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## Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

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# **Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial**

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**Attn: Ascension Providence Hospital Graduate Medical Education**

## 32 **Abstract**

## 33 **Introduction**

34 Delayed cerebral ischemia due to cerebral vasospasm remains the foremost contributor to  
35 morbidity and mortality following aneurysmal subarachnoid hemorrhage. Past effort in  
36 preventing and treating delayed cerebral ischemia have failed to make any significant progress.  
37 To date, our most effective treatment involves the use of nimodipine, a calcium channel blocker.  
38 Recent studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent  
39 cerebral vasospasm. Thus far, no study has evaluated the effect of cilostazol plus nimodipine on  
40 the rate of delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage.

## 41 **Methods and Analysis**

42 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial  
43 investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of  
44 delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of ICU stay, and  
45 long-term functional and quality of life outcomes will be recorded. All data will be collected  
46 with the aim of demonstrating that the use of cilostazol plus nimodipine will not only safely  
47 decrease the incidence of delayed cerebral ischemia, but decrease the rates of both radiographic  
48 and symptomatic vasospasm with subsequent improvement in long-term functional and quality-  
49 of-life outcomes when compared to nimodipine alone.

## 50 **Ethics and Dissemination**

51 Ethical approval was obtained at all participating hospitals by the institutional review board. The  
52 results of this study will be submitted for publication in peer-reviewed journals.

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58

## 59 **Article Summary**

### 60 **Strengths and limitations of this study:**

- 61 • First randomized controlled trial in the US to evaluate the effect of cilostazol and  
62 nimodipine on delayed cerebral ischemia and cerebral vasospasm
- 63 • Adequately powered study
- 64 • Primary outcome improvement may not lead to secondary clinical outcome improvement

65 **Title:** Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral  
66 Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-  
67 Blinded, Placebo-Controlled Trial

68 **FDA IND Application:** Approved on 4/5/2019 (FDA IND# 143368) for off-label use

69 **Registry:** NCT04148105

70 **Study Dates:** November 2019 – October 2023

71 **Institutional Approvals:** The protocol was approved by the Ascension Providence Hospital  
72 Institutional Review Board (IRB)

73 **Funding Agency:** This study is supported by the Ascension Providence Hospital Institutional  
74 research grant. This project is not an industry-sponsored study. The investigators are solely  
75 responsible for the protocol design, data collection, analysis and interpretation, writing of the  
76 report, or decision to submit this publication

77 **Investigators: Research Site:** Investigators and their subsequent roles are detailed in the  
78 authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital,  
79 Michigan State University, College of Human Medicine  
80 Southfield, MI 48075  
81 248-849-3403

## 83 **Introduction**

84 Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating condition which affects  
85 approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been  
86 made in the treatment of ruptured aneurysms, however, there has been little progress in the  
87 treatment and prevention of delayed cerebral ischemia (DCI) due to cerebral vasospasm  
88 (cVS).[1,2] Cerebral vasospasm and subsequent DCI remain to be the most prominent cause of

1  
2  
3 89 morbidity and mortality following aSAH.[3] Although the mechanism and pathogenesis of cVS  
4 90 is not fully understood, it is considered a vital underlying mechanism in DCI.[4,5] Cerebral  
5 91 vasospasm is known to take effect between days 3 and 21 post-aSAH with a peak incidence  
6 92 between days 6 and 10.[2] Current therapy includes definitive treatment of the ruptured  
7 93 aneurysm through either open clipping or endovascular therapy followed by a 21-day course of  
8 94 nimodipine after the onset of SAH.[6–8] Nimodipine is a dihydropyridine calcium channel  
9 95 blocker which is recommended for the postprocedural treatment of aneurysmal subarachnoid  
10 96 hemorrhage (aSAH) for the prevention of cerebral vasospasm.[8,9] This regimen has shown  
11 97 long-term outcome improvement following aSAH.[7,10] Multiple other modalities have been  
12 98 investigated for the treatment and/or prevention of cVS including mechanical removal of blood,  
13 99 cisternal irrigation, Rho kinase inhibitors, triple-H therapy, and numerous endovascular  
14 100 treatments – all of which demonstrated minimal efficacy or limited use.[11–18] Despite years of  
15 101 investigation and improvement, the risk of symptomatic and radiographic vasospasm remains  
16 102 unacceptably high between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23]  
17 103 This also continues to be prevalent at our institution as we observed rates of symptomatic  
18 104 vasospasm and DCI to be 40% and 60%, respectively.

19 105 Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic  
20 106 intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory  
21 107 and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral  
22 108 arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26]  
23 109 Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both  
24 110 radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30]  
25 111 In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol  
26 112 effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in  
27 113 patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated  
28 114 the combined application of nimodipine and cilostazol. This combination therapy of nimodipine  
29 115 and cilostazol with possible synergistic effect require further investigation.[31]

30 116 Our randomized superiority trial seeks to investigate the combined effect of cilostazol  
31 117 plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when  
32 118 compared to nimodipine alone.

## 119 **Study Goals and Objectives**

120 Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine  
121 alone in the prevention of DCI in patients with aSAH.

### 122 **Primary Objective**

- 123 • To demonstrate that the combined use of cilostazol plus nimodipine when compared to  
124 nimodipine alone will decrease the rate of DCI in patients following aSAH

### 125 **Secondary Objectives**

- 126 • To demonstrate that the combined use of cilostazol plus nimodipine is not associated with  
127 increased drug-related serious adverse events
- 128 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of  
129 symptomatic and radiographic vasospasm
- 130 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
131 average length of intensive care unit (ICU) stay
- 132 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
133 incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- 134 • To demonstrate that the combined use of cilostazol plus nimodipine will improve  
135 Modified Rankin Scores (mRS) and Quality-of-life (QoL) outcomes at 6-months.

## 136 **Methods and Analysis**

137 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in  
138 adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design  
139 without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow  
140 chart.

141 Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This  
142 protocol was approved by our Institutional Review Board (IRB) and published on  
143 ClinicalTrials.gov.

144 Over a three-year period, consecutive adult patients over the age of 18 who present to our  
145 tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT



1  
2  
3 146 angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those  
4  
5 147 adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). After  
6  
7 148 satisfying inclusion/exclusion criteria, patients/family members are consented for full  
8  
9 149 participation in the trial. Once consented, patients are randomized to receive either placebo or  
10  
11 150 intervention with a centralized treatment allocation mechanism and block randomization to  
12  
13 151 assure the two arms achieve equal proportion of patients over time.

14 152 All patients, treatment providers, investigators, and statisticians are blinded to the allocation.  
15  
16 153 Blinding is achieved by allocation sequence being concealed to personnel involved in the  
17  
18 154 enrolling, care and evaluation of the patient. The study coordinator will keep the randomization  
19  
20 155 schedule in a cloud-based, secure and encrypted database. Only the study coordinator who  
21  
22 156 monitors the trial, the pharmacist who executes the allocation, the supervising investigator who  
23  
24 157 is not involved in the patients' care or enrollment will have access to the randomization schedule.  
25  
26 158 Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will  
27  
28 159 conceal the identity of the medications.

29 160 All participating patients, after undergoing treatment of their ruptured aneurysm (open  
30  
31 161 clipping vs. endovascular coiling) and confirmation of a stable head CT will be randomized and  
32  
33 162 scheduled to receive their allocation within 48 hours of surgery/intervention for a total of 14  
34  
35 163 days. In addition to their randomized allocation, all patients will receive a standard aSAH  
36  
37 164 treatment protocol,[7] including 21 days of nimodipine as endorsed by the Congress of  
38  
39 165 Neurological Surgeons. The standardized treatment regimen is summarized in Table 2. Each  
40  
41 166 patient is followed according to the data collection schedule (Figure 2). While in the hospital, the  
42  
43 167 patients are monitored frequently (every hour while in the ICU and every 4 hours while on the  
44  
45 168 floor) throughout the day for any adverse/serious adverse events (Table 3). Adverse and serious  
46  
47 169 adverse events (SAE) are defined using a validated classification scheme (Table 4).[33] SAE are  
48  
49 170 defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the  
50  
51 171 study medication will be recorded and reported immediately to the principal investigator and the  
52  
53 172 IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in  
54  
55 173 which knowledge of the allocation will aid in the clinical management of the patient and  
56  
57 174 therefore warrant unblinding of the allocation.

1  
2  
3 175 The primary outcome will be defined as low-density areas on CT or signal changes on MRI  
4  
5 176 performed at 1-week and 1-month following initial presentation determined by blinded  
6  
7 177 neuroradiologists. Secondary outcomes including length of ICU stay, QoL, and mRS at 1-month,  
8  
9 178 3-months, & 6-months postoperatively will be prospectively collected. Length of ICU stay will  
10  
11 179 be determined by standardized discharge criteria. Rates of symptomatic vasospasm will be  
12  
13 180 collected and defined as development of a new focal or global neurological deficit or  
14  
15 181 deterioration of at least 2 points on the Glasgow Coma Scale,[34] which was not explained by  
16  
17 182 initial hemorrhage, re-bleeding, hydrocephalus, surgical complications, fever, infections, or  
18  
19 183 electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI  
20  
21 184 and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or CTA.[14,35,36]  
22  
23 185 Radiographic vasospasm will be assessed by either CTA or DSA between 7 and 10 days  
24  
25 186 postoperatively. Radiographic vasospasm will be defined as arterial narrowing not attributable to  
26  
27 187 atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of stenosis compared  
28  
29 188 to previous baseline CTA or DSA as determined by blinded neuroradiologists.[14] In each  
30  
31 189 patient, the smallest diameters of 10 arterial segments of the bilateral distal internal carotid  
32  
33 190 arteries (ICA), M1 and M2 segments of the middle cerebral artery (MCA), and A1 and A2  
34  
35 191 segments of the anterior cerebral artery (ACA) will be measured. Severity of the radiographic  
36  
37 192 vasospasm will be categorized as none or mild (0%-25% decrease in vessel diameter from baseline),  
38  
39 193 moderate (25%-50% decrease in vessel diameter from baseline), or severe (greater than 50%  
40  
41 194 decrease in vessel diameter from baseline). The most affected segment will be used to determine  
42  
43 195 severity of radiographic vasospasm.

40 196 To demonstrate superiority, an 80% power is used to minimize chances of false negatives.  
41  
42 197 Assuming an effect size of 50% with the use of cilostazol and a baseline rate of DCI of 60%, a  
43  
44 198 total sample size was estimated to be 100 patients with an alpha of 0.05. In anticipation for any  
45  
46 199 unforeseen events and those lost to follow-up, we plan to enroll a total of 120 patients.

## 200 **Patient and Public Involvement**

50 201 At the time of 1-month postoperative follow-up, patients or their families will be asked to  
51  
52 202 participate as study advisers in our data monitoring and safety committee. There will be 2-4  
53  
54 203 patient advisers at any given time during the study period, each with a term of 6 months. These

1  
2  
3 204 patient advisers will share their experience regarding the recruitment process, surgery, and  
4  
5 205 postoperative care in order to help ensure patient safety and satisfaction throughout the study.  
6

## 7 206 **Trial Status**

8  
9  
10 207 At the time of manuscript submission, the trial is ongoing.  
11

## 12 208 **Safety Considerations**

13  
14  
15 209 All study-related adverse events (AE) are recorded and reported immediately to the  
16  
17 210 principal investigator and subsequently to the IRB within 24 hours of the event as previously  
18  
19 211 stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional  
20  
21 212 data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical  
22  
23 213 safety of the study and review adverse events reported to the IRB to determine risk and benefits.  
24  
25 214 Any SAE related to the study medication represents a circumstance under which unblinding is  
26  
27 215 permissible in order to ensure the safety of the participant. At that time, the intervention will be  
28  
29 216 stopped, and any clinical intervention required at the discretion of the attending surgeon will  
30  
31 217 ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be  
32  
33 218 surgeons and related experts who will meet to review the results and any adverse events  
34  
35 219 biannually to evaluate study safety.

## 36 220 **Follow-up**

37  
38 221 Postoperatively, patients will be followed according to the data collection schedule  
39  
40 222 (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome  
41  
42 223 and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled  
43  
44 224 follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be  
45  
46 225 designated at the discretion of the treating attending physician.

## 47 226 **Data Management and Statistical Analysis**

48  
49 227 During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will  
50  
51 228 observe all the steps of the intervention and data collection to ensure proper execution. The  
52  
53 229 progress of data entry, follow-up and recruitment are logged and monitored regularly by the  
54  
55 230 CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and  
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1  
2  
3 231 the database will be maintained to within one week of the data collection. CRC will coordinate  
4  
5 232 the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month  
6  
7 233 and 6-months.

8  
9 234 Comparability between groups will be evaluated by descriptive and univariate analyses.  
10  
11 235 Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-  
12  
13 236 value less than or equal to 0.05 will be considered statistically significant. Bonferroni's  
14  
15 237 correction will be applied when appropriate. Descriptive statistics will be used in each arm for  
16  
17 238 proportion who did not receive allocated intervention, lost to follow-up, excluded from primary  
18  
19 239 analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses  
20  
21 240 will be performed. An interim analysis will be conducted after 50 patients (25 per arm) have  
22  
23 241 been enrolled and completed study procedures. This is a superiority trial. Early discontinuation  
24  
25 242 of the study will be dependent on overwhelming positive results for the primary outcome. We  
26  
27 243 will discontinue the trial if we achieve  $p < 0.001$  threshold at the time of interim analysis.[37]

## 27 244 **Quality Assurance**

28  
29 245 Standardized medication orders will conceal the treatment allocation. The study  
30  
31 246 coordinator will be responsible for managing the quality of patient data recorded in the study. All  
32  
33 247 participating research staff will be trained and given written copies of a standard operating  
34  
35 248 procedure to ensure consistency during recruitment, consent, handling of data, and follow-up  
36  
37 249 evaluation. The study coordinator along with the PI will check weekly the content of the forms  
38  
39 250 and database to ensure accurate and timely entry. Compliance at all study timepoints including  
40  
41 251 enrollment, randomization, intervention, data, and outcome collection will be documented daily  
42  
43 252 on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered  
44  
45 253 into a cloud-based, secure and encrypted database by the research staff. Access to the database  
46  
47 254 will be restricted. Data validation tool has been embedded in the database. Data entered will  
48  
49 255 undergo monthly verification with the source document.

## 49 256 **Expected Outcome of the Study**

50  
51  
52 257 This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe  
53  
54 258 and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We  
55  
56 259 expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally,

260 we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and  
261 radiographic vasospasm.

## 262 **Duration of the Project**

263 Given our institutional volume, we anticipate a study period of 1-3 years assuming 50%  
264 of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment  
265 and subject to discontinuation if all previously defined criteria are met.

## 266 **Project Management**

267 Neurosurgery staff will counsel and recruit subjects according to their initial screening to  
268 participate in this trial. The neurosurgery staff will check for eligibility using inclusion and  
269 exclusion criteria listed in Table 1. They will also explain the study principles, including the  
270 detailed experimental in-hospital & postoperative protocol, investigational treatment, potential  
271 risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed  
272 in a cloud-based, secure, and encrypted database. The designated lead pharmacists will execute  
273 the randomized allocation assignment according to the block randomization schedule to maintain  
274 masking of allocation. The neuroscience ICU charge nurse will be responsible for overseeing and  
275 monitoring administration of the study medication. The neuroscience trained intensive care  
276 nursing staff will administer the study medication to the study participants. The PI and support  
277 staff will record all perioperative and postoperative data including study-related adverse events.  
278 The study coordinator will ensure and maintain follow-up visits for postoperative secondary  
279 outcomes. The neuroradiologists will evaluate and determine primary and secondary outcomes of  
280 DCI and vasospasm, respectively. The clinical research methodologist will function as the CRC,  
281 supervise the overall execution of the study, and participate in the writing of the protocol and  
282 manuscript.

## 283 **Ethics and Dissemination**

284 The study will be conducted according to the Helsinki Declaration[38], the NIH human  
285 subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good  
286 Clinical Practice.[39] This protocol is written following the SPIRIT 2013 guidelines and was

287 approved by the hospital IRB. The results of this study will be submitted for publication in peer-  
288 reviewed journals and the key findings will be presented at national conferences.

### 289 **Author Contribution**

290 TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this  
291 trial including organization and execution over two hospital campuses. DS contributed to the  
292 design and execution of the study drug protocol including randomization, blinding and placebo.  
293 MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard  
294 operating procedures, and maintaining quality assurance among study participants and their  
295 subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT  
296 contributed to the drafting of the original manuscript, participated in critically revising the  
297 manuscript and agree to be accountable for all aspects of the work.

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299 This trial is supported by the Ascension Providence Hospital Institutional research grant.

### 300 **Disclaimer**

301 This project is not an industry-sponsored study. The investigators are solely responsible  
302 for the protocol design, data collection, analysis and interpretation, writing of the report, or  
303 decision to submit this publication.

### 305 **Competing Interests**

306 None declared.

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431 **Figure Legend:**

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433 **Figure 1. Study Design CONSORT Flow Diagram**434 **Figure 2. Data Collection Schedule & Timeline**

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**Table 1.** Inclusion, Exclusion, and Withdrawal Criteria

| Inclusion  | Exclusion   |
|--|---|
| 18 years of age or older   | Non-aneurysmal subarachnoid hemorrhage  |
| Anterior circulation aneurysm  | Multiple ruptured aneurysms   |
| Patients who have undergone surgical intervention  | Patients with congestive heart failure  |
| Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan                     | Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)   |
| Consent to study participation   | Active pathological bleeding  |
|  | Allergy to cilostazol   |
|  | Positive pregnancy test   |
|  | Coagulopathy not caused by anti-coagulant use   |
|  | History of hemorrhagic complications (gastrointestinal bleeding, etc.)  |
|  | Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol  |
|  | Patients requiring anticoagulant/antiplatelet treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm) |
| <b>Criteria for discontinuing follow-up:</b>   |   |
| Subject wishing to terminate participation in the study at any time throughout his/her participation |   |
| CT, computed tomography  |   |

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**Table 2.** Standardized Treatment Regimen

| Location  | Treatment  |
|---|--|
| NSICU and floor   | <p data-bbox="456 506 727 537"><b>Intervention group:</b></p> <ul data-bbox="505 548 1425 779" style="list-style-type: none"> <li data-bbox="505 548 967 579">• 60 mg nimodipine Q4H for 21 days</li> <li data-bbox="505 590 967 621">• 100 mg cilostazol b.i.d. for 14 days</li> <li data-bbox="505 632 1425 663">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="505 674 1425 737">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="505 747 1227 779">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> <p data-bbox="456 789 662 821"><b>Control group:</b></p> <ul data-bbox="505 831 1425 1066" style="list-style-type: none"> <li data-bbox="505 831 967 863">• 60mg nimodipine Q4H for 21 days</li> <li data-bbox="505 873 967 905">• Cilostazol placebo b.i.d. for 14 days</li> <li data-bbox="505 915 1425 947">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="505 957 1425 1020">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="505 1031 1227 1062">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> |
| NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography |  |

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**Table 3.** List of Adverse or Serious Adverse Events

| <b>Cilostazol</b>             |   | <b>Nimodipine</b>             |   |
|-------------------------------|---|-------------------------------|---|
| <b>Adverse events</b>         | Headache<br>Diarrhea<br>Abnormal Stools<br>Palpitations<br>Dizziness<br>Peripheral Edema<br>Dyspepsia<br>Abdominal pain<br>Tachycardia  | <b>Adverse events</b>         | Hypotension (mild)<br>Diarrhea<br>Dyspepsia<br>Rash<br>Headache<br>Flushing   |
| <b>Serious adverse events</b> | Hypotension<br>Bleeding<br>Stevens Johnson<br>Syndrome<br>Anaphylaxis<br>Hypersensitivity<br>Reaction<br>Leukopenia<br>Thrombocytopenia<br>Tachyarrhythmias<br>Myocardial<br>Infarction<br>Angina | <b>Serious adverse events</b> | Hypotension (severe)<br>EKG changes<br>CHF<br>Thromboembolism<br>Thrombocytopenia<br>Anemia<br>GI bleeding<br>Ileus<br>Intestinal obstruction |

EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal

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**Table 4.** Definition and Classification of Surgical Complications

| <b>Grade</b>   | <b>Definition</b>  |
|--|--|
| Grade 1  | Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions  |
| Grade 2  | Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.  |
| Grade 3  | Requiring surgical, endoscopic, or radiological intervention   |
| 3a)  | Intervention not under general anesthesia  |
| 3b)  | Intervention under general anesthesia  |
| Grade 4  | Life-threatening complication (including CNS complications)* requiring IC/ICU management   |
| 4a)  | Single organ dysfunction (including dialysis)  |
| 4b)  | Multiorgan dysfunction   |
| Grade 5  | Death of a patient   |
| Suffix   | If the patient suffers from a complication at the time of discharge, the suffix “d” is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication |
| *Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit |  |

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Figure 1. CONSORT flow diagram

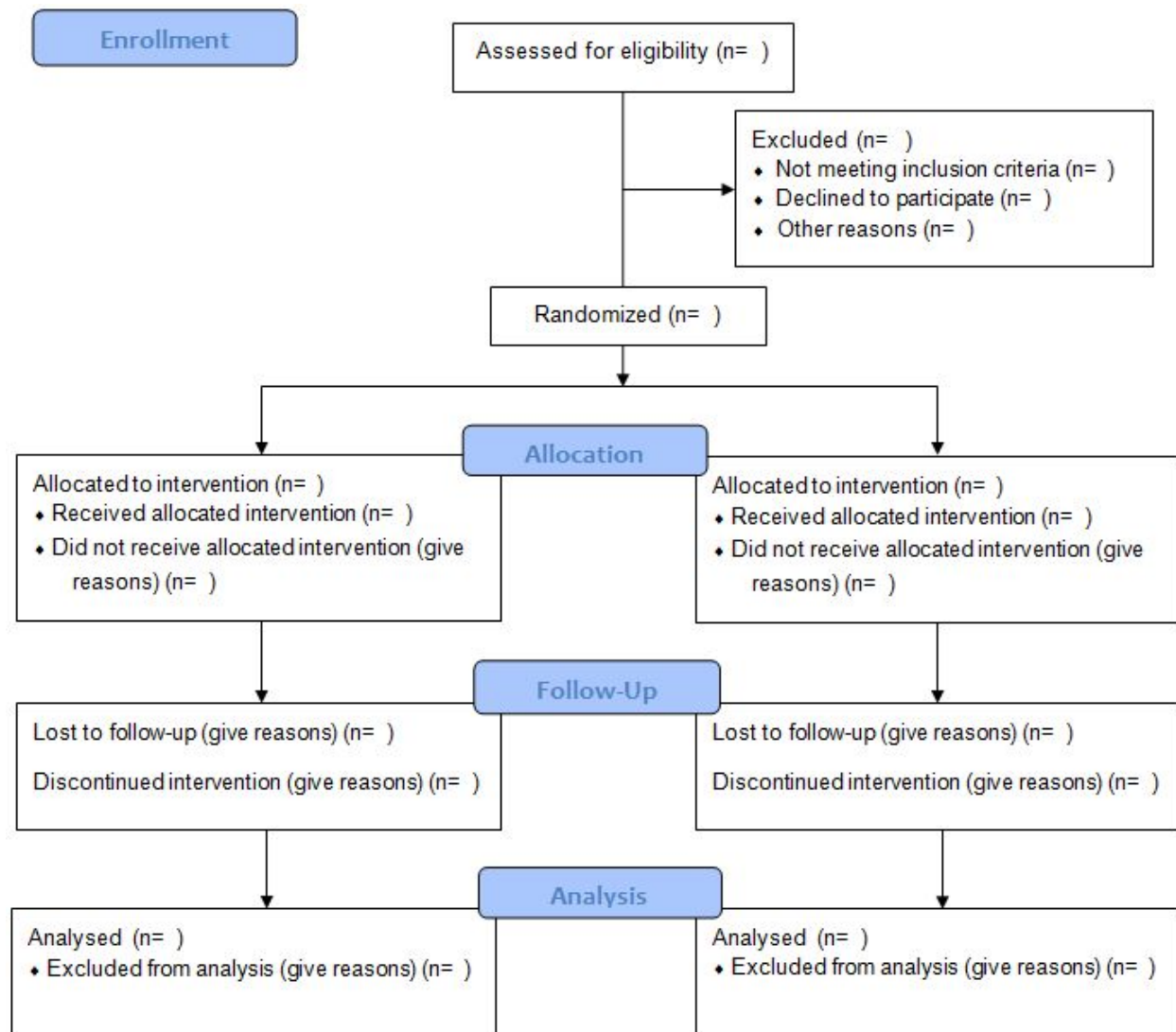


Figure 2. Data Collection Schedule

|                                   | PreOp | D0 | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 | D15 | D16 | D17 | D18 | D19 | D20 | D21 | D/C |
|-----------------------------------|-------|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Eligibility                       |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Recruit                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Consent                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clinical Exam                     |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mFisher                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Hunt Hess                         |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EKG/ECHO                          | X     |    |    |    |    |    |    |    |    |    | X  |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pregnancy                         | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Randomise                         |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Cilostazol /Placebo               |       |    | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   |     |     |     |     |     |     |     |     |
| Nimodipine                        |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| CT Scan                           |       | X  | X  |    |    |    |    |    | X  |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| DSA/CTA                           |       | X  |    |    |    |    |    |    |    | X  | X  | X   |     |     |     |     |     |     |     |     |     |     |     |     |
| Coiling                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| All AE                            |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mRS                               |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EVD (Y/N)                         |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Symptomatic Vasospasm? (Mark "Y") |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | _____1_____              |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | _____3_____              |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | _____n/a_____            |
| Protocol version                  | 3       | Date and version identifier  | _____3_____              |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____3_____              |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____11_____             |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____3_____              |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | _____11_____             |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | _____n/a_____            |



1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant \_\_\_\_\_ 3, 4 \_\_\_\_\_

4 rationale studies (published and unpublished) examining benefits and harms for each intervention

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6 6b Explanation for choice of comparators \_\_\_\_\_ 3, 4 \_\_\_\_\_

7

8 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 4, 5 \_\_\_\_\_

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), \_\_\_\_\_ 5 \_\_\_\_\_

11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will \_\_\_\_\_ 5 \_\_\_\_\_

17 be collected. Reference to where list of study sites can be obtained

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and \_\_\_\_\_ 5, 6 Table 1 \_\_\_\_\_

20 individuals who will perform the interventions (eg, surgeons, psychotherapists)

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be \_\_\_\_\_ 5, 6 \_\_\_\_\_

23 administered

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose \_\_\_\_\_ 5, 6 \_\_\_\_\_

26 change in response to harms, participant request, or improving/worsening disease)

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence \_\_\_\_\_ 9 \_\_\_\_\_

29 (eg, drug tablet return, laboratory tests)

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 5, 6 \_\_\_\_\_

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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

37 efficacy and harm outcomes is strongly recommended

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40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for \_\_\_\_\_ 6, 7, 8, Figure 2\_ \_\_\_\_\_

41 participants. A schematic diagram is highly recommended (see Figure)

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|   |             |    |   |               |
|---|-------------|----|---|---------------|
| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | _____7_____   |
| 2 |             |    |   |               |
| 3 |             |    |   |               |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | _____n/a_____ |
| 5 |             |    |   |               |

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

|    |                    |     |  |             |
|----|--------------------|-----|--|-------------|
| 8  |                    |     |  |             |
| 9  |                    |     |  |             |
| 10 | Sequence           | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | _____5_____ |
| 11 | generation         |     |  |             |
| 12 |                    |     |  |             |
| 13 |                    |     |  |             |
| 14 |                    |     |  |             |
| 15 |                    |     |  |             |
| 16 | Allocation         | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | _____6_____ |
| 17 | concealment        |     |  |             |
| 18 | mechanism          |     |  |             |
| 19 |                    |     |  |             |
| 20 | Implementation     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | _____6_____ |
| 21 |                    |     |  |             |
| 22 |                    |     |  |             |
| 23 |                    |     |  |             |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | _____6_____ |
| 25 |                    |     |  |             |
| 26 |                    |     |  |             |
| 27 |                    | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | _____6_____ |
| 28 |                    |     |  |             |
| 29 |                    |     |  |             |
| 30 |                    |     |  |             |

### 31 **Methods: Data collection, management, and analysis**

|    |                 |     |  |                |
|----|-----------------|-----|--|----------------|
| 32 |                 |     |  |                |
| 33 | Data collection | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | _____8, 9_____ |
| 34 | methods         |     |  |                |
| 35 |                 |     |  |                |
| 36 |                 |     |  |                |
| 37 |                 |     |  |                |
| 38 |                 |     |  |                |
| 39 |                 | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | _____8_____    |
| 40 |                 |     |  |                |
| 41 |                 |     |  |                |
| 42 |                 |     |  |                |

|    |                                 |     |   |       |
|----|---------------------------------|-----|---|-------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | 8, 9  |
| 2  |                                 |     |   |       |
| 3  |                                 |     |   |       |
| 4  |                                 |     |   |       |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | 8, 9  |
| 6  |                                 |     |   |       |
| 7  |                                 |     |   |       |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8, 9  |
| 9  |                                 |     |   |       |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | 9     |
| 11 |                                 |     |   |       |
| 12 |                                 |     |   |       |
| 13 |                                 |     |   |       |
| 14 | <b>Methods: Monitoring</b>      |     |   |       |
| 15 |                                 |     |   |       |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 9, 10 |
| 17 |                                 |     |   |       |
| 18 |                                 |     |   |       |
| 19 |                                 |     |   |       |
| 20 |                                 |     |   |       |
| 21 |                                 |     |   |       |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | 9     |
| 23 |                                 |     |   |       |
| 24 |                                 |     |   |       |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | 6     |
| 26 |                                 |     |   |       |
| 27 |                                 |     |   |       |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 8, 9  |
| 29 |                                 |     |   |       |
| 30 |                                 |     |   |       |
| 31 |                                 |     |   |       |
| 32 | <b>Ethics and dissemination</b> |     |   |       |
| 33 |                                 |     |   |       |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 5, 10 |
| 35 |                                 |     |   |       |
| 36 |                                 |     |   |       |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | n/a   |
| 38 |                                 |     |   |       |
| 39 |                                 |     |   |       |
| 40 |                                 |     |   |       |
| 41 |                                 |     |   |       |
| 42 |                                 |     |   |       |

|    |                               |     |   |                 |
|----|-------------------------------|-----|---|-----------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | ___ 8, 9 ___    |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | ___ n/a ___     |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | ___ 6, 7, 8 ___ |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | ___ 11 ___      |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | ___ 10 ___      |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | ___ n/a ___     |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ___ 7 ___       |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | ___ 11 ___      |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | ___ n/a ___     |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | ___ n/a ___     |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | ___ n/a ___     |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

|                                 |   |
|---------------------------------|---|
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3  
4 1 **Efficacy and Safety of Cilostazol-Nimodipine Combined**  
5 2 **Therapy on Delayed Cerebral Ischemia after Aneurysmal**  
6 3 **Subarachnoid Hemorrhage: A Prospective, Randomized,**  
7 4 **Double-Blinded, Placebo-Controlled Trial Protocol**  
8  
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10

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## 32 **Abstract**

## 33 **Introduction**

34 Delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS) remains the foremost  
35 contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH).  
36 Past efforts in preventing and treating DCI have failed to make any significant progress. To date,  
37 our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent  
38 studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cVS. Thus  
39 far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of DCI following  
40 aSAH.

## 41 **Methods and Analysis**

42 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial  
43 investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of  
44 delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of intensive care unit  
45 (ICU) stay, and long-term functional and quality of life outcomes will be recorded. All data will  
46 be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not  
47 only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both  
48 radiographic and symptomatic vasospasm with subsequent improvement in long-term functional  
49 and quality-of-life (QoL) outcomes when compared to nimodipine alone.

## 50 **Ethics and Dissemination**

51 Ethical approval was obtained at all participating hospitals by the Ascension Providence Hospital  
52 Institutional Review Board (IRB). The results of this study will be submitted for publication in  
53 peer-reviewed journals.

54  
55 **Trial registration number:** NCT04148105

## 60 **Article Summary**

### 61 **Strengths and limitations of this study:**

- 62 • First randomized controlled trial in the US to evaluate the effect of cilostazol and  
63 nimodipine on delayed cerebral ischemia and cerebral vasospasm
- 64 • Adequately powered study
- 65 • Includes both objective outcomes (DCI and angiographic vasospasm) and subjective  
66 patient-reported-outcomes.
- 67 • We limited the study population to anterior circulation aSAH, thereby limiting the  
68 generalizability of the results to other patient populations

69 **Title:** Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral  
70 Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-  
71 Blinded, Placebo-Controlled Trial

72 **FDA IND Application:** Approved on 4/5/2019 (FDA IND# 143368) for off-label use

73 **Trial Registration Number:** NCT04148105

74 **Study Dates:** November 2019 – October 2023

75 **Institutional Approvals:** The protocol was approved by the Ascension Providence Hospital  
76 Institutional Review Board (IRB)

77 **Funding Agency:** This study is supported by the Ascension Providence Hospital Institutional  
78 research grant. This project is not an industry-sponsored study. The investigators are solely  
79 responsible for the protocol design, data collection, analysis and interpretation, writing of the  
80 report, or decision to submit this publication

81 **Investigators: Research Site:** Investigators and their subsequent roles are detailed in the  
82 authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital,  
83 Michigan State University, College of Human Medicine  
84 Southfield, MI 48075

85 248-849-3403

86

## 87 **Introduction**

88 Aneurysmal subarachnoid hemorrhage is a devastating condition which affects  
89 approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been  
90 made in the treatment of ruptured aneurysms, however, there has been little progress in the

1  
2  
3 91 treatment and prevention of DCI due to cVS.[1,2] Cerebral vasospasm and subsequent DCI  
4  
5 92 remain to be the most prominent cause of morbidity and mortality following aSAH.[3] Although  
6  
7 93 the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital  
8  
9 94 underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3  
10  
11 95 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes  
12  
13 96 definitive treatment of the ruptured aneurysm through either open clipping or endovascular  
14  
15 97 therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a  
16  
17 98 dihydropyridine calcium channel blocker which is recommended for the postprocedural  
18  
19 100 improvement following aSAH.[7,10] Multiple other modalities have been investigated for the  
20  
21 101 treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation,  
22  
23 102 Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which  
24  
25 103 demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and  
26  
27 104 improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high  
28  
29 105 between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to  
30  
31 106 be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be  
32  
33 107 40% and 60%, respectively.

33 108 Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic  
34  
35 109 intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory  
36  
37 110 and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral  
38  
39 111 arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26]  
40  
41 112 Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both  
42  
43 113 radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30]  
44  
45 114 In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol  
46  
47 115 effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in  
48  
49 116 patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated  
50  
51 117 the combined application of nimodipine and cilostazol. This combination therapy of nimodipine  
52  
53 118 and cilostazol with possible synergistic effect require further investigation.[31]

1  
2  
3 119 Our randomized superiority trial seeks to investigate the combined effect of cilostazol  
4 plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when  
5 120 compared to nimodipine alone.  
6  
7 121

## 8 9 122 **Study Goals and Objectives**

10  
11  
12 123 Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine  
13 124 alone in the prevention of DCI in patients with aSAH.

### 15 16 125 **Primary Objective**

- 17  
18 126 • To demonstrate that the combined use of cilostazol plus nimodipine when compared to  
19 127 nimodipine alone will decrease the rate of DCI in patients following aSAH

### 22 23 128 **Secondary Objectives**

- 24  
25 129 • To demonstrate that the combined use of cilostazol plus nimodipine is not associated with  
26 130 increased drug-related serious adverse events
- 27  
28 131 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of  
29 132 symptomatic and radiographic vasospasm
- 30  
31 133 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
32 134 average length of ICU stay
- 33  
34 135 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
35 136 incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- 36  
37 137 • To demonstrate that the combined use of cilostazol plus nimodipine will improve  
38 138 Modified Rankin Scores (mRS) and QoL outcomes at 6-months.

## 42 43 139 **Methods and Analysis**

44  
45  
46 140 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in  
47 141 adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design  
48 142 without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow  
49 143 chart.  
50  
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1  
2  
3 144 Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This  
4  
5 145 protocol was approved by the Ascension Providence Hospital IRB and published on  
6  
7 146 ClinicalTrials.gov.

8  
9 147 Over a three-year period, consecutive adult patients over the age of 18 who present to our  
10  
11 148 tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT  
12  
13 149 angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those  
14  
15 150 adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). Patients  
16  
17 151 with posterior circulation aSAH are known to be lower risk for developing symptomatic  
18  
19 152 vasospasm and were therefore excluded to avoid bias.[33] After satisfying inclusion/exclusion  
20  
21 153 criteria, patients/family members are consented for full participation in the trial. Once consented,  
22  
23 154 patients are randomized to receive either placebo or intervention with a centralized treatment  
24  
25 155 allocation mechanism and block randomization to assure the two arms achieve equal proportion  
26  
27 156 of patients over time.

28  
29 157 All patients, treatment providers, investigators, and statisticians are blinded to the allocation.  
30  
31 158 Blinding is achieved by allocation sequence being concealed to personnel involved in the  
32  
33 159 enrolling, care and evaluation of the patient. The study coordinator will keep the randomization  
34  
35 160 schedule in a cloud-based, secure and encrypted database. Only the study coordinator who  
36  
37 161 monitors the trial, the pharmacist who executes the allocation, the supervising investigator who  
38  
39 162 is not involved in the patients' care or enrollment will have access to the randomization schedule.  
40  
41 163 Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will  
42  
43 164 conceal the identity of the medications.

44  
45 165 All participating patients, after undergoing treatment of their ruptured aneurysm (open  
46  
47 166 clipping vs. endovascular coiling) and confirmation of a stable head CT 24-hours post-  
48  
49 167 intervention will be randomized and scheduled to receive their allocation within 48 hours of  
50  
51 168 surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients  
52  
53 169 will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed  
54  
55 170 by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in  
56  
57 171 Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in  
58  
59 172 the hospital, the patients are monitored frequently (every hour while in the ICU and every 4  
60  
173 173 hours while on the floor) for any adverse/serious adverse events (Table 3). Adverse and serious

1  
2  
3 174 adverse events (SAE) are defined using a validated classification scheme (Table 4).[34] SAE are  
4  
5 175 defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the  
6  
7 176 study medication will be recorded and reported immediately to the principal investigator and the  
8  
9 177 IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in  
10  
11 178 which knowledge of the allocation will aid in the clinical management of the patient and  
12  
13 179 therefore warrant unblinding of the allocation.

14 180 The primary outcome will be defined as new ischemic areas on CT performed at 1-month  
15  
16 181 following initial presentation and not observed on postoperative CT (24-hours post-intervention)  
17  
18 182 determined by blinded neuroradiologists.[35] Ischemic areas or low-density areas on CT  
19  
20 183 performed the day after intervention will be defined as rupture-related or procedural-related  
21  
22 184 infarctions and/or brain injury (such as ventriculostomy tract, craniotomy changes, etc.).  
23  
24 185 Secondary outcomes including symptomatic vasospasm, angiographic vasospasm, length of ICU  
25  
26 186 stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively  
27  
28 187 collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of  
29  
30 188 symptomatic vasospasm will be collected and defined as development of a new focal or global  
31  
32 189 neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[36] which  
33  
34 190 was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications,  
35  
36 191 fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT  
37  
38 192 scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or  
39  
40 193 CTA.[14,37,38] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and  
41  
42 194 10 days postoperatively. Radiographic vasospasm will be defined as arterial narrowing not  
43  
44 195 attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of  
45  
46 196 stenosis compared to previous baseline CTA or DSA as determined by blinded  
47  
48 197 neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the  
49  
50 198 bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery  
51  
52 199 (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured.  
53  
54 200 Severity of the radiographic vasospasm will be categorized as none or mild (0%-25% decrease in  
55  
56 201 vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline),  
57  
58 202 or severe (greater than 50% decrease in vessel diameter from baseline). The most affected  
59  
60 203 segment will be used to determine severity of radiographic vasospasm.

1  
2  
3 204 To demonstrate superiority, an 80% power is used to minimize chances of false negatives.  
4  
5 205 Assuming an relative effect size of 25% and absolute effect size of 16% with the use of  
6  
7 206 cilostazol and a baseline rate of DCI of 50%, a total sample size was estimated to be 126 patients  
8  
9 207 with an alpha of 0.05. In anticipation for any unforeseen events and those lost to follow-up, we  
10  
11 208 plan to enroll a total of 138 patients.

## 12 209 **Patient and Public Involvement**

15 210 At the time of 1-month postoperative follow-up, patients or their families will be asked to  
16  
17 211 participate as study advisers in our data monitoring and safety committee. There will be 2-4  
18  
19 212 patient advisers at any given time during the study period, each with a term of 6 months. These  
20  
21 213 patient advisers will share their experience regarding the recruitment process, surgery, and  
22  
23 214 postoperative care in order to help ensure patient safety and satisfaction throughout the study.

## 24 215 **Trial Status**

26  
27 216 At the time of manuscript submission, the trial is ongoing.

## 29 217 **Safety Considerations**

31  
32 218 All study-related adverse events (AE) are recorded and reported immediately to the  
33  
34 219 principal investigator and subsequently to the IRB within 24 hours of the event as previously  
35  
36 220 stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional  
37  
38 221 data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical  
39  
40 222 safety of the study and review adverse events reported to the IRB to determine risk and benefits.  
41  
42 223 Any SAE related to the study medication represents a circumstance under which unblinding is  
43  
44 224 permissible in order to ensure the safety of the participant. At that time, the intervention will be  
45  
46 225 stopped, and any clinical intervention required at the discretion of the attending surgeon will  
47  
48 226 ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be  
49  
50 227 surgeons and related experts who will meet to review the results and any adverse events  
51  
52 228 biannually to evaluate study safety.

## 53 229 **Follow-up**



1  
2  
3 230 Postoperatively, patients will be followed according to the data collection schedule  
4  
5 231 (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome  
6  
7 232 and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled  
8  
9 233 follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be  
10  
11 234 designated at the discretion of the treating attending physician.

## 12 235 **Data Management and Statistical Analysis**

13  
14  
15 236 During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will  
16  
17 237 observe all the steps of the intervention and data collection to ensure proper execution. The  
18  
19 238 progress of data entry, follow-up and recruitment are logged and monitored regularly by the  
20  
21 239 CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and  
22  
23 240 the database will be maintained to within one week of the data collection. CRC will coordinate  
24  
25 241 the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month  
26  
27 242 and 6-months.

28 243 Comparability between groups will be evaluated by descriptive and univariate analyses.  
29  
30 244 Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-  
31  
32 245 value less than or equal to 0.05 will be considered statistically significant. Bonferroni's  
33  
34 246 correction will be applied when appropriate. Descriptive statistics will be used in each arm for  
35  
36 247 proportion who did not receive allocated intervention, lost to follow-up, excluded from primary  
37  
38 248 analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses  
39  
40 249 will be performed. An interim analysis will be conducted quarterly during the trial, i.e. after a  
41  
42 250 total of 35, 70, and 105 patients have been enrolled. This is a superiority trial. Early  
43  
44 251 discontinuation of the study will be dependent on overwhelming positive results for the primary  
45  
46 252 outcome. We will discontinue the trial if we achieve  $p < 0.001$  threshold at the time of interim  
47  
48 253 analysis.[39]

## 49 254 **Quality Assurance**

50 255 Standardized medication orders will conceal the treatment allocation. The study  
51  
52 256 coordinator will be responsible for managing the quality of patient data recorded in the study. All  
53  
54 257 participating research staff will be trained and given written copies of a standard operating  
55  
56 258 procedure to ensure consistency during recruitment, consent, handling of data, and follow-up



1  
2  
3 259 evaluation. The study coordinator along with the PI will check weekly the content of the forms  
4  
5 260 and database to ensure accurate and timely entry. Compliance at all study timepoints including  
6  
7 261 enrollment, randomization, intervention, data, and outcome collection will be documented daily  
8  
9 262 on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered  
10  
11 263 into a cloud-based, secure and encrypted database by the research staff. Access to the database  
12  
13 264 will be restricted. Data validation tool has been embedded in the database. Data entered will  
14  
15 265 undergo monthly verification with the source document.

## 16 266 **Expected Outcome of the Study**

17  
18 267 This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe  
19  
20 268 and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We  
21  
22 269 expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally,  
23  
24 270 we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and  
25  
26 271 radiographic vasospasm.

## 27 272 **Duration of the Project**

28  
29  
30 273 Given our institutional volume, we anticipate a study period of 1-3 years assuming 50%  
31  
32 274 of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment  
33  
34 275 and subject to discontinuation if all previously defined criteria are met.

## 35 276 **Project Management**

36  
37  
38  
39 277 Neurosurgery staff will counsel and recruit subjects according to their initial screening to  
40  
41 278 participate in this trial. The neurosurgery staff will check for eligibility using inclusion and  
42  
43 279 exclusion criteria listed in Table 1. They will also explain the study principles, including the  
44  
45 280 detailed experimental in-hospital & postoperative protocol, investigational treatment, potential  
46  
47 281 risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed  
48  
49 282 in a cloud-based, secure, and encrypted database. The designated lead pharmacists will execute  
50  
51 283 the randomized allocation assignment according to the block randomization schedule to maintain  
52  
53 284 masking of allocation. The neuroscience ICU charge nurse will be responsible for overseeing and  
54  
55 285 monitoring administration of the study medication. The neuroscience trained intensive care  
56  
57 286 nursing staff will administer the study medication to the study participants. The PI and support

1  
2  
3 287 staff will record all perioperative and postoperative data including study-related adverse events.  
4  
5 288 The study coordinator will ensure and maintain follow-up visits for postoperative secondary  
6  
7 289 outcomes. The neuroradiologists will evaluate and determine primary and secondary outcomes of  
8  
9 290 DCI and vasospasm, respectively. The clinical research methodologist will function as the CRC,  
10  
11 291 supervise the overall execution of the study, and participate in the writing of the protocol and  
12  
13 292 manuscript.

### 14 293 **Ethics and Dissemination**

16  
17 294 The study will be conducted according to the Helsinki Declaration[40], the NIH human  
18  
19 295 subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good  
20  
21 296 Clinical Practice.[41] This protocol is written following the SPIRIT 2013 guidelines and was  
22  
23 297 approved by the hospital IRB. The results of this study will be submitted for publication in peer-  
24  
25 298 reviewed journals and the key findings will be presented at national conferences.

### 26 299 **Author Contribution**

28  
29 300 TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this  
30  
31 301 trial including organization and execution over two hospital campuses. DS contributed to the  
32  
33 302 design and execution of the study drug protocol including randomization, blinding and placebo.  
34  
35 303 MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard  
36  
37 304 operating procedures, and maintaining quality assurance among study participants and their  
38  
39 305 subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT  
40  
41 306 contributed to the drafting of the original manuscript, participated in critically revising the  
42  
43 307 manuscript and agree to be accountable for all aspects of the work.

### 44 308 **Funding**

46 309 This trial is supported by the Ascension Providence Hospital Institutional research grant.

### 48 310 **Disclaimer**

50  
51 311 This project is not an industry-sponsored study. The investigators are solely responsible  
52  
53 312 for the protocol design, data collection, analysis and interpretation, writing of the report, or  
54  
55 313 decision to submit this publication.

314

315 **Competing Interests**

316 None declared.

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**448 Figure Legend:**

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**450 Figure 1. Study Design CONSORT Flow Diagram****451 Figure 2. Data Collection Schedule & Timeline**

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**Table 1.** Inclusion, Exclusion, and Withdrawal Criteria

| Inclusion  | Exclusion   |
|--|---|
| 18 years of age or older   | Non-aneurysmal subarachnoid hemorrhage  |
| Anterior circulation aneurysm rupture  | Multiple ruptured aneurysms   |
| Patients who have undergone surgical intervention  | Patients with congestive heart failure  |
| Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan                     | Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)   |
| Consent to study participation   | Active pathological bleeding  |
|  | Allergy to cilostazol   |
|  | Positive pregnancy test   |
|  | Coagulopathy not caused by anti-coagulant use   |
|  | History of hemorrhagic complications (gastrointestinal bleeding, etc.)  |
|  | Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol  |
|  | Patients requiring anticoagulant/antiplatelet treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm) |
| <b>Criteria for discontinuing follow-up:</b>   |   |
| Subject wishing to terminate participation in the study at any time throughout his/her participation |   |
| CT, computed tomography  |   |

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**Table 2.** Standardized Treatment Regimen

| Location  | Treatment  |
|---|--|
| NSICU and floor   | <p data-bbox="451 277 727 312"><b>Intervention group:</b></p> <ul data-bbox="500 321 1425 558" style="list-style-type: none"> <li data-bbox="500 321 967 357">• 60 mg nimodipine Q4H for 21 days</li> <li data-bbox="500 363 964 399">• 100 mg cilostazol b.i.d. for 14 days</li> <li data-bbox="500 405 1390 441">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="500 447 1354 516">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="500 522 1227 558">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> <p data-bbox="451 564 662 600"><b>Control group:</b></p> <ul data-bbox="500 609 1425 842" style="list-style-type: none"> <li data-bbox="500 609 959 644">• 60mg nimodipine Q4H for 21 days</li> <li data-bbox="500 651 972 686">• Cilostazol placebo b.i.d. for 14 days</li> <li data-bbox="500 693 1390 728">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="500 735 1354 804">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="500 810 1227 842">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> |
| NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PO, post-operative; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography |  |

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**Table 3.** List of Adverse or Serious Adverse Events

| <b>Cilostazol</b>   |   | <b>Nimodipine</b>             |   |
|---|---|-------------------------------|---|
| <b>Adverse events</b>   | Headache<br>Diarrhea<br>Abnormal Stools<br>Palpitations<br>Dizziness<br>Peripheral Edema<br>Dyspepsia<br>Abdominal pain<br>Tachycardia  | <b>Adverse events</b>         | Hypotension (mild)<br>Diarrhea<br>Dyspepsia<br>Rash<br>Headache<br>Flushing   |
| <b>Serious adverse events</b>   | Hypotension<br>Bleeding<br>Stevens Johnson<br>Syndrome<br>Anaphylaxis<br>Hypersensitivity<br>Reaction<br>Leukopenia<br>Thrombocytopenia<br>Tachyarrhythmias<br>Myocardial<br>Infarction<br>Angina | <b>Serious adverse events</b> | Hypotension (severe)<br>EKG changes<br>CHF<br>Thromboembolism<br>Thrombocytopenia<br>Anemia<br>GI bleeding<br>Ileus<br>Intestinal obstruction |
| EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal |   |                               |   |

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**Table 4.** Definition and Classification of Surgical Complications

| <b>Grade</b>   | <b>Definition</b>  |
|--|--|
| Grade 1  | Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions  |
| Grade 2  | Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.  |
| Grade 3  | Requiring surgical, endoscopic, or radiological intervention   |
| 3a)  | Intervention not under general anesthesia  |
| 3b)  | Intervention under general anesthesia  |
| Grade 4  | Life-threatening complication (including CNS complications)* requiring IC/ICU management   |
| 4a)  | Single organ dysfunction (including dialysis)  |
| 4b)  | Multiorgan dysfunction   |
| Grade 5  | Death of a patient   |
| Suffix   | If the patient suffers from a complication at the time of discharge, the suffix “d” is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication |
| *Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit |  |

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**Cilostazol-Nimodipine Randomized Controlled Trial (CONSORT Flow Diagram)**

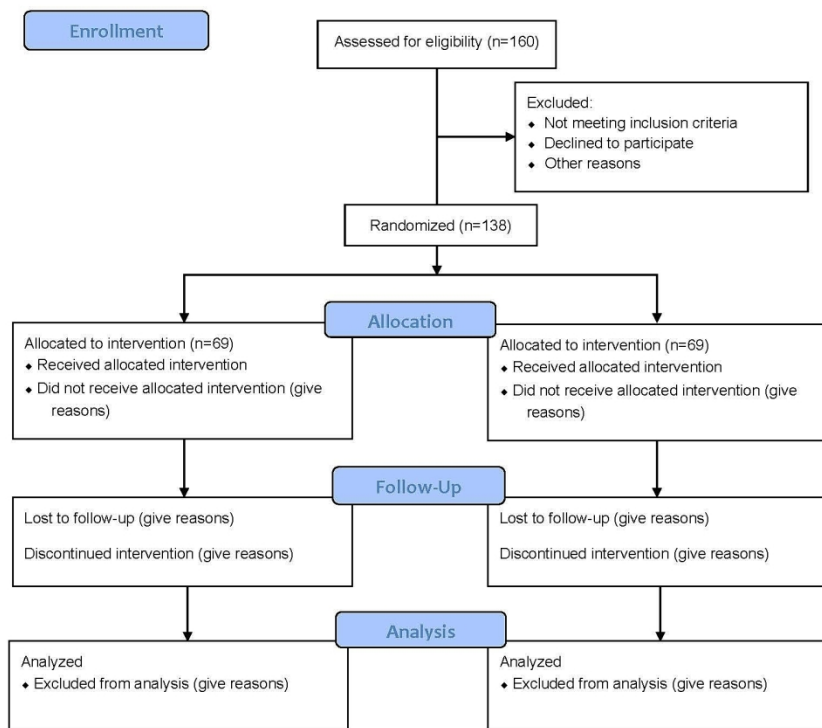


Figure 1. Study Design CONSORT Flow Diagram

143x186mm (300 x 300 DPI)

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Figure 2. Data Collection Schedule

|                                   | PreOp | D0 | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 | D15 | D16 | D17 | D18 | D19 | D20 | D21 | D/C |
|-----------------------------------|-------|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Eligibility                       |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Recruit                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Consent                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clinical Exam                     |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mFisher                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Hunt Hess                         |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EKG/ECHO                          | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pregnancy                         | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Randomise                         |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clofazolin/Placebo                |       |    | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   |     |     |     |     |     |     |     |     |
| Nimodipine                        |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| CT Scan                           |       | X  | X  |    |    |    |    |    | X  |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| DSA/CTA                           |       | X  |    |    |    |    |    |    | X  | X  | X  |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Colling                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| All AE                            |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mRS                               |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EVD (Y/N)                         |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Symptomatic Vasospasm? (Mark "Y") |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |

Figure 2. Data Collection Schedule & Timeline

181x117mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | _____1_____              |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | _____3_____              |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | _____n/a_____            |
| Protocol version                  | 3       | Date and version identifier  | _____3_____              |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____3_____              |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____11_____             |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____3_____              |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | _____11_____             |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | _____n/a_____            |

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant \_\_\_\_\_ 3, 4 \_\_\_\_\_

4 rationale studies (published and unpublished) examining benefits and harms for each intervention

5

6 6b Explanation for choice of comparators \_\_\_\_\_ 3, 4 \_\_\_\_\_

7

8 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 4, 5 \_\_\_\_\_

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), \_\_\_\_\_ 5 \_\_\_\_\_

11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will \_\_\_\_\_ 5 \_\_\_\_\_

17 be collected. Reference to where list of study sites can be obtained

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and \_\_\_\_\_ 5, 6 Table 1 \_\_\_\_\_

20 individuals who will perform the interventions (eg, surgeons, psychotherapists)

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be \_\_\_\_\_ 5, 6 \_\_\_\_\_

23 administered

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose \_\_\_\_\_ 5, 6 \_\_\_\_\_

26 change in response to harms, participant request, or improving/worsening disease)

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence \_\_\_\_\_ 9 \_\_\_\_\_

29 (eg, drug tablet return, laboratory tests)

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 5, 6 \_\_\_\_\_

32

33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

37 efficacy and harm outcomes is strongly recommended

38

39

40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for \_\_\_\_\_ 6, 7, 8, Figure 2\_ \_\_\_\_\_

41 participants. A schematic diagram is highly recommended (see Figure)

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|   |             |    |   |               |
|---|-------------|----|---|---------------|
| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | _____7_____   |
| 2 |             |    |   |               |
| 3 |             |    |   |               |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | _____n/a_____ |
| 5 |             |    |   |               |

### 6 **Methods: Assignment of interventions (for controlled trials)**

#### 7 Allocation:

|    |                    |     |  |             |
|----|--------------------|-----|--|-------------|
| 8  |                    |     |  |             |
| 9  |                    |     |  |             |
| 10 | Sequence           | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | _____5_____ |
| 11 | generation         |     |  |             |
| 12 |                    |     |  |             |
| 13 |                    |     |  |             |
| 14 |                    |     |  |             |
| 15 |                    |     |  |             |
| 16 | Allocation         | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | _____6_____ |
| 17 | concealment        |     |  |             |
| 18 | mechanism          |     |  |             |
| 19 |                    |     |  |             |
| 20 | Implementation     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | _____6_____ |
| 21 |                    |     |  |             |
| 22 |                    |     |  |             |
| 23 |                    |     |  |             |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | _____6_____ |
| 25 |                    |     |  |             |
| 26 |                    |     |  |             |
| 27 |                    | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | _____6_____ |
| 28 |                    |     |  |             |
| 29 |                    |     |  |             |
| 30 |                    |     |  |             |

### 31 **Methods: Data collection, management, and analysis**

|    |                 |     |  |                |
|----|-----------------|-----|--|----------------|
| 32 |                 |     |  |                |
| 33 | Data collection | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | _____8, 9_____ |
| 34 | methods         |     |  |                |
| 35 |                 |     |  |                |
| 36 |                 |     |  |                |
| 37 |                 |     |  |                |
| 38 |                 |     |  |                |
| 39 |                 | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | _____8_____    |
| 40 |                 |     |  |                |
| 41 |                 |     |  |                |
| 42 |                 |     |  |                |

|    |                                 |     |   |       |
|----|---------------------------------|-----|---|-------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | 8, 9  |
| 2  |                                 |     |   |       |
| 3  |                                 |     |   |       |
| 4  |                                 |     |   |       |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | 8, 9  |
| 6  |                                 |     |   |       |
| 7  |                                 |     |   |       |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8, 9  |
| 9  |                                 |     |   |       |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | 9     |
| 11 |                                 |     |   |       |
| 12 |                                 |     |   |       |
| 13 |                                 |     |   |       |
| 14 | <b>Methods: Monitoring</b>      |     |   |       |
| 15 |                                 |     |   |       |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 9, 10 |
| 17 |                                 |     |   |       |
| 18 |                                 |     |   |       |
| 19 |                                 |     |   |       |
| 20 |                                 |     |   |       |
| 21 |                                 |     |   |       |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | 9     |
| 23 |                                 |     |   |       |
| 24 |                                 |     |   |       |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | 6     |
| 26 |                                 |     |   |       |
| 27 |                                 |     |   |       |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 8, 9  |
| 29 |                                 |     |   |       |
| 30 |                                 |     |   |       |
| 31 |                                 |     |   |       |
| 32 | <b>Ethics and dissemination</b> |     |   |       |
| 33 |                                 |     |   |       |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 5, 10 |
| 35 |                                 |     |   |       |
| 36 |                                 |     |   |       |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | n/a   |
| 38 |                                 |     |   |       |
| 39 |                                 |     |   |       |
| 40 |                                 |     |   |       |
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| 42 |                                 |     |   |       |
| 43 |                                 |     |   |       |
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| 46 |                                 |     |   |       |



|    |                               |     |   |                 |
|----|-------------------------------|-----|---|-----------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | ___ 8, 9 ___    |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | ___ n/a ___     |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | ___ 6, 7, 8 ___ |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | ___ 11 ___      |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | ___ 10 ___      |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | ___ n/a ___     |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ___ 7 ___       |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | ___ 11 ___      |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | ___ n/a ___     |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | ___ n/a ___     |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | ___ n/a ___     |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| Manuscript ID                   | bmjopen-2019-036217.R2  |
| Article Type:                   | Protocol  |
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| Complete List of Authors:       | Dawley, Troy; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Claus, Chad; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Tong, Doris; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Rajamand, Sina; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Sigler, Diana; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Department of Pharmacy<br>Bahoura , Matthew; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Garmo, Lucas; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Soo, Teck; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Kelkar, Prashant; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Richards, Boyd; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery |
| <b>Primary Subject Heading</b>: | Surgery   |
| Secondary Subject Heading:      | Intensive care, Neurology, Pharmacology and therapeutics, Complementary medicine, Emergency medicine  |
| Keywords:                       | Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurology < INTERNAL MEDICINE, Stroke medicine < INTERNAL MEDICINE, Neurological injury < NEUROLOGY, Stroke < NEUROLOGY, NEUROSURGERY  |
|                                 |   |

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4 1 **Efficacy and Safety of Cilostazol-Nimodipine Combined**  
5 2 **Therapy on Delayed Cerebral Ischemia after Aneurysmal**  
6 3 **Subarachnoid Hemorrhage: A Prospective, Randomized,**  
7 4 **Double-Blinded, Placebo-Controlled Trial Protocol**  
8  
9  
10

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## 32 **Abstract**

## 33 **Introduction**

34 Delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS) remains the foremost  
35 contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH).  
36 Past efforts in preventing and treating DCI have failed to make any significant progress. To date,  
37 our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent  
38 studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cVS. Thus  
39 far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of DCI following  
40 aSAH.

## 41 **Methods and Analysis**

42 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial  
43 investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of  
44 delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of intensive care unit  
45 (ICU) stay, and long-term functional and quality of life outcomes will be recorded. All data will  
46 be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not  
47 only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both  
48 radiographic and symptomatic vasospasm with subsequent improvement in long-term functional  
49 and quality-of-life (QoL) outcomes when compared to nimodipine alone.

## 50 **Ethics and Dissemination**

51 Ethical approval was obtained at all participating hospitals by the Ascension Providence Hospital  
52 Institutional Review Board (IRB). The results of this study will be submitted for publication in  
53 peer-reviewed journals.

54  
55 **Trial registration number:** NCT04148105

## 60 Article Summary

### 61 Strengths and limitations of this study:

- 62 • First randomized controlled trial in the US to evaluate the effect of cilostazol and  
63 nimodipine on delayed cerebral ischemia and cerebral vasospasm
- 64 • Adequately powered study
- 65 • Includes both objective outcomes (DCI and angiographic vasospasm) and subjective  
66 patient-reported-outcomes.
- 67 • We limited the study population to anterior circulation aSAH, thereby limiting the  
68 generalizability of the results to other patient populations

69 **Title:** Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral  
70 Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-  
71 Blinded, Placebo-Controlled Trial

72 **FDA IND Application:** Approved on 4/5/2019 (FDA IND# 143368) for off-label use

73 **Trial Registration Number:** NCT04148105

74 **Study Dates:** November 2019 – October 2023

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76 Institutional Review Board (IRB)

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79 responsible for the protocol design, data collection, analysis and interpretation, writing of the  
80 report, or decision to submit this publication

81 **Investigators: Research Site:** Investigators and their subsequent roles are detailed in the  
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## 87 Introduction

88 Aneurysmal subarachnoid hemorrhage is a devastating condition which affects  
89 approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been  
90 made in the treatment of ruptured aneurysms, however, there has been little progress in the

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3 91 treatment and prevention of DCI due to cVS.[1,2] Cerebral vasospasm and subsequent DCI  
4  
5 92 remain to be the most prominent cause of morbidity and mortality following aSAH.[3] Although  
6  
7 93 the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital  
8  
9 94 underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3  
10  
11 95 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes  
12  
13 96 definitive treatment of the ruptured aneurysm through either open clipping or endovascular  
14  
15 97 therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a  
16  
17 98 dihydropyridine calcium channel blocker which is recommended for the postprocedural  
18  
19 100 improvement following aSAH.[7,10] Multiple other modalities have been investigated for the  
20  
21 101 treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation,  
22  
23 102 Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which  
24  
25 103 demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and  
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27 104 improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high  
28  
29 105 between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to  
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31 106 be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be  
32  
33 107 40% and 60%, respectively.

33 108 Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic  
34  
35 109 intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory  
36  
37 110 and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral  
38  
39 111 arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26]  
40  
41 112 Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both  
42  
43 113 radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30]  
44  
45 114 In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol  
46  
47 115 effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in  
48  
49 116 patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated  
50  
51 117 the combined application of nimodipine and cilostazol. This combination therapy of nimodipine  
52  
53 118 and cilostazol with possible synergistic effect require further investigation.[31]



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2  
3 119 Our randomized superiority trial seeks to investigate the combined effect of cilostazol  
4 plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when  
5 120 compared to nimodipine alone.  
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## 8 9 122 **Study Goals and Objectives**

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11  
12 123 Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine  
13 124 alone in the prevention of DCI in patients with aSAH.

### 15 16 125 **Primary Objective**

- 17  
18 126 • To demonstrate that the combined use of cilostazol plus nimodipine when compared to  
19 127 nimodipine alone will decrease the rate of DCI in patients following aSAH

### 22 23 128 **Secondary Objectives**

- 24  
25 129 • To demonstrate that the combined use of cilostazol plus nimodipine is not associated with  
26 130 increased drug-related serious adverse events
- 27  
28 131 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of  
29 132 symptomatic and radiographic vasospasm
- 30  
31 133 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
32 134 average length of ICU stay
- 33  
34 135 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
35 136 incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- 36  
37 137 • To demonstrate that the combined use of cilostazol plus nimodipine will improve  
38 138 Modified Rankin Scores (mRS) and QoL outcomes at 6-months.

## 42 43 139 **Methods and Analysis**

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45  
46 140 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in  
47 141 adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design  
48 142 without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow  
49 143 chart.  
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3 144 Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This  
4  
5 145 protocol was approved by the Ascension Providence Hospital IRB and published on  
6  
7 146 ClinicalTrials.gov.

8  
9 147 Over a three-year period, consecutive adult patients over the age of 18 who present to our  
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11 148 tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT  
12  
13 149 angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those  
14  
15 150 adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). Patients  
16  
17 151 with posterior circulation aSAH are known to be lower risk for developing symptomatic  
18  
19 152 vasospasm and were therefore excluded to avoid bias.[33] After satisfying inclusion/exclusion  
20  
21 153 criteria, patients/family members are consented for full participation in the trial. Once consented,  
22  
23 154 patients are randomized to receive either placebo or intervention with a centralized treatment  
24  
25 155 allocation mechanism and block randomization to assure the two arms achieve equal proportion  
26  
27 156 of patients over time.

28  
29 157 All patients, treatment providers, investigators, and statisticians are blinded to the allocation.  
30  
31 158 Blinding is achieved by allocation sequence being concealed to personnel involved in the  
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33 159 enrolling, care and evaluation of the patient. The study coordinator will keep the randomization  
34  
35 160 schedule in a cloud-based, secure and encrypted database. Only the study coordinator who  
36  
37 161 monitors the trial, the pharmacist who executes the allocation, the supervising investigator who  
38  
39 162 is not involved in the patients' care or enrollment will have access to the randomization schedule.  
40  
41 163 Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will  
42  
43 164 conceal the identity of the medications.

44  
45 165 All participating patients, after undergoing treatment of their ruptured aneurysm (open  
46  
47 166 clipping vs. endovascular coiling) and confirmation of a stable head CT 24-hours post-  
48  
49 167 intervention will be randomized and scheduled to receive their allocation within 48 hours of  
50  
51 168 surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients  
52  
53 169 will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed  
54  
55 170 by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in  
56  
57 171 Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in  
58  
59 172 the hospital, the patients are monitored frequently (every hour while in the ICU and every 4  
60  
173 172 hours while on the floor) for any adverse/serious adverse events (Table 3). Adverse and serious

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3 174 adverse events (SAE) are defined using a validated classification scheme (Table 4).[34] SAE are  
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5 175 defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the  
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7 176 study medication will be recorded and reported immediately to the principal investigator and the  
8  
9 177 IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in  
10  
11 178 which knowledge of the allocation will aid in the clinical management of the patient and  
12  
13 179 therefore warrant unblinding of the allocation.

14 180 The primary outcome will be defined as new ischemic areas on CT performed at 1-month  
15  
16 181 following initial presentation and not observed on postoperative CT (24-hours post-intervention)  
17  
18 182 determined by blinded neuroradiologists.[35] Ischemic areas or low-density areas on CT  
19  
20 183 performed the day after intervention will be defined as rupture-related or procedural-related  
21  
22 184 infarctions and/or brain injury (such as ventriculostomy tract, craniotomy changes, etc.).  
23  
24 185 Secondary outcomes including symptomatic vasospasm, angiographic vasospasm, length of ICU  
25  
26 186 stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively  
27  
28 187 collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of  
29  
30 188 symptomatic vasospasm will be collected and defined as development of a new focal or global  
31  
32 189 neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[36] which  
33  
34 190 was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications,  
35  
36 191 fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT  
37  
38 192 scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or  
39  
40 193 CTA.[14,37,38] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and  
41  
42 194 10 days postoperatively. Radiographic vasospasm will be defined as arterial narrowing not  
43  
44 195 attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of  
45  
46 196 stenosis compared to previous baseline CTA or DSA as determined by blinded  
47  
48 197 neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the  
49  
50 198 bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery  
51  
52 199 (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured.  
53  
54 200 Severity of the radiographic vasospasm will be categorized as none or mild (0%-25% decrease in  
55  
56 201 vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline),  
57  
58 202 or severe (greater than 50% decrease in vessel diameter from baseline). The most affected  
59  
60 203 segment will be used to determine severity of radiographic vasospasm.

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2  
3 204 To demonstrate superiority, an 80% power is used to minimize chances of false negatives.  
4  
5 205 Assuming a relative effect size of 15% with the use of cilostazol and a baseline rate of DCI of  
6  
7 206 50%, a total sample size was estimated to be 349 patients with an alpha of 0.05. In anticipation  
8  
9 207 for any unforeseen events and those lost to follow-up, we plan to enroll a total of 390 patients.

## 10 11 208 **Patient and Public Involvement**

12  
13 209 At the time of 1-month postoperative follow-up, patients or their families will be asked to  
14  
15 210 participate as study advisers in our data monitoring and safety committee. There will be 2-4  
16  
17 211 patient advisers at any given time during the study period, each with a term of 6 months. These  
18  
19 212 patient advisers will share their experience regarding the recruitment process, surgery, and  
20  
21 213 postoperative care in order to help ensure patient safety and satisfaction throughout the study.

## 22 23 214 **Trial Status**

24  
25 215 At the time of manuscript submission, the trial is ongoing.

## 26 27 28 216 **Safety Considerations**

29  
30 217 All study-related adverse events (AE) are recorded and reported immediately to the  
31  
32 218 principal investigator and subsequently to the IRB within 24 hours of the event as previously  
33  
34 219 stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional  
35  
36 220 data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical  
37  
38 221 safety of the study and review adverse events reported to the IRB to determine risk and benefits.  
39  
40 222 Any SAE related to the study medication represents a circumstance under which unblinding is  
41  
42 223 permissible in order to ensure the safety of the participant. At that time, the intervention will be  
43  
44 224 stopped, and any clinical intervention required at the discretion of the attending surgeon will  
45  
46 225 ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be  
47  
48 226 surgeons and related experts who will meet to review the results and any adverse events  
49  
50 227 biannually to evaluate study safety.

## 51 52 228 **Follow-up**

53 229 Postoperatively, patients will be followed according to the data collection schedule  
54  
55 230 (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome

231 and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled  
232 follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be  
233 designated at the discretion of the treating attending physician.

## 234 **Data Management and Statistical Analysis**

235 During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will  
236 observe all the steps of the intervention and data collection to ensure proper execution. The  
237 progress of data entry, follow-up and recruitment are logged and monitored regularly by the  
238 CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and  
239 the database will be maintained to within one week of the data collection. CRC will coordinate  
240 the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month  
241 and 6-months.

242 Comparability between groups will be evaluated by descriptive and univariate analyses.  
243 Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-  
244 value less than or equal to 0.05 will be considered statistically significant. Bonferroni's  
245 correction will be applied when appropriate. Descriptive statistics will be used in each arm for  
246 proportion who did not receive allocated intervention, lost to follow-up, excluded from primary  
247 analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses  
248 will be performed. An interim analysis will be conducted quarterly during the trial, i.e. after a  
249 total of 75, 150, and 250 patients have been enrolled. This is a superiority trial. Early  
250 discontinuation of the study will be dependent on overwhelming positive results for the primary  
251 outcome. We will discontinue the trial if we achieve  $p < 0.001$  threshold at the time of interim  
252 analysis.[39]

## 253 **Quality Assurance**

254 Standardized medication orders will conceal the treatment allocation. The study  
255 coordinator will be responsible for managing the quality of patient data recorded in the study. All  
256 participating research staff will be trained and given written copies of a standard operating  
257 procedure to ensure consistency during recruitment, consent, handling of data, and follow-up  
258 evaluation. The study coordinator along with the PI will check weekly the content of the forms  
259 and database to ensure accurate and timely entry. Compliance at all study timepoints including

1  
2  
3 260 enrollment, randomization, intervention, data, and outcome collection will be documented daily  
4  
5 261 on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered  
6  
7 262 into a cloud-based, secure and encrypted database by the research staff. Access to the database  
8  
9 263 will be restricted. Data validation tool has been embedded in the database. Data entered will  
10  
11 264 undergo monthly verification with the source document.

## 12 265 **Expected Outcome of the Study**

15 266 This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe  
16  
17 267 and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We  
18  
19 268 expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally,  
20  
21 269 we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and  
22  
23 270 radiographic vasospasm.

## 24 271 **Duration of the Project**

27 272 Given our institutional volume, we anticipate a study period of 1-3 years assuming 50%  
28  
29 273 of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment  
30  
31 274 and subject to discontinuation if all previously defined criteria are met.

## 32 275 **Project Management**

33  
34  
35 276 Neurosurgery staff will counsel and recruit subjects according to their initial screening to  
36  
37 277 participate in this trial. The neurosurgery staff will check for eligibility using inclusion and  
38  
39 278 exclusion criteria listed in Table 1. They will also explain the study principles, including the  
40  
41 279 detailed experimental in-hospital & postoperative protocol, investigational treatment, potential  
42  
43 280 risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed  
44  
45 281 in a cloud-based, secure, and encrypted database (see supplementary text). The designated lead  
46  
47 282 pharmacists will execute the randomized allocation assignment according to the block  
48  
49 283 randomization schedule to maintain masking of allocation. The neuroscience ICU charge nurse  
50  
51 284 will be responsible for overseeing and monitoring administration of the study medication. The  
52  
53 285 neuroscience trained intensive care nursing staff will administer the study medication to the  
54  
55 286 study participants. The PI and support staff will record all perioperative and postoperative data  
56  
57 287 including study-related adverse events. The study coordinator will ensure and maintain follow-up

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2  
3 288 visits for postoperative secondary outcomes. The neuroradiologists will evaluate and determine  
4  
5 289 primary and secondary outcomes of DCI and vasospasm, respectively. The clinical research  
6  
7 290 methodologist will function as the CRC, supervise the overall execution of the study, and  
8  
9 291 participate in the writing of the protocol and manuscript.

## 10 11 292 **Ethics and Dissemination**

12  
13 293 The study will be conducted according to the Helsinki Declaration[40], the NIH human  
14  
15 294 subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good  
16  
17 295 Clinical Practice.[41] This protocol is written following the SPIRIT 2013 guidelines and was  
18  
19 296 approved by Ascension Providence Hospital IRB. The results of this study will be submitted for  
20  
21 297 publication in peer-reviewed journals and the key findings will be presented at national  
22  
23 298 conferences.

## 24 25 299 **Author Contribution**

26  
27 300 TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this  
28  
29 301 trial including organization and execution over two hospital campuses. DS contributed to the  
30  
31 302 design and execution of the study drug protocol including randomization, blinding and placebo.  
32  
33 303 MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard  
34  
35 304 operating procedures, and maintaining quality assurance among study participants and their  
36  
37 305 subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT  
38  
39 306 contributed to the drafting of the original manuscript, participated in critically revising the  
40  
41 307 manuscript and agree to be accountable for all aspects of the work.

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44  
45 309 This trial is supported by the Ascension Providence Hospital Institutional research grant.

## 46 47 310 **Disclaimer**

48  
49 311 This project is not an industry-sponsored study. The investigators are solely responsible  
50  
51 312 for the protocol design, data collection, analysis and interpretation, writing of the report, or  
52  
53 313 decision to submit this publication.

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## 315 Competing Interests

316 None declared.

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**448 Figure Legend:**

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**450 Figure 1. Study Design CONSORT Flow Diagram****451 Figure 2. Data Collection Schedule & Timeline**

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**Table 1.** Inclusion, Exclusion, and Withdrawal Criteria

| Inclusion  | Exclusion   |
|--|---|
| 18 years of age or older   | Non-aneurysmal subarachnoid hemorrhage  |
| Anterior circulation aneurysm rupture  | Multiple ruptured aneurysms   |
| Patients who have undergone surgical intervention  | Patients with congestive heart failure  |
| Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan                     | Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)   |
| Consent to study participation   | Active pathological bleeding  |
|  | Allergy to cilostazol   |
|  | Positive pregnancy test   |
|  | Coagulopathy not caused by anti-coagulant use   |
|  | History of hemorrhagic complications (gastrointestinal bleeding, etc.)  |
|  | Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol  |
|  | Patients requiring anticoagulant treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm)  |
|  | <i>Exception:</i> patients who require the use of aspirin as determined by the staff member performing the coil embolization for thromboembolic event protection due to a small amount of coil extrusion from the aneurysm neck with be allowed to be included into the trial |
| <b>Criteria for discontinuing follow-up:</b>   |   |
| Subject wishing to terminate participation in the study at any time throughout his/her participation |   |
| CT, computed tomography  |   |

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**Table 2.** Standardized Treatment Regimen

| Location  | Treatment  |
|---|--|
| NSICU and floor   | <p data-bbox="453 352 727 384"><b>Intervention group:</b></p> <ul data-bbox="501 394 1393 632" style="list-style-type: none"> <li data-bbox="501 394 967 426">• 60 mg nimodipine Q4H for 21 days</li> <li data-bbox="501 436 967 468">• 100 mg cilostazol b.i.d. for 14 days</li> <li data-bbox="501 478 1393 510">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="501 520 1354 590">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="501 600 1227 632">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> <p data-bbox="453 642 662 674"><b>Control group:</b></p> <ul data-bbox="501 684 1393 913" style="list-style-type: none"> <li data-bbox="501 684 967 716">• 60mg nimodipine Q4H for 21 days</li> <li data-bbox="501 726 967 758">• Cilostazol placebo b.i.d. for 14 days</li> <li data-bbox="501 768 1393 800">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="501 810 1354 879">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="501 890 1227 921">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> |
| NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PO, post-operative; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography |  |

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**Table 3.** List of Adverse or Serious Adverse Events

| <b>Cilostazol</b>             |   | <b>Nimodipine</b>             |   |
|-------------------------------|---|-------------------------------|---|
| <b>Adverse events</b>         | Headache<br>Diarrhea<br>Abnormal Stools<br>Palpitations<br>Dizziness<br>Peripheral Edema<br>Dyspepsia<br>Abdominal pain<br>Tachycardia  | <b>Adverse events</b>         | Hypotension (mild)<br>Diarrhea<br>Dyspepsia<br>Rash<br>Headache<br>Flushing   |
| <b>Serious adverse events</b> | Hypotension<br>Bleeding<br>Stevens Johnson<br>Syndrome<br>Anaphylaxis<br>Hypersensitivity<br>Reaction<br>Leukopenia<br>Thrombocytopenia<br>Tachyarrhythmias<br>Myocardial<br>Infarction<br>Angina | <b>Serious adverse events</b> | Hypotension (severe)<br>EKG changes<br>CHF<br>Thromboembolism<br>Thrombocytopenia<br>Anemia<br>GI bleeding<br>Ileus<br>Intestinal obstruction |

EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal

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**Table 4.** Definition and Classification of Surgical Complications

| <b>Grade</b>   | <b>Definition</b>  |
|--|--|
| Grade 1  | Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions  |
| Grade 2  | Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.  |
| Grade 3  | Requiring surgical, endoscopic, or radiological intervention   |
| 3a)  | Intervention not under general anesthesia  |
| 3b)  | Intervention under general anesthesia  |
| Grade 4  | Life-threatening complication (including CNS complications)* requiring IC/ICU management   |
| 4a)  | Single organ dysfunction (including dialysis)  |
| 4b)  | Multiorgan dysfunction   |
| Grade 5  | Death of a patient   |
| Suffix   | If the patient suffers from a complication at the time of discharge, the suffix “d” is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication |
| *Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit |  |

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**Cilostazol-Nimodipine Randomized Controlled Trial (CONSORT Flow Diagram)**

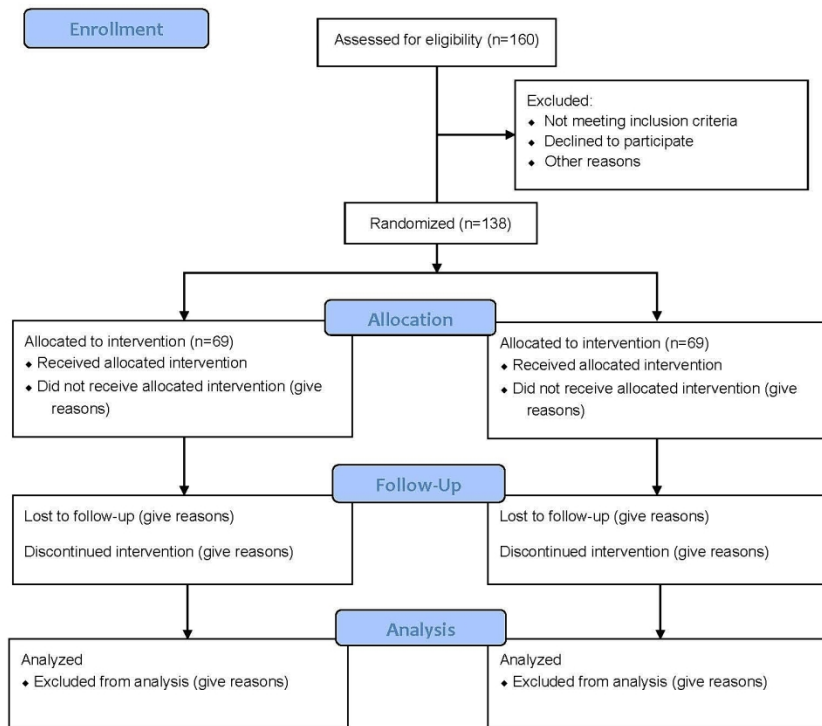


Figure 1. Study Design CONSORT Flow Diagram

143x186mm (300 x 300 DPI)



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Figure 2. Data Collection Schedule

|                                   | PreOp | D0 | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 | D15 | D16 | D17 | D18 | D19 | D20 | D21 | D/C |
|-----------------------------------|-------|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Eligibility                       |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Recruit                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Consent                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clinical Exam                     |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mFisher                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Hunt Hess                         |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EKG/ECHO                          | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pregnancy                         | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Randomise                         |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clofazolin/Placebo                |       |    | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   |     |     |     |     |     |     |     |     |
| Nimodipine                        |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| CT Scan                           |       | X  | X  |    |    |    |    |    | X  |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| DSA/CTA                           |       | X  |    |    |    |    |    |    | X  | X  | X  |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Colling                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| All AE                            |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mRS                               |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EVD (Y/N)                         |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Symptomatic Vasospasm? (Mark "Y") |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |

Figure 2. Data Collection Schedule & Timeline

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3 **Ascension Providence Hospital**  
4 **16001 West Nine Mile Road, Southfield, MI**  
5

6  
7 **CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY**

8 **AND**

9  
10 **AUTHORIZATION TO USE OR DISCLOSE PROTECTED HEALTH INFORMATION**  
11 **FOR RESEARCH TO BE CONDUCTED AT PROVIDENCE HOSPITAL,**  
12 **PROVIDENCE PARK HOSPITAL AND MEDICAL CENTERS**  
13

14  
15 **Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed**  
16 **Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage (SAH): A Multicenter,**  
17 **Randomized, Double-blinded, Placebo-controlled Trial**  
18

19 **Principal Investigator:**

20  
21  
22 Boyd Richards D.O. Neurological Surgery  
23

24 **Co-Investigators:**

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26  
27 Doris Tong, MD; Chad F. Claus; Sina Rajamand, DO; Ascher Kaufmann, MD; Troy Dawley,  
28 DO; Prashant Kelkar, DO; Teck M Soo, MD  
29

30 Office Phone: (248) 569-7745  
31

32  
33 Please read the following material to ensure that you are informed of the nature of this clinical  
34 research study and how you will participate in it. Signing this form will indicate that you have  
35 been informed and that you give your consent to participate in a free manner. Federal regulations  
36 require written informed consent prior to participation in this clinical research study.  
37

38 **INTRODUCTION**  
39

40  
41 This is an important form. Please read it carefully. It tells you what you need to know about this  
42 research study. If you agree to take part in this study, you need to sign this form. Your signature  
43 means that you have been told about the study and any applicable risks. Your signature on this  
44 form also means that you want to take part in this study. This is a randomized multi-center  
45 double-blinded controlled clinical trial. Your doctor will explain the clinical research study to  
46 you. Research studies or clinical trials only include people who choose to take part. Please take  
47 your time to make your decision about taking part. You may discuss your decision with your  
48 friends and family. You can also discuss it with your health care team. If you have any questions,  
49 you can ask your study doctor for more explanation.  
50

51  
52 You are being asked to take part in this research study because you recently underwent either a  
53 surgical or endovascular intervention for the treatment of intracranial hemorrhage and are being  
54 seen at Ascension Providence Hospital.  
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58 APH IRB Approved: 2/5/20-8/4/20  
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## BACKGROUND

This research study is designed to evaluate the effects of the combination between Cilostazol and Nimodipine on delayed cerebral ischemia due to cerebral vasospasm after anterior circulation aneurysmal subarachnoid hemorrhage. Cilostazol is a selective phosphodiesterase-3 inhibitor which exerts a vasodilatory and antithrombotic effect. Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postoperative treatment of aneurysmal subarachnoid hemorrhage. We seek to compare the incidence of delayed cerebral ischemia when treated with Cilostazol and Nimodipine versus when treated with Nimodipine alone. The researchers will compare two different groups. With your consent, you will be randomly assigned to a group who receives conventional post-intervention treatment with Nimodipine or to a group who receives conventional post-intervention treatment with Nimodipine in addition to 100mg Cilostazol twice daily for 14 days after your intervention. Your chances of being in one group are 1 in 2, much like flipping a coin. This is a double-blind study, which means neither you nor your doctor will know which group you are in until the study is completed.

Imaging will be taken 1 day after your intervention,  $7 \pm 2$  days after your intervention, approximately 1 month and 6 months after discharge as part of your standard of care. More imaging, including but not limited to CTA or MRI scans, may be needed depending on the individual care management plan.

## PURPOSE OF THE STUDY

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will decrease the rate of delayed cerebral ischemia during your hospital stay
- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will not lead to significant increase in bleeding disorders
- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone, will lead to significant improvement in the following:
  - The rates of symptomatic vasospasm
  - The rates of angiographic vasospasm
  - Quality-of-life outcomes: Modified Rankin Scores (mRS) at Pre, 1, 3 and 6 months postoperatively and SF-12 at 1, 3 and 6 months postoperatively
  - Length of hospitalization
  - Length of stay in the intensive care unit (ICU)
  - Duration of ventriculostomy use

### **How many people will take part in this study?**

Approximately 120 men and/or women of at least 18 years of age will be in this study.

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### **How long will I be in this study?**

You will participate in this study for 6 months. Your part in the study is completed once you have completed your 6-month follow-up visit with your surgeon including completion of the modified Rankin Scores and SF-12 questionnaires.

### **What will happen if I take part in this research study?**

You have recently undergone either a surgical or endovascular intervention for the treatment of intracranial hemorrhage and your surgeon has determined that you meet eligibility criteria to participate in this research study.

After your enrollment, you will receive the necessary post-intervention care. If you are randomly selected into the treatment group, you will receive the drug Cilostazol in addition to your standard care regimen. If you are not, you will receive the standard care regimen plus a placebo. However, your knowledge of which group you are assigned to, as well as the administration of that drug will not be known to you. Throughout your hospital stay, data will be collected including any Cilostazol-related adverse events, occurrence of symptomatic vasospasm, and length of stay, among others. This all will be collected from either your electronic medical record or directly from you by a blinded member our staff. You will follow-up in clinic with your surgeon for standard post-interventional evaluation which includes 1, 3, and 6-month follow-up visit along with completion of modified Rankin Score and SF-12 questionnaires.

### **Risk to patients**

Important risks and side effects of 100mg Cilostazol may include:

Frequent side effects:

- Headche
- Abnormal stools
- Diarrhea

Infrequent side effects:

- Abdominal pain
- Back pain
- Infection
- Palpitation
- Tachycardia
- Flatulence
- Nausea
- Peripheral edema
- Myalgia
- Dizziness
- Cough increased
- Pharyngitis
- Rhinitis

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Rare side effects:

- Chills
- Vertigo
- Other rare side effects

***Frequent (occurs in 10-25% of people – 10 to 25 out of 100 people)***

***Infrequent (occurs in 1-10% of people – 1 to 10 out of 100 people)***

***Rare (occurs in less than 1% of people – less than 1 out of 100 people)***

Every effort will be made to minimize any discomfort and these risks. There may be other risks that are unknown at this time.

You should tell the person obtaining your consent if you are currently participating in any other medical research studies.

### **What are the benefits of the study?**

There may be no direct benefit to you in participating in the study. However, it is possible that you may have less chance of delayed cerebral ischemia or symptomatic and angiographic cerebral vasospasm following your surgery. You may also experience an improvement in postoperative quality-of-life. In the future, other patients may benefit from the results of this study, when they become known.

### **What other options are there?**

One option is to not participate. You do not have to participate in this research study in order to continue receiving treatment for your condition. Electing to not participate in this study will not affect your care whatsoever.

### **Do I have to participate in this study?**

Your participation in this study is voluntary. Your refusal to participate will cause no penalty or loss of benefits which you would otherwise receive. If you decide to participate, you may change your mind about being in the study and may quit at any time without penalty of loss of benefits regarding your future care. If new information becomes available during the study that may affect your willingness to continue in the study, your doctor and/or his/her associate will discuss this information with you. Also, your doctor may stop your participation at any time if he/she feels it is in your best interest.

### **Will it cost anything to participate?**

We do not expect there to be any additional costs to you if you participate in this study. Besides the drug treatment, the additional care you would receive during this study is considered standard of care and would not otherwise be different.

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### **Compensation to patients – None**

There is no compensation or pay offered for your medical care if you are injured as a result of participating in this study. You and/or your medical insurance may have to pay for your medical care if you are injured as a result of participating in this study. You are not giving up any of your legal rights by signing this consent form.

### **Confidentiality of Records**

The principal investigators will have access to your medical records and your test results. While absolute confidentiality cannot be guaranteed, all research material which could identify you will be kept as confidential as possible within the state and federal laws. You should be aware that your medical records could be examined by the study staff, the Institutional Review Board (a group of people who review the research to protect your rights), or government agencies in order to verify the data collected during this research study. If the results of this study are presented in any public forum, you will not be personally identified.

### **Participant HIPAA Authorization to Use and Disclose Protected Health Information (PHI)**

Your participation in this study will require the use and disclosure of certain medical and other information about you. The information that may be used or disclosed includes any and all health care records such as: laboratory, pathology and/or radiology results, CT scans, MRI, and Protected Health Information (PHI) previously collected for research purposes.

Your PHI will be used in the following ways: To conduct the research and to ensure that the research meets legal, institutional or accreditation requirements.

Your authorization to use and disclose the above information has no expiration date.

Your PHI may be seen, used or disclosed to the following:

- The researchers and members of the research team
- Other health care providers or employees of Ascension Providence Hospital
- Representatives of the Institutional Review Board (IRB), the FDA (Food and Drug Administration), or other governmental agencies involved in research monitoring.
- Other agencies as required by law.

You have the right to review your PHI. However, if you agree to participate in the research study and sign below, you will not be able to look at your research information until the research study is completed.

You do not have to sign this authorization. If you decide not to sign the authorization it will not affect your treatment or eligibility for health benefits. However, if you do not sign this authorization you may not participate in this study.

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3 You may withdraw your authorization at any time by notifying the principal investigator in  
4 writing, but the withdrawal will not affect any information already disclosed. However, you need  
5 to be aware that your written withdrawal of this Authorization may result in the termination of  
6 the research-related treatment being provided to you.  
7

8  
9 This study and more information will be available at ClinicalTrials.gov which is a registry and  
10 results database of publicly and privately supported research studies conducted in the United  
11 States and around the world. Sponsors or investigators of certain clinical trials are required by  
12 U.S. law to register their trials on and submit summary results to ClinicalTrials.gov. Each study  
13 record includes a summary of the study protocol, including the purpose, recruitment status, and  
14 eligibility criteria. Study locations and specific contact information are listed to assist with  
15 enrollment. You can visit ClinicalTrials.gov for more information regarding this study.  
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17

### 18 **Who do I call with questions about the study or to report an injury?**

19  
20 If you have any questions regarding a research-related injury, you can contact:  
21 Troy Dawley, DO  
22 [22250 Providence Dr Ste 601, Southfield, MI 48075](mailto:Troy.Dawley@Ascension.org)  
23 (214) 886-6111  
24  
25

26 If you have any questions about your rights as a subject in this clinical research study, you may  
27 contact the IRB representative at 248-849-8889 at Ascension Providence Hospital.  
28

### 29 **CONSENT**

30  
31 You have had the opportunity to fully discuss the purpose of this clinical research study  
32 and how it will be carried out. Your questions have been answered. Your participation in  
33 this study is fully voluntary and you may withdraw at any time.  
34  
35

36  
37 Your signature below acknowledges that you voluntarily agree to participate in this  
38 clinical research study, and you will receive a signed copy of this form.  
39  
40  
41

42  
43 \_\_\_\_\_  
44 Printed Name of Research Subject  
45  
46

47  
48 \_\_\_\_\_  
49 Signature of Research Subject  
50  
51

52  
53 \_\_\_\_\_  
54 Date  
55  
56  
57

58 APH IRB Approved: 2/5/20-8/4/20  
59

**Legally Authorized Representative (if applicable):**

\_\_\_\_\_  
 Printed Name of Legally Authorized Representative

\_\_\_\_\_  
 Signature of Legally Authorized Representative

\_\_\_\_\_  
 Date

Check Relationship to Subject:\*

Legal Guardian or Legally Authorized Representative for Medical Care (LARM)

Spouse

Adult Son or Daughter    Mother or Father    Adult Brother or Sister    Other,  
 explain:

Reason subject is unable to sign for self:

*\*If a Legal Guardian or Legally Authorized Representative for Medical Care (LARM) has not been appointed, then consent should be obtained from the closest next of kin (in the order listed above). When that individual is unavailable or refuses to act the next in order should be contacted.*

*\* If there is a disagreement among next of kin regarding the appropriateness of the treatment plan, Clinical Safety Risk Management may be contacted. Outside of business hours, Clinical Safety Risk Management can be contacted through any St. John Hospital operator.*

\_\_\_\_\_  
 Printed Name of Person Obtaining Consent

\_\_\_\_\_  
 Signature of Person Obtaining Consent

\_\_\_\_\_  
 Date





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | _____1_____              |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | _____3_____              |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | _____n/a_____            |
| Protocol version                  | 3       | Date and version identifier  | _____3_____              |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____3_____              |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____11_____             |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____3_____              |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | _____11_____             |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | _____n/a_____            |

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention \_\_\_\_\_ 3, 4 \_\_\_\_\_

4

5

6 6b Explanation for choice of comparators \_\_\_\_\_ 3, 4 \_\_\_\_\_

7

8 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 4, 5 \_\_\_\_\_

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_\_\_ 5 \_\_\_\_\_

11

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained \_\_\_\_\_ 5 \_\_\_\_\_

17

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) \_5, 6 Table 1\_ \_\_\_\_\_

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered \_\_\_\_\_ 5, 6 \_\_\_\_\_

23

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) \_\_\_\_\_ 5, 6 \_\_\_\_\_

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) \_\_\_\_\_ 9 \_\_\_\_\_

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 5, 6 \_\_\_\_\_

32

33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

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39

40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) \_6, 7, 8, Figure 2\_ \_\_\_\_\_

41

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43

44

45

46

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including \_\_\_\_\_7\_\_\_\_\_

2 clinical and statistical assumptions supporting any sample size calculations

3

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size \_\_\_\_\_n/a\_\_\_\_\_

5

6 **Methods: Assignment of interventions (for controlled trials)**

7

8 Allocation:

9

10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any \_\_\_\_\_5\_\_\_\_\_

11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction

12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants

13 or assign interventions

14

15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, \_\_\_\_\_6\_\_\_\_\_

17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

18 mechanism

19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to \_\_\_\_\_6\_\_\_\_\_

21 interventions

22

23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome \_\_\_\_\_6\_\_\_\_\_

25 assessors, data analysts), and how

26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's \_\_\_\_\_6\_\_\_\_\_

28 allocated intervention during the trial

29

30

31 **Methods: Data collection, management, and analysis**

32

33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related \_\_\_\_\_8, 9\_\_\_\_\_

34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of

35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.

36 Reference to where data collection forms can be found, if not in the protocol

37

38

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_8\_\_\_\_\_

40 collected for participants who discontinue or deviate from intervention protocols

41

42

|    |                                 |     |   |       |
|----|---------------------------------|-----|---|-------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | 8, 9  |
| 2  |                                 |     |   |       |
| 3  |                                 |     |   |       |
| 4  |                                 |     |   |       |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | 8, 9  |
| 6  |                                 |     |   |       |
| 7  |                                 |     |   |       |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8, 9  |
| 9  |                                 |     |   |       |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | 9     |
| 11 |                                 |     |   |       |
| 12 |                                 |     |   |       |
| 13 |                                 |     |   |       |
| 14 | <b>Methods: Monitoring</b>      |     |   |       |
| 15 |                                 |     |   |       |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 9, 10 |
| 17 |                                 |     |   |       |
| 18 |                                 |     |   |       |
| 19 |                                 |     |   |       |
| 20 |                                 |     |   |       |
| 21 |                                 |     |   |       |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | 9     |
| 23 |                                 |     |   |       |
| 24 |                                 |     |   |       |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | 6     |
| 26 |                                 |     |   |       |
| 27 |                                 |     |   |       |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 8, 9  |
| 29 |                                 |     |   |       |
| 30 |                                 |     |   |       |
| 31 |                                 |     |   |       |
| 32 | <b>Ethics and dissemination</b> |     |   |       |
| 33 |                                 |     |   |       |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 5, 10 |
| 35 |                                 |     |   |       |
| 36 |                                 |     |   |       |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | n/a   |
| 38 |                                 |     |   |       |
| 39 |                                 |     |   |       |
| 40 |                                 |     |   |       |
| 41 |                                 |     |   |       |
| 42 |                                 |     |   |       |
| 43 |                                 |     |   |       |
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| 46 |                                 |     |   |       |

|    |                               |     |   |                 |
|----|-------------------------------|-----|---|-----------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | ___ 8, 9 ___    |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | ___ n/a ___     |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | ___ 6, 7, 8 ___ |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | ___ 11 ___      |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | ___ 10 ___      |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | ___ n/a ___     |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ___ 7 ___       |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | ___ 11 ___      |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | ___ n/a ___     |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | ___ n/a ___     |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | ___ n/a ___     |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
 40  
 41  
 42

# BMJ Open

## Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| Manuscript ID                   | bmjopen-2019-036217.R3  |
| Article Type:                   | Protocol  |
| Date Submitted by the Author:   | 28-Jul-2020   |
| Complete List of Authors:       | Dawley, Troy; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Claus, Chad; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Tong, Doris; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Rajamand, Sina; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Sigler, Diana; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Department of Pharmacy<br>Bahoura , Matthew; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Garmo, Lucas; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Soo, Teck; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Kelkar, Prashant; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery<br>Richards, Boyd; Ascension Providence Hospital, Michigan State University, College of Human Medicine, Division of Neurosurgery |
| <b>Primary Subject Heading</b>: | Surgery   |
| Secondary Subject Heading:      | Intensive care, Neurology, Pharmacology and therapeutics, Complementary medicine, Emergency medicine  |
| Keywords:                       | Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Neurology < INTERNAL MEDICINE, Stroke medicine < INTERNAL MEDICINE, Neurological injury < NEUROLOGY, Stroke < NEUROLOGY, NEUROSURGERY  |
|                                 |   |

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3  
4 1 **Efficacy and Safety of Cilostazol-Nimodipine Combined**  
5 2 **Therapy on Delayed Cerebral Ischemia after Aneurysmal**  
6 3 **Subarachnoid Hemorrhage: A Prospective, Randomized,**  
7 4 **Double-Blinded, Placebo-Controlled Trial Protocol**  
8  
9  
10

11 5 Troy Dawley DO,<sup>1</sup> \*Chad F. Claus DO,<sup>1</sup> Doris Tong MD,<sup>1</sup> Sina Rajamand DO,<sup>1</sup> Diana Sigler  
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26 16 **Attn: Ascension Providence Hospital Graduate Medical Education**  
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## 32 **Abstract**

## 33 **Introduction**

34 Delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS) remains the foremost  
35 contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH).  
36 Past efforts in preventing and treating DCI have failed to make any significant progress. To date,  
37 our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent  
38 studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cVS. Thus  
39 far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of DCI following  
40 aSAH.

## 41 **Methods and Analysis**

42 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial  
43 investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of  
44 delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of intensive care unit  
45 (ICU) stay, and long-term functional and quality of life outcomes will be recorded. All data will  
46 be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not  
47 only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both  
48 radiographic and symptomatic vasospasm with subsequent improvement in long-term functional  
49 and quality-of-life (QoL) outcomes when compared to nimodipine alone.

## 50 **Ethics and Dissemination**

51 Ethical approval was obtained at all participating hospitals by the Ascension Providence Hospital  
52 Institutional Review Board (IRB). The results of this study will be submitted for publication in  
53 peer-reviewed journals.

54  
55 **Trial registration number:** NCT04148105

## 60 **Article Summary**

### 61 **Strengths and limitations of this study:**

- 62 • First randomized controlled trial in the US to evaluate the effect of cilostazol and  
63 nimodipine on delayed cerebral ischemia and cerebral vasospasm
- 64 • Adequately powered study
- 65 • Includes both objective outcomes (DCI and angiographic vasospasm) and subjective  
66 patient-reported-outcomes.
- 67 • We limited the study population to anterior circulation aSAH, thereby limiting the  
68 generalizability of the results to other patient populations

69 **Title:** Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral  
70 Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-  
71 Blinded, Placebo-Controlled Trial

72 **FDA IND Application:** Approved on 4/5/2019 (FDA IND# 143368) for off-label use

73 **Trial Registration Number:** NCT04148105

74 **Study Dates:** November 2019 – October 2023

75 **Institutional Approvals:** The protocol was approved by the Ascension Providence Hospital  
76 Institutional Review Board (IRB)

77 **Funding Agency:** This study is supported by the Ascension Providence Hospital Institutional  
78 research grant (1478832-5). This project is not an industry-sponsored study. The investigators  
79 are solely responsible for the protocol design, data collection, analysis and interpretation, writing  
80 of the report, or decision to submit this publication

81 **Investigators: Research Site:** Investigators and their subsequent roles are detailed in the  
82 authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital,  
83 Michigan State University, College of Human Medicine  
84 Southfield, MI 48075

85 248-849-3403

86

## 87 **Introduction**

88 Aneurysmal subarachnoid hemorrhage is a devastating condition which affects  
89 approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been  
90 made in the treatment of ruptured aneurysms, however, there has been little progress in the

1  
2  
3 91 treatment and prevention of DCI due to cVS.[1,2] Cerebral vasospasm and subsequent DCI  
4  
5 92 remain to be the most prominent cause of morbidity and mortality following aSAH.[3] Although  
6  
7 93 the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital  
8  
9 94 underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3  
10  
11 95 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes  
12  
13 96 definitive treatment of the ruptured aneurysm through either open clipping or endovascular  
14  
15 97 therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a  
16  
17 98 dihydropyridine calcium channel blocker which is recommended for the postprocedural  
18  
19 99 treatment of aSAH for the prevention of DCI.[8,9] This regimen has shown long-term outcome  
20  
21 100 improvement following aSAH.[7,10] Multiple other modalities have been investigated for the  
22  
23 101 treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation,  
24  
25 102 Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which  
26  
27 103 demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and  
28  
29 104 improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high  
30  
31 105 between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to  
32  
33 106 be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be  
34  
35 107 40% and 60%, respectively.

33 108 Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic  
34  
35 109 intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory  
36  
37 110 and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral  
38  
39 111 arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26]  
40  
41 112 Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both  
42  
43 113 radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30]  
44  
45 114 In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol  
46  
47 115 effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in  
48  
49 116 patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated  
50  
51 117 the combined application of nimodipine and cilostazol. This combination therapy of nimodipine  
52  
53 118 and cilostazol with possible synergistic effect require further investigation.[31]

1  
2  
3 119 Our randomized superiority trial seeks to investigate the combined effect of cilostazol  
4 plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when  
5 120 compared to nimodipine alone.  
6  
7 121

## 8 9 122 **Study Goals and Objectives**

10  
11  
12 123 Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine  
13 124 alone in the prevention of DCI in patients with aSAH.

### 15 16 125 **Primary Objective**

- 17  
18 126 • To demonstrate that the combined use of cilostazol plus nimodipine when compared to  
19 127 nimodipine alone will decrease the rate of DCI in patients following aSAH

### 22 23 128 **Secondary Objectives**

- 24  
25 129 • To demonstrate that the combined use of cilostazol plus nimodipine is not associated with  
26 130 increased drug-related serious adverse events
- 27  
28 131 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of  
29 132 symptomatic and radiographic vasospasm
- 30  
31 133 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
32 134 average length of ICU stay
- 33  
34 135 • To demonstrate that the combined use of cilostazol plus nimodipine will decrease the  
35 136 incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- 36  
37 137 • To demonstrate that the combined use of cilostazol plus nimodipine will improve  
38 138 Modified Rankin Scores (mRS) and QoL outcomes at 6-months.

## 42 43 139 **Methods and Analysis**

44  
45  
46 140 This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in  
47 141 adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design  
48 142 without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow  
49 143 chart.  
50  
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1  
2  
3 144 Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This  
4  
5 145 protocol was approved by the Ascension Providence Hospital IRB and published on  
6  
7 146 ClinicalTrials.gov.

8  
9 147 Over a three-year period, consecutive adult patients over the age of 18 who present to our  
10  
11 148 tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT  
12  
13 149 angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those  
14  
15 150 adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). Patients  
16  
17 151 with posterior circulation aSAH are known to be lower risk for developing symptomatic  
18  
19 152 vasospasm and were therefore excluded to avoid bias.[33] After satisfying inclusion/exclusion  
20  
21 153 criteria, patients/family members are consented for full participation in the trial. Once consented,  
22  
23 154 patients are randomized to receive either placebo or intervention with a centralized treatment  
24  
25 155 allocation mechanism and block randomization to assure the two arms achieve equal proportion  
26  
27 156 of patients over time.

28  
29 157 All patients, treatment providers, investigators, and statisticians are blinded to the allocation.  
30  
31 158 Blinding is achieved by allocation sequence being concealed to personnel involved in the  
32  
33 159 enrolling, care and evaluation of the patient. The study coordinator will keep the randomization  
34  
35 160 schedule in a cloud-based, secure and encrypted database. Only the study coordinator who  
36  
37 161 monitors the trial, the pharmacist who executes the allocation, the supervising investigator who  
38  
39 162 is not involved in the patients' care or enrollment will have access to the randomization schedule.  
40  
41 163 Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will  
42  
43 164 conceal the identity of the medications.

44  
45 165 All participating patients, after undergoing treatment of their ruptured aneurysm (open  
46  
47 166 clipping vs. endovascular coiling) and confirmation of a stable head CT 24-hours post-  
48  
49 167 intervention will be randomized and scheduled to receive their allocation within 48 hours of  
50  
51 168 surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients  
52  
53 169 will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed  
54  
55 170 by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in  
56  
57 171 Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in  
58  
59 172 the hospital, the patients are monitored frequently (every hour while in the ICU and every 4  
60  
173 173 hours while on the floor) for any adverse/serious adverse events (Table 3). Adverse and serious

1  
2  
3 174 adverse events (SAE) are defined using a validated classification scheme (Table 4).[34] SAE are  
4  
5 175 defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the  
6  
7 176 study medication will be recorded and reported immediately to the principal investigator and the  
8  
9 177 IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in  
10  
11 178 which knowledge of the allocation will aid in the clinical management of the patient and  
12  
13 179 therefore warrant unblinding of the allocation.

14 180 The primary outcome will be defined as new ischemic areas on CT performed at 1-month  
15  
16 181 following initial presentation and not observed on postoperative CT (24-hours post-intervention)  
17  
18 182 determined by blinded neuroradiologists.[35] Ischemic areas or low-density areas on CT  
19  
20 183 performed the day after intervention will be defined as rupture-related or procedural-related  
21  
22 184 infarctions and/or brain injury (such as ventriculostomy tract, craniotomy changes, etc.).  
23  
24 185 Secondary outcomes including symptomatic vasospasm, angiographic vasospasm, length of ICU  
25  
26 186 stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively  
27  
28 187 collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of  
29  
30 188 symptomatic vasospasm will be collected and defined as development of a new focal or global  
31  
32 189 neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[36] which  
33  
34 190 was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications,  
35  
36 191 fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT  
37  
38 192 scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or  
39  
40 193 CTA.[14,37,38] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and  
41  
42 194 10 days postoperatively. Radiographic vasospasm will be defined as arterial narrowing not  
43  
44 195 attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of  
45  
46 196 stenosis compared to previous baseline CTA or DSA as determined by blinded  
47  
48 197 neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the  
49  
50 198 bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery  
51  
52 199 (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured.  
53  
54 200 Severity of the radiographic vasospasm will be categorized as none or mild (0%-25% decrease in  
55  
56 201 vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline),  
57  
58 202 or severe (greater than 50% decrease in vessel diameter from baseline). The most affected  
59  
60 203 segment will be used to determine severity of radiographic vasospasm.



1  
2  
3 204 To demonstrate superiority, an 80% power is used to minimize chances of false negatives.  
4  
5 205 Assuming a relative effect size of 29% with the use of cilostazol and a baseline rate of DCI of  
6  
7 206 50%, a total sample size was estimated to be 100 patients with an alpha of 0.05. In anticipation  
8  
9 207 for any unforeseen events and those lost to follow-up, we plan to enroll a total of 120 patients.

## 10 11 208 **Patient and Public Involvement**

12  
13 209 At the time of 1-month postoperative follow-up, patients or their families will be asked to  
14  
15 210 participate as study advisers in our data monitoring and safety committee. There will be 2-4  
16  
17 211 patient advisers at any given time during the study period, each with a term of 6 months. These  
18  
19 212 patient advisers will share their experience regarding the recruitment process, surgery, and  
20  
21 213 postoperative care in order to help ensure patient safety and satisfaction throughout the study.

## 22 23 214 **Trial Status**

24  
25 215 At the time of manuscript submission, the trial is ongoing.

## 26 27 28 216 **Safety Considerations**

29  
30 217 All study-related adverse events (AE) are recorded and reported immediately to the  
31  
32 218 principal investigator and subsequently to the IRB within 24 hours of the event as previously  
33  
34 219 stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional  
35  
36 220 data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical  
37  
38 221 safety of the study and review adverse events reported to the IRB to determine risk and benefits.  
39  
40 222 Any SAE related to the study medication represents a circumstance under which unblinding is  
41  
42 223 permissible in order to ensure the safety of the participant. At that time, the intervention will be  
43  
44 224 stopped, and any clinical intervention required at the discretion of the attending surgeon will  
45  
46 225 ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be  
47  
48 226 surgeons and related experts who will meet to review the results and any adverse events  
49  
50 227 biannually to evaluate study safety.

## 51 52 228 **Follow-up**

53 229 Postoperatively, patients will be followed according to the data collection schedule  
54  
55 230 (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome



231 and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled  
232 follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be  
233 designated at the discretion of the treating attending physician.

## 234 **Data Management and Statistical Analysis**

235 During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will  
236 observe all the steps of the intervention and data collection to ensure proper execution. The  
237 progress of data entry, follow-up and recruitment are logged and monitored regularly by the  
238 CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and  
239 the database will be maintained to within one week of the data collection. CRC will coordinate  
240 the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month  
241 and 6-months.

242 Comparability between groups will be evaluated by descriptive and univariate analyses.  
243 Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-  
244 value less than or equal to 0.05 will be considered statistically significant. Bonferroni's  
245 correction will be applied when appropriate. Descriptive statistics will be used in each arm for  
246 proportion who did not receive allocated intervention, lost to follow-up, excluded from primary  
247 analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses  
248 will be performed. An interim analysis will be conducted quarterly during the trial, i.e. after a  
249 total of 75, 150, and 250 patients have been enrolled. This is a superiority trial. Early  
250 discontinuation of the study will be dependent on overwhelming positive results for the primary  
251 outcome. We will discontinue the trial if we achieve  $p < 0.001$  threshold at the time of interim  
252 analysis.[39]

## 253 **Quality Assurance**

254 Standardized medication orders will conceal the treatment allocation. The study  
255 coordinator will be responsible for managing the quality of patient data recorded in the study. All  
256 participating research staff will be trained and given written copies of a standard operating  
257 procedure to ensure consistency during recruitment, consent, handling of data, and follow-up  
258 evaluation. The study coordinator along with the PI will check weekly the content of the forms  
259 and database to ensure accurate and timely entry. Compliance at all study timepoints including

1  
2  
3 260 enrollment, randomization, intervention, data, and outcome collection will be documented daily  
4  
5 261 on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered  
6  
7 262 into a cloud-based, secure and encrypted database by the research staff. Access to the database  
8  
9 263 will be restricted. Data validation tool has been embedded in the database. Data entered will  
10  
11 264 undergo monthly verification with the source document.

## 12 265 **Expected Outcome of the Study**

15 266 This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe  
16  
17 267 and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We  
18  
19 268 expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally,  
20  
21 269 we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and  
22  
23 270 radiographic vasospasm.

## 24 271 **Duration of the Project**

27 272 Given our institutional volume, we anticipate a study period of 1-3 years assuming 50%  
28  
29 273 of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment  
30  
31 274 and subject to discontinuation if all previously defined criteria are met.

## 32 275 **Project Management**

33  
34  
35 276 Neurosurgery staff will counsel and recruit subjects according to their initial screening to  
36  
37 277 participate in this trial. The neurosurgery staff will check for eligibility using inclusion and  
38  
39 278 exclusion criteria listed in Table 1. They will also explain the study principles, including the  
40  
41 279 detailed experimental in-hospital & postoperative protocol, investigational treatment, potential  
42  
43 280 risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed  
44  
45 281 in a cloud-based, secure, and encrypted database (see supplementary text). The designated lead  
46  
47 282 pharmacists will execute the randomized allocation assignment according to the block  
48  
49 283 randomization schedule to maintain masking of allocation. The neuroscience ICU charge nurse  
50  
51 284 will be responsible for overseeing and monitoring administration of the study medication. The  
52  
53 285 neuroscience trained intensive care nursing staff will administer the study medication to the  
54  
55 286 study participants. The PI and support staff will record all perioperative and postoperative data  
56  
57 287 including study-related adverse events. The study coordinator will ensure and maintain follow-up

288 visits for postoperative secondary outcomes. The neuroradiologists will evaluate and determine  
289 primary and secondary outcomes of DCI and vasospasm, respectively. The clinical research  
290 methodologist will function as the CRC, supervise the overall execution of the study, and  
291 participate in the writing of the protocol and manuscript.

## 292 **Ethics and Dissemination**

293 The study will be conducted according to the Helsinki Declaration[40], the NIH human  
294 subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good  
295 Clinical Practice.[41] This protocol is written following the SPIRIT 2013 guidelines and was  
296 approved by Ascension Providence Hospital IRB. The results of this study will be submitted for  
297 publication in peer-reviewed journals and the key findings will be presented at national  
298 conferences.

## 299 **Author Contribution**

300 TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this  
301 trial including organization and execution over two hospital campuses. DS contributed to the  
302 design and execution of the study drug protocol including randomization, blinding and placebo.  
303 MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard  
304 operating procedures, and maintaining quality assurance among study participants and their  
305 subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT  
306 contributed to the drafting of the original manuscript, participated in critically revising the  
307 manuscript and agree to be accountable for all aspects of the work.

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## 311 **Disclaimer**

312 This project is not an industry-sponsored study. The investigators are solely responsible  
313 for the protocol design, data collection, analysis and interpretation, writing of the report, or  
314 decision to submit this publication.

315

316 **Competing Interests**

317 None declared.

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40 446 *Transnational Economic Governance Regimes*. Brill 2009. 1041–54.  
41 447 doi:10.1163/ej.9789004163300.i-1081.897

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**Figure Legend:**

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451 **Figure 1. Study Design CONSORT Flow Diagram**452 **Figure 2. Data Collection Schedule & Timeline**

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**Table 1.** Inclusion, Exclusion, and Withdrawal Criteria

| Inclusion  | Exclusion   |
|--|---|
| 18 years of age or older   | Non-aneurysmal subarachnoid hemorrhage  |
| Anterior circulation aneurysm rupture  | Multiple ruptured aneurysms   |
| Patients who have undergone surgical intervention  | Patients with congestive heart failure  |
| Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan                     | Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)   |
| Consent to study participation   | Active pathological bleeding  |
|  | Allergy to cilostazol   |
|  | Positive pregnancy test   |
|  | Coagulopathy not caused by anti-coagulant use   |
|  | History of hemorrhagic complications (gastrointestinal bleeding, etc.)  |
|  | Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol  |
|  | Patients requiring anticoagulant treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm)  |
|  | <i>Exception:</i> patients who require the use of aspirin as determined by the staff member performing the coil embolization for thromboembolic event protection due to a small amount of coil extrusion from the aneurysm neck with be allowed to be included into the trial |
| <b>Criteria for discontinuing follow-up:</b>   |   |
| Subject wishing to terminate participation in the study at any time throughout his/her participation |   |
| CT, computed tomography  |   |

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**Table 2.** Standardized Treatment Regimen

| Location  | Treatment  |
|---|--|
| NSICU and floor   | <p data-bbox="453 352 727 384"><b>Intervention group:</b></p> <ul data-bbox="501 394 1393 632" style="list-style-type: none"> <li data-bbox="501 394 967 426">• 60 mg nimodipine Q4H for 21 days</li> <li data-bbox="501 436 964 468">• 100 mg cilostazol b.i.d. for 14 days</li> <li data-bbox="501 478 1393 510">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="501 520 1354 590">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="501 600 1227 632">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> <p data-bbox="453 642 662 674"><b>Control group:</b></p> <ul data-bbox="501 684 1393 913" style="list-style-type: none"> <li data-bbox="501 684 964 716">• 60mg nimodipine Q4H for 21 days</li> <li data-bbox="501 726 972 758">• Cilostazol placebo b.i.d. for 14 days</li> <li data-bbox="501 768 1393 800">• CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week</li> <li data-bbox="501 810 1354 879">• DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm</li> <li data-bbox="501 890 1227 921">• Standard subarachnoid hemorrhage treatment pathway [4]</li> </ul> |
| NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PO, post-operative; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography |  |

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**Table 3.** List of Adverse or Serious Adverse Events

| <b>Cilostazol</b>   |   | <b>Nimodipine</b>             |   |
|---|---|-------------------------------|---|
| <b>Adverse events</b>   | Headache<br>Diarrhea<br>Abnormal Stools<br>Palpitations<br>Dizziness<br>Peripheral Edema<br>Dyspepsia<br>Abdominal pain<br>Tachycardia  | <b>Adverse events</b>         | Hypotension (mild)<br>Diarrhea<br>Dyspepsia<br>Rash<br>Headache<br>Flushing   |
| <b>Serious adverse events</b>   | Hypotension<br>Bleeding<br>Stevens Johnson<br>Syndrome<br>Anaphylaxis<br>Hypersensitivity<br>Reaction<br>Leukopenia<br>Thrombocytopenia<br>Tachyarrhythmias<br>Myocardial<br>Infarction<br>Angina | <b>Serious adverse events</b> | Hypotension (severe)<br>EKG changes<br>CHF<br>Thromboembolism<br>Thrombocytopenia<br>Anemia<br>GI bleeding<br>Ileus<br>Intestinal obstruction |
| EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal |   |                               |   |

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**Table 4.** Definition and Classification of Surgical Complications

| <b>Grade</b>   | <b>Definition</b>  |
|--|--|
| Grade 1  | Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions  |
| Grade 2  | Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.  |
| Grade 3  | Requiring surgical, endoscopic, or radiological intervention   |
| 3a)  | Intervention not under general anesthesia  |
| 3b)  | Intervention under general anesthesia  |
| Grade 4  | Life-threatening complication (including CNS complications)* requiring IC/ICU management   |
| 4a)  | Single organ dysfunction (including dialysis)  |
| 4b)  | Multiorgan dysfunction   |
| Grade 5  | Death of a patient   |
| Suffix   | If the patient suffers from a complication at the time of discharge, the suffix “d” is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication |
| *Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit |  |

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Cilostazol-Nimodipine Randomized Controlled Trial (CONSORT Flow Diagram)

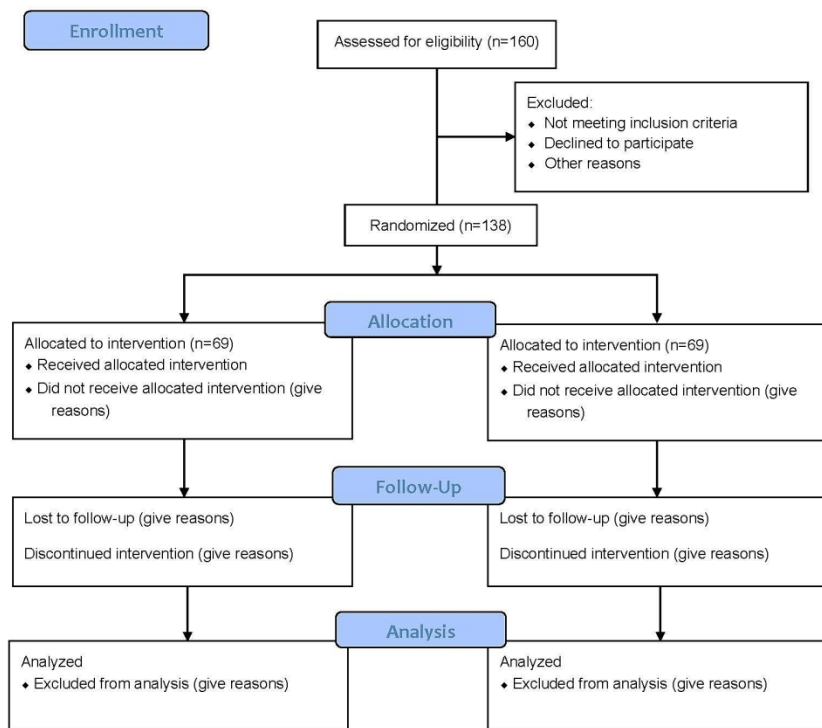


Figure 1. Study Design CONSORT Flow Diagram

143x186mm (300 x 300 DPI)

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Figure 2. Data Collection Schedule

|                                   | PreOp | D0 | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 | D15 | D16 | D17 | D18 | D19 | D20 | D21 | D/C |
|-----------------------------------|-------|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Eligibility                       |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Recruit                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Consent                           |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clinical Exam                     |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mFisher                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Hunt Hess                         |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EKG/ECHO                          | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pregnancy                         | X     |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Randomise                         |       |    | X  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Clofazolin /Placebo               |       |    | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   |     |     |     |     |     |     |     |     |
| Nimodipine                        |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| CT Scan                           |       | X  | X  |    |    |    |    |    | X  |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| DSA/CTA                           |       | X  |    |    |    |    |    |    | X  | X  | X  |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Colling                           |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| All AE                            |       | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |
| mRS                               |       | X  |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| EVD (Y/N)                         |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Symptomatic Vasospasm? (Mark "Y") |       |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |

Figure 2. Data Collection Schedule & Timeline

181x117mm (300 x 300 DPI)

1  
2  
3 **Ascension Providence Hospital**  
4 **16001 West Nine Mile Road, Southfield, MI**  
5

6  
7 **CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY**

8 **AND**

9  
10 **AUTHORIZATION TO USE OR DISCLOSE PROTECTED HEALTH INFORMATION**  
11 **FOR RESEARCH TO BE CONDUCTED AT PROVIDENCE HOSPITAL,**  
12 **PROVIDENCE PARK HOSPITAL AND MEDICAL CENTERS**  
13

14  
15 **Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed**  
16 **Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage (SAH): A Multicenter,**  
17 **Randomized, Double-blinded, Placebo-controlled Trial**  
18

19 **Principal Investigator:**

20  
21  
22 Boyd Richards D.O. Neurological Surgery  
23

24 **Co-Investigators:**

25  
26  
27 Doris Tong, MD; Chad F. Claus; Sina Rajamand, DO; Ascher Kaufmann, MD; Troy Dawley,  
28 DO; Prashant Kelkar, DO; Teck M Soo, MD  
29

30 Office Phone: (248) 569-7745  
31

32  
33 Please read the following material to ensure that you are informed of the nature of this clinical  
34 research study and how you will participate in it. Signing this form will indicate that you have  
35 been informed and that you give your consent to participate in a free manner. Federal regulations  
36 require written informed consent prior to participation in this clinical research study.  
37

38 **INTRODUCTION**  
39

40  
41 This is an important form. Please read it carefully. It tells you what you need to know about this  
42 research study. If you agree to take part in this study, you need to sign this form. Your signature  
43 means that you have been told about the study and any applicable risks. Your signature on this  
44 form also means that you want to take part in this study. This is a randomized multi-center  
45 double-blinded controlled clinical trial. Your doctor will explain the clinical research study to  
46 you. Research studies or clinical trials only include people who choose to take part. Please take  
47 your time to make your decision about taking part. You may discuss your decision with your  
48 friends and family. You can also discuss it with your health care team. If you have any questions,  
49 you can ask your study doctor for more explanation.  
50

51  
52 You are being asked to take part in this research study because you recently underwent either a  
53 surgical or endovascular intervention for the treatment of intracranial hemorrhage and are being  
54 seen at Ascension Providence Hospital.  
55

56  
57  
58 APH IRB Approved: 2/5/20-8/4/20  
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## BACKGROUND

This research study is designed to evaluate the effects of the combination between Cilostazol and Nimodipine on delayed cerebral ischemia due to cerebral vasospasm after anterior circulation aneurysmal subarachnoid hemorrhage. Cilostazol is a selective phosphodiesterase-3 inhibitor which exerts a vasodilatory and antithrombotic effect. Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postoperative treatment of aneurysmal subarachnoid hemorrhage. We seek to compare the incidence of delayed cerebral ischemia when treated with Cilostazol and Nimodipine versus when treated with Nimodipine alone. The researchers will compare two different groups. With your consent, you will be randomly assigned to a group who receives conventional post-intervention treatment with Nimodipine or to a group who receives conventional post-intervention treatment with Nimodipine in addition to 100mg Cilostazol twice daily for 14 days after your intervention. Your chances of being in one group are 1 in 2, much like flipping a coin. This is a double-blind study, which means neither you nor your doctor will know which group you are in until the study is completed.

Imaging will be taken 1 day after your intervention,  $7 \pm 2$  days after your intervention, approximately 1 month and 6 months after discharge as part of your standard of care. More imaging, including but not limited to CTA or MRI scans, may be needed depending on the individual care management plan.

## PURPOSE OF THE STUDY

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will decrease the rate of delayed cerebral ischemia during your hospital stay
- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will not lead to significant increase in bleeding disorders
- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone, will lead to significant improvement in the following:
  - The rates of symptomatic vasospasm
  - The rates of angiographic vasospasm
  - Quality-of-life outcomes: Modified Rankin Scores (mRS) at Pre, 1, 3 and 6 months postoperatively and SF-12 at 1, 3 and 6 months postoperatively
  - Length of hospitalization
  - Length of stay in the intensive care unit (ICU)
  - Duration of ventriculostomy use

### **How many people will take part in this study?**

Approximately 120 men and/or women of at least 18 years of age will be in this study.

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### **How long will I be in this study?**

You will participate in this study for 6 months. Your part in the study is completed once you have completed your 6-month follow-up visit with your surgeon including completion of the modified Rankin Scores and SF-12 questionnaires.

### **What will happen if I take part in this research study?**

You have recently undergone either a surgical or endovascular intervention for the treatment of intracranial hemorrhage and your surgeon has determined that you meet eligibility criteria to participate in this research study.

After your enrollment, you will receive the necessary post-intervention care. If you are randomly selected into the treatment group, you will receive the drug Cilostazol in addition to your standard care regimen. If you are not, you will receive the standard care regimen plus a placebo. However, your knowledge of which group you are assigned to, as well as the administration of that drug will not be known to you. Throughout your hospital stay, data will be collected including any Cilostazol-related adverse events, occurrence of symptomatic vasospasm, and length of stay, among others. This all will be collected from either your electronic medical record or directly from you by a blinded member our staff. You will follow-up in clinic with your surgeon for standard post-interventional evaluation which includes 1, 3, and 6-month follow-up visit along with completion of modified Rankin Score and SF-12 questionnaires.

### **Risk to patients**

Important risks and side effects of 100mg Cilostazol may include:

Frequent side effects:

- Headche
- Abnormal stools
- Diarrhea

Infrequent side effects:

- Abdominal pain
- Back pain
- Infection
- Palpitation
- Tachycardia
- Flatulence
- Nausea
- Peripheral edema
- Myalgia
- Dizziness
- Cough increased
- Pharyngitis
- Rhinitis

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Rare side effects:

- Chills
- Vertigo
- Other rare side effects

***Frequent (occurs in 10-25% of people – 10 to 25 out of 100 people)***

***Infrequent (occurs in 1-10% of people – 1 to 10 out of 100 people)***

***Rare (occurs in less than 1% of people – less than 1 out of 100 people)***

Every effort will be made to minimize any discomfort and these risks. There may be other risks that are unknown at this time.

You should tell the person obtaining your consent if you are currently participating in any other medical research studies.

### **What are the benefits of the study?**

There may be no direct benefit to you in participating in the study. However, it is possible that you may have less chance of delayed cerebral ischemia or symptomatic and angiographic cerebral vasospasm following your surgery. You may also experience an improvement in postoperative quality-of-life. In the future, other patients may benefit from the results of this study, when they become known.

### **What other options are there?**

One option is to not participate. You do not have to participate in this research study in order to continue receiving treatment for your condition. Electing to not participate in this study will not affect your care whatsoever.

### **Do I have to participate in this study?**

Your participation in this study is voluntary. Your refusal to participate will cause no penalty or loss of benefits which you would otherwise receive. If you decide to participate, you may change your mind about being in the study and may quit at any time without penalty of loss of benefits regarding your future care. If new information becomes available during the study that may affect your willingness to continue in the study, your doctor and/or his/her associate will discuss this information with you. Also, your doctor may stop your participation at any time if he/she feels it is in your best interest.

### **Will it cost anything to participate?**

We do not expect there to be any additional costs to you if you participate in this study. Besides the drug treatment, the additional care you would receive during this study is considered standard of care and would not otherwise be different.

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### **Compensation to patients – None**

There is no compensation or pay offered for your medical care if you are injured as a result of participating in this study. You and/or your medical insurance may have to pay for your medical care if you are injured as a result of participating in this study. You are not giving up any of your legal rights by signing this consent form.

### **Confidentiality of Records**

The principal investigators will have access to your medical records and your test results. While absolute confidentiality cannot be guaranteed, all research material which could identify you will be kept as confidential as possible within the state and federal laws. You should be aware that your medical records could be examined by the study staff, the Institutional Review Board (a group of people who review the research to protect your rights), or government agencies in order to verify the data collected during this research study. If the results of this study are presented in any public forum, you will not be personally identified.

### **Participant HIPAA Authorization to Use and Disclose Protected Health Information (PHI)**

Your participation in this study will require the use and disclosure of certain medical and other information about you. The information that may be used or disclosed includes any and all health care records such as: laboratory, pathology and/or radiology results, CT scans, MRI, and Protected Health Information (PHI) previously collected for research purposes.

Your PHI will be used in the following ways: To conduct the research and to ensure that the research meets legal, institutional or accreditation requirements.

Your authorization to use and disclose the above information has no expiration date.

Your PHI may be seen, used or disclosed to the following:

- The researchers and members of the research team
- Other health care providers or employees of Ascension Providence Hospital
- Representatives of the Institutional Review Board (IRB), the FDA (Food and Drug Administration), or other governmental agencies involved in research monitoring.
- Other agencies as required by law.

You have the right to review your PHI. However, if you agree to participate in the research study and sign below, you will not be able to look at your research information until the research study is completed.

You do not have to sign this authorization. If you decide not to sign the authorization it will not affect your treatment or eligibility for health benefits. However, if you do not sign this authorization you may not participate in this study.

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2  
3 You may withdraw your authorization at any time by notifying the principal investigator in  
4 writing, but the withdrawal will not affect any information already disclosed. However, you need  
5 to be aware that your written withdrawal of this Authorization may result in the termination of  
6 the research-related treatment being provided to you.  
7

8  
9 This study and more information will be available at ClinicalTrials.gov which is a registry and  
10 results database of publicly and privately supported research studies conducted in the United  
11 States and around the world. Sponsors or investigators of certain clinical trials are required by  
12 U.S. law to register their trials on and submit summary results to ClinicalTrials.gov. Each study  
13 record includes a summary of the study protocol, including the purpose, recruitment status, and  
14 eligibility criteria. Study locations and specific contact information are listed to assist with  
15 enrollment. You can visit ClinicalTrials.gov for more information regarding this study.  
16  
17

### 18 **Who do I call with questions about the study or to report an injury?**

19  
20 If you have any questions regarding a research-related injury, you can contact:  
21 Troy Dawley, DO  
22 [2250 Providence Dr Ste 601, Southfield, MI 48075](mailto:Troy.Dawley@Ascension.org)  
23 (214) 886-6111  
24  
25

26 If you have any questions about your rights as a subject in this clinical research study, you may  
27 contact the IRB representative at 248-849-8889 at Ascension Providence Hospital.  
28

### 29 **CONSENT**

30  
31 You have had the opportunity to fully discuss the purpose of this clinical research study  
32 and how it will be carried out. Your questions have been answered. Your participation in  
33 this study is fully voluntary and you may withdraw at any time.  
34  
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36  
37 Your signature below acknowledges that you voluntarily agree to participate in this  
38 clinical research study, and you will receive a signed copy of this form.  
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42  
43 \_\_\_\_\_  
44 Printed Name of Research Subject  
45  
46

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48 \_\_\_\_\_  
49 Signature of Research Subject  
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53 \_\_\_\_\_  
54 Date  
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58 APH IRB Approved: 2/5/20-8/4/20  
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**Legally Authorized Representative (if applicable):**

\_\_\_\_\_  
 Printed Name of Legally Authorized Representative

\_\_\_\_\_  
 Signature of Legally Authorized Representative

\_\_\_\_\_  
 Date

Check Relationship to Subject:\*

Legal Guardian or Legally Authorized Representative for Medical Care (LARM)

Spouse

Adult Son or Daughter    Mother or Father    Adult Brother or Sister    Other,  
 explain:

Reason subject is unable to sign for self:

*\*If a Legal Guardian or Legally Authorized Representative for Medical Care (LARM) has not been appointed, then consent should be obtained from the closest next of kin (in the order listed above). When that individual is unavailable or refuses to act the next in order should be contacted.*

*\* If there is a disagreement among next of kin regarding the appropriateness of the treatment plan, Clinical Safety Risk Management may be contacted. Outside of business hours, Clinical Safety Risk Management can be contacted through any St. John Hospital operator.*

\_\_\_\_\_  
 Printed Name of Person Obtaining Consent

\_\_\_\_\_  
 Signature of Person Obtaining Consent

\_\_\_\_\_  
 Date



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | _____1_____              |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | _____3_____              |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | _____n/a_____            |
| Protocol version                  | 3       | Date and version identifier  | _____3_____              |
| Funding                           | 4       | Sources and types of financial, material, and other support  | _____3_____              |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | _____11_____             |
|                                   | 5b      | Name and contact information for the trial sponsor   | _____3_____              |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | _____11_____             |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | _____n/a_____            |

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention \_\_\_\_\_ 3, 4 \_\_\_\_\_

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6 6b Explanation for choice of comparators \_\_\_\_\_ 3, 4 \_\_\_\_\_

7

8 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 4, 5 \_\_\_\_\_

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_\_\_ 5 \_\_\_\_\_

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14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained \_\_\_\_\_ 5 \_\_\_\_\_

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) \_5, 6 Table 1\_\_\_\_\_

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered \_\_\_\_\_ 5, 6 \_\_\_\_\_

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25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) \_\_\_\_\_ 5, 6 \_\_\_\_\_

26

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) \_\_\_\_\_ 9 \_\_\_\_\_

29

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 5, 6 \_\_\_\_\_

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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended \_\_\_\_\_ 5, 6, 7 \_\_\_\_\_

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40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) \_6, 7, 8, Figure 2\_

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including \_\_\_\_\_7\_\_\_\_\_

2 clinical and statistical assumptions supporting any sample size calculations

3

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size \_\_\_\_\_n/a\_\_\_\_\_

5

6 **Methods: Assignment of interventions (for controlled trials)**

7

8 Allocation:

9

10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any \_\_\_\_\_5\_\_\_\_\_

11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction

12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants

13 or assign interventions

14

15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, \_\_\_\_\_6\_\_\_\_\_

17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

18 mechanism

19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to \_\_\_\_\_6\_\_\_\_\_

21 interventions

22

23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome \_\_\_\_\_6\_\_\_\_\_

25 assessors, data analysts), and how

26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's \_\_\_\_\_6\_\_\_\_\_

28 allocated intervention during the trial

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31 **Methods: Data collection, management, and analysis**

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33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related \_\_\_\_\_8, 9\_\_\_\_\_

34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of

35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.

36 Reference to where data collection forms can be found, if not in the protocol

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39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_8\_\_\_\_\_

40 collected for participants who discontinue or deviate from intervention protocols

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|    |                                 |     |   |       |
|----|---------------------------------|-----|---|-------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | 8, 9  |
| 2  |                                 |     |   |       |
| 3  |                                 |     |   |       |
| 4  |                                 |     |   |       |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | 8, 9  |
| 6  |                                 |     |   |       |
| 7  |                                 |     |   |       |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 8, 9  |
| 9  |                                 |     |   |       |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | 9     |
| 11 |                                 |     |   |       |
| 12 |                                 |     |   |       |
| 13 |                                 |     |   |       |
| 14 | <b>Methods: Monitoring</b>      |     |   |       |
| 15 |                                 |     |   |       |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 9, 10 |
| 17 |                                 |     |   |       |
| 18 |                                 |     |   |       |
| 19 |                                 |     |   |       |
| 20 |                                 |     |   |       |
| 21 |                                 |     |   |       |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | 9     |
| 23 |                                 |     |   |       |
| 24 |                                 |     |   |       |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | 6     |
| 26 |                                 |     |   |       |
| 27 |                                 |     |   |       |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 8, 9  |
| 29 |                                 |     |   |       |
| 30 |                                 |     |   |       |
| 31 |                                 |     |   |       |
| 32 | <b>Ethics and dissemination</b> |     |   |       |
| 33 |                                 |     |   |       |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 5, 10 |
| 35 |                                 |     |   |       |
| 36 |                                 |     |   |       |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | n/a   |
| 38 |                                 |     |   |       |
| 39 |                                 |     |   |       |
| 40 |                                 |     |   |       |
| 41 |                                 |     |   |       |
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| 44 |                                 |     |   |       |
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|----|-------------------------------|-----|---|-----------------|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | ___ 8, 9 ___    |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | ___ n/a ___     |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | ___ 6, 7, 8 ___ |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | ___ 11 ___      |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | ___ 10 ___      |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | ___ n/a ___     |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ___ 7 ___       |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | ___ 11 ___      |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | ___ n/a ___     |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | ___ n/a ___     |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | ___ n/a ___     |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
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