

⑥ The incidence of major adverse events after 3 months of surgery;

⑦ The incidence of major adverse events in 3 months and 6 months later after operation;

⑧ The incidence of major adverse events in 6 months and 12 months later after operation.

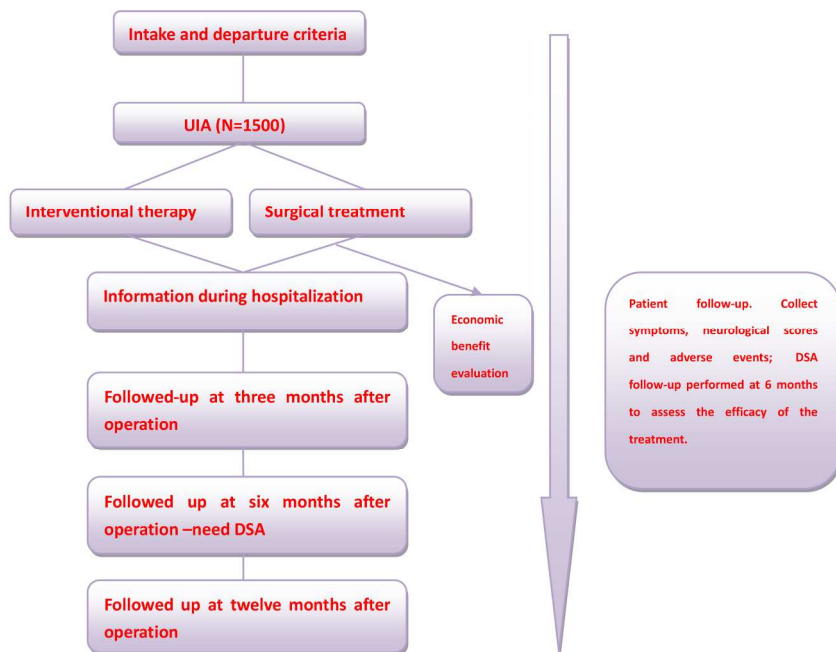
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Figure legends

Figure 1. Research flowchart

Figure 2. Participants visit and evaluation schedule

Figure 1. Research flowchart:



UJA: un-ruptured aneurysms; DSA: digital subtraction angiography

169x243mm (300 x 300 DPI)

Figure 2. Participants visit and evaluation schedule.

Visit number	Screening period	Treatment period		follow-up period		
	1	2	3	4	5	6
Study	Preoperative screening	In operation	Before discharge	3 months±14 days	6 months±30 days	12 months±30 days
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

210x297mm (300 x 300 DPI)

# BMJ Open

## The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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Complete List of Authors:	Chen, Yunchang; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Fan, Haiyan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery He, Xuying; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Guo, Shenquan; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery Li, Xifeng; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery He, Min; West China Hospital, Sichuan University, Department of Neurosurgery Qu, Yan; Tangdu Hospital, Fourth Military Medical University, Department of Neurosurgery Yang, Xinjian; Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Department of Interventional Neuroradiology Zhang, Hongqi; Xuanwu Hospital, Capital Medical University, Department of Neurosurgery Sun, Xiaochuan; The 1st Affiliated Hospital of Chongqing Medical University, Department of Neurosurgery Wang, Liqun; The Second Hospital of Hebei Medical University, Department of Neurosurgery wang, Zhong; The First Affiliated Hospital of Soochow University, Department of Neurosurgery Tong, Xiaoguang; Tianjin Huanhu Hospital, Department of Neurosurgery Zhong, Ming; The First Affiliate of Wenzhou Medical University, Department of Neurosurgery Maimaitili, Aisha; The First Affiliated Hospital of Xinjiang Medical University, Department of Neurosurgery Tong, Zhiyong; The First Hospital of China Medical University, Department of Neurosurgery Duan, Chuazhi; Southern Medical University, Zhujiang Hospital, Department of Neurosurgery
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Surgery
Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

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4 **The China intracranial aneurysm project (CIAP): protocol for a**  
5 **prospective cohort study of interventional treatment and craniotomy**  
6 **for un-ruptured aneurysms**  
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13 Yunchang Chen<sup>1</sup>, Haiyan Fan<sup>1</sup>, Xuying He<sup>1</sup>, Shenquan Guo<sup>1</sup>, Xifeng Li<sup>1</sup>,  
14 Min He<sup>2</sup>, Yan Qu<sup>3</sup>, Xinjian Yang<sup>4</sup>, Hongqi Zhang<sup>5</sup>, Xiaochuan Sun<sup>6</sup>, Liquan  
15 Wang<sup>7</sup>, Zhong Wang<sup>8</sup>, Xiaoguang Tong<sup>9</sup>, Ming Zhong<sup>10</sup>, Maimaitili  
16 Aisha<sup>11</sup>, Zhiyong Tong<sup>12</sup>, Chuanzhi Duan<sup>1</sup>  
17  
18  
19  
20  
21  
22  
23  
24

25 <sup>1</sup>Department of Neurosurgery, Southern Medical University, Zhujiang Hospital, 253#  
26 Industry road, Guangzhou, Guangdong, 510282, RP China.

27 <sup>2</sup>Department of Neurosurgery, West China Hospital, Sichuan University, Guoxue  
28 Street 37#, Chengdu, Sichuan, 610041, RP China.

29 <sup>3</sup>Department of Neurosurgery, Tangdu Hospital, Fourth Military Medical University,  
30 Xi'an, Shaanxi, 710038, RP China.

31 <sup>4</sup>Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and  
32 Beijing Tiantan Hospital, Capital Medical University, Beijing, 100050, RP China.

33 <sup>5</sup>Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing  
34 100053, RP China

35 <sup>6</sup>Department of Neurosurgery, The 1st Affiliated Hospital of Chongqing Medical  
36 University, No.1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing, 400016, RP  
37 China

38 <sup>7</sup>Department of Neurosurgery, The Second Hospital of Hebei Medical University,  
39 No.215 Hepingxi Road Shijiazhuang City, Hebei Province, 050000, RP China

40 <sup>8</sup>Department of Neurosurgery, The First Affiliated Hospital of Soochow University,  
41 188 Shizi Street, Suzhou, Jiangsu Province, 215006, RP China

42 <sup>9</sup>Department of Neurosurgery, Tianjin Huanhu Hospital, No.6, JiZhao Road, Jinnan  
43 District, Tianjin, 300350, RP China

44 <sup>10</sup>Department of Neurosurgery, The First Affiliate of Wenzhou Medical University,  
45 The New Campus of First Affiliate of Wenzhou Medical University, Street of  
46 Nanbaixiang, Ouhai District, Wenzhou, Zhe Jiang Province, 325000, RP China

47 <sup>11</sup>Department of Neurosurgery, The First Affiliated Hospital of Xinjiang Medical  
48 University, No.137 Of Liyushannan Road Urumqi, Xinjiang Uyghur Autonomous  
49 Region, 830054, RP China

50 <sup>12</sup>Department of Neurosurgery, The First Hospital of China Medical University,  
51  
52  
53  
54  
55  
56  
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1  
2  
3 No.155, Nanjingbei Road, Heping District, Shenyang, Liaoning Province, 110001, RP  
4 China  
5  
6  
7

8  
9 *Corresponding Author: Director and Professor Chuan-Zhi Duan*

10  
11 *Tel: +86-013539962233; Fax: +86-020-61643269; E-mail:*

12  
13 *doctor\_duanZJ@163.com*  
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## ABSTRACT

**Introduction:** There are two approaches for the treatment of IA: interventional therapy and craniotomy, both of which have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms (UIA), to save valuable medical resources, and to reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. In this study, we propose a refined, prospective, multicentre study for the Chinese population with strictly defined patient inclusion criteria along with the selection of representative clinical participating centres.

**Methods and analysis:** This report describes a multicentre, prospective cohort study. As IA is extremely harmful if it ruptures, ethical issues need to be taken into account with regard to this study. Researchers are therefore not able to use randomized controlled trials. The study will be conducted by 12 clinical centres located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be completed in 2020. We expect 1500 participants with UIA to be included. Clinical information relating to the participants will be recorded objectively. The primary endpoints are an evaluation of the safety and efficiency of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up. The second endpoint is the evaluation of safety and the efficacy of interventional therapy and craniotomy clipping when participants are treated for 12 months. We also address the success of treatment and the incidence of adverse events.

**Ethics and dissemination:** The research protocol and the informed consent form (ICF) for participants in this study were approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001). The results of this study are expected to be disseminated in peer reviewed journals in 2021.

**Clinical trial registration number:** NTC03133598

**Keywords:** Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

### Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus, it can fully represent the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been adopted in the light of China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size to but ensures that the study can be completed on time.
3. The research process will be coordinated by several departments to ensure the quality and reliability of the research data.
4. The study considers a variety of clinical control factors and the research efficiency

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3 may be reduced as a result.

- 4 5. To evaluate the economic benefits of treatment, we considered many factors, after  
5 statistical analysis of these factors, the total cost of hospitalization was directly  
6 compared, this method may not rigorously reflect the differences in economic  
7 benefits.  
8

## 9 10 INTRODUCTION

11 IA is a common cause of subarachnoid haemorrhage (SAH) that is estimated to affect  
12 between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs  
13 (UIAs) in healthy people can be as high as 3%, these detection rates differ across  
14 various countries.<sup>1</sup> According to recent research, the overall prevalence of UIA was  
15 7.0% in Chinese adults aged 35 to 75 years, with women being more affected than  
16 men (8.4% *versus* 5.5%, respectively).<sup>2</sup> In the case of un-ruptured cerebral aneurysms  
17 (UCAS), the natural course of UIA varies according to the size, location, and shape of  
18 the aneurysm.<sup>3</sup> Interventional therapy and craniotomy represent the two main methods  
19 for treating UIAs. However, despite our current knowledge of UIA, and even when  
20 we consider information relating to pathological, radiological, and clinical studies,  
21 there are no specific criteria that can be used to select the appropriate treatment  
22 strategy. Consequently, there is an urgent global requirement to develop methods  
23 which will help to select the most appropriate treatment for UIA.<sup>4</sup>  
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28 A large number of researchers have investigated the treatment options available for IA  
29 and many of these studies have indicated that the postoperative complications  
30 associated with interventional therapy are lower than those of craniotomy. However,  
31 the short and long-term occlusion rate was lower for interventional therapy than for  
32 craniotomy.<sup>5-9</sup> These studies have also highlighted that the size and anatomical  
33 location of aneurysms can exert a significant influence on the effect of treatment.<sup>5-9</sup>  
34 Interestingly, research failed to identify any significant difference in costs when  
35 treatment was compared between endovascular and neurosurgical approaches over the  
36 short term.<sup>10</sup> The International Subarachnoid Aneurysm Trial (ISAT) further showed  
37 that compared with craniotomy, interventional treatment can clearly improve patient  
38 outcome; however, most of the participants in that study had small aneurysms.  
39 Consequently, the trial could not definitively conclude that coiling was safer than  
40 clipping for all cases of IA.<sup>11-14</sup> While controversial, the ISAT did provide us with a  
41 degree of understanding of IA.<sup>15 16</sup>  
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46 Previous research has also shown that the risk of IA rupture was 1% to 2%, leading to  
47 intracranial haemorrhage, a dangerous condition that is associated with a high  
48 mortality and disability rate.<sup>17</sup> However, while UIAs do not generally rupture during  
49 long-term follow-up, medical treatment can increase the bleeding rate and the rate of  
50 rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms,  
51 the aim of this study was to assess the safety, efficacy and economic benefits of  
52 interventional treatment *versus* craniotomy and to propose a scientific strategy for  
53 selecting the appropriate form of surgical treatment for UIA that could be deployed  
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3 across clinics worldwide.  
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## 5 **METHODS AND ANALYSIS**

### 6 **Study design**

7  
8 CIAP is an ongoing, multicentre trial supported by the National Key Research  
9 Development Program. CIAP predominantly studies five different aspects of  
10 aneurysms: 1) the risk of antithrombotic therapy in patients with UIAs complicated by  
11 ischaemic cardio cerebrovascular diseases; 2) the rate of rupture; 3) the risk of rupture  
12 and developing a model to predict rupture; 4) treatment options for UIAs and 5) the  
13 development of standardized treatments for early stage UIA bleeding. This study  
14 dealing with one of the sub-topics is an observational study.  
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18 This study evaluates the treatment options for UIAs from the point of view of safety,  
19 efficacy and economic benefits, and compares these factors between interventional  
20 therapy and craniotomy. The incidence of aneurysms is relatively high among the  
21 population, and China is a large country with a wide population distribution. Thus, in  
22 order to fully reflect the population more objectively, the researchers will conduct this  
23 multicentre, prospective cohort study for five continuous years. Furthermore, referring  
24 to previous related research studies and taking into account the characteristics and  
25 hazards of UIA, the researchers will not include the random division of participants  
26 into groups<sup>3</sup>; a total of 1500 UIA participants are expected to be included. Each  
27 participant will be followed up at fixed time points by researchers, and the normal  
28 procedures of treatment will not be affected by participants joining the CIAP study.  
29 Follow-up data and other clinical information, relating to the participants are recorded  
30 in detail, and data are analysed statistically. A concise flow chart of the entire study is  
31 shown in Figure 1. The study protocol was approved by the Ethics Committee of  
32 Zhujiang Hospital of Southern Medical University (Reference Number:  
33 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has  
34 been registered at ClinicalTrials.gov with reference number NTC03133598.  
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### 39 **Participation centre qualification**

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41 To evaluate UIA treatment objectively, it is important to avoid participant bias and to  
42 ensure that an adequate number of cases is included in the study. We involved  
43 participants in multiple centres at the same time and documented the diagnosis and  
44 treatment process in detail objectively. The researchers selected 12 clinical centres  
45 (each centre covering more than 2 community or referral units) to conduct this study  
46 in collaboration distributed across several regions of China (South east, Southwest,  
47 Northwest and Northeast). According to an incomplete dataset, in 2015, a total of  
48 6000 IA patients had been evaluated across the 12 clinical centres. Consequently, the  
49 researchers believe that each centre can adequately represent the actual level of IA  
50 diagnosis and treatment at a regional and national level. The 12 clinical centres used in  
51 this study are therefore representative.  
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56 There are no specific guidelines for the treatment of UIA. As such, differences exist in  
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3 the diagnosis and treatment of IA across different regions, different centres, and even  
4 between different neurosurgeons. In this study, the basic requirement of the  
5 neurosurgeons who perform surgery on participants is that they are able to complete  
6 more than 30 cases of aneurysm surgery per year independently. The study also  
7 features an imaging interpretation centre (Internationally Recognized Image  
8 Interpretation Laboratory, established by Xuanwu Hospital and the Image Centre of  
9 the University of California, Los Angeles, UCLA). This centre is responsible for the  
10 unified standard interpretation of imaging data arising from the 12 clinical centres.  
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### 13 14 **Participant selection and screening**

15 The purpose of this study is to recruit patients who are suffering from IA without  
16 rupture. First, participants are diagnosed with UIA, either by computed tomography  
17 angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction  
18 angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting  
19 aneurysms, or with SAH of unknown origin, are excluded. These types of patients,  
20 involving other vascular diseases (arteriovenous malformation [AVM], arteriovenous  
21 fistula [AVF]), malignant tumours, or poor physical condition factors, are expected to  
22 live less than a year and are not suitable for study. In order not to disturb the  
23 objectivity of the study and to provide good opportunities for follow-up, the  
24 researchers also emphasize the ability of participants to live independently (using the  
25 modified Rankin scale (mRS) and including those with a score of  $\leq 3$ ). Patients are  
26 also excluded if they are unable to communicate normally due to serious mental  
27 illness; Patients are also excluded if they receive flow diversion as part of their  
28 aneurysm treatment (as flow diversion becomes a standard of care for many large,  
29 wide-necked aneurysms that are located in the internal carotid artery), if the size of  
30 the aneurysm was less than 3 mm, or if aneurysm diagnosis is unclear or difficult. The  
31 specific inclusion and exclusion criteria for the trial are provided in Tables 1 and 2,  
32 respectively.  
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38 The study involves twelve recruiting centres, each of which require IRB approval  
39 before recruiting cases. Patients diagnosed with UIA not only receive formal  
40 diagnosis and treatment for their aneurysms but also, along with their families, receive  
41 full communication from the researchers regarding to the aims of the study. Patients  
42 can later voluntarily join the study and sign the ICF. Once these steps are taken, the  
43 participant's imaging data will be transmitted to the imaging interpretation centre to  
44 re-confirm the diagnosis. If the two diagnoses are not consistent, then the participant  
45 is excluded. The participants can withdraw from the study at any time, and the  
46 researchers can determine whether the participants continue the study according to  
47 their physical status. When serious adverse events occur during the course of the trial,  
48 the researchers must terminate the study in advance and report to the ethics committee;  
49 adverse events are also entered into the case report form (CRF). This study is an  
50 observational study that does not interfere with the normal course of clinical diagnosis  
51 and treatment; even if participants withdraw from the study, it will not affect their  
52 treatment.  
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### Sample size calculation

Sample size is calculated based on the formula:

$$n = \frac{(z_{\alpha} \sqrt{(1 + 1/R)pq} + z_{\beta} \sqrt{p_1q_1 + p_0q_0/R})^2}{(P_1 - P_0)^2}$$

( $\alpha = 0.05$ , two-sided test, 80% of the degree of control.)

According to the results of the ISUA test, the mortality rate of the intervention group was 8.7% at one year and that of the craniotomy group was 14.1%, and in the intervention group, it was two times as much in the participants as those in the craniotomy group. We calculated  $n=1185$  (intervention group:  $n = 395$ ; craniotomy group:  $n = 790$ ). During the study, 20% of the patients would be lost during follow-up, thus, the study requires 1,422 participants. Ultimately, we decided to include 1,500 participants.

### Data collection

Once participants are included in the study, all information regarding the course of diagnosis and treatment are recorded in the CRF-A. This study also uses an electronic data collection system (EDC) developed by the National Centre for Cardiovascular Diseases; information stored on CRFs is entered into the EDC by a designated person on each site, and each site shares data with the EDC. The objective of this study is to objectively compare the safety, efficacy and economic benefits of the two treatment methods for UIA, and each participant is followed for at least one year (at 3, 6, and 12 months). Consequently, each participant will have at least one year of follow-up data, and when the study is finished, participants will be followed at least once a year up to 5 years. All participants undergo DSA at 18 months. Follow-up data will be acquired by a neurosurgeon either by telephone or by social tools as soon as possible and recorded in the CRF-B. In most cases, DSA examination should be conducted six months after the operation to confirm the effect of treatment, which is the vital end point of this study. Furthermore, data acquired at three and twelve months after surgery are also an important aspect of the study. A detailed follow-up plan is given in Figure 2. During the study, the researchers will be obliged to protect the personal privacy and medical information of each participant, and strictly adhere to ethical guidelines.

### Data management

As all data will be collected using CRFs and the EDC, the CIAP have established a data management committee (DMC, located in Xuanwu hospital) to supervise data quality and have hired a specialist data management company responsible for constructing the EDC and ensuring data security, integrity and accuracy. Before the participants are formally enrolled, the DMC will hold CRF and EDC data entry study

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3 classes for the main studies in each collaboration clinical centre regarding data entry,  
4 modification and retrieval, and setting permissions for the main researchers in the  
5 EDC. A clinical research operator (CRO) supervises project progress and quality of  
6 data implementation, and the researcher assigned. The clinical research associate  
7 (CRA) will regularly visit each participating centre to ensure that all contents of the  
8 research programme are strictly followed. If not, the CRA promptly submits  
9 information to the investigators. Throughout the project, a research summary  
10 conference will be held every 6 months to discuss progress and solve any problems  
11 that may arise. This study holds a study summary meeting every 6 months to discuss  
12 and solve research question and outcome measures informed by patients' priorities,  
13 experience, and preferences.  
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16

### 17 **Data analysis**

18 The Department of Medical Statistics at the National Centre for Cardiovascular  
19 Diseases will be responsible for all data management and statistical analysis. SPSS  
20 V21.0 statistical software (IBM Corp, Armonk, New York, USA) will be used to  
21 analyse the results, with normally distributed data being represented by  $\bar{x} \pm SD$ .  
22 Skewed distribution data will be described by the median ( $M$ ) and the four-quartile  
23 range ( $P25$ ;  $P75$ ) using an independent t test or rank sum test. Categorical variables  
24 will be described by frequency, percentage and grouped data, and rate or percentages  
25 between the groups will be compared with the Chi-square test or by the Fisher exact  
26 test. Rank data will be analysed by the rank sum test.  $P < 0.05$  will be considered to  
27 indicate statistical significance.  
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### 32 **Endpoints of the study**

33 The endpoints of the study have also been divided into primary and secondary  
34 endpoints. The safety and efficacy of interventional treatment and craniotomy are  
35 considered as the primary endpoint of the study and represent the key goals of  
36 investigators. Using participant mortality and morbidity rates to evaluate the safety of  
37 interventional and craniotomy, and by considering ipsilateral stroke and neurological  
38 deficits within 30 days, we shall enhance the safety evaluation of our study, and these  
39 features will play a positive role in our findings. Efficacy will be evaluated by  
40 aneurysm recurrence rate, re-bleeding rate and complete occlusion rate. The  
41 secondary endpoint mainly considers the time of postoperative evaluation and the  
42 occurrence of adverse events. The primary and the secondary endpoints are described  
43 in Table 3.  
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### 48 **Methods of evaluating the economic benefits of treatment**

49 The study combines the following three aspects of patient evaluation in terms of the  
50 economic benefits of treatment: admission (GCS, WFNS, mRS, MMSE), the third day  
51 after surgery (GCS, WFNS, mRS, MMSE) and the total cost of hospitalization.  
52 Multivariate logistic regression analyses will be used to adjust for GCS, WFNS, mRS,  
53 MMSE (admission and the third day after surgery), and then to compare the total cost  
54 of hospitalization for both treatments with control of other economic factors, such as  
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length of ICU stay, length of hospital stay, readmission rate, drug changes, adverse events, intraoperation complications and postoperative complications, etc..

#### Ethics and dissemination

The study was approved by the China's Ministry of Science and Technology as a national key research programme in 2016. During the research process, the investigators strictly followed the Declaration of Helsinki and Human Biomedical Research Ethical Issues. Participants will not be affected the normal course of clinical diagnosis and treatment of aneurysms because of participating in the study. Professor Chuanzhi Duan is the principal investigator who will supervise the successful implementation of the study. The results of this study will be disseminated in peer-reviewed journals in 2021.

#### Patient and Public Involvement

Patients or the public were not directly involved in the study design or conduct of the study. When the participants were included, we told them that this study will take about 5 years to complete and after the results of the study are published, we will inform them by telephone immediately.

### **DISCUSSION**

To the best of our knowledge, CIAP is a project exploring the characteristics of intracranial aneurysms nationwide among the Chinese people and does so from a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of rupture; and the emergency treatment required for ruptured aneurysms; etc. In particular, this study compares two different treatment methods for UIA. IA is a common cause of SAH, but this does not imply that if the SAH rate is high, the incidence of IA is therefore also high;<sup>18</sup> to a certain extent, SAH can lead to an erroneous understanding of IA. Consequently, we should exclude the unknown causes of SAH.<sup>19</sup> DSA has traditionally been considered the gold standard for detecting aneurysms. However, combined with existing data, the present study suggests that the incidence of UIA within the population varies according to the method of examination. The main reason for this finding is that the accuracy of different diagnostic methods is affected by the size of aneurysms. Studies have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm) and that the efficacy of computed tomographic (CT) angiography for diagnosing intracranial aneurysms is increasingly being recognized;<sup>1 20-23</sup> this study excludes patients with small aneurysms and in doing so increases the accuracy of the study. However, this finding means that the study can be considered to be incomplete, as it only targets aneurysms of a certain size.

The treatment of IA cannot be separated from interventional treatment and craniotomy. Interventional therapy is becoming increasingly popular among neurosurgeons, but selecting which of the two approaches to use for treatment has been controversial.<sup>24-26</sup> Most scholars believe that interventional therapy is associated with lower mortality than is craniotomy; the recurrence and re-bleeding rate of interventional therapy is

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3 higher,<sup>12</sup> and combined with other techniques, interventional therapy may achieve  
4 better results.<sup>5 27 28</sup> The recurrence rate of interventional therapy is higher because for  
5 certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not  
6 satisfactory. However, as the intervention materials and technology improve, many  
7 scholars have adopted this approach for the treatment of aneurysms and have obtained  
8 good results.<sup>29-33</sup> Comparing the two methods in terms of safety and efficacy, it is  
9 necessary to consider a range of factors, including age, gender, subarachnoid  
10 haemorrhage and aneurysm size because these are the principal factors which can  
11 influence the re-bleeding of aneurysms.<sup>34 35</sup> Surgery can cause haemodynamic  
12 changes in an aneurysm, but there is no conclusive evidence to show that this plays a  
13 positive role in the recurrence of aneurysms; the study does not take into account the  
14 effects of haemodynamics on the results,<sup>36 37</sup> but rather, the researchers, with the help  
15 of a professional statistical team, can try to minimize the impact of baseline data  
16 differences upon the results.  
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21 The authors believe that the most obvious limitations of this study are the following.  
22 First, we have included many factors in order to fully evaluate the economic benefits  
23 of treatment. Although there are statistical methods to address these factors, error still  
24 exists, and directly comparing total hospital costs, this method may not be highly  
25 rigorous. Second, in the study process, there are many factors affecting outcome,  
26 including treatment time, drug changes and adverse events, etc. Investigators  
27 primarily use retrospective methods to record these data, and the research method is  
28 single, resulting in convincing evidence that needs improvement. In addition, our  
29 study includes 1,500 participants. Whether this sample accurately represents the  
30 Chinese patients with IA is unknown. There are no national studies to indicate the  
31 overall incidence of IA in China, and we can only refer to the existing literature. CIAP  
32 sub-project 1 aims to indicate the incidence of IA in China.  
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35 With careful research design, it is possible to consider and exclude the factors that  
36 could potentially influence the results, and by referring to foreign research  
37 programmes, this study may provide helpful information for therapeutic strategies for  
38 UIA in clinical practice. Results from this study may provide us with a chance of  
39 using normative interventions for UIA before deploying interventional treatment and  
40 craniotomy, thereby providing significant benefit for patients with aneurysms.  
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#### 44 **Contributors**

45 CD obtained the research funding and is the principal investigator of this study. YC,  
46 HF, XL, MH, YQ, XY and HZ have developed the study protocol and YC is the main  
47 author of this article. HF, XH, SG and XL have revised the manuscript. XS, LW, ZW,  
48 XT, MZ, MA and ZT are the main people responsible for the seven clinical centers  
49 and responsible for implementing this study. CD has approved publication of the final  
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57  
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### Conflict of interest

None declared

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18 Environment in Ruptured and Unruptured Brain Aneurysms. *AM J NEURORADIOL* 2010.

1  
2  
3 Table 1. Inclusion criteria.

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- 4 1. At least 1 intracranial un-ruptured aneurysm confirmed by
  - 5 imaging(CTA/MRA/DSA), whether or not there are clinical symptoms
  - 6 2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless
  - 7 of whether they have been treated or not
  - 8 3. Patients currently have the ability to live independently and have an mRS scale
  - 9 score of  $\leq 3$
  - 10 4. Age is  $> 14$  years old
  - 11 5. Patients or family members agree to provide informed written consent
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15  
16 Table 2. Exclusion criteria.

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- 17 1. Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for
  - 18 30 days
  - 19 2. Patients with other intracranial vascular malformations, such as AVM or AVF
  - 20 3. Patients with intracranial or other parts of the body suffering from malignancy
  - 21 4. Fusiform, traumatic, bacterial, or dissecting aneurysms
  - 22 5. Patients with severe mental illness who are unable to communicate when disease is
  - 23 diagnosed
  - 24 6. Patients with poor overall state, expected survival time less than 1 year or poor
  - 25 physical status, cannot tolerate general anesthesia or aneurysm surgeries
  - 26 7. Patients involved in other clinical studies of intracranial aneurysms
  - 27 8. Patients undergoing surgical clipping or endovascular treatment simultaneously
  - 28 9. Patients who receive flow diversion as aneurysm treatment
  - 29 10. Patients who refused to follow up
  - 30 11. The size of the aneurysm  $\leq 3$  mm
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36 CTA: computed tomography angiography; MRA: magnetic resonance angiography;  
37 DSA: digital subtraction angiography; AVM: arteriovenousmalformation; AVF:  
38 arteriovenous fistula; mRS: modified Rankin scale  
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### Table 3. Endpoints of the study

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#### 1. The primary endpoint

① The main security endpoint:

The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including participants' mortality (mRS = 6), morbidity ( $3 \leq \text{mRS} \leq 5$  points); the emergency of ipsilateral stroke and neurological deficits within 30 days are also recognized as reliability measures to evaluate the security of interventional and craniotomy.

② The main effectiveness endpoint:

The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including the recurrence (Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects.

#### 2. The secondary endpoints

① The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including participants' mortality (mRS = 6), morbidity ( $3 \leq \text{mRS} \leq 5$  points);

② The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including the recurrence (Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects;

③ The success rate of treatment;

④ The success rate of 6 months after interventional therapy or craniotomy clipping (the DSA hint: aneurysm completely or nearly total occlusion, re-canalization or re-growth did not appear);

⑤ The incidence of major adverse events during hospitalization;

⑥ The incidence of major adverse events after 3 months of surgery;

⑦ The incidence of major adverse events in 3 months and 6 months later after operation;

⑧ The incidence of major adverse events in 6 months and 12 months later after operation.

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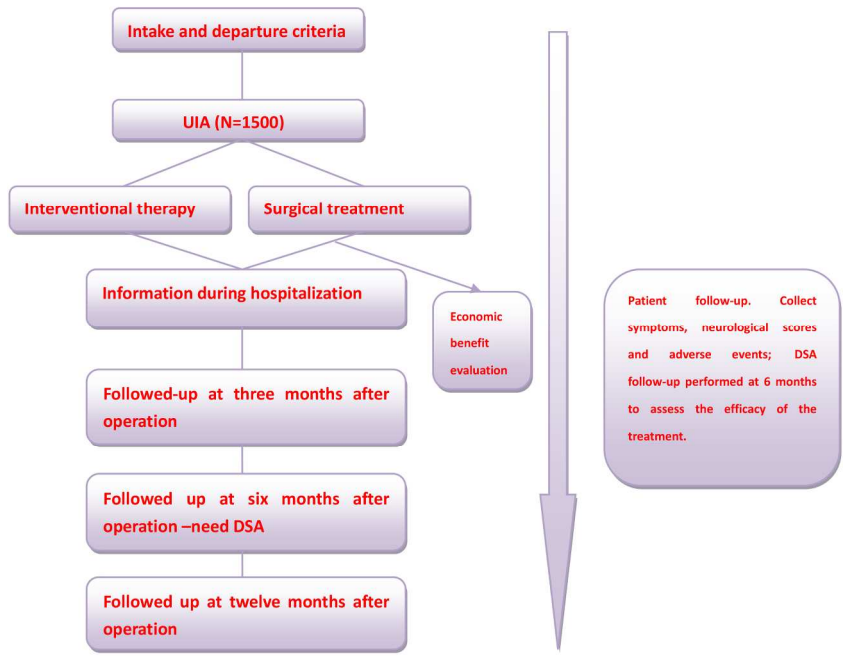
Figure legends

Figure 1. Research flowchart

Figure 2. Participants visit and evaluation schedule

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Figure 1. Research flowchart:



UJA: un-ruptured aneurysms; DSA: digital subtraction angiography

169x243mm (300 x 300 DPI)



Figure 2. Participants visit and evaluation schedule.

Visit number	Screening period	Treatment period		follow-up period		
	1	2	3	4	5	6
Study	Preoperative screening	In operation	Before discharge	3 months±14 days	6 months±30 days	12 months±30 days
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

210x297mm (300 x 300 DPI)