Neurocognitive Impairment Assessment in Symptomatic Carotid Occlusion Recanalized Endovascularly

Protocol Number: 01

National Clinical Trial (NCT) Identified Number: NCT03176420

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.2	Wording changes for medical management	Promoting clarity and consistency
1.3	Defined Visit windows	Promoting clarity and consistency

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

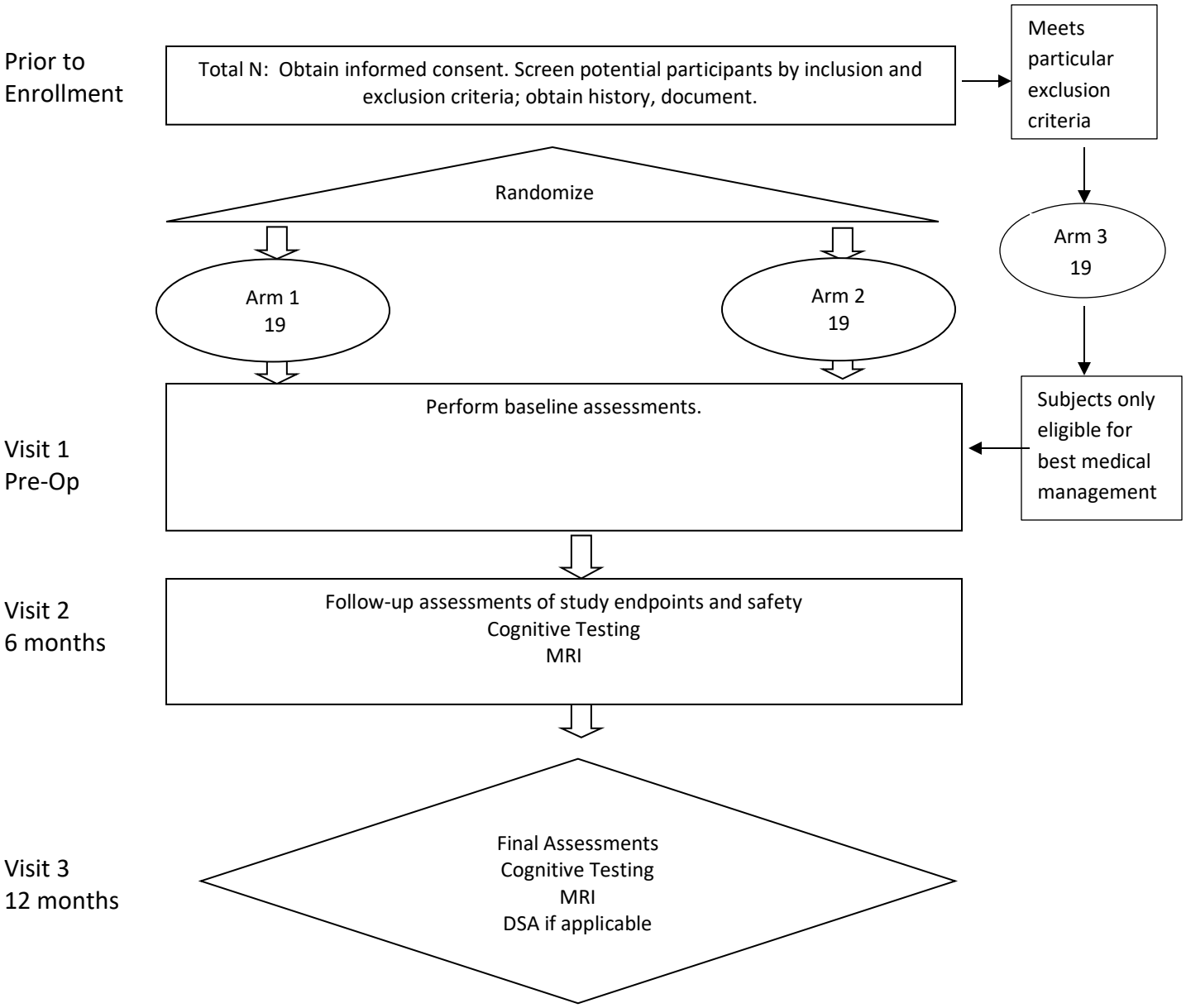
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Neurocognitive Impairment Assessment in Symptomatic Carotid Occlusion Recanalized Endovascularly
Study Description:	This is a phase 2 randomized single-center open label clinical trial with randomization of 1:1 to either best medical management vs. best medical management and endovascular revascularization of COICA. The study will utilize best medical management and will randomize patients to endovascular balloon angioplasty and stenting. • A third study group will be included that meet selected exclusion criteria. This group will not be randomized, only eligible for best medical management and prospective observation.
Objectives:	**Primary Objective:** To test the hypothesis that endovascular revascularization of COICA improves significantly cognitive function assessed by a specifically designed battery of 14 cognitive tests including the Montreal Cognitive Assessment (MoCA). **Secondary Objective:** To test the safety of endovascular revascularization of chronically occluded ICA. **Tertiary/exploratory Objectives:** To test the hypothesis that subjects with symptomatic COICAs and mild/moderate cognitive dysfunction have the following biomarkers:

	A) Presence of lactate and decreased Naa/Cr in the watershed area (specifically centrum semiovale) on 1H-MRI-spectroscopy, and B) Decreased size of the hippocampus and amygdala on MRI. C) increased MTT and/or PTT on CTP in the ipsilateral side of the occluded ICA specifically in the MCA territory when compared to the opposite unaffected hemisphere.
Endpoints:	**Primary endpoints:** 1. Cognitive outcome at 12-month follow-up assessed mainly by a specifically designed battery of 14 cognitive tests including the MoCA. **Secondary Endpoints:** 1. Safety: Occurrence of Stroke, Cerebral Hemorrhage, or Death **Exploratory endpoints:** Biomarkers: 1. Resolution/improvement of previously increased of MTT and/ or PTT (normalization of MTT/ PTT) on CTP specifically in the ipsilateral MCA territory. 2. The presence/absence of lactate on 1H-MRI spectroscopy in centrum semiovale in the ipsilateral side of COICA; 3. The change in size of amygdala and hippocampus in the ipsilateral side of COICA. 4.Subgroups: Gender difference
Study Population:	Age ≥ 21 Patients with complete occlusion of cervical ICA on imaging studies (MRA or CTA) and confirmed with DSA, a history of TIA or stroke , increased MTT and/or TPP on CTP in the ipsilateral side of the occluded ICA specifically in the MCA territory when compared to the opposite unaffected hemisphere, all occlusion is due to atherosclerotic disease and MoCA < 26 or abnormal result on another test in the battery (abnormal defined as 1.5 SD below age/ gender/ education matched norms). • Subjects without increased MTT or TPP on CTP may still be included in the unrandomized prospective observational 3rd arm.
Phase:	Phase 2
Description of Sites/Facilities Enrolling Participants:	University of Iowa Hospitals and Clinics
Description of Study Intervention:	Endovascular balloon angioplasty and stenting
Study Duration:	5 years
Participant Duration:	12 months

1.2 SCHEMA


Prior to Enrollment
Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Meets particular exclusion criteria
Randomize
Arm 1
19
Arm 2
19
Arm 3
19
Subjects only eligible for best medical management
Visit 1
Pre-Op
Perform baseline assessments.
Visit 2
6 months
Follow-up assessments of study endpoints and safety
Cognitive Testing
MRI
Visit 3
12 months
Final Assessments
Cognitive Testing
MRI
DSA if applicable

Baseline visit day -30 to -10 days — Screening /Baseline assessments

- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

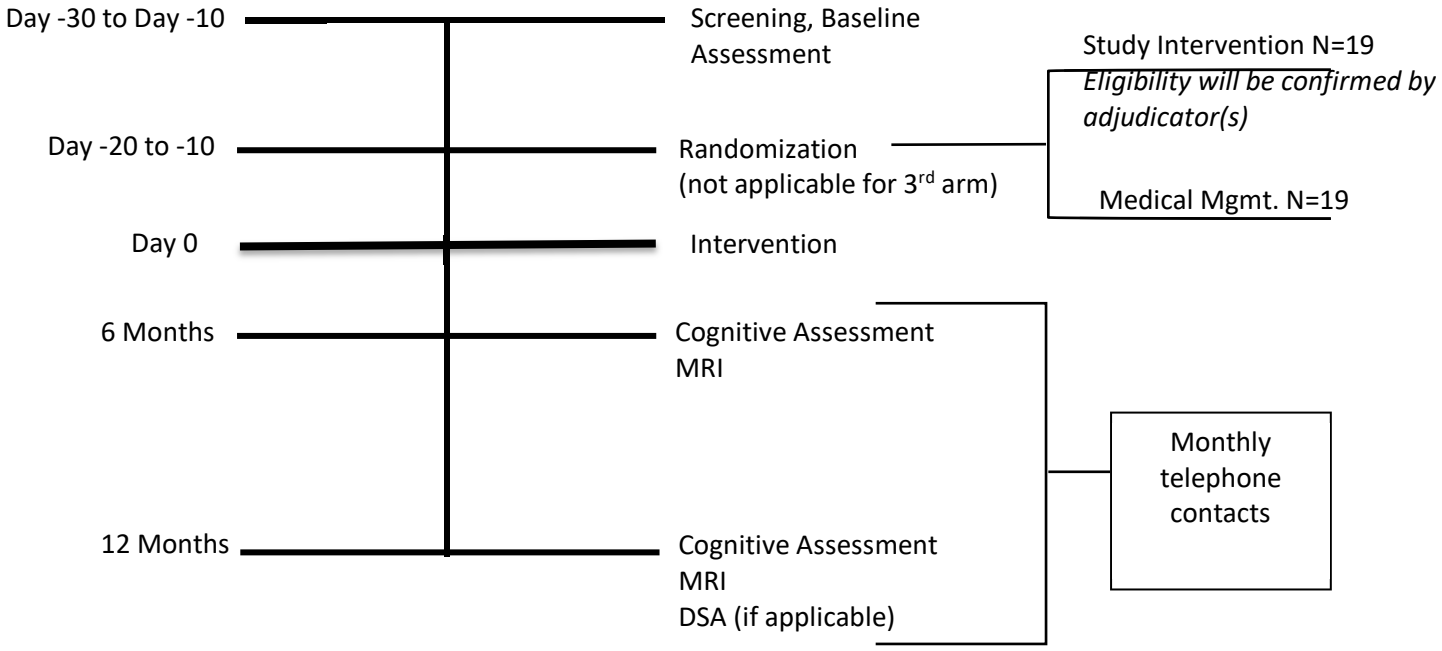
day -20 to -10 days — Randomization 1:1 (not applicable for 3rd arm)

- Intervention Group 1 (n=19)
- Placebo (n=19)

Day 0 — Study Intervention

Day 100-140; Day 160-200 — Follow-up assessments of study endpoints and safety

Day 330- 390 — End of Study Assessments


Day -30 to Day -10
Screening, Baseline Assessment
Study Intervention N=19
Eligibility will be confirmed by adjudicator(s)
Day -20 to -10
Randomization
(not applicable for 3rd arm)
Medical Mgmt. N=19
Day 0
Intervention
6 Months
Cognitive Assessment
MRI
Monthly telephone contacts
12 Months
Cognitive Assessment
MRI
DSA (if applicable)

1.3 SCHEDULE OF ACTIVITIES (SOA)

The schedule below is provided as an example and should be modified as appropriate.

Procedures	Screening Day -30 to -1	Enrollment/Baseline Visit 1, Day 0[f]	Study Visit 4 6 Months +/- 6 weeks	Final Study Visit 12 monthsh +/- 6 weeks
Informed consent	X			
Demographics	X			
Medical history	X			
Randomization[a]	X			
Administer study intervention		X[e]		
Concomitant medication review	X	X		
Physical exam (including height and weight)	X	X	X	X
Vital signs	X	X	X	X
Height	X			
Weight	X			
Performance status	X			
Hematology	X			
Serum chemistry [a]	X			
Pregnancy test [b]	X			
Blood Test [c]		X		
EKG (as indicated)	X			
Adverse event review and evaluation	X	X		
CTP	X	X		
MRA or CTA	X			
Radiologic/Imaging assessment (MRI of the brain)	X		X	X
Cognitive testing	X		X	X
Complete Case Report Forms (CRFs)	X	X	X	X
Diagnostic angiogram	X[d]			X[c]
Medication check			X	X

a- Not applicable to 3rd study arm
b- Only if necessary, to confirm surgery eligibility
c- Surgical arm only
d- Only applicable if the subject has not had one in the past 6 months
e- Prior to surgical intervention eligibility will be confirmed by adjudicator(s)
f- Enrollment for surgical arm may be delayed due to OR schedule

g- 6-month follow up visit timeframe is based on the date of randomization for non-surgical arms, date of surgery for surgical arm

h- 12-month follow up visit timeframe is based on same dates as 6-month visit

2 INTRODUCTION

2.1 STUDY RATIONALE

Complete occlusion of the Internal carotid artery (ICA) by atherosclerotic disease (COICA) causes approximately 15%–25% of ischemic strokes in the carotid artery distribution. (11,17,48,54,57,70,71,84,92,98) Patients treated with medical therapy have a 7%–10% risk of recurrent stroke per year for any stroke and a 5%–8% risk per year for ipsilateral ischemic stroke during the first 2 years after ICA occlusion. (41,42,46,49,50,68,69) Internal carotid artery occlusion causes an estimated 61,000 first-ever strokes per year in the US (1,15,34,57,70,92,105) an incidence more than twice the annual occurrence of ruptured intracranial aneurysms (14) Additionally, 40% of subjects with COICA who present with TIA and 70% of COICA who present with stroke have cognitive decline with increased risk of vascular dementia and Alzheimer's' disease (AD) with time (2,3).

Symptomatic COICA subjects are at increased risk of developing cognitive impairment and progressive development of vascular dementia and AD with time. Our proposal leverages several compelling retrospective and prospective preliminary data from human to perform this exploratory trial with go/no-go criteria to proceed to a phase 3 based on the data generated

2.2 BACKGROUND

A. New COICA classification based on anatomy and radiographic findings:
We analyzed the diagnostic cerebral angiogram (DSA) for 100 consecutive subjects with a diagnosis of COICA in the interval of 2009–2017 at the University of Iowa Hospitals and Clinics 43. Initial diagnosis of the occluded cervical ICA along with an assessment of collateral filling was reported by a member of our neuroradiology team based on MRA and/or CTA. Then, an endovascular neurosurgeon (lead PI) used the morphology and location of the occlusion, as well as the presence or absence of reconstitution of the distal ICA on DSA, to stratify this cohort into 4 categories. The rationale for this classification was to determine whether it could predict upfront which COICA subject would be a viable candidate for the revascularization procedure using endovascular techniques. For the type A category (Figs. 1A and 2A–C), occlusion of the cervical ICA is tapered with proximal ICA lumen patency. In addition, the cavernous and/or petrous segments are reconstituted by collateral vessels from the external carotid artery (ECA) and/or retrograde filling from the supraclinoid segment. For the type A category (Figs. 1A and 2A–C), occlusion of the cervical ICA is tapered with proximal ICA lumen patency. In addition, the cavernous and/or petrous segments are reconstituted by collateral vessels from the external carotid artery (ECA) and/or retrograde filling from the supraclinoid segment. For type B (Figs. 1B and 2D–F), occlusion of the cervical ICA is not tapered; instead, a stump is present, and the immediate proximal portion of the cervical ICA lumen is patent. In addition, the cavernous and/or petrous segments are reconstituted by collateral vessels from the ECA and/or retrograde filling from the supraclinoid segment. For type C (Figs. 1C and 3A–C), occlusion of the cervical ICA is at the common carotid artery bifurcation (the cervical ICA appears completely amputated at the bifurcation), and no ICA lumen is observed. The common carotid artery continues as the ECA. However, the cavernous and/or petrous segment is reconstituted by either

collateral vessels from the ECA and/or retrograde filling from the supraclinoid segment. Type D (Figs. 1D and 3D–F) is the same as type C, except that there is no reconstitution of the cavernous and/ or petrous segments. In our analysis of the radiographic images for 100 consecutive subjects with a diagnosis of COICA, we found type A represented 29/100 (29%) COICAs; type B: 28/100 (28%); type C: 33/100 (33%); and type D: 10/100 (10%). We then assessed whether our proposed classification could predict upfront the technical feasibility and safety of endovascular revascularization for symptomatic COICA.

B. Proof-of-concept and pilot study of the feasibility and safety of revascularizing symptomatic COICA based of the proposed new radiographic classification of COICA mentioned above:
Using the above classification, we conducted a pilot study 43 in which we treated 31 subjects for their symptomatic COICAs in the interval of 2016–2017. Institutional Review Board approval was obtained. Subjects were included in the study if they had a COICA with ischemic symptoms refractory to medical therapy, i.e., subjects who were having recurrent ipsilateral hemispheric stroke (emboli or watershed infarcts) while on dual antiplatelet therapy or anticoagulation. Symptoms were evaluated based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) 31criteria. Asymptomatic subjects with COICA were not included in this study. All occlusions were due to atherosclerosis; those that were not, such as dissection, were excluded from the study. Acute carotid artery occlusions were not included in the study. Carotid occlusion was defined as 100% cross-sectional obliteration of the vessel lumen as documented on CTA or MRA and confirmed with DSA. In the pilot study, 31 subjects, five (16.12%) of whom were female, had 32 symptomatic COICAs and underwent endovascular recanalization and stent deployment across the occluded section of the vessel. The mean age was 65.77 years (range 49–84 years). The mean (± standard deviation) follow-up among the 31 patients since diagnosis of the ICA occlusion was 13.70 ± 3.77 months (median 11 months, range 7 days–4.5 years). Among the revascularized group, the mean follow-up was 10 months and the median was 12 months. Sixteen subjects had only right ICA occlusion, 14 had only left ICA occlusion, and one subject had bilateral ICA occlusion. Recanalization was successful in 68.75% (22/32) of symptomatic COICAs. Among type A, 8/8 (100%) COICAs were successfully revascularized (Fig. 2A–C). Among type B, 8/8 (100%) had successful revascularization (Fig. 2D–F). As for types C and D, the success rate was 50.00% (4/8) and 25.00% (2/8), respectively (Fig. 2). The perioperative complication rate was 18.75% (6/32), and 4 of the cases were transient. Persistent complications were limited to a minor/silent hemorrhagic transformation in the right parietooccipital lobe and the right basal ganglia in 2 subjects who had type C& D occlusions. None of the subjects with type A or B COICAs had any perioperative complications. Overall, none of the complications resulted in any permanent morbidity or death. Twenty (64.52%) of 31 subjects had improvement in their neurological symptoms at the 6 months' follow-up. Four of the subjects that did not have successful revascularization (12.90%; 3 with type D, 1 with type C) had a recurrent TIA/stroke after 30 days postprocedure. Hence, the rate of TIA/stroke more than 30 days after the procedure was 4/10 (40.00%) in the cohort in which revascularization had failed. None of the successfully revascularized subjects suffered any ischemic events at follow-up

In a literature search for any studies published in English language that addressed endovascular revascularization of COICA, we identified 16 studies that satisfied our inclusion criteria. Studies that did not involve endovascular treatment for COICA or that did not present data amenable to meta-analysis were excluded. A total of 333 patients with COICA underwent endovascular recanalization. The mean age of the patient sample was 67.2 years old (SD = 9.3). Male patients represented 85% of the population. The mean duration of known occlusion was 7.4 months (SD = 9.4). Seventy percent (70%) of patients had a successful recanalization. A total of 13 patients (3.9%) experienced major complications following the procedure, whereas only 8 patients (2.4%) experienced minor complications. Among the most common complications were hemorrhagic complications [n = 8, (2.4%)], and ischemic strokes [n =7

(2.1%)]. The incidence of periprocedural complication was 5.4%. Periprocedural hypotension / bradycardia was not included in the complication rates unless it was severe enough alter the treatment course. Hyperperfusion syndrome occurred in 0.6%. The rate of restenosis of follow-up was 7.8%. Lin et al 54, were the first to show improvement in cognitive function after stenting in COICA subjects with objective hemispheric ischemia. They found that subjects with successful recanalization had improvement in ipsilateral brain perfusion after the procedure, which was associated with a significant improvement in the scores on the Alzheimer Disease Assessment Scale–Cognitive Subtest (before: 7.7±8.9 versus after: 5.7±7.1; p=0.024), Mini-Mental State Examination (before: 25.8±3.8 versus after: 27.7±2.7; p=0.015), and Color Trail Making A (before: 123.2±68.6 versus after: 99.3±51.5; p=0.017), compared to those who failed recanalization. Fan et al 27, also conducted a prospective, controlled, single center study on endovascular recanalization of symptomatic COICA, reporting a success rate of 88.9%. Additionally, they reported a noticeable clinically and statistically significant cognitive improvement (greater than 5 points on MoCA score) in the group that underwent successful endovascular recanalization compared to the group receiving conservative management (Table 1).

	Group A	Group B	P
Baseline	14.67 ± 3.56	14.91 ± 3.39	.83
Postintervention			
1 week	15.33 ± 3.25	16.14 ± 3.88	.49
1 month	20.56 ± 4.06	18.18 ± 2.75	.03
3 months	24.17 ± 3.55	18.18 ± 2.68	0
6 months	24.72 ± 2.85	19.1 ± 2.97	0

Table 1: Fan et al[27] reported a noticeable clinically and statistically significant neurocognitive improvement (greater than 5 points on MoCA score) in the group that underwent successful endovascular recanalization compared to the group receiving conservative management

Summary
1. As of today there is no definitive treatment for symptomatic COICA.
2. A subset of subjects with COICA has mild to moderate cognitive impairment with accelerated progression to vascular dementia. This is supported by several animal studies (mentioned above)
3. Preliminary data from several studies including ours suggest that recanalization of COICA is feasible and safe especially if our COICA classification is used to guide intervention.
4. Three studies (1 retrospective and 2 prospective studies) including ours demonstrated significant improvement of cognitive impairment when symptomatic COICA revascularized using endovascular techniques.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks include:
1. Ischemic stroke
2. hemorrhagic stroke

3. Seizure
4. Carotid cavernous fistula
5. Visual acuity deficits.
6. Extravasation of contrast secondary to injury to cervical ICA during the procedure; and
7. Contrast allergy
8. Radiation exposure from CTP and x-rays associated with diagnostic angiograms and intervention.
9. renal dysfunction

Additional risks:
There is a very minimal risk of violation of confidentiality as some patient identifiers will be collected as part of the data collection process. Emotional or psychological risk could ensue if this were to occur. No financial, legal, social or physical risks are anticipated.

2.3.2 KNOWN POTENTIAL BENEFITS

Revascularization that may improve cognitive status and may prevent future recurrence of stroke and TIAs.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The research team have devised a classification system that helps select subjects that are suitable for the procedure and minimize the risks associated with intervention. The research team will use that classification to enroll subjects. This classification was tested in pilot study among 4 institutions and was very effective.

The study is designed to reduce the risks by careful pre-screening, monitoring and follow up visits.
To reduce the risk of loss of confidentiality, precautions will be taken to ensure privacy. The investigators and the study team will maintain appropriate medical and research records for the study, in compliance with ICH E6 GCP, section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Research records generated in this study will be stored in a file cabinet in a locked room and/or on a secure electronic database. Only the authorized study team will have access to the data. Research team members have separate usernames and passwords. Imaging collected during the study will be identified by a subject number, IRB protocol number, and date of collection. All personal data will be de-identified and kept separately from patients' identifiers. A subject will be assigned a research study ID and all research data will be identified with this research study ID. Whenever possible, all personal information will be blacked out on all hard copy records and replaced with research study ID; if research team writes an article or report about the study or share the data with others, all personal information that can identify a subject will be removed.

Data and Safety Monitoring Board [DSMB]:
The DSMB will be appointed by the NIA to monitor the performance of the study. The Steering Committee will prepare regular reports summarizing patient accrual and the morbidity and mortality experienced in the study, The DSMB will also review the cumulative outcome data at regular intervals (every 6 months).

During hospitalization and for the intervention arm, Dr. Samaniego will monitor for adverse events. He will check on the subjects post op and every day while in hospital.

Definitions:
Stroke: any new ischemic changes found either on head CT and/or MRI of the brain and associated with new neurological deficits that were not present prior to intervention.
TIA: any new neurological deficits resolved within 24 hours of symptom onset.

For medical arm: The subjects will be asked to return for clinical visits and follow up at 3 montes, 6 months and 12 months. The PI and his research nurse will check on medications, compliance, and any side effects.
Also, the subjects will be given a direct number to clinic and research nurse to contact if there are any side effects encountered. At initiation of medication, they will be instructed/educated about side effects of aspirin, Plavix, and statin.
Additionally the research team will partner with local primary care physician who will help will monitor for any side effects and will report that to the research team.

Risks associated with procedure and strategies to mitigate them:
Potential risks to research subjects are:

- 1. Ischemic stroke
- 2. hemorrhagic stroke
- 3. Seizure
- 4. Carotid cavernous fistula
- 5. Visual acuity deficits.
- 6. Extravasation of contrast secondary to injury to cervical ICA during the procedure; and
- 7. Contrast allergy
- 8. Radiation exposure from CTP and x-rays associated with diagnostic angiograms and intervention
- 9. Renal dysfunction

Strategies to mitigate risks to subjects in the trial include 1) exclusion of subjects with COICA type D, 2) strict perioperative blood pressure management to minimize hypoperfusion pre-procedure (maintain MAP ≥ 80mmHg and ≤120mmHg) and hyper-perfusion post procedure 9maintian MAP≤ 80mmHg and ≥60mmHg, 4) admission to neuro-intensive critical for management post procedure, and 5) use of IV maintenance dose Tirofiban immediately post procedure as a monotherapy for the first 24 hours (no aspirin or clopidogrel) to reverse the effect of anti-platelet effect within 90 minutes in case of dreaded intracranial hemorrhage secondary hyper-perfusion (from our series, no subjects suffered intracranial hemorrhage). If the subject is with signs or symptoms of intracranial hemorrhage, then at the end of 24 hours, the subject will be given a loading dose of clopidogrel (600 mg) and aspirin (325mg) and Tirofiban continued for another 2 hours to allow for the loading dose of aspirin and clopidogrel to reach therapeutic effect

Stopping rules or safety triggers for the study:
The occurrence of following potential side effects and risks associated with procedure will trigger a prompt reporting and review by the DSMB to discuss the events and decide on the continuation of the trial. The following adverse events will be reported to the DSMB: 1) Any intracranial hemorrhage within 72 hours post procedure, 2) Any stroke within 30 days post procedure; 3) Any seizure within 72 hours post procedure; and 4) Any injury to cervical ICA during the procedure.

Based on complication rates in the trial to date (June 2021), the occurrence of one additional event in these categories will trigger a suspension of enrollment in the trial and meeting of the DSMB to discuss the events and decide on the continuation of the trial
A combined rate of > 20% of the above adverse events at any time during the study will lead evaluation by the DSMB. The cumulative rate of these events will also be assessed at different time points: A) after completed enrolment of the first 10 subjects, B) completed enrollment of first 20 subjects, and C) Completed enrollment of first 30 subjects. If any of these thresholds are crossed, the study will automatically be placed on hold until the investigators and the DSMB can conduct a review of events. All adverse events (AEs) will be collected, recorded, and analyzed. Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor (Dr. Edgar Samaniego).

Adverse Event (AE) Reporting:
Any potential adverse event or a serious adverse event mentioned above will be reported during the trial. An AE will be defined as any unfavorable and/or unintended sign, symptom, or injury temporally associated with the procedure or other study medication. A serious adverse event (SAE) is defined as any untoward/undesirable adverse experience related to a study intervention/medication that results in any of the following outcomes: 1) death; 2) a life-threatening adverse experience; 3) need for additional surgery; 4) a permanent or significant disability/incapacity; 5) important medical events that may not result in death, be life-threatening, or require additional surgery.
Adverse events or a serious adverse events which occur during surgery will be communicated to the study coordinator and the independent Medical Safety Monitor (Dr. Edgar Samaniego) within 3 hours of occurrence by the surgical team. Dr. Samaniego and the study coordinator will then report the necessary information to the DSMB, NIH, and or IRB within 24 hours or as quickly as feasible.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Endovascular revascularization that improves cognitive outcome	Cognitive outcome at 12-month follow-up assessed mainly by a specifically designed battery of 14 cognitive tests including the MoCA.	The battery of 14 tests including MoCA are designed to test tight hemisphere domain, left hemisphere domain, and global domain to assess for cognitive improvement
Secondary		
To test the safety of the procedure	1. Safety: Occurrence of Stroke, Cerebral Hemorrhage, or Death	1. These are the expected adverse events from this procedure and hence will be used to monitor safety
Tertiary/Exploratory		
To test the hypothesis that subjects with symptomatic COICAs and mild/moderate cognitive dysfunction have associated, measurable biomarkers	1. Biomarkers: A) The presence/absence of lactate on 1H-MRI spectroscopy in centrum semiovale in the ipsilateral side of COICA; B)The change in size of amygdala and hippocampus in the ipsilateral side of COICA; C) Resolution/improvement of increased MTT and/or PTT (normalization of MTT and/or PTT) on CTP. 2. Gender difference.	These are objective biomarkers of improved cerebral perfusion and improved cognitive outcome.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Primary Hypothesis:
Revascularizing symptomatic chronically occluded cervical ICA (COICA) using endovascular techniques will significantly improve cognitive outcome.
Primary Objective:
To test the hypothesis that endovascular revascularization of COICA (via endovascular techniques) improves significantly cognitive function assessed by a specifically designed battery of 14 cognitive tests including the MoCA.

Secondary Objectivs:
To test the safety of endovascular revascularization of chronically occluded ICA.

Tertiary/Exploratory Objectives:
To test the hypothesis that subjects with symptomatic COICAs and mild/moderate cognitive dysfunction have the following biomarkers:

A) increased MTT or TTP on CTP in the ipsilateral side of the occluded ICA specifically in the MCA territory when compared to the opposite unaffected hemisphere
B) Presence of lactate and decreased Naa/Cr in the watershed area (specifically centrum semiovale) on 1H-MRI-spectroscopy, and
C) Decreased size of the hippocampus and amygdala on MRI.

Primary endpoints:

Cognitive outcome at 12-month follow-up assessed mainly by a specifically designed battery of 14 cognitive tests including MoCA.

Secondary endpoints:

1. Safety: Occurrence of Stroke, Cerebral Hemorrhage, or Death

Exploratory endpoints:
Biomarkers:

A) The presence/absence of lactate on 1H-MRI spectroscopy in centrum semiovale in the ipsilateral side of COICA;
B) The change in size of amygdala and hippocampus in the ipsilateral side of COICA.
C) Improvement/ normalization of MTT and/or PTT on CTP specifically in the ipsilateral MCA territory.
D) subgroup difference (Gender)

Study Design:
This is a phase 2 randomized single-center open label clinical trial with randomization of 1:1 to either best medical management vs. best medical management and endovascular revascularization of COICA. Subjects who meet all inclusion criteria but have a normal CTP may be included in the unrandomized prospective observational 3rd arm.

Intervention: Surgical intervention - endovascular balloon angioplasty and stenting

Protocol:

Screening, Enrolling, & Randomization:

All subjects who presents to our tertiary hospital with a diagnosis of COICA will undergo full evaluation including 1) documenting previous history of TIA and/or stroke; 2) cervical and brain CTA to document complete occlusion; 3) CTP to assess for presence of penumbra evident by increased MTT and/or PTT in the ipsilateral side of COICA; and 4) MoCA. If any subject is found to have complete occlusion of COICA, evident of abnormal/prolongation of MTT/ PTT on CTP, previous history of TIA and or stroke, and MoCA <26 or one abnormal neuropsychological test, then further evaluation is obtained including: 1H-MRI spectroscopy to assess for presence/absence of lactate in the ipsilateral watershed area (centrum semiovale), ratio of Naa/Cr, and size of ipsilateral hippocampus and amygdala, additional cognitive testing battery, and DSA to document adequately the type of COICA the subject have (type A-D).

If any subject has complete occlusion, and/or MoCA >26 or abnormal neuropsychological test but no abnormalities on CTP, then the subject is eligible for arm 3. This arm will only be prospective observational with best medical management. No randomization will be completed for these subjects.

If the subject does not meet inclusion/ exclusion criteria (except for the circumstance described above) the subject's participation will be discontinued. No further testing will be required.

If the subject meets all inclusion criteria, then a baseline of complete neurological testing, full demographics, CTA or MRA, CTP, MoCA, additional neurological testing (see below), 1H-MRI sectroscopy and DSA are obtained and subject is randomized 1:1 to either best medical management or best medical management + endovascular balloon angioplasty and stenting. If the subject is randomized to this treatment, their pre-op visit will include a blood draw (CBC and chemistry/BMP)

Follow up clinic visits are arranged at 6 and 12 months. Repeat testing of MoCA and additional cognitive testing battery are done at these clinical follow-up visits (6 and 12 months). MRI of the brain and DSA is performed at 6 month and 1 year follow-up to assess brain biomarkers and revascularization respectively. All MRI images required by the protocol may be completed under sedative, if subject requests and PI deems them eligible.

Definitions

1. Stroke: ischemic changes noted on CT/MRI of brain and associated with new neurological deficits within 120 days prior to enrolment.
2. TIA: New neurological deficits that resolve within 24 hours of onset and within 120 days prior to enrolment.
3. Abnormal neuropsychological test: any tests included in the screening battery that is scored below 1.5 SDs below the gender, age, and education matched norms.

Procedure:

Procedure will be performed under general anesthesia. Prior to induction of general anesthesia, A-line will be paced to monitor for blood pressure. The mean arterial pressure (MAP) will be maintained above 80mmHG during the procedure till complete revascularization of the occluded cervical ICA. At that time MAP will be lowered to < 80mmHG. The anesthesia team will use their standard of care medications to maintain the pressure as describe d above.

The groin area will be prepped and draped in the usual sterile fashion. Femoral access will be obtained using 18 gauge needle. Nine French sheet will be placed over the guide wire provided. 5 French Bernstein catheter and 6 French Cook shuttle catheter will be advanced over 0.038 Terumo guide wide to the common carotid artery of the occluded cervical ICA. At the time, the 5 French Bernstein catheter will be withdrawn and contrast will be injected to obtain selective images. After that, attempt to cross the occluded segment will be done, first using SL-10 microcatheter and 0.014 synchro soft microwire, if unsuccessful, then will use the 0.038 exchange Terumo guide wire. If not successful, then will use the stiffer end of the 0.038 exchange Terumo guide wire. If not successful, then abort procedure. If successful, then advance the microwire or the Terumo wire across the occlusion till identifying normal lumen. Following that, angioplasty and stenting using approved angioplasty balloons and carotid stents will be sued to recanalize the occluded ICCA. During that time, anesthesia will monitor for bradycardia. If any bradycardia, they treat per standard care and use atropine. Once recanalization is achieved, the MAP will be lowered to < 80mm Hg using standard care medication per anesthesia. IV maintenance dose Tirofiban (0.1 microgram/kg/min) immediately post procedure as a monotherapy for the first 24 hour Following that the puncture site will be closed using angioseal device. The patient will be extubated and transferred to surgical ICU for BP monitoring. If the subject is doing well, he/she is transferred to the normal floor. Aspirin and plavix will be continued for 12 months.

Strategies to mitigate risks to subjects during hospitalization include:
1) exclusion of subjects with COICA type D, 2) performing the procedure only by the PI, 3) strict perioperative blood pressure management to minimize hypoperfusion pre-procedure (maintain MAP ≥ 80mmHg and ≤120mmHg) and hyper-perfusion post procedure (maintain MAP≤ 80mmHg and ≥60mmHg, 4) admission to neuro-intensive critical for management post procedure, and 5) use of IV maintenance dose Tirofiban immediately post procedure as a monotherapy for the first 24 hours (no aspirin or clopidogrel) to reverse the effect of anti-platelet effect within 90 minutes in case of dreaded intracranial hemorrhage secondary hyper-perfusion (from our series, no subjects suffered intracranial hemorrhage). If the subject is with no signs or symptoms of intracranial hemorrhage, then at the end of 24 hours, the subject will be given a loading dose of clopidogrel (600 mg) and aspirin (325mg) and Tirofiban continued for another 2 hours in order for the loading dose of aspirin and clopidogrel to reach therapeutic effect.

Diagnostic and Follow- up angiograms:
These procedures will be done under monitored anesthetic are per standard care. The groin area will be prepped and draped in the usual sterile fashion. Femoral access will be obtained using 18 gauge needle. Five French sheet will be placed over the guide wire provided.
5 French Bernstein catheter will be advanced over 0.038 Terumo guide wide to the common carotid artery of the same side of previous recanalization. Dye will be injected and multiple images will be obtained to assess patency of stents. Following that, the puncture site will be closed using angioseal device. The subject will then be transferred to second stage and kept flat for 2 hours then discharged home.

Cognitive Testing:
Participants who are enrolled in this study will undergo a standardized neuropsychological test battery at 3 time points with the test score calculated at 12-month follow-up is considered the primary endpoint for the trial:

(1) Baseline: prior to procedure.

(2) Early Post-op: At 6 months post-discharge from hospital, to investigate short-term cognitive outcome;
(3) Late Post-op: At 12 months post-discharge from hospital, to investigate long-term cognitive outcome.

We selected a battery of tests that includes a standard screening measure (the MoCA), to facilitate comparisons to other studies that have used this as the primary cognitive outcome measure. The battery includes a number of well-standardized, widely used cognitive tests that measure various aspects of cognitive and behavioral functioning, including intelligence, attention, processing speed, memory, speech and language, visuoconstruction, and executive functioning. We selected a set of tests that can be administered in a one-hour session, and that are highly efficient (providing the highest yield for time required). Also, for all of these tests we have standardized information about the effects of repeat assessment, and/or multiple forms of the tests that allow practice effects to be either obviated or measured and factored into the analyses. A general reference for the neuropsychological assessment battery we are proposing is Lezak, Howiesen, Bigler, and Tranel (2012)53 , the standard textbook on neuropsychological assessment on which one of the current co-investigators (Tranel) is a co-author.

The test battery at each time point will include the following measures:
1. Montreal Cognitive Assessment (MoCA): This is a widely used screening instrument designed for the detection of cognitive impairment 62. Total points possible on this test range from 0 – 30.
2. Wide Range Achievement Test-5 (WRAT-5)104, Word Reading subtest: This is a single-word oral reading test, well-validated as an estimate of baseline general intelligence (Wilkinson & Robertson, 2017). The number of correctly read words is converted to an age-adjusted standard score (mean = 100, standard deviation = 15).
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7. Benton Visual Retention Test (BVRT) 7: This test measures attention, working memory, and visual
perceptual-constructional skills. The participant is shown a page containing one to three geometric

designs for 10 seconds, and then is instructed to draw the design(s) immediately after the stimulus is removed 88. Scores are the total number of correct designs (range 0 – 10) and total number of errors, converted to z-scores.

8. Controlled Oral Word Association (COWA) Test: This test measures flexible thinking and verbal fluency. The participant is asked to orally generate as many words as possible in 60 seconds, for each of three letters 7:. The score (age- and gender-corrected) is the total number of words generated across the three trials; this is converted to a percentile score.

9. Boston Naming Test (BNT): This is a test of confrontation naming in which the participant is presented line-drawn pictures and asked to name them 47 . The overall test contains 60 items, from which three equivalent short-form versions (20 items each) will be used in the current study 5. The score is the number of correctly named items (range 0 – 20), converted to a z-score.

10. Boston Diagnostic Aphasia Examination, Complex Ideational Material subtest (CIM): This is an auditory comprehension test developed to measure sustained attention and receptive language skills. It consists of yes/no questions of increasing difficulty in which the participant must recall common facts, and infer details contained in short, aurally presented stories 38. The range of scores on this test is 0 – 12, and raw scores are converted to T-scores.

11. Trail-Making Test, part A (TMT-A): This test measures attention, processing speed, and visuomotor skills. Participants are asked to connect 25 numbered circles as quickly and accurately as possible 78. The score is the time to completion (in seconds), converted to a T-score.

12. Trail-Making Test, part B (TMT-B): This test measures divided attention, processing speed, cognitive flexibility, and executive function. The participant is asked to connect 25 numbered and lettered circles, alternating between the two in numerical and alphabetical order (e.g., 1, A, 2, B, 3, C, etc.). The score is the time to completion (in seconds), converted to a T-score.

13. Beck Depression Inventory-Fast Screen (BDI-FS): This is a self-report inventory of depressive symptomatology, designed for use in persons with medical illnesses6. Scores are converted to a range of depression severity (none, mild, moderate, severe).

14. Iowa Scales of Personality Change (ISPC): On this measure, a collateral of the patient (e.g., spouse, child) rates behavioral and personality characteristics of the patient before and after a particular event (for the current study, this will be the surgical intervention) 4. The ISPC measures changes in personality and behavior, and will be administered only at the post-surgery evaluations (to the collateral). Scores are converted to z-scores.

The score on the MoCA will serve as an overall proxy for cognitive outcome, and can be used to measure change (e.g., pre to post). Scores from tests 2-12 in the proposed neuropsychological battery will be converted to z-scores, to facilitate direct comparisons across the test battery for pre to post (including short- and long-term outcomes). These will also be used to analyze changes in specific cognitive domains. The score from the BDI-FS will be used as a covariate to assess the role of depressive symptomatology in cognitive performance.

Demographics collected:

We will collect the following demographics during initial screening visit: age, gender, education level, antiplatelets and anticoagulation therapy, statin therapy, NIHSS, pre-procedure modified Rankin Scale (mRS), employment, history of depression, use of antidepressant medications, history of hypertension, history of stroke/TIA, history of seizures, comorbid diseases, and history of head injury.

CTP protocol (adopted from Kamath et al; Neuroradiology. 2008 Sep; 50(9): 745–751; Bathla et al, J NeuroIntervent Surg 2019;0:1–5. doi:10.1136/neurintsurg-2019-014810):

CTP is performed in the radiology department using Siemens CT scanner. Images will be acquired on either a 128 slice (SOMATOM definition AS; Siemens AG, Forchheim, Germany) or a 192 slice (SOMATOM Force, Siemens AG) scanner.
18 French IV access is obtained. Then 40 ml bolus of iodine contrast (Isovue-370, iopamidol, 370 mg iodine/mL; Bracco Diagnostics, Princeton, New Jersey, USA) is administered into a vein using a power injector (Stellant D; MedRad Inc, Indianola, Pennsylvania, USA), with a 2 s delay between contrast injection and scan initiation. The acquisition parameters are 80 kV and 9.6 cm scan range. he radiation dose is 2 mSv. Data are acquired using the protocol recommended: with 4 scans 3 s apart followed by 15 scans 1.5 s apart, and another 9 scans 3 s apart, totaling 28 scans over approximately 60 s. We will utilize the software in the Siemens CT scanner in our radiology department [The Syngo software (Syngo.via CT Neuro Perfusion VB30; Siemens Healthineers, Erlangen, Germany)]. Initial post-processing using the vendor specified parameters to include initial motion correction, bone removal and brain segmentation, 4D noise reduction, and reference vessel and arterial input function detection. The software is programmed to use the central volume principle will apply the curve fitting by least mean squares to obtain mathematical descriptions of the time-density curves for each pixel. A closed-form (non-iterative) deconvolution that accounts for delay-related errors is then applied to calculate the mean transit time (MTT) map. The deconvolution operation requires a reference arterial input function (AIF). The cerebral blood volume (CBV) map is calculated from the area under the time-density curves. Cerebral blood flow (CBF) is calculated as the CBV/MTT ratio. In Syngo, infarct core/non-viable tissue (NVT) is defined as rCBF <threshold. Voxels not treated as NVT are classified as 'tissue at risk' (TAR) if Tmax >6 s. MR was calculated as MR=(TAR+NVT)/NVT.

MRI protocol:
MR Image Acquisition MR imaging will be performed on a GE 750W 3T scanner using a 32-channel head coil. Anatomical images will include volumetric T1 MPRAGE (TI=900ms, TE=3ms, TR=3000ms, flip angle=10°, FOV=210x210x210mm, matrix=420x420x420, bandwidth= 244Hz/pixel, acceleration=4) and T2 CUBE (TE= 90ms, TR= 3000ms, echo train length=130, FOV=210x210x210mm, matrix=420x420x420, bandwidth= 488Hz/pixel, acceleration=4) sagittal scans with a 0.5 mm isotropic spatial resolution. The 1H MRS data will be acquired from voxels placed in the centrum semiovale in the ipsilateral side of COICA using a single-voxel semi-LASER sequence with the following parameters: TE=288, TR=4000ms, Voxel size = 20x20x20mm, Spectral Width=5000Hz, Vector size=4096, and NEX=32. Data will be collected with and without water suppression.

Volumetric Anatomical Image Analysis: The volumetric anatomical T1- and T2-weighted images will be analyzed using BRAINS AutoWorkup 72 that includes a FreeSurfer 22,32,33 module using Nipype 39. The default FreeSurfer pipeline will be updated to segment the brain and generate the cortical surface using a 0.5mm resolution for the reconstruction. The original images and the automated pipeline results will be checked for validity by a trained technician who is blind to subject status. Of primary interest for this analysis is the volume of the hippocampus and amygdala as generated by this pipeline

MRI-Specteroscpy (MRS) Analysis. The 1H MRS data will be analyzed using LCModel 77. The water suppressed and non-water suppressed data will be analyzed to generate absolute concentrations after performing phase and eddy current correction. We will obtain concentrations measurements for NAA, glutamate+glutamine (Glx), total creatine (Cr+PCr), total choline (tCho), and lactate from

the 1H data. Only metabolites with a Cramer-Rao lower bound of less than 20% will be included in further analyses. Lactate concentrations will be the primary metabolite of interest for this study.

MRI protocol for checking silent infarcts/strokes will contain the same sequences described previously in addition to adding T2 and SWI sequences. Each will add 2-3 minutes with a total of 4-6 minutes

All MRI images required by the protocol may be completed under sedative, if subject requests and PI deems them eligible.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Control is observation and best medical management for the carotid occlusion which is the standard of care.

4.3 JUSTIFICATION FOR DOSE

Not applicable here.

4.4 END OF STUDY DEFINITION

1) Successful completion is 1-year cognitive assessment
2) Early termination due to intracranial hemorrhage, stroke, death, seizure or injury to cervical ICA

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- Age ≥ 21
- Complete occlusion of cervical ICA on imaging studies (MRA or CTA) and confirmed with DSA
- History of TIA or stroke
- Increased MTT and/or TTP on CTP as defined as TMax threshold of > 10cc > 4 seconds in the territory of the occluded carotid specifically in the MCA territory when compared to the opposite unaffected hemisphere
- All occlusion is due to atherosclerotic disease
- MoCA < 26 and/or one abnormal test on the rest of the neuropsychological battery administered at screening
- Occlusion is class A or B using COICA classification
- Study team able to gain consent from subject or LAR
- 7. Failed best medical treatment (continued TIA symptoms despite medical management)

5.2 EXCLUSION CRITERIA

- History of Moyamoya or Moyamoya like disease
- Tandem occlusion
- No evidence of increased MTT or TTP on CT perfusion ✧

- Severe co-morbid diseases: renal insufficiency, end-stage renal disease, liver cirrhosis, COPD requiring home oxygen, terminal illness such as cancer, Parkinson disease or other neurodegenerative diseases, severe cognitive heart failure, seizures, debilitating stroke, mRS ≥3.
- Short life expectancy due to cancer or other co-morbid diseases
- Class C or D on COICA classification ✧
- Occlusion of the Common Carotid Artery
- Normal neuropsychological battery results ✧
- Subject unwilling to participate in follow up and/ or unwilling to be randomized to surgery✧

✧ If subject meets any combination of these exclusion criteria, they may be applicable for the non-randomized third arm.

If a subject meets all criteria and is randomized to surgery their eligibility will be confirmed by 1 outside adjudicator. If this decision is not in agreement with the PI then a second adjudicator will review. Despite ruling, inclusion will be confirmed by two clinicians (PI and adjudicator or both adjudicators).

5.3 LIFESTYLE CONSIDERATIONS

Smoking cessation.

5.4 SCREEN FAILURES

These subjects will be monitored longitudinally per standard of care for any signs of stroke/TIAs or other neurological deterioration including cognitive decline. If during the study period, the subjects re-meet the criteria of inclusion, then they will be approached again for enrollment.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment

Participants will present to either to the emergency department and/or neurosurgery/neurology clinic for evaluation of symptomatic chronic cervical internal carotid artery (ICA) occlusion (COICA). Imaging studies will be obtained to confirm diagnosis of COICA.

To be recruited and enrolled for the trial, the following inclusion/exclusion criteria must be satisfied:

E.2 Inclusion and Exclusion Criteria:

Inclusion Criteria	Exclusion Criteria
Age ≥ 21	History of Moyamoya or Moyamoya like disease
Complete occlusion of cervical ICA on imaging studies (MRA or CTA) and confirmed with DSA	Tandem occlusion
History of TIA or stroke	No evidence of penumbra (increased MTT and/or PTT) on CT perfusion ✧
Increased MTT and/or TTP on CTP as defined as TMax threshold of > 10cc > 4 seconds in the territory of the occluded carotid specifically in the MCA territory when compared to the opposite unaffected hemisphere	Severe co-morbid diseases: end-stage renal disease, liver cirrhosis, COPD requiring home oxygen, terminal illness such as cancer, Parkinson disease or other neurodegenerative diseases,

	severe congetive heart failure, seizures, debilitating stroke, mRS ≥3.
All occlusion is due to atherosclerotic disease	Short life expectancy due to cancer or other co-morbid diseases
MoCA < 26 and/or one or more abnormal test on the rest of the neuropsychological battery administered at screening	MoCA ≥ 26 and normal screening battery✧
Study team able to gain consent from subject or LAR	Subject unwilling to participate in follow up and/ or unwilling to be randomized to surgery ✧
Class A or B occlusion based on COICA classification	Class Cor D occlusion based on COICA classification ✧
	Occlusion of the Common Carotid Artery

✧ If a subject meets any combination of these exclusion criteria, they may be applicable for the non-randomized third arm.

E.3 Definitions:

- Chronically Occluded Cervical ICA (COICA): documented complete occlusion of cervical ICA evident on CTA, and/or MRA for at least 4 weeks.
- Symptomatic (COICA): subjects with chronically occluded ICA with a presentation of TIA and/or stroke corresponding to anatomical structures supplied by the ipsilateral COICA.
- Abnormal test is considered 1.5 SD below age, gender, and education norms
- Severity of impairment
    - Mild cognitive impairment: MoCA score < 26 but ≥23
    - Moderate cognitive impairment: MoCA score < 23 but ≥18
    - Severe cognitive impairment: MoCA < 18

I. The proposed NIA SCORE trial is committed to aggressively recruit and include women and members of minority groups.

II. MINORITY RECRUITMENT

The investigators have set a goal of enrolling at least 15-30% of minorities in this trial. To ensure adequate recruitment and enrolment of minorities to the trial, we will employ the following strategies:

1. The research team will be educated and made aware of the attention that must be given to cultural, historical, social, and political factors that may influence minority participation. In focus groups with African-Americans, many of them needed clarification of a clinical trial, and the term "research study" had more meaning. Most indicated that certain criteria had to be in place before they would consider participating: benefit to family/community, pastor's encouragement, type of research, understanding of study, and who is conducting the research.
2. Social workers will be involved to help arrange for transportation for these study subjects who lack them, which is important for follow-up in clinic.
3. Clinic office hours may need to be extended to allow for the schedules of working individuals or those with caregiving responsibilities.
4. The accessibility and location of the clinic/hospital would also be considered to encourage compliance with follow-up appointments.

III. RECRUITMENT OF WOMEN:

The investigators have set a goal of enrolling at least 30-50% women in this trial. The staff and investigators will make it a priority to make extra time and commitment to understand other issues in the subject's personal life that may affect her enrollment and compliance.

IV. Specific strategies that we will use to enhance recruitment and retention of underrepresented minorities and women into your trial:

The research team will employ the following additional strategies to ensure adequate enrolment of women and minorities in the trial by suing these specific strategies:

1. The research team will be urged to appropriately present the trial to women and all minority patients with emphasis on presenting the facts in regard to the potential impact of the study on their health and standard care.
2. The nurse research coordinator will periodically communicate with women and minority subjects to address their concerns and attempt to facilitate compliance and retention and minimize drop out.
3. Financial voucher ($75) per annual clinic visit will be provided to cover gas mileage, parking, and a small meal.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Endovascular balloon angioplasty and stenting
Medical management: Aspirin 325 mg po daily; Plavix 75 mg po daily; Statin.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

1) Randomized 1:1 ratio
2) Blinded assessment of cognition, MRI and exploratory endpoints

6.3 STUDY INTERVENTION COMPLIANCE

Percent revascularized

6.4 CONCOMITANT THERAPY

Best Medical Management: daily dual antiplatelet therapy (aspirin: 325 mg p.o. qd and Clopidogrel: 75 mg p.o. qd), optimization of systolic blood pressure (120 -140 mmHg), smoking cessation, and statin therapy. These primary risk factors (systolic blood pressure, smoking, and cholesterol level) will be managed mainly by the local primary care physician with inputs from the research team. The goal is targeting a systolic blood pressure (SBP) 120-140 mmHg and smoking cessation. Subjects will be monitored by the primary care physician after enrollment and then every four months for management

of risk factors during the first year, then annually thereafter. Also during follow up visits, the research team will ensure compliance with medications.
Also keeping the SBP > 120mmHg will ensure prevention of potential hypoperfusion of the brain resulting into cerebral hemodynamic compromise and potential TIA and/or stroke.
Statin: the subject will be started on Lipitor 20 mg po qd. Lipid profile will be monitored by the primary care physician.

Smoking Cessation: We chose a target level of complete cessation of smoking in our trial for the following reasons: 1. Several studies have shown that smoking is associated with worsening atherosclerotic disease and stroke. 2. Smoking cessation is recommended for all patients by the US Department of Health and Human Services and by the AHA/ASA guidelines for the Primary Prevention of stroke. and management of UIA. 3. Light and intermittent smoking have been associated with increased cardiopulmonary and cerebrovascular risks and death. If the patient doesn't quit smoking, he/she will continue to be encouraged to quit smoking and he/she will be kept enrolled in the study.

To insure compliance with recommendation and best medical management plan, we will implement the following: A) The study will provide each subject with a blood pressure cuff to measure blood pressure in siting position biweekly and document pressure measurements in a diary notebook. These measurements will be taken at home and in clinic. The measurements will be reviewed by the PCP of the study, the research nurse, and local PCP. Family member will be educated on how to take the blood pressure. The nurse research will observe the family member perform BP measurements on the subject during the initial training and in random visits to ensure adequate technique. B) Counting bills by the research team during clinic visits will be used to monitor for compliance. C) Lipid profile panel will be used to monitor compliance for using statin. D) A survey of over the counter medications will be obtain during each clinic visit.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

None

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention such as development of cancer, severe COPD, end stage renal disease, …
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the REDCap Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

Enrolled subjects in the study are expected to be followed for 12 months post intervention. The followup included assessment of cognitive function using the designed battery of tests (including Moca), DSA, CTP and MRI of the brain.
Participants are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures.
To minimize that:

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The research nurse will attempt to contact the participant and reschedule the missed visit within 30 days from scheduled visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the PI will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Cognitive Testing:
Participants who are enrolled in this study will undergo a standardized neuropsychological test battery at 3 time points with the test score calculated at 12-month follow-up is considered the primary endpoint for the trial:
(1) Baseline: prior to procedure.
(2) Early Post-op: At 6 months post-discharge from hospital, to investigate short-term cognitive outcome;
(3) Late Post-op: At 12 months post-discharge from hospital, to investigate long-term cognitive outcome.

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repeat assessment, and/or multiple forms of the tests that allow practice effects to be either obviated or measured and factored into the analyses. A general reference for the neuropsychological assessment battery we are proposing is Lezak, Howiesen, Bigler, and Tranel (2012)53 , the standard textbook on neuropsychological assessment on which one of the current co-investigators (Tranel) is a co-author. The test battery at each time point will include the following measures:

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12. Trail-Making Test, part B (TMT-B): This test measures divided attention, processing speed, cognitive flexibility, and executive function. The participant is asked to connect 25 numbered and lettered circles, alternating between the two in numerical and alphabetical order (e.g., 1, A, 2, B, 3, C, etc.). The score is the time to completion (in seconds), converted to a T-score.
13. Beck Depression Inventory-Fast Screen (BDI-FS): This is a self-report inventory of depressive symptomatology, designed for use in persons with medical illnesses6. Scores are converted to a range of depression severity (none, mild, moderate, severe).
14. Iowa Scales of Personality Change (ISPC): On this measure, a collateral of the patient (e.g., spouse, child) rates behavioral and personality characteristics of the patient before and after a particular event (for the current study, this will be the surgical intervention) 4. The ISPC measures changes in personality and behavior, and will be administered only at the post-surgery evaluations (to the collateral). Scores are converted to z-scores.

The score on the MoCA will serve as an overall proxy for cognitive outcome, and can be used to measure change (e.g., pre to post). Scores from tests 2-12 in the proposed neuropsychological battery will be converted to z-scores, to facilitate direct comparisons across the test battery for pre to post (including short- and long-term outcomes). These will also be used to analyze changes in specific cognitive domains. The score from the BDI-FS will be used as a covariate to assess the role of depressive symptomatology in cognitive performance.

MR Image Acquisition MR imaging will be performed on a GE 750W 3T scanner using a 32-channel head coil. Anatomical images will include volumetric T1 MPRAGE (TI=900ms, TE=3ms, TR=3000ms, flip angle=10°, FOV=210x210x210mm, matrix=420x420x420, bandwidth= 244Hz/pixel, acceleration=4) and T2 CUBE (TE= 90ms, TR= 3000ms, echo train length=130, FOV=210x210x210mm, matrix=420x420x420, bandwidth= 488Hz/pixel, acceleration=4) sagittal scans with a 0.5 mm isotropic spatial resolution. The 1H MRS data will be acquired from voxels placed in the centrum semiovale in the ipsilateral side of COICA using a single-voxel semi-LASER sequence with the following parameters: TE=288, TR=4000ms, Voxel size = 20x20x20mm, Spectral Width=5000Hz, Vector size=4096, and NEX=32. Data will be collected with and without water suppression.

Volumetric Anatomical Image Analysis: The volumetric anatomical T1- and T2-weighted images will be analyzed using BRAINS AutoWorkup 72 that includes a FreeSurfer 22,32,33 module using Nipype 39. The default FreeSurfer pipeline will be updated to segment the brain and generate the cortical surface using a 0.5mm resolution for the reconstruction. The original images and the automated pipeline results will be checked for validity by a trained technician who is blind to subject status. Of primary interest for this analysis is the volume of the hippocampus and amygdala as generated by this pipeline
MRI-Specteroscpy (MRS) Analysis. The 1H MRS data will be analyzed using LCModel 77. The water suppressed and non-water suppressed data will be analyzed to generate absolute concentrations after performing phase and eddy current correction. We will obtain concentrations measurements for NAA, glutamate+glutamine (Glx), total creatine (Cr+PCr), total choline (tCho), and lactate from the 1H data. Only metabolites with a Cramer-Rao lower bound of less than 20% will be included in further analyses. Lactate concentrations will be the primary metabolite of interest for this study

All MRI images required by the protocol may be completed under sedative, if subject requests and PI deems them eligible.

8.2 SAFETY AND OTHER ASSESSMENTS

Stopping rules or safety triggers for the study:
The occurrence of the following potential side effects and risks associated with procedure will trigger prompt reporting and review by the DSMB to discuss the events and decide on the continuation of the trial. The following adverse events, will be reported to the DSMB: 1) Any intracranial hemorrhage within 72 hours post procedure, 2) Any stroke within 30 days post procedure; 3)Any seizure within 72 hours post procedure; and 4) any injury to cervical ICA during the procedure.
Based on complication rates in the trial to date (June 2021), the occurrence of one additional event in these categories will trigger a suspension of enrollment in the trial and meeting of the DSMB to discuss the events and decide on the continuation of the trial
The cumulative rates will also be assessed at different time points: A) after completed enrollment of the first 10 subjects, B) completed enrollment of first 20 subjects, & C) Completed enrollment of first 30 subjects. A rate of > 20% will lead to automatic stop and evaluation by the DSMB.
Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor (Dr. Edgar Samaniego).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Potential risks to research subjects are: 1. Intracranial hemorrhage secondary to re-perfusion injury; 2. Stroke; 3. Seizures; 4. Extravasation of contrast secondary to injury to cervical ICA during the procedure; and 5. Contrast allergy. Strategies to mitigate risks to subjects in the trial include 1) exclusion of subjects with COICA type D, 2) performing the procedure only by the PI, 3) strict perioperative blood pressure management to minimize hypoperfusion pre-procedure (maintain MAP ≥ 80mmHg and ≤120mmHg) and hyper-perfusion post procedure maintain MAP≤ 80mmHg and ≥60mmHg, 4) admission to neuro-intensive critical for management post procedure, and 5) use of IV maintenance dose Tirofiban immediately post procedure as a monotherapy for the first 24 hours (no aspirin or clopidogrel) to reverse the effect of anti-platelet effect within 90 minutes in case of dreaded intracranial hemorrhage secondary hyper-perfusion (from our series, no subjects suffered intracranial hemorrhage). If the subject is with no signs or symptoms of intracranial hemorrhage, then at the end of 24 hours, the subject will be given a loading dose of clopidogrel (600 mg) and aspirin (325mg) and Tirofiban continued for another 2 hours in order for the loading dose of aspirin and clopidogrel to reach therapeutic effect

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse Event (AE) Reporting:

Any potential adverse event or a serious adverse event mentioned above will be reported during the trial. An AE will be defined as any unfavorable and/or unintended sign, symptom, or injury temporally associated with the procedure or other study medication. A serious adverse event (SAE) is defined as any untoward/undesirable adverse experience related to a study intervention/medication that results in any of the following outcomes: 1) death; 2) a life-threatening adverse experience; 3) need for additional surgery; 4) a permanent or significant disability/incapacity; 5) important medical events that may not result in death, be life-threatening, or require additional surgery.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

All adverse events (AEs) will be collected, recorded, and analyzed. Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor (Dr. Edgar Samaniego).
All AEs will be classified as related to the intervention based on severity, relatedness and outcome.

8.3.3.2 EXPECTEDNESS

Potential risks to research subjects are: 1. Intracranial hemorrhage secondary to re-perfusion injury; 2. Stroke; 3. Seizures; 4. Extravasation of contrast secondary to injury to cervical ICA during the procedure; and 5. Contrast allergy, 6. carotid fistula, 7. Radiation exposure

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Strategies to mitigate risks to subjects in the trial include 1) exclusion of subjects with COICA type D, 2) performing the procedure only by the PI, 3) strict perioperative blood pressure management to minimize hypoperfusion pre-procedure (maintain MAP ≥ 80mmHg and ≤120mmHg) and hyper-perfusion post procedure (maintain MAP≤ 80mmHg and ≥60mmHg, 4) admission to neuro-intensive critical for management post procedure, and 5) use of IV maintenance dose Tirofiban immediately post procedure as a monotherapy for the first 24 hours (no aspirin or clopidogrel) to reverse the effect of anti-platelet effect within 90 minutes in case of dreaded intracranial hemorrhage secondary hyper-perfusion (from our series, no subjects suffered intracranial hemorrhage). If the subject is with no signs or symptoms of intracranial hemorrhage, then at the end of 24 hours, the subject will be given a loading dose of clopidogrel (600 mg) and aspirin (325mg) and Tirofiban continued for another 2 hours in order for the loading dose of aspirin and clopidogrel to reach therapeutic effect.

All AEs will be followed until resolution with treatment by best medical or surgical management.

8.3.5 ADVERSE EVENT REPORTING

Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor (Dr. Edgar Samaniego). Reports will be done of comparison of the intervention groups every 10 patients to the DSMB.

Data and Safety Monitoring Board [DSMB]:
The DSMB will be appointed by the NIA to monitor the performance of the study. The Steering Committee will prepare regular reports summarizing patient accrual and the morbidity and mortality experienced in the study, The DSMB will also review the cumulative outcome data at regular intervals (every 6 months).

Stopping rules or safety triggers for the study:
The occurrence of the following potential side effects and risks associated with procedure will trigger prompt reporting and review by the DSMB to discuss the events and decide on the continuation of the trial.
The following adverse events will be reported to the DSMB: 1) Any intracranial hemorrhage within 72 hours post procedure, 2) Any stroke within 30 days post procedure; 3) Any seizure within 72 hours post procedure; and 4) Any injury to the cervical ICA during the procedure.
Based on complication rates in the trial to date (June 2021), the occurrence of one additional event in these categories will trigger a suspension of enrollment in the trial and meeting of the DSMB to discuss the events and decide on the continuation of the trial.
Safety oversight for this study will be provided by both the DSMB and the Independent Medical Safety Monitors.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

AEs will be reported as they occur to the medical monitor. Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor (Dr. Edgar Samaniego). Serious AEs will be reported to the DSMB and IRB as required.

Any potential adverse event or a serious adverse event mentioned above will be reported during the trial. An AE will be defined as any unfavorable and/or unintended sign, symptom, or injury temporally associated with the procedure or other study medication. A serious adverse event (SAE) is defined as any untoward/undesirable adverse experience related to a study intervention/medication that results in any of the following outcomes: 1) death; 2) a life-threatening adverse experience; 3) need for additional surgery; 4) a permanent or significant disability/incapacity; 5) important medical events that may not result in death, be life-threatening, or require additional surgery.

Study Monitoring

Local IRB monitors will conduct yearly monitoring visit. Review of the protocol and all data collection forms will be conducted, confirming the investigators' compliance and thereby ensuring appropriate and accurate data collection, regulatory committee approval, and informed consent procedures. Any minor concerns in data collection issues will be dealt with by the IRB. All significant concerns regarding either data collection or the nature of an investigator's participation which are not immediately solved will be reported by the IRB designated monitor and further evaluated by the IRB. Should an investigators deviate from the study protocol, the IRB will raise the issue with the Steering Committee, which will determine an appropriate course of action.

Participant Confidentiality

All imaging studies (MRA, CTA, and/or DSA), case report/evaluation forms, laboratory specimens, and other records will be de-identified and assigned Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a secure and locked file cabinet with keys to this cabinet only kept by the PI and/or nurse research coordinator. No clinical information will be shared or released without the written permission/consent of the patient, except as necessary for minoring by the IRB.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Adverse Event (AE) Reporting:

Any potential adverse event or a serious adverse event mentioned above will be reported during the trial. An AE will be defined as any unfavorable and/or unintended sign, symptom, or injury temporally associated with the procedure or other study medication. A serious adverse event (SAE) is defined as any untoward/undesirable adverse experience related to a study intervention/medication that results in any of the following outcomes: 1) death; 2) a life-threatening adverse experience; 3) need for additional surgery; 4) a permanent or significant disability/incapacity; 5) important medical events that may not result in death, be life-threatening, or require additional surgery.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Definition of unanticipated problems: unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

This includes:
1. Development of carotid cavernous fistula
2. loss of vision
3. renal dysfunction due to contrast toxicity
4. seizures

An incident, experience, or outcome that meets the definition of an UP generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Other UPs may warrant corrective actions. Examples of corrective actions or changes that might need to be considered in response to an UP include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The PI will report unanticipated problems (UPs) to the reviewing DSMB and the Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary endpoints:
Cognitive outcome at 12-month follow-up assessed mainly by a specifically designed battery of 14 cognitive tests including MoCA.

Secondary endpoints:
1. Safety: Occurrence of Stroke/TIA, Cerebral Hemorrhage, or Death

Exploratory endpoints:
1. Biomarkers: A) The presence/absence of lactate on 1H-MRI spectroscopy in centrum semiovale in the ipsilateral side of COICA; B) The change in size of amygdala and hippocampus in the ipsilateral side of

COICA; C) improved and/or normalization of MTT and/or PTT on CTP specifically in the ipsilateral MCA territory.

Subgroups: Gender difference.

9.2 SAMPLE SIZE DETERMINATION

To maximize success of the intervention, we will only enroll subjects with classification of A, B, or C. The current success rate for revascularizing types A & B using EVT is 100% and type C using the Hybrid technique is 80% making the success rate for the whole sub-cohort is 93%. Based on our preliminary data and others, the mean difference in the pre- and post-procedure MoCA score was between 5-8 points. Using two comparisons: A) comparison between intervention vs. best medical management and B) pre- and post-intervention for successful vs unsuccessful intervention. We pooled the data for these studies, and then used the lower and upper ends of the confidence interval calculated between the suggested groups for the trial (best medical management vs. intervention). Doing so, we will assume the difference between pre- and post-procedure MoCA score to be 2 points and standard deviation to be 2 points. Assuming α=0.05; β=0.8; and power of 80%, then our total sample size needed is 34 (Table 2). Based on our previous clinical trial experiences, we anticipate maximum of 10% drop out. Given that, then total sample size needed is 38 subjects with 19 subjects in each group.

Sample size estimates: Total N							
MoCA Score	Difference in total points between pre and post procedure	1		2		3	
	Standard Deviation difference between pre & post procedure	1	2	1	2	1	2
Power :							
0.8		34	128	5	34	6	16
0.85		38	146	12	38	8	18
0.9		46	172	14	46	8	20
0.95		54	210	16	54	8	26

9.3 POPULATIONS FOR ANALYSES

Data analysis will be performed based on Intention-to-Treat (ITT).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The analysis will be intention to treat.

1) Comparison of treatment groups of baseline variables
2) Comparison of primary endpoint
    a. MOCA change
    b. Cognitive battery summary score
3) Comparison of secondary endpoints
4) Exploratory analysis of associations of exploratory endpoints with cognitive change

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary Endpoint: Montreal Cognitive Assessment (MoCA) and cognitive battery of tests. They will be administered by a neuropsychologist masked to treatment at the pre-treatment, at 3 month and 12 month assessments. The battery is designed to assess left hemisphere function, right hemisphere function, and global function. All tests had published age-adjusted norms 10,12,38,59,60,76,80,95,101,108. All subjects will undergo all 14 cognitive tests. The order of test administration will remain constant, accommodating the delays required for recall intervals and minimizing stimulus interference in memory tasks. The raw score for each test for each subject will be converted into test-specific z score for each test in the battery. Then a composite z score based on average z score for the tests for each subject (sum of the z scores divided by the number of tests included) will be calculated. A two-sided type I error rate of 0.05 will be used.

A linear mixed effect model (PROC MIXED in SAS, Version 9.4) will be used to compare the two groups (medical management vs. surgical intervention) with the change in MoCA as the dependent variable across the repeated measures of 6 months and 12 months. The main independent variable is the intervention. The multivariable model will be adjusted for the following covariates: age, gender, education level (≤8th grade, 9th–12th grade [high school], or ≥13 years [some college]), ICA side, and pre-treatment depression (as measured by the Center for Epidemiologic Studies–Depression scale). The correlation coefficient between MoCA change and the composite cognitive score will be calculated. A second comparative model of the interventions will be performed to support the primary analysis. It will use the change in composite cognitive z score as the dependent variable. Similar analysis using mixed linear models and covariates will be done.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The safety measures of occurrence of Stroke/TIA, cerebral hemorrhage, or death will be analyzed as frequency within the 30-day post-procedure period. Analysis will be done in aggregate of the events combined and individually using a Kaplan-Meier survival estimation with a Logrank test. Adjustment for age, etiology of ischemia, and side of occlusion will be done using a Cox Model Regression. A two-sided type I error rate of 0.05 will be used.

Analysis of the Tertiary/exploratory Endpoint

Tertiary/exploratory endpoints will be analyzed individually. The presence/absence of lactate will be estimated by a proportion and evaluated using a Fisher's Exact Test. The change in sizes of amygdala and hippocampus in the ipsilateral side of COICA will be using a T-Test of the difference. Improved and/or normalization of MTT and/or PTT on CTP specifically in the ipsilateral MCA territory will be analyzed using a T-Test.

9.4.4 SAFETY ANALYSES

Event rates by treatment group will be reported with 95% confidence intervals. The distribution by severity will be compared. Kaplan-Meier time to event curves will be done for AEs and deaths. Logrank tests will be performed.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Baseline descriptive statistics will be done for each treatment group and compared using Chi-Square Tests and t-tests as determined by variable type.

9.4.6 PLANNED INTERIM ANALYSES

Interim analysis for safety every 10 patients

9.4.7 SUB-GROUP ANALYSES

By gender

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Cognitive measures at baseline, 6 months and 12 months

9.4.9 EXPLORATORY ANALYSES

The presence/absence of lactate will be estimated by a proportion and evaluated using a Fisher's Exact Test. The change in sizes of amygdala and hippocampus in the ipsilateral side of COICA will be using a T-Test of the difference. Improved and/or normalization of MTT and/or PTT on CTP specifically in the ipsilateral MCA territory will be analyzed using a T-Test.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Informed consent will be obtained after study details are explained in full to the patient, and the patient was provided with written informed consent to read it. The patient will be informed that the study is a research effort, that participation is fully voluntary and that refusal to participate will in no way compromise the patient's clinical care, with full disclosure of potential risks and benefits for participation.

At presentation to neurosurgery/neurology clinic, the patient will undergo neurologic, neuro-imaging evaluation, DSA, and cognitive testing as part of standard clinical care at the participating center. If the patient appears eligible on the basis of clinical and imaging (see above), the patient will be be approached to obtain written consent. The consent form will contain the background of the proposed study and the benefits and risks of the procedures and will be explained in detail to the patient. Informed consent must be signed by the patient prior to enrollment. Failure to obtain a signed informed consent renders the patient ineligible for the study. Copies of the signed informed consent will be kept in the patients' file and in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

An IRB approved consent form will be utilized.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The consent form will contain the background of the proposed study and the benefits and risks of the procedures and will be explained in detail to the patient. Informed consent must be signed by the patient prior to enrollment. Failure to obtain a signed informed consent renders the patient ineligible for the study. Copies of the signed informed consent will be kept in the patients' file and in the medical record.

Unless otherwise stated, all consents are done following the strictest Good Clinical Practice (GCP) protocol. This includes proper assessment of ability to consent, time to consider enrollment with loved ones, opportunity to discuss consent with study staff, time to ask questions and receive all appropriate answers, and all other applicable components.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Participants will be informed if the study is closed prematurely or at the end of the study.

Recruitment and Enrolment will be assessed every 6 months. We anticipate enrolling 1 subject every 5 weeks and allowing for 12 months follow up visit. If the recruitment/enrolment is averaged at 1 subject per 10 weeks for 24 months, then the study will be futile and will be stopped for failure of accrual.

10.1.3 CONFIDENTIALITY AND PRIVACY

All research activities will be conducted in as private a setting as possible.

All imaging studies (MRA, CTA, and/or DSA), case report/evaluation forms, laboratory specimens, and other records will be de-identified and assigned Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a secure and locked file cabinet with keys to this cabinet only kept by the PI and/or nurse research coordinator. No clinical information will be shared or released without the written permission/consent of the patient, except as necessary for minoring by the IRB.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting will be stored on secure servers. Password access for data collection and analysis will be used.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Specimens will be retained for assessment of biomarkers only with permission of the participants through the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
David Hasan, MD	TBN
University of Iowa	
University of Iowa Hospitals and Clinics	
Phone Number	
david-hasan@uiowa.edu	

10.1.6 SAFETY OVERSIGHT

Data and Safety Monitoring Board [DSMB]:
The DSMB will be appointed by the NIA to monitor the performance of the study. The Steering Committee will prepare regular reports summarizing patient accrual and the morbidity and mortality experienced in the study, The DSMB will also review the cumulative outcome data at regular intervals (every 6 months) or every 10 patients.

All adverse events (AEs) will be collected, recorded, and analyzed. Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor (Dr. Edgar Samaniego).

10.1.7 CLINICAL MONITORING

The DSMB and Medical Safety Monitor (Dr. Edgar Samaniego) will assess the performance of the study including accrual, intervention execution, adverse events and clinical outcome assessment.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

10.1.9 DATA HANDLING AND RECORD KEEPING

Data collection will be in compliance with ICH GCP and regulatory and UI institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored or NIH-affiliated study, the records and data will be available for authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Records will be available to study staff and to IRB staff for review.

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be done through case report forms created and utilized via REDCap software.
Quality control will examine range checks, missing data and incomplete data.
Data analysis for reporting and statistical analysis will be done with SAS Version 9.4.

10.1.9.2 STUDY RECORDS RETENTION

Study records will be maintained for access and review for at least 3 years after the last patient follow-up.

10.1.10 PROTOCOL DEVIATIONS

Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.]

10.1.12 CONFLICT OF INTEREST POLICY

10.2 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
COICA	Chronically occluded cervical ICA
MRI	Magnetic resonance imaging
CTP	CT perfusion
CTA	CT angiogram
MTT	Mean transient time
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
V3.0	8/13/20	Revision to study design to reflect I/E adjustment	Including changes to make study endpoints consistent with I/E criteria
V3.0	8/13/20	Change 3 month visit to 6 month follow up	Makes study protocol more consistent with surgical/ clinical procedures
V3.0	8/13/20	Inclusion/ exclusion criteria adjusted	Includes more subjects and reflects issues we have faced so far with recruitment
V3.0	8/13/20	Added blood draw, if subject is randomized to intervention	
V4.0	1/25/21	Updated study to include study arm 3	Allows study to follow subjects who are relevant to study aims but not eligible for treatment
V4.0	1/25/21	Inclusion/ exclusion criteria adjusted	Includes subject who are impaired but do not show impairment on MoCA
V4.0	1/25/21	Updated MRI protocol	Allows study team to measure white matter integrity.
V4.0	2/4/2021	Added 6 month MRI	Allows the study team to compare 6 months post op
V5.0	5/15/2021	Inclusion of DSA to confirm COICA classification	Definitive COICA classification
V5.0	5/15/2021	Inclusion/ exclusion criteria adjusted	Based on DSMB recommendations
V5.0	5/15/21	Further definition of 3rd non-randomized arm	Necessitated by adjustments to I/E criteria
V.50	5/15/2021	Inclusion of adjudicators to confirm eligibility of surgical arm	Included to minimize surgical risk
V5.0	6/21/21	Adjusted stopping rules	Protocol adherence with DSMB ruling
V6.0	9/3/21	Added Co-PI Dr. Derdeyn	New study requirements
V6.0	9/3/21	Inclusion criteria adjustment	Provided specifications on MTT/TTP measurements
V6.0	9/3/21	Removed inaccurate wording of primary objective	Clerical mistake corrected
V6.0	9/3/21	Clarified AE reporting workflow	Included for more thorough team roles
V6.1	10/12/21	Wording changes for medical management	Promoting clarity and consistency
V6.1	10/12/2021	Defined Visit windows	Promoting clarity and consistency