

**Carotid Revascularization and Medical Management for Asymptomatic Carotid  
stenosis - Hemodynamics (CREST-H)**

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## LIST OF ABBREVIATIONS

AE Adverse Event  
CAS carotid artery stenting  
CCC Clinical Coordinating Center  
CEA carotid endarterectomy  
CFR Code of Federal Regulations  
CLIA Clinical Laboratory Improvement Amendments  
CMP Clinical Monitoring Plan  
CMS Centers for Medicare and Medicaid Services  
CRF Case Report Form  
CTA Computed tomography angiogram  
CTP Computerized tomography perfusion scan  
DSA digital subtraction angiography  
DCC Data Coordinating Center  
DHHS Department of Health and Human Services  
DSMB Data Safety Monitoring Board  
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  
HIPAA Health Insurance Portability and Accountability Act  
IB Investigator's brochure  
ICA Internal carotid artery  
ICH International Conference on Harmonisation  
IDE Investigational Device Exemption  
IMM intensive medical management  
IND Investigational New Drug Application  
IRB Investigational Review Board  
ISO International Organization for Standardization  
MED Optimal Medical Management Group  
MedDRA Medical Dictionary for Regulatory Activities  
MOP Manual of Procedures  
MRA magnetic imaging angiography  
MRI magnetic resonance imaging  
MRP magnetic resonance perfusion imaging  
MSDS Material Safety Data Sheet  
NIH National Institutes of Health  
NINDS National Institute of Neurological Diseases and Stroke  
OHRP Office for Human Research Protections  
PI Principal Investigator  
PWI perfusion weighted imaging  
QA Quality Assurance  
QC Quality Control  
REVASC Revascularization + Optimal Medical Management Group  
SAE Serious Adverse Event

SAP Statistical Analysis Plan  
SMC Safety Monitoring Committee  
SOC System Organ Class  
SOP Standard Operating Procedure  
UP Unanticipated Problem  
US United States  
WMHV white matter hyperintensity volume

## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following (*use applicable regulations depending on study location and sponsor requirements; examples follow*): 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)

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

\_\_\_\_\_ Print/Type Name

Signed:

\_\_\_\_\_ Signature

Date: \_\_\_\_\_

## PROTOCOL SUMMARY

**Title:** Carotid Revascularization and Medical Management for Asymptomatic Carotid stenosis - Hemodynamics (CREST-H)

**Précis:** This is an ancillary study to the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis study (CREST-2). We will enroll 500 patients from CREST-2, all of whom receive cognitive assessments at baseline and yearly thereafter as part of the CREST-2 protocol. All subjects enrolled in CREST-H will get an MR or CT perfusion scan to look for hemodynamic flow impairment. Our study groups will be CREST-2 patients randomized to either revascularization (CEA or CAS) or to IMM alone. Among those who are found to be hemodynamically impaired and have baseline cognitive impairment, the cognitive exam at 1 year will determine if those assigned to revascularization arm in CREST-2 will have better cognitive outcomes than those in the medical-only arm. We further hypothesize that those who have baseline cognitive impairment without flow impairment will not benefit from revascularization. Cognitive exams will take place at baseline and at follow up yearly up to 4 years to examine long-term outcomes. Perfusion scans will be done at baseline, with follow-up scans at 1 year for those who had baseline flow impairment. Linear regression will be used to assess if the magnitude of the treatment

differences (revascularization versus medical management alone) differs between those with flow impairment compared to those without flow impairment.

**Objectives:**

To determine whether cognition can be improved by revascularization among the subset of CREST-2 patients with hemodynamic impairment and mild cognitive impairment at baseline.

**Endpoint**

The primary outcome is cognition at 1 year

**Population:**

Patients with asymptomatic high grade carotid artery stenosis

**Phase:**

Ancillary study on a Phase 3 parent trial

**Number of Sites**

**enrolling participants:**

75

**Description of Study Agent :**

No additional intervention. This will be a comparison of the cognitive outcomes in a subset of those being randomized in the parent trial to revascularization vs IMM alone

**Study Duration:**

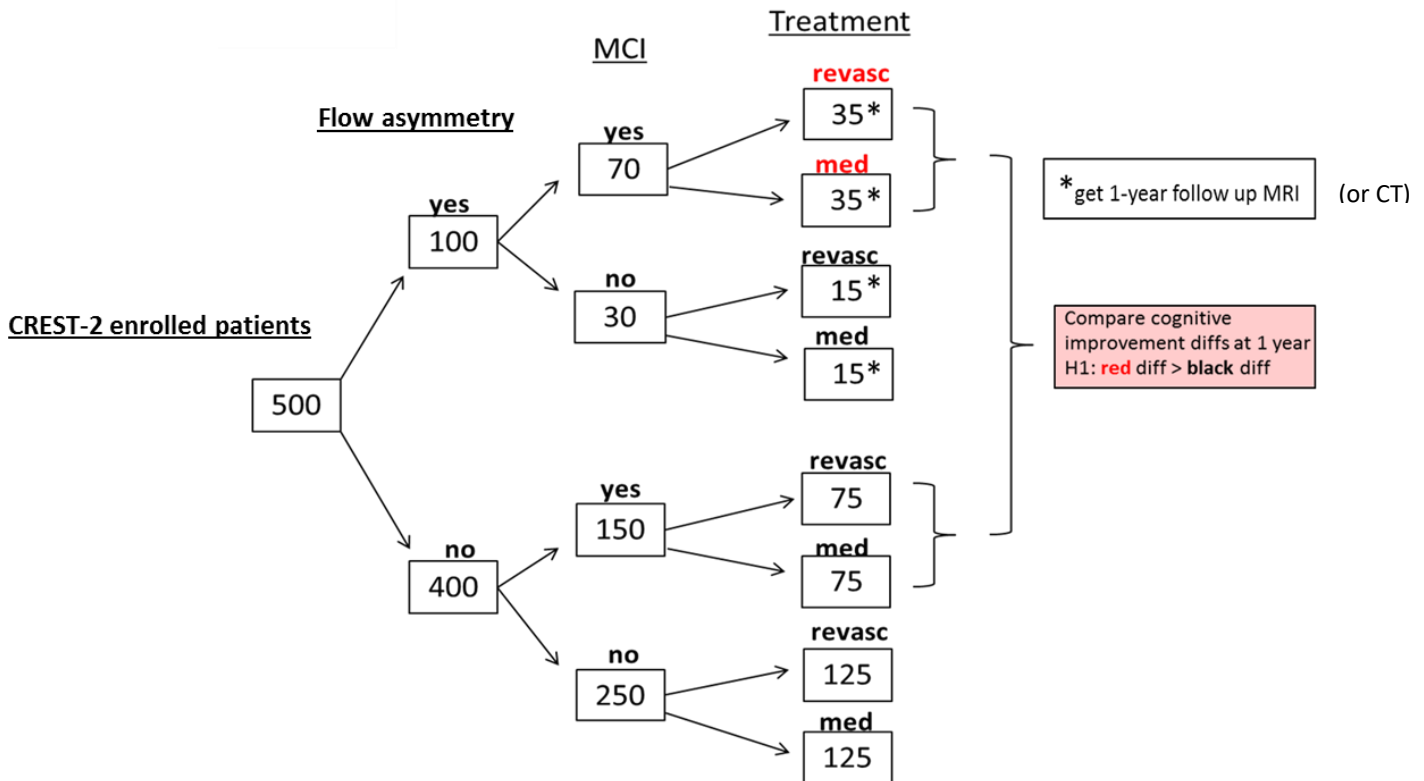
60 months

**Participant Duration:**

Up to 48 months

**SCHEMATIC OF STUDY DESIGN**

The primary hypothesis is to assess if the magnitude of the treatment differences (revascularization versus medical management alone) differs between those with cerebral hemodynamic impairment compared to those without flow impairment. Figure 1 illustrates the anticipated breakdown of comparison



groups. The main comparison will be the treatment difference between the top two cells (red groups, with flow impairment/asymmetry) versus the treatment difference between the 5<sup>th</sup> and 6<sup>th</sup> cells (black groups, without flow asymmetry), indicated by the brackets on the right. The upper 4 cells will get follow up scans at 1 year (see Secondary aims).

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## 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

### 2.1 BACKGROUND INFORMATION

#### Preclinical Models

De la Torre et al subjected middle-aged rats to bilateral common carotid artery and left subclavian artery occlusion that produced chronic cerebrovascular insufficiency, causing selective CA1 damage in the hippocampus and resulting in poorer performance on the water maze memory test.<sup>1</sup> Three groups of rats had their cerebral blood flow restored after 1, 2 or 3 weeks by de-occlusion of the vessels. The rats were then assessed behaviorally and histopathologically at 9 weeks and were compared to another group that did not undergo de-occlusion. The investigators found that rats in the permanent occlusion and 3-week occlusion groups failed to regain their memory function and had a high degree of reactive astrocytic hypertrophy in the hippocampus. In contrast, de-occlusion at 1 or 2 weeks resulted in less neuronal damage and less reactive astrocytic hypertrophy. At 9 weeks, the early de-occlusion groups performed well on the spatial memory tasks. Local cerebral blood flow (LCBF) was measured at baseline and at 9 weeks later in all groups. At the end of the 9-week experimental period, all three de-occluded rat groups had LCBF levels similar to intact controls, whereas permanent ischemia resulted in a significant decrease in LCBF in the fronto-parietal cortex. Authors concluded that neuronal cells may exist in a prolonged state of reversible ischemia, thus supporting the concept of reversible chronic ischemia.

This study met several current criteria for pre-clinical experimental rigor: 1) controls were used by comparing occlusion at different time points and to groups that were not occluded and permanently occluded, 2) steps were taken to minimize bias by automating cell counts and using aged rats to better approximate a human stroke model, 3) confirmation was obtained that the intervention target was reached by quantitatively measuring CBF, and 4) a dose-response approach was used by testing reversibility at 1, 2 and 3 weeks of occlusion.

Additional animal model evidence exists that hypoperfusion can independently alter brain structure, with an impact as late as 1 to 6 weeks following carotid occlusion. Ni J, et al<sup>3</sup> and Pappas et al.<sup>4</sup> showed that behavioral impairment was evident before hippocampal damage was seen, indicating that hypoperfusion in the absence of frank stroke can produce learning and memory deficits. Supporting this notion was a multi-stage carotid occlusion technique by Wang and Han, which showed that persistent cognitive impairment was established within 4 weeks, but hippocampal neuronal loss only after 49 days.<sup>5</sup>

A more recent rat study added imaging data to earlier histopathological findings to support the notion of chronic ischemia in large vessel disease. Using a bilateral carotid artery occlusion model, Soria et al<sup>6</sup> identified delayed white-matter changes on diffusion tensor MR imaging over 12 weeks that were correlated with pathological myelinated-fiber degeneration. These delayed white-matter tract findings also correlated with behavior changes, particularly tests of executive functions. It is notable that the behavioral changes in the rodents parallel a similar loss of frontal executive functions in humans,<sup>7-9</sup> also found in our own preliminary studies (See Section B.2.20), and which will be tested in the proposed study.

Taken as a group these animal models establish a scientific premise for human studies (see below) that hypoperfusion can produce cognitive impairment in the absence of overt infarction, and that the effects of hemodynamic impairment are potentially reversible.

## Clinical Studies

Our primary specific aim hypotheses are based on the role of hemodynamics in patients with carotid atherosclerotic disease, represented both in the literature<sup>10-14</sup> and in our own preliminary work, but these questions have never been tested in the setting of a randomized clinical trial. Although artery-to-artery embolism is another mechanism by which carotid artery stenosis may affect cognition (refs), this mechanism will be tested only indirectly by identification of new silent infarcts:

1. Hemodynamic impairment in high-grade carotid artery stenosis is associated with lower cognitive scores.

European investigators demonstrated an increased probability of developing cognitive deterioration among 210 subjects with unilateral asymptomatic severe carotid stenosis compared to 109 healthy controls. The presence of impaired cerebral hemodynamics ipsilateral to the stenosis was associated with an increased incidence of reduction in cognitive performance (OR 14.66 [95% CI 7.51-28.59];  $p < 0.001$ ).<sup>15</sup> This investigator group also published results showing that impaired vasomotor reactivity (VMR) was associated with cognitive impairment for cognitive tests specific to the ipsilateral hemisphere among 83 patients with unilateral high-grade carotid stenosis, further supporting the cognitive impairment hypothesis because of the hemispherical specificity for the hemodynamic impairment.<sup>16</sup>

2. Reversal of hemodynamic impairment from asymptomatic carotid artery disease is associated with cognitive improvement.

A recent case series showed that among 24 patients with >60% asymptomatic carotid artery stenosis, 22% had flow impairment in the MCA territory. Among all patients, there was a 16% post-operative improvement in MCA flow. All patients with improvement in MCA flow had a significant improvement in attention; if there was no MCA flow improvement, only 56% of patients showed an increase in attention function, which was statistically significant for those with flow impairment at baseline ( $p < 0.01$ ).<sup>17</sup> In another case series, 25 patients with asymptomatic carotid stenosis underwent CAS and showed improvement in global cognitive scores ( $p = .002$ ).<sup>18</sup> Finally, a meta-analysis reviewed 16 studies for the impact of carotid stenting on cognition and found overall improvements in the modified Mini-Mental State Exam (MMSE) and tests of attention/psychomotor speed and memory.<sup>13</sup>

3. Hemodynamic impairment is present at baseline in at least 20% of patients with severe carotid artery disease as measured by PWI TTP, and is reversible with revascularization.

a) Teng et al found that among 10 patients (symptomatic and asymptomatic) with unilateral  $\geq 75\%$  ICA stenosis, 5 (50%) had asymmetrically increased TTP in brain tissue with no infarct present.<sup>19</sup>

b) Kluytmans et al showed that there was significantly increased TTP on the stenosis side among all 66 patients with ICA >70% stenosis or occlusion, including 12 who were asymptomatic.<sup>20</sup> Of note, when circle of Willis collateral flow was poor, there were also abnormalities in MTT, a marker of worse hemodynamic status. We will derive MTT in our PWI protocol, and examine this and other perfusion markers in our exploratory aim.

c) Pinero et al showed PWI TTP to be a sensitive MRI marker of hemodynamic impairment in unilateral asymptomatic stenosis.<sup>21</sup> Among 33 patients with unilateral stenosis, 12 of whom were asymptomatic; asymmetry was present in all at baseline and normalized 30 days after CAS.

## 2.2 RATIONALE

Vascular cognitive impairment is widely described as a step-wise or progressive disease resulting from accumulated ischemic injury.<sup>23-26</sup> Cerebral hemodynamic impairment in patients with high-grade carotid artery stenosis can also impair cognition, even if no overt clinical stroke has occurred<sup>27-28</sup>, contributing

independently to cognitive decline either directly<sup>29</sup>, or as a consequence of a higher occurrence of silent infarction by thrombosis or embolism. Although there is compelling preliminary evidence from case series and physiological studies that hemodynamic impairment affects cognition in patients with carotid occlusive disease, treatment of this condition has never been tested in a randomized clinical trial. CREST-2 is a pair of outcome-blinded, Phase 3 clinical trials in patients with asymptomatic high-grade carotid artery stenosis, which compares stroke prevention and death for carotid endarterectomy (CEA) plus intensive medical management (IMM) versus IMM alone, and carotid artery stenting (CAS) plus IMM versus IMM alone. Our proposal addresses the intriguing question regarding the potential reversibility of cognitive decline when it arises from abnormal cerebral hemodynamics. Five hundred CREST-2 patients will undergo perfusion-weighted MRI (PWI)/CT to identify patients with hemodynamic impairment. If cognitive impairment is identified, and reversed or stabilized in these patients, then we will have established a new indication for carotid revascularization, independent of the risk of stroke and, importantly, reducing the public health burden of vascular cognitive impairment.

Primary Hypothesis. Among patients randomized in CREST-2 who have impaired cognition at baseline (as measured by CREST-2 cognitive battery baseline Z-score  $\leq -1.0$ ), those assigned to revascularization by CEA or CAS plus IMM will have greater improvement in cognition at 1 year compared to those assigned to IMM alone if they had flow impairment at baseline (as measured by longer PWI time to peak (TTP) on the side of occlusion), and compared with an identical group of patients without flow impairment, adjusting for age, baseline cognitive performance, depression, prior cerebral infarcts, subsequent silent infarction, WMH volume, and microbleeds.

## 2.3 POTENTIAL RISKS AND BENEFITS

### 2.3.1 KNOWN POTENTIAL RISKS

Cognitive testing. There are no significant risks to the subjects for the neuropsychological tests, except for the psychological burden of being tested for 20 minutes.

MR and CT imaging. Contraindications and safety considerations for MRI will be managed at the local site per published guidelines and updated references on minimizing risks to the patient. ACR guidelines will be followed for considerations in MRI and CT contrast agents, including radiation risk for CT perfusion and the recent reports of brain deposits in patients who receive 4 or more MRI contrast studies, which has been reviewed by the FDA. The latter question will be addressed in our consent form with appropriate language to explain that the risk is unknown at this time. Discussion of risk of multiple administrations of perfusion agent will be mentioned. Should evidence of greater risk emerge during the course of the trial, the CREST-2/H DSMB will decide this matter. All risks associated with scanning will be discussed as part of the informed consent process. Blinding to results of perfusion imaging. Although there have been some reviews advocating for the clinical utility of perfusion imaging, the clinical significance of this test is not known. We will nonetheless make every attempt to maintain the blinded status of the patients so as not to provide any information that could falsely alter their clinical course.

### 2.3.2 KNOWN POTENTIAL BENEFITS

There will be no clear, direct benefit to the patients in the study, although many patients involved in studies of this type feel their care is improved by the frequent follow up and examinations as part of the study. A safety read at each institution will provide any alerts for unexpected findings on the MRI/CTscan, which will be communicated to the CREST-H PI. We anticipate that knowledge gained from this study will provide additional treatment options for stroke patients to enhance their long-term outcomes, particularly with regard to cognitive function.

### 3 OBJECTIVES AND PURPOSE

#### A. Specific Aims

Vascular cognitive impairment is widely described as a step-wise or progressive disease resulting from accumulated ischemic injury.<sup>23-26</sup> Cerebral hemodynamic impairment in patients with high-grade carotid artery stenosis can also impair cognition even if no overt clinical stroke has occurred<sup>27-28</sup>, contributing independently to cognitive decline either directly<sup>29</sup>, or as a consequence of a higher occurrence of silent infarction by thrombosis or embolism. Although there is compelling preliminary evidence from case series and physiological studies that hemodynamic impairment affects cognition in patients with carotid occlusive disease, treatment of this condition has never been tested in a randomized clinical trial. CREST-2 is a pair of outcome-blinded, Phase 3 clinical trials in patients with asymptomatic high-grade carotid artery stenosis, which compares stroke prevention and death for carotid endarterectomy (CEA) plus intensive medical management (IMM) versus IMM alone, and carotid artery stenting (CAS) plus IMM versus IMM alone. Our proposal addresses the intriguing question regarding the potential reversibility of cognitive decline when it arises from abnormal cerebral hemodynamics. Five hundred CREST-2 patients will undergo perfusion-weighted MRI (PWI) or CT perfusion (CTP) to identify patients with hemodynamic impairment. If cognitive impairment is identified, and reversed or stabilized in these patients, then we will have established a new indication for carotid revascularization, independent of the risk of stroke and importantly, reducing the public health burden of vascular cognitive impairment.

Specific Aim. To determine whether cognition can be improved by revascularization among a subset of CREST-2 patients with hemodynamic impairment at baseline.

Hypothesis 1. Among patients randomized in CREST-2 who have impaired cognition at baseline (as measured by CREST-2 cognitive battery baseline Z-score  $\leq -1.0$ ), those assigned to revascularization by CEA or CAS plus IMM will have greater improvement in cognition at 1 year compared to those assigned to IMM alone if they had flow impairment at baseline (as measured by longer PWI or CTP time to peak (TTP) on the side of occlusion), and compared to an identical group of patients without flow impairment, adjusting for age, baseline cognitive performance, depression, prior cerebral infarcts, subsequent silent infarction, WMH volume, and microbleeds.

Hypothesis 2. Among those with baseline cognitive and hemodynamic impairment assigned to revascularization by CEA or CAS, degree of improvement in cognition will correlate with degree of improvement in TTP.

Hypothesis 3. Among CREST-2 patients with hemodynamic and cognitive impairment at baseline, the difference in cognitive performance between the revascularization versus medical-only groups will be maintained during yearly CREST-2 follow exams up to 4 years.

Secondary aims:

Secondary Aim 1 (MRI only): To determine if the number of silent infarcts at 1 year is different between the revascularization and the medical-only arms.

Hypothesis S1: Among CREST-2 patients with hemodynamic impairment at baseline, there will be fewer new silent infarcts (e.g. due to embolization) at 1 year among those assigned to revascularization compared with patients in the medical-only arm

Secondary Aim 2 (MRI only): To determine if the WMH volume is different at 1 year between the revascularization and the medical-only arms.

Hypothesis S2: Among CREST-2 patients with hemodynamic impairment at baseline, change in WMH volumes at 1 year will be less among those assigned to revascularization compared with patients in the medical-only arm.

Exploratory Aim (MRI only): We will assess additional imaging markers including TTP delay >4 sec, circle of Willis collateral pattern, mean transit time (MTT), Tmax, CBF, and cerebral blood volume (CBV) to determine with greater specificity possible physiological mechanisms.

## 4 STUDY DESIGN AND ENDPOINTS

### 4.1 DESCRIPTION OF THE STUDY DESIGN

Study type: This is an ancillary study of the multi-center Phase 3 Outcome-blinded Randomized Clinical trial, Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis study (CREST-2).

Number of study groups for this study: 2

Multicenter vs single: multicenter.

Study agent: The parent trial from which our cognitive and demographic data will be drawn is run as a pair of outcome-blinded, Phase 3 clinical trials in patients with asymptomatic high-grade carotid artery stenosis, which compares stroke prevention and death for carotid endarterectomy (CEA) plus intensive medical management (IMM) versus IMM alone, and carotid artery stenting (CAS) plus IMM versus IMM alone. For the purposes of CREST-H, the two revascularization arms will be analyzed as one, and compared to those randomized to IMM from either part of the parent trial (CEA or CAS).

There are no dose escalations and no stratifications.

#### 4.2.1 PRIMARY ENDPOINT

Our primary end point is the difference in cognitive score from baseline to 1 year. Although cognitive exams address secondary aims as part of the parent trial, the cognitive outcome is chosen as primary outcome for this study because the hypothesis is that there is a subset of CREST-2 patients (those who have cerebral hypoperfusion by MR/CT perfusion scanning) who will have cognitive impairment at baseline that may be reversible with revascularization. The cognitive outcome at 1 year is therefore distinct from the parent trial primary endpoint which is a measure of recurrent ischemic events. Cognition as an endpoint is extremely important in the field of carotid artery stenosis treatment because it represents a unique opportunity to treat a potentially reversible cause of cognitive impairment.

Additional endpoint under Specific Aim 1: Correlation between improvement in cognition and improvement in cerebral perfusion. As a proof of principle, we will obtain follow up MR or CT perfusion scans on those with hemodynamic impairment at baseline. We hypothesize that our primary endpoint – improvement in cognition from revascularization – will be accompanied by an improvement in cerebral perfusion. This secondary endpoint will be examined both as continuous and dichotomous variables (i.e. presence or absence of hemodynamic impairment and improvement). Although not necessary for the primary endpoint to be proven, demonstrating an effect with our secondary endpoints will help support the primary hypothesis.

Special consideration for parent study endpoint of stroke. CREST-2 primary endpoint includes clinical stroke. If this specific parent trial endpoint is reached, subsequent composite cognitive Z-scores will be changed to the score at the lowest end of the range of scores in the cohort.

#### 4.2.2 Secondary Endpoints

Secondary endpoint 1 (MRI only): Number of new silent infarcts at 1 year compared with baseline among the subset of patients with hemodynamic impairment at baseline. This endpoint will help answer the question of cause of cognitive change over the course of the year since silent infarcts are known to be associated with cognitive decline. We hypothesize that the number of new silent infarcts at 1 year will be greater in the IMM only group vs the revascularization group.

Secondary endpoint 2 (MRI only): Change in of white matter hyperintensity volume over 1 year compared with baseline among the subset of patients with hemodynamic impairment at baseline. This endpoint will help answer the question of cause of cognitive change over the course of the year since WMHV is known to be associated with cognitive decline. We hypothesize that WMHV at 1 year will be greater in the IMM only group vs the revascularization group.

---

#### 4.2.3 EXPLORATORY ENDPOINTS

Exploratory endpoints: We will look for other correlates of cognitive change among our two treatment groups in the subset of patients with hemodynamic impairment at baseline, including TTP delay >4 sec, circle of Willis collateral pattern, MTT, Tmax, CBF, CBV, and cortical thickness (MRI only).

## 5 STUDY ENROLLMENT AND WITHDRAWAL

### 5.1 PARTICIPANT INCLUSION CRITERIA

Participants must meet all inclusion criteria in order to be eligible for the study.

Inclusion criteria include randomization in CREST-2 . Specifically:

Age 35-86 years

provision of appropriate consent

willingness and ability to participate in study procedures

≥70% ICA stenosis

No ipsilateral stroke or TIA within 180 days of randomization

No chronic or paroxysmal atrial fibrillation requiring anticoagulation

Anatomy amenable to stenting (CAS trial); No surgical contraindication (for CEA trial)

### 5.2 PARTICIPANT EXCLUSION CRITERIA

All individuals meeting any of the exclusion criteria at baseline will be excluded from study participation.

(for MRI only) unable to undergo MRI (e.g. non-compatible metal in body, pacemaker)

known allergy to gadolinium (MRI) or iodinated (CT) contrast dye

Either creatinine ≥ 2.5 mg/dl or GFR < 30cc/min

pre-existing diagnosis of dementia

contralateral ICA stenosis >70% by MRA, CTA or Doppler ultrasound

history of severe head trauma defined by loss of consciousness >30 minutes, or seizure

major depression

education less than 8 years

### 5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will involve 500 adult patients enrolled in CREST-2 with high grade asymptomatic carotid artery disease who have had no recent prior stroke. Patients will be recruited in the first 4 years of the study, with planned yearly follow-up for up to 4 years per patient. The vulnerability of the study

population will be limited to the fact that they are patients with risk of stroke, and some will have had stroke symptoms.

Women and minority recruitment. An effort to recruit women and minorities will be made as per the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects. Women will be represented in the study in proportion to the population prevalence of carotid artery disease (50% female). Women of childbearing potential will not be excluded, although assurance of non-pregnancy status will be required at the time of the scanning.

Minority patients will be included in the study population in proportion to the population of carotid stenosis patients nationwide, with a goal of including a higher minority population from sites where there is a higher representation. At Columbia University Medical Center, for example, the ethnicity distribution for stroke overall is roughly 30% white, 35% hispanic, 30% African-American, 5% other. Extracranial carotid disease is more common in whites compared to other race-ethnic groups, in whom intracranial atherosclerosis is more common. The projected gender and ethnic distribution is 50% female gender, 75% white, 15% African American, 6% Asian/Pacific Islander/other. Every effort will be made to recruit minorities to the study.

Site enrollment, accrual rate, and infrastructure support from parent study: The total number of CREST-2 (parent study) patients anticipated to be enrolled is 2,480, from among approximately 120 CREST-2 sites.

For CREST-H our target enrollment is 500, approximately 20% of the total CREST-2 population, making enrollment in CREST-H highly feasible. We anticipate needing recruiting from 75 sites, which would enroll an average of 6-7 patients each over the course of the 4-year enrollment period (1-2 per year). To facilitate CREST-H site enrollment and start-up, as well as to ensure smooth implementation of study procedures, startup costs will be provided to participating sites to cover IRB application and other logistics. In addition, we will take advantage of the existing infrastructure of the CREST-2 Clinical Coordinating team at Mayo, Jacksonville. They will execute the CREST-H subcontracts, be responsible for disbursement of start-up funds, handle per-patient reimbursements for the CREST-H MR/CTscans and completion of CREST-H CRFs over the study period, and monitor CREST-H source data as part of the CREST-2 site monitoring plan. Additional components of the CREST-2 infrastructure are the Data management team at UAB, who will be responsible for data management and statistics for CREST-H, and the vascular imaging core at U Maryland that will handle uploading, transferring, and archiving of the MRI/CT image files generated at each participating sit. A central IRB at U Cincinnati, which currently handles approximately 40% of the CREST-2 sites (and performs this function for the NIH StrokeNet program) will be responsible for developing and executing the IRB documents for CREST-H.

Subject enrollment and recruitment protocol: Patients will be approached for enrollment in CREST-H once they have been enrolled and consented in CREST-2 by the CREST-2 site PI or study-affiliated designee. Participation in CREST-H is voluntary, but we anticipate very high participation rates because the additional patient burden is minimal. From the patient perspective, it consists only of undergoing a baseline MR or CT perfusion scan (500 CREST-2 patients), and follow up scan at 1 year (for those 100



subjects who are found to have hemodynamic flow impairment on baseline scanning). Cognitive assessments are already performed as part of the CREST-2 protocol, and are done by telephone by trained personnel UAB.

A separate informed consent form will be signed for CREST-H.

## 5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

### 5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate the involvement of a participant in the study 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

-The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

-Inability to obtain the baseline study MRI or CT

-Baseline scan data are uninterpretable

### 5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

We will make every effort to continue follow up of participants who withdraw or terminate. Because all participants will be CREST-2 participants, our coordinator or PI will assist in any way needed with the CREST-2 protocol, which includes the following:

When a patient has missed one follow-up visit without advance warning, then the coordinator will contact the patient by phone, utilizing any additional contact information for the patient, such as multiple telephone numbers (i.e., home, work, cell), contact information for next of kin, or contact information for someone who does not live in the same household as patient (in case of emergencies). If the patient cannot be contacted by telephone and there is contact information for other persons, then an attempt should be made to contact the proxy of the patient. The proxy may be asked to have the patient contact the study staff or to find out whether the patient is still in the area and his/her status. The coordinator may also send a letter by certified mail, asking the patient to contact the study staff (verify with your local IRB or central IRB if this letter needs approval before sending out to the patient). Record the results of all attempts to contact the patient either by phone or by mail in a narrative.

One exception to attempt to retain withdrawn participants are those for whom adequate baseline MRP imaging was not obtained because further participation would not be valuable without baseline imaging

data. Patients with clinical stroke as a CREST-2 outcome will have their composite cognitive Z-scores changed to the score at the lowest end of the range of scores in the cohort.

## 5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to NINDS and all participating sites. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

We do not anticipate any safety concerns that would necessitate early termination of the study since the imaging protocol includes only well-known, standard MR/CT imaging sequences. There are no expected AEs for our study. Nonetheless it is possible that the parent trial, CREST-2 would be terminated early for for futility, efficacy, or safety, in which case our study would be terminated as well. The CREST-2 DSMB will be reviewing CREST-H data, and will be responsible for any decision for termination. Of note, no interim analysis is planned for CREST-H.

## 6 STUDY AGENT

### 6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

#### 6.1.1 ACQUISITION

No agent or device will be tested for efficacy or safety in CREST-H.

#### 6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

N/A

#### 6.1.3 PRODUCT STORAGE AND STABILITY

N/A

#### 6.1.4 PREPARATION

N/A

#### 6.1.5 DOSING AND ADMINISTRATION

N/A

#### 6.1.6 ROUTE OF ADMINISTRATION

N/A

#### 6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

<Insert text>

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#### 6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

N/A

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#### 6.1.9 DURATION OF THERAPY

There is no therapy being tested in isolation from the parent trial, which is revascularization plus intensive medical management vs intensive medical management alone.

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#### 6.1.10 TRACKING OF DOSE

N/A

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#### 6.1.11 DEVICE SPECIFIC CONSIDERATIONS

N/A

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### 6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

N/A

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## 7 STUDY PROCEDURES AND SCHEDULE

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### 7.1 STUDY PROCEDURES/EVALUATIONS

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#### 7.1.1 STUDY SPECIFIC PROCEDURES

Medical history and medication history will be performed at time of CREST-2 enrollment as part of the CREST-2 protocol and most elements will not need to be duplicated in CREST-H. Specific exclusion criteria for CREST-H will be obtained by interview at the time of CREST-H enrollment (contraindications to MRI, allergy to contrast dye, diagnosis of dementia, major depression, education level, history of severe head trauma, substance abuse)

#### Cognitive Assessments

CREST-H will utilize the already-existing CREST-2 protocol to obtain the cognitive assessments. The telephone-based test battery uses well-validated measures in an aural format that are administered in standardized fashion to participants from centers around the US who are enrolled in CREST-H. Test administrators undergo rigorous training and are re-certified on a scheduled basis. The inter-tester reliability is ~98%. Added to the current CREST-2 battery will be Oral Trail Making A & B as an additional measure of executive function, which will be administered to every CREST-2 patient, regardless of their participation in CREST-H. Cognitive assessments in CREST-2 take place after enrollment and randomization to revascularization plus IMM or IMM alone. The assessments must take place prior to revascularization or within two weeks after assignment to IMM alone. Testing in CREST-2 is repeated at 44 days, and every year thereafter up to 4 years. At each test interval, a composite (mean) Z-score is

derived from published normative samples for each test outcome. The CREST-H primary outcome will be at 1 year in which the change in the composite Z-score from baseline will be calculated. Covariates will include age, education and depression. The test battery is administered the same way for all CREST-2 and CREST-H enrolled patients, but the elements used to generate the composite Z-score will differ in CREST-H, based on known sensitivity to hemodynamic compromise. Table 3 shows the CREST-2 and CREST-H batteries, with the domain and behavior outcome measures for each, and indicates which measures will be used to determine the primary cognitive outcomes, respectively. The domains being assessed in CREST-2/H are entirely consistent with those encompassed within the NINDS Common Data Elements (CDE).

Domain	Test	Behavior Outcome	CREST-2 Composite	CREST-H Composite
Learning	CERAD Word List Learning	Sum of 3 trials	x	
Attention	Digit Span	Number of sequences correctly repeated (forward + backward)	x	
Memory	CERAD Delayed Recall	Number Correct	x	<b>x</b>
Executive Function	Animal Fluency	Number correct in 1 min	x	<b>x</b>
	Letter Fluency (Controlled Oral Word Association)	Number correct in 1 min for each of F, A and S.	x	<b>x</b>
	Oral Trail Making A & B	Time to complete Part B		<b>x</b>

Imaging protocol.

The following imaging acquisition protocol for CREST H comprises standard MRI and CT sequences available at nearly all clinical performance sites that perform carotid revascularization procedures, so that a vast majority of CREST-2 sites will have them available and therefore be eligible to be CREST-H sites: Imaging will take place within 14 days after CREST-H enrollment and prior to any CREST 2 intervention for those randomized to CEA or CAS. If a patient is randomized to IMM only, the imaging may take place up to and including the 44-day CREST-2 follow up visit.

Standardized contrast agent injection protocol (see below) and appropriate preparation or IV setup is required to reproducibly administer an adequate bolus of contrast material that will ensure good scan quality. An antecubital vein IV catheter of 18-20 gauge is required. A test injection will be performed with approximately 10 ml of normal saline solution.

MRI image acquisition:

DWI/ADC (b=0, 1000 s/mm<sup>2</sup> applied in each of three principal gradient directions), FLAIR, high-resolution T1, and GRE sequences will be acquired on 1.5-3.0T scanners equipped with echo-planar imaging capability, using the standard clinical protocol at participating CREST-H sites (see Table below for recommended image acquisition parameters). Total scanning time will be approximately 40 minutes. PWI acquisition protocol will be standardized across all CREST-H sites, using sequential T2\*-weighted

(gradient echo) EPI time sequence scanning. A modified 2-phase contrast injection scheme will be used to perform CEMRA and DSC perfusion imaging, without need for additional contrast.<sup>37</sup> To accomplish this, a total of 0.1 mmol/kg of gadolinium (MultiHance, Bracco Diagnostics, Princeton, New Jersey) that is used routinely for MR perfusion will be diluted with normal saline to a total volume of 50 mL. Three mL of contrast solution will be injected and flushed with 20 mL of saline to determine the transit time from the arm vein to the cervical carotid arteries. A total of 22mL of contrast solution will then be injected and flushed with 20 mL of saline for the CE-MRA acquisition. The contrast injection rate for timing run and CE-MRA will be 1.5 mL/s. Subsequently, the remaining 25 mL of contrast solution will be injected and flushed with 20 mL of saline at 5 mL/s for the MR perfusion scan, which will be performed last. Because patients with Cr. $\geq$ 2.5 mg/dl or GFR<40 cc/min are excluded from CREST-2 participation, no adjustments for gadolinium dosing will be required. Prior to site initiation, the UCLA imaging core lab will request and review a sample dataset of PWI source images to ensure adequate image quality. Training and assistance with implementation of the PWI protocol will be performed as needed. All imaging files submitted to the UCLA core lab for enrolled subjects will be monitored with every uploaded scan for data quality and consistency.

Table of MR parameters for CREST-H Image acquisition protocol

Sequence	Orientation	Time	Slice (mm)	Gap	Slices	TR	TE	TI	FOV (cm)	Frequency	Phase	Mode
High Res T1	Sagittal	7:23	1.2	0	160	NA	Full Min	900	24	192	192	3D
T2 FLAIR	Axial	4:36	4	0	36	11000	147	2460	22	256	192	2D
DWI/ADC	Axial	0:50	4	0	36	10000	Min	NA	22	128	256	2D
2D PC scout	Coronal	1:33	90	0	1	40	Min	NA	22	256	224	2D
MRA Intra	Axial	4:18	1.4 (0.7)	0	3 x 32	Min	Min	NA	18	384	224	3D
Perfusion	Axial	3:00	5	0	Max for TR	2225	60	NA	24	128	96	2D
GRE	Axial	0:09	4	0	36	1700	Full Min	NA	22	128	128	2D

Abbreviations: TR=repetition time, TE=echo time, FA=flip angle, ST=slice thickness (mm), FOV=field of view

CT perfusion imaging acquisition

CT perfusion (CTP) is a commonly performed imaging study especially in the setting of acute stroke. All CREST-H centers likely perform CTP on a routine basis with established protocols for brain perfusion studies. While a single protocol is not mandatory at participating sites, the following parameters can be used as a guide based upon a Siemen’s Flash scanner utilizing the common shuttle mode:

	Non-contrast head (optional)	CT Perfusion (required)
Coverage	Top C1 lamina to vertex	Top C1 lamina to vertex
Scan type	Spiral	Dynamic Multi 4D
Rotation Time (sec)	1	0.28
Collimation	128 x 0.6	32 x 1.2
4D Range	NA	100 mm 1.5 sec
Multi Cycle time	NA	1.5/Multiple ON

Pitch	0.6	None
kVp	120	80
Effective mAs	350	200
CARE Dose 4D	Off	NA
Scan Field (mm)	300	300
Prep Delay	Min allowable	2 sec
Min. Retro (mm)	0.6	1.5
CTDI-vol (mGy)	53	8.6/scan, 1.5 sec scan time
Recon Kernel	J40	H20

An 18 or 20 gauge peripheral IV is inserted, preferentially within the right arm. A contrast agent such as Omnipaque 350 is administered by a split does as follows: 50 mL Omnipaque 350 IV at 7 mL/second, followed by 50 mL 0.9% NaCL at 7 mL/second (we have found that if the contrast cannot be given at 7ml/second a suboptimal CTP exam may occur). The images will be processed with a semi-automated system such as the OleaSphere software platform that computes quantitative perfusion maps using deconvolution of the tissue and arterial signal in an expedited manner, yielding standardized data regardless of the acquisition system at each site. As with CREST-H MRI perfusion studies, hemodynamic impairment will be defined as longer Time-To-Peak in the middle cerebral artery and anterior cerebral artery territories of the ipsilateral hemisphere to the carotid lesion compared with the same territory in the opposite hemisphere. Training and assistance for CTP imaging will be provided as needed.

Image de-identification and blinding:

All scan image files will be de-identified under the supervision of an Investigator at each Crest-H site and uploaded to the CREST-2 Imaging Core site at U Maryland. In order to assure that the perfusion scan information from CREST-H does not compromise the integrity of the parent trial, the results of the perfusion scan will be blinded to the treating investigator team. Note that imaging will not impact CREST-2 randomization because the imaging will be done after CREST-2 randomization has taken place. See section 10.6.1 for full discussion of the impact of this blinding to minimize bias.

Image upload and transfer.

The CREST-2 Vascular Imaging Core facility (VIC) at U Maryland has already established electronic linkages with each CREST-2 clinical center approved to randomize patients in the parent trial. Individual centers will utilize the same file transfer protocol (ftp) to transfer images to U Maryland for CREST-H. The CCC at Mayo Clinic-Jacksonville and the CREST-H Study team will interact with participating centers to ensure that they upload all appropriate images in a timely fashion. The images will be stored in a HIPAA-compliant, firewall protected server within the U Maryland archival system. The system undergoes daily integrity checks, daily backups locally, weekly backups remotely, and monthly tape backups remotely. A CREST-2 dedicated ftp linkage already exists between the VIC at U Maryland and UCLA; and the VIC at U Maryland and Mayo-Rochester. These linkages will be utilized to make each perfusion image file available for transfer to UCLA (Liebeskind lab) and each structural image (DWI/ADC, FLAIR, high res T1, GRE) to Mayo-Rochester (Huston lab). Dr. Huston will review images sent to him for QA of image acquisition at each site (other than the perfusion imaging, which will be assessed by Dr. Liebeskind). If there are any concerns for the data quality, Dr. Liebeskind, Dr. Huston or Dr. Marshall will

contact the participating site PI for review and remediation of the problem. If image quality cannot be maintained, that site will be terminated for CREST-H participation.

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### 7.1.2 STANDARD OF CARE STUDY PROCEDURES

Standard of care for revascularization procedures and IMM are part of the CREST-2 parent study protocol. No other standard of care procedures are included in CREST-H.

## 7.2 LABORATORY PROCEDURES/EVALUATIONS

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### 7.2.1 CLINICAL LABORATORY EVALUATIONS

Standard of care laboratory evaluations for revascularization procedures and IMM are part of the CREST-2 parent study protocol. No other standard of care laboratory procedures are included in CREST-H.

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### 7.2.2 OTHER ASSAYS OR PROCEDURES

N/A

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### 7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

N/A

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### 7.2.4 SPECIMEN SHIPMENT

N/A

## 7.3 STUDY SCHEDULE

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### 7.3.1 SCREENING

Timing of all procedures is provided in Schedule of Events Table, section 7.3.7. Workflow for imaging data is shown in Figure 2.

The following screening procedures for CREST-H will take place on the day of enrollment of a participant into the parent study, CREST-2:

1. Review medical history and existing CREST-2 carotid imaging data to determine CREST-H eligibility based on inclusion/exclusion criteria. Data to be reviewed will include the qualifying carotid Doppler information, and/or CTA, MRA, or DSA for exclusion criteria of contralateral stenosis >70%.
2. Obtain informed consent of potential participant verified by signature on written informed consent for screening form.

3. Schedule baseline MRI/CT study visit to take place within 2 weeks of CREST-2 randomization and before any revascularization procedure for participants randomized to a revascularization arm (CEA or CAS).

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### 7.3.2 ENROLLMENT/BASELINE

Baseline visit (MRI or CT scanning) for CREST-H requires confirmation of randomization into parent study, CREST-2.

1. Confirm randomization into CREST-2
2. Confirm that baseline cognitive exam has been performed or scheduled.
3. Proceed with scheduled baseline MRI or CTP scan, anonymization, and upload to U Maryland Image transfer center per imaging protocol.
4. Note that both the baseline scan and the baseline cognitive exam must take place before any revascularization procedure, and prior to the 44-day CREST-2 follow up visit for those in the medical only arm.
5. Images transferred by U Maryland Image transfer center to UCLA for perfusion (flow impairment) analysis (Hi res-T1, PWI, MRA, or CT perfusion), and to Mayo Rochester for structural analysis (DWI/ADC, FLAIR, GRE).
6. SDCC confirms data completion for cognitive exam, image acquisition, image transfer.

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### 7.3.3 FOLLOW-UP

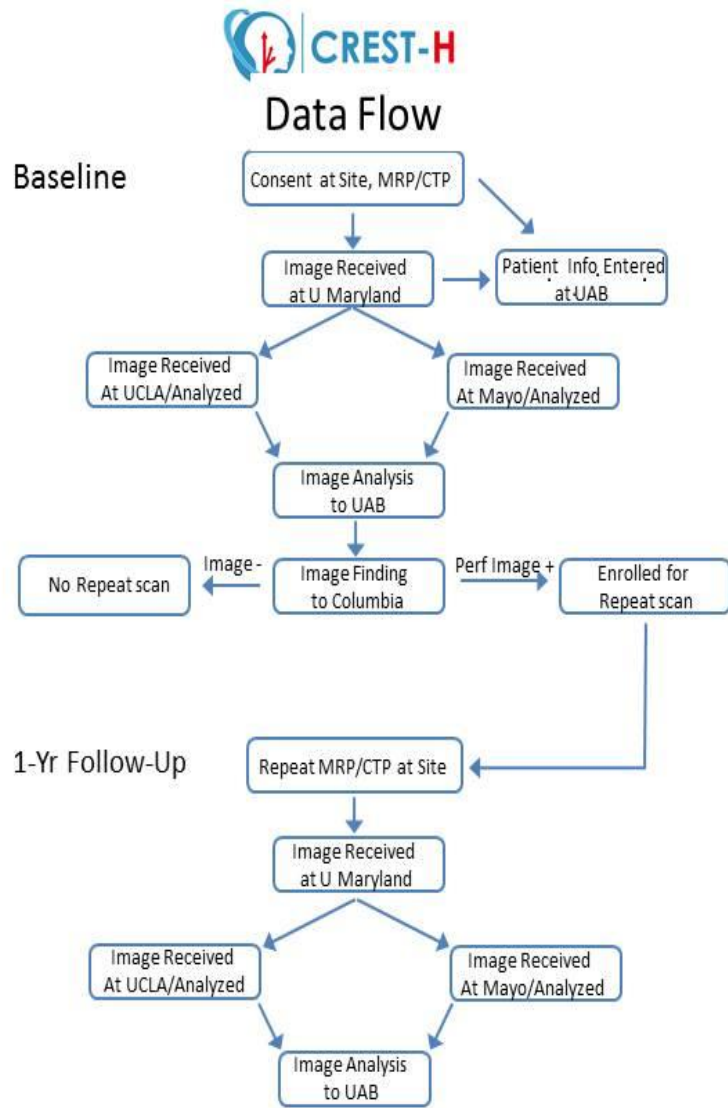
Follow up cognitive exams will take place under the CREST-2 parent study protocol at 1 year, and yearly up to 4 years.

1. Confirm cognitive exam has taken place at 1 year, 2 years, 3 years, 4 years. The acceptable time window for these follow up visits is 30 days before or after the target date.

Follow up MRI or CT perfusion scan will take place at 1 year for those participants who met the baseline criteria for hemodynamic flow impairment by PWI or CTP. Data from UCLA baseline image analysis will be transmitted to the UAB SDCC to determine which participants will need to be scheduled for 1 year follow up scan

1. UCLA Image analysis center transmits hemodynamic flow status (flow impairment/no flow impairment) to SDCC (and from SDCC to Columbia for confirmation) within 1 month of baseline MRI/CT.
2. SDCC notifies site if a follow up MRI or CT scan is needed.
3. Site schedules 1-year follow up MRI/CT for participants who met baseline MRP/CTP criteria for hemodynamic flow impairment and cognitive impairment.
4. 1-year follow up scanning performed (30-day window on either side of target date) at site, using identical protocol to baseline MRI or CT, including upload of de-identified images, image transfer to UCLA and Mayo Rochester.





### 7.3.4 FINAL STUDY VISIT

At the 4-year follow up visit, or at the end of the parent trial CREST-2 recruitment period, a data review will take place to ensure data completion, including baseline and follow up cognitive exams, structural and perfusion MRI /CT data, and any AEs/SAEs. The site investigator should also make sure no diagnosis of non-vascular dementia was made during the course of the study.

### 7.3.5 EARLY TERMINATION VISIT

There will be no separate early termination visits. Patients with clinical stroke as a CREST-2 outcome will have their composite cognitive Z-scores changed to the score at the lowest end of the range of scores in the cohort. If a stroke occurs after 1 year, the patient’s data will be retained for the primary analysis, but will not be included in the secondary end-point of subsequent year cognitive outcomes.

### 7.3.6 UNSCHEDULED VISITS

There will be no unscheduled visits.

### 7.3.7 SCHEDULE OF EVENTS TABLE

	Screening/ Enrollment	Baseline	Follow up visit 1 yr	Follow up visit 2 yr	Follow up visit 3 yr	Follow up visit 4 yr	Final Visit							
<b>Procedures</b>														
Medical history screen	X													
Carotid image screen	X													
Informed consent	X													
Schedule baseline MRI or CT	X													
Confirm CREST-2 randomization completed		X												
Confirm cognitive exam completed	X	X	X	X	X	X	X							
Scanning protocol: acquisition, anonymization, file upload		X	X*											
Adverse event evaluation							X							
*for patients with hemodynamic flow impairment														

## 7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

N/A

## 7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

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#### 7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

#### 7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

#### 7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

#### 7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

#### 7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

N/A>

### 8 ASSESSMENT OF SAFETY

#### 8.1 SPECIFICATION OF SAFETY PARAMETERS

The primary endpoint is change in cognitive exam at one year compared to baseline. Because the cognitive outcomes will be analyzed by group at the end of the study there will be no cognitive change data to report during the course of the study. There are no expected adverse events for this study that uses standard MRI/CT acquisition sequences. Serious adverse events related to imaging would be allergic reaction to contrast dye or other unexpected event during standard scanning sessions. Secondary endpoints include changes in number of silent infarcts, change in white matter hyperintensity volume, or microbleeds. Unexpected findings on MRI or CT will be identified by a safety read that accompanies each MRI/ CT scan acquisition.

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##### 8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

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##### 8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth

defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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### 8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

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## 8.2 CLASSIFICATION OF AN ADVERSE EVENT

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### 8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

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### 8.2.2 RELATIONSHIP TO STUDY AGENT

The clinician’s assessment of an AE’s relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – The AE is known to occur with the study procedure, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event.

Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

- Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

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### 8.2.3 EXPECTEDNESS

The monitoring team of the SDCC will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

## 8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

## 8.4 REPORTING PROCEDURES

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### 8.4.1 ADVERSE EVENT REPORTING

AEs will be reported by the study coordinator or study investigator to the CIRB within 7 days of discovery using the study AE CRF. There are no expected AEs for the standard imaging protocol used in this study.

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#### 8.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the SDCC sponsor within 24 hours of site awareness. See **Section 1, Key Roles** for contact information.
- Other SAEs regardless of relationship, will be submitted to the SDCC within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the SDCC and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

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#### 8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the SDCC/. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the cIRB (StrokeNet sites) or local IRB (non-StrokeNet Sites) 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the cIRB (StrokeNet sites) or local IRB (non-StrokeNet sites) and to the SDCC as soon as possible but within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the SDCC within 14 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IRB's receipt and review of the report of the problem from the investigator.

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#### 8.4.4 EVENTS OF SPECIAL INTEREST

N/A

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#### 8.4.5 REPORTING OF PREGNANCY

A urine pregnancy test will be required for study subjects who are of child-bearing potential prior to performing the MRP/ CTP. Positive pregnancy test will preclude MRP/CTP, and further participation in the study.

## 8.5 STUDY HALTING RULES

There are no halting rules that will be used in this study except that the study will be halted if the parent trial is halted.

## 8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the CREST-2 (parent study) DSMB, composed of individuals with the appropriate expertise, including vascular neurology, interventional neuroradiology, neurosurgery, and radiology. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NIH/NINDS staff. The CREST-2 DSMB will be responsible for safety oversight of CREST-H.

## 9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- The CREST-2 (parent study) CCC will conduct centralized monitoring of CREST-H sites for protocol adherence and data accuracy throughout the study at the time of CREST-2 monitoring visits, with random review of imaging and work flow CRFs. Monitoring reports will be provided to NIH/NINDS staff as part of the parent study monitoring reports
- Independent audits of imaging data will be conducted by the UCLA image analysis center to ensure image acquisition and transfer procedures are performed consistently across all participating sites.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

## 10 STATISTICAL CONSIDERATIONS

### 10.1 STATISTICAL AND ANALYTICAL PLANS

The statistical plan is outlined below.

### 10.2 STATISTICAL HYPOTHESES

Hypothesis 1. Among patients randomized in CREST-2 who have impaired cognition at baseline (as measured by CREST-2 cognitive battery baseline Z-score  $\leq -1.0$ ), those assigned to revascularization by CEA or CAS plus IMM will have greater improvement in cognition at 1 year compared to those assigned to IMM alone if they had flow impairment on the side of occlusion at baseline (as measured by longer PWI or CTP time to peak (TTP) ), and compared to an identical group of patients without flow impairment, adjusting for age, baseline cognitive performance, depression, prior cerebral infarcts, subsequent silent infarction, WMH volume, and microbleeds. The null hypothesis is that there is no difference in cognitive change scores between the two groups.

Hypothesis 2. Among those with baseline cognitive and hemodynamic impairment assigned to revascularization by CEA or CAS, degree of improvement in cognition will correlate with degree of improvement in TTP.

Hypothesis 3. Among CREST-2 patients with hemodynamic and cognitive impairment at baseline, the difference in cognitive performance between the revascularization versus medical-only groups will be maintained during yearly CREST-2 follow exams up to 4 years.

Hypothesis S2: Among CREST-2 patients with hemodynamic impairment at baseline, there will be fewer new silent infarcts (e.g. due to embolization) at 1 year among those assigned to revascularization compared with patients in the medical-only arm

Hypothesis S3: Among CREST-2 patients with hemodynamic impairment at baseline, change in WMH volumes at 1 year will be less among those assigned to revascularization compared with patients in the medical-only arm.

### 10.3 ANALYSIS DATASETS

The analysis data set will be the cognitive scores and imaging data from the 500 CREST-2 patients who underwent MRI/CTP at baseline and were randomized in CREST-2 to revascularization plus IMM vs IMM alone. The difference in cognitive outcomes by treatment group will be compared between those with hemodynamic flow impairment vs those without flow impairment. We will use the treatment assignments from CREST-2 , MRI/CT-based hemodynamics and cognitive status to group the patients for statistical analysis.

### 10.4 DESCRIPTION OF STATISTICAL METHODS

#### 10.4.1 GENERAL APPROACH

Linear regression analysis will be used to estimate the treatment differences among those with flow impairment vs those without flow impairment, controlling for a number of covariates of age, baseline cognitive performance, depression, prior cerebral infarcts, subsequent silent infarction, WMH volume, and microbleeds. The (two-tailed) significance level will be  $p=0.05$ .

#### 10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)



## Primary Hypothesis

The primary hypothesis is to assess if the magnitude of the treatment differences (revascularization versus medical management alone) differs between those with flow impairment compared to those without flow impairment. Thus, the primary hypothesis is an interaction hypothesis that will be assessed using linear regression, specifically:  $(C1 - C0) = \beta_0 + \beta_1T + \beta_2F + \beta_3TF + \beta_4C0 + (\text{other covariates})$ , where C1 is the cognitive z-score at year 1, C0 the cognitive z-score at baseline, T the treatment indicator variable, F the flow impairment indicator variable, and  $\beta_i$  the regression parameters to be estimated. The parameter of interest for the primary hypothesis is then  $\beta_3$  that would assess if the magnitude of treatment difference in the change in cognitive score between baseline and 1-year is similar for those with versus without flow impairment. Given our experience from the original CREST trial, we anticipate that fewer than 5% of the patients will be missing the 1-year data; however, to reflect the intention-to-treat principle, this difference will be assessed using the mixed model approach of Laird and Ware.<sup>23</sup> Covariates will include baseline cognitive status, age, depression, prior cerebral infarcts, silent infarction, WMH volume, and microbleeds.

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### 10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Hypothesis 2: The assessment of whether the improvement in cognition is correlated with improvement in hemodynamic impairment as measured by TTP in patients will be assessed in those with MCI assigned to revascularization ( $\approx 35$  patients), where the average change in the z-score is an analysis restricted to those with hemodynamic impairment, where the change in z-score will be correlated with the continuous measure of the hemodynamic impairment.

Hypothesis 3: The determination of whether differences in the change in cognition is related to the presence/absence of hemodynamic impairment will be assessed using approaches identical to that for the primary aim.

### Secondary Hypotheses

S1 and S2: We will calculate the number of new silent cerebral infarctions occurring over the first year, and the change in the WMH volume for each patient. The approach for analysis of the number of new silent infarcts will depend on the average number and distribution of the number of new infarctns. The analytic approach will be linear regression if the number of new infarcts is large (considered more likely the case), or Poisson Regression if the number is smaller (considered less likely the case). The analysis of the change in WMH will use a linear regression approach.

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### 10.4.4 SAFETY ANALYSES

No safety analyses will be performed as part of this study.

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### 10.4.5 ADHERENCE AND RETENTION ANALYSES

A comprehensive plan to assure adherence to medical therapy exists as part of the parent trial, including regular telephone calls, an assigned medical management physician, and an independent lifestyle advocacy program, all of which will support the CREST-H participants. Measures to minimize loss to follow up are described in section 5.4.2.

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#### 10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be compared between treatment groups, including demographics, cognitive scores, depression scores, and imaging data for silent infarcts, microbleeds, and white matter hyperintensity volumes. We will be taking advantage of the randomization within the parent trial to achieve equivalence between groups.

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#### 10.4.7 PLANNED INTERIM ANALYSES

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##### 10.4.7.1 SAFETY REVIEW

There are no safety endpoints for this study and therefore no safety interim analyses are planned for this study. The parent study DSMB will be responsible for safety review throughout the duration of the study. See sections 5.5 and 8.5 for considerations of premature termination and halting rules.

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##### 10.4.7.2 EFFICACY REVIEW

No interim analyses for efficacy are planned.

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#### 10.4.8 ADDITIONAL SUB-GROUP ANALYSES

The study is not powered for subgroup analysis but will use demographics as covariates in the primary and secondary analysis.

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#### 10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

N/A

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#### 10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

The analysis will be at the group level, and will not report individual response data.

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#### 10.4.11 EXPLORATORY ANALYSES

Exploratory Analysis: A linear regression analysis will be used to determine the relationship between cognitive impairment and other imaging measures including TTP delay >4 sec, circle of Willis collateral pattern, MTT, Tmax, CBF, and CBV.

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### 10.5 SAMPLE SIZE

Primary endpoint.

It is anticipated that at least 100 (20%) of the 500 CREST-2 enrolled patients will have hemodynamic impairment. Based on Preliminary Study 4, 70 of these will have baseline composite cognitive Z-scores  $\leq -1.0$ . By CREST-2 randomization, 35 of these patients will have revascularization, and 35 will be managed with OMT alone. Since Preliminary Study 2 suggests that 44% (220) of all 500 CREST-H patients will have composite cognitive Z-scores  $\leq -1.0$  at baseline, and 70 of these will be in the flow impairment group,

those with MCI who do not have hemodynamic impairment will number 150, half of whom will be randomized to revascularization and half to OMT alone. This leads to an anticipated 35 patients in each treatment group for MCI and flow impairment, and 75 in each group for the MCI and no flow impairment. While the null-hypothesis is the treatment change will be the same for those with and without flow impairment, power calculations require the specification of an alternative difference. Specifically, in the flow-impairment group we would speculate that there would be a 0.6 SD increase in the score for those assigned to revascularization and 0.0 SD change in those assigned to medical management alone (i.e., a 0.6 treatment difference). In contrast, we would speculate that both treatment groups would have a 0.2 change in those with no flow impairment (i.e., no treatment difference). That is, the analysis is attempting to detect a differential treatment effect of 0.6 SD. Monte Carlo analysis suggests that there is 98% power to detect such a difference (see Appendix for program). Sensitivity analysis suggests there is 93% power to detect a differential treatment effect of 0.5 SD, 82% power to detect differential treatment effects of 0.4 SD, but only 56% power to detect different effects of 0.3 SD. Since a minimum clinically meaningful effect is 0.4 SD (ref), we will have adequate power to identify a clinically important effect. [other methods include reliable change index and using 1xSEM]

Analysis will be performed by z-scoring the outcome from each of the cognitive instruments (using REGARDS and other normative data), then calculating the average change across the cognitive domains, allowing incorporation of all patients. Patients with clinical stroke as a CREST-2 outcome will have their composite cognitive Z-scores changed to the score at the lowest end of the range of scores in the cohort.

Power calculation for Secondary endpoints -- Hypothesis 2 and 3, S1 and S2.

Hypothesis 2: With 37 patients, there is 80% power to detect a correlation of 0.38, and 90% power to detect a correlation of 0.44.

Hypothesis 3: All 500 patients with baseline scans can be used in the analysis (anticipated 100 with hemodynamic impairment, 400 without). With this larger sample size, differences of 0.3 SD can be detected with 80% power, and 0.4 with 90% power (corresponding to differences of 0.15 to 0.16 in the average change in the z-score).

S1 and S2: Under the assumption that linear regression is used, similar to the primary aim, there will be 80% to 90% power to detect differences that are as large or larger as 0.6 to 0.7 times the within-group standard deviations of the number of new lesions.

## 10.6 MEASURES TO MINIMIZE BIAS

### 10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

In order to minimize bias (and cross-over resulting from the perfusion information) the CREST-H PI at the participating institution will oversee all research scan information once it is acquired, and facilitate the upload of de-identified scans for centralized processing at U Maryland via links already established as part of CREST-2. It is recommended that a co-investigator be assigned to carry out these functions. No processed scan information will be made available to the treating team at the site, who, as a condition

of participating in CREST-H, will agree to remain blinded to the perfusion scan information for the duration of the patient's participation in the study.

The CREST-H PI or assigned co-investigator will act as the local "imaging liaison officer." He or she will agree to receive any official safety reads from the local institution or the central image processing and analysis site, and will alert the site PI with any clinically relevant information, such as brain tumor, hemorrhage, vascular malformation, etc. No perfusion data will be considered clinically relevant since the use of MR and CT perfusion is not standard of care for asymptomatic carotid stenosis, and clinical relevance will be established only after the proposed study is completed.

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#### 10.6.2 EVALUATION OF SUCCESS OF BLINDING

There will be no specific evaluation of the success of blinding for this study, except to show that no more than expected cross-overs occurred.

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#### 10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Because the safety of the main intervention (revascularization vs IMM alone) falls under the management of the parent trial, the only blinding that is important with respect to CREST-H is the classification of patients into those with hemodynamic flow impairment vs those with normal flow. Only if there were an SAE concerning the MRI/ CT protocol would the blind need to be broken. As described above, there will be a safety read for the structural imaging sequences, and any unexpected imaging findings such as a hemorrhage, tumor or other clinically relevant pathology, will be transmitted to the primary treating physicians.

### 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

As part of participating in a NIH IC-sponsored or NIH IC -affiliated study, each site will permit authorized representatives of the NIH IC 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. Access to clinical records will be provided to the local and central IRB (for those sites who are using the StrokeNet cIRB) and representatives of the sponsor, NIH/NINDS.

### 12 QUALITY ASSURANCE AND 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 sites for clarification/resolution.

For MRP/CTP imaging each CREST-H participating site will submit a test file of MRP/CTP acquisition data according to the protocol. These files will de-identified, uploaded to the Image Data Management center at U Maryland, and transferred to UCLA Image analysis center. Study personnel at UCLA will

confirm that the images are of good quality and adequate for analysis. Confirmation of adequacy of images will be confirmed, and the participating site notified prior to that site enrolling its first patient.

Following written SOPs, the monitors will verify that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all study related locations, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

### 13.1 ETHICAL STANDARD

The investigators will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

### 13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the cIRB (StrokeNete sites) or local IRB (non-StrokeNet sites) 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

### 13.3 INFORMED CONSENT PROCESS

#### 13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol:

Consent form for CREST-H

#### 13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and

review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

#### 13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB 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 IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the SDCC at the University of Alabama at Birmingham. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the SDCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the SDCC.

A certificate of confidentiality has been granted for the study.

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##### 13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Data to be stored: There are no biological or genetic specimens for this study. De-identified MRI/CT data will be archived at the Imaging Management Center at University of Maryland for the duration of the study and up to 7 years thereafter. Processed data including cognitive exams and numerical results of

the imaging analysis will be stored at the SDCC at U Alabama at Birmingham as part of the parent study (CREST-2) data storage.

Storage: For the duration of the study, access to stored MRI /CTP data will be limited. Data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the MRIs/CTPs and data.

Tracking: Data will be tracked by the SDCC through the use of CRFs that used log data collection, transfer, and completion.

### 13.5 FUTURE USE OF STORED SPECIMENS

In accordance with NIH policy regarding data sharing, the study data will be made available to the research community broadly defined after the final data set has been cleaned and locked and the primary and main secondary outcomes analyses have been published in the peer-reviewed scientific literature.

## 14 DATA HANDLING AND RECORD KEEPING

### 14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Paper CRFs generated by the SDCC will be used, with direct data entry to a password-secured website at the SDCC. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the SDCC website, a 21 CFR Part 11-compliant data capture system provided by U Alabama at Birmingham. The data system includes password protection and internal quality checks, such as automatic range and logic checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

### 14.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after study completion in accordance with NIH policy.

### 14.3 PROTOCOL DEVIATIONS

Protocol deviations are not allowed. A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NINDS Program Official and U Alabama at Birmingham SDCC. Protocol deviations must be sent to the local IRB or the cIRB (StrokeNet sites) per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

#### 14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the 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.

### 15 STUDY ADMINISTRATION

#### 15.1 STUDY LEADERSHIP

The following roles from key personnel comprise the Study Leadership and form the steering committee which will meet at least twice a year during the conduct of the study.

**Randolph S Marshall, MD**, Professor of Neurology (Co-PI – contact/administrative)

Dr. Marshall will be responsible for the overall conduct of the study, including the recruitment of sites. He will be responsible for overseeing patient recruitment across all 75 CREST-H sites. He will interface with the administrative operations at Mayo Jacksonville, the database and statistics operations at UAB, and ongoing QA procedures at Mayo Rochester and UCLA. He will participate in the analysis of the main results of the trial, and sit on the Steering Committee.

**Ronald M Lazar, PhD**, Professor of Neuropsychology (Co-PI - cognitive)

Dr. Lazar at University of Alabama Birmingham is the Cognitive PI for the parent trial CREST-2 and will serve this function for CREST-H; he will thus be the liaison between the parent and ancillary study, reporting on progress at the weekly CREST-2 Executive Committee meeting. He will also attend the CREST-2 DSMB meetings and report on the progress of this project. He will be in charge of interpreting results correlating hemodynamic with the cognitive outcomes in this project, and sit on the Steering Committee.



**E Sander Connolly, MD**, Professor of Neurological Surgery (Co-PI – surgical)

Dr. Connolly has presence and national visibility in the academic Neurosurgical community. He will provide neurosurgical leadership to interface with the surgical and interventional investigators across CREST-2 participating sites to help facilitate recruitment, and assist sites with timing and coordination of the MRI/CT scanning for CREST-H within the CREST-2 interventional arm. He will sit on the Steering Committee.

**David S Liebeskind, MD**, Professor of Clinical Neurology (Co-PI – imaging)

Dr. Liebeskind will oversee image acquisition, post-processing, analysis and provide QA oversight for all perfusion imaging for CREST-H. His expertise in stroke imaging, measurement of cerebral blood flow with perfusion MRI techniques and collateral circulation is unique for the project and his leadership will be crucial to the success of the study. He will also sit on the Steering Committee

**George Howard, Dr.PH.** Professor of Biostatistics (Co-I - data management, statistics)

Dr. Howard is the PI of the Statistical and Data Management Center for the Carotid Revascularization for Primary Prevention of Stroke Trial (CREST-2), the parent trial for CREST-H He is also the immediate past PI of the Coordinating Centers the Carotid Revascularization Endarterectomy Stenting Trial (CREST) a randomized trial of 2,502 patients contrasting endarterectomy versus carotid stenting. He will be responsible for the management of all clinical data uploaded from CREST-H participating sites and the integration of clinical and imaging output data from UCLA and Mayo Rochester. He will supervise the statistical data analysis for the grant, and will sit on the Steering Committee.

**Brajesh K Lal, MD**, Professor of Surgery (Co-I - Image data management)

Dr. Lal is Professor and Chief of Vascular Surgery at the Baltimore VA Medical Center at University of Maryland. He is in charge of the CREST-2 Vascular Imaging Core facility (VIC) at U Maryland which has already established electronic linkages with each CREST-2 clinical center approved to randomize patients in the trial. He will be responsible for file transfer protocol (ftp) to transfer images to U Maryland for CREST-H, interacting with participating centers to ensure timely transfer. The images will be stored in a HIPAA-compliant, firewall protected server within the U Maryland archival system. He will also be responsible for the transfer of PWI image files to Dr. Liebeskind's Imaging lab at UCLA, and of structural MRI/CT files to Dr. Huston's lab at Mayo Rochester. He will sit on the Steering Committee.

**John Huston, III, MD**, Professor of Radiology (Co-I - structural imaging analysis)

Dr. Huston will interpret study standard MRI/CT imaging (other than the perfusion imaging) utilizing NIH NINDS Common Data Elements developed for the CREST-2 grant. These reviews provide the data to quantify the presence of prior cerebral infarcts, white matter hyperintensity volumes, cerebral microbleeds and subsequent silent infarcts. He will monitor the quality of the images submitted from each participating site, and contact the site PI to discuss quality of the images if they are not satisfactory. He will sit on the Steering Committee.

**Thomas Brott, MD**, Professor of Neurology, Mayo Jacksonville (CREST-2 Co-PI)

Dr. Brott will be responsible for the conduct of the CREST-H study as it pertains to the interface with CREST-2, ensuring that the conduct of CREST-H does not interfere with recruitment, retention or completion of the parent study. He will sit on the Steering Committee.

**James Meschia, MD**, Professor of Neurology, Mayo Jacksonville (CREST-2 Co-PI)

Dr. Meschia will assist with the operational interface between CREST-H and CREST-2, to ensure that coordination between the two protocols is made as efficient and productive as possible. He will sit on the Steering Committee.

## 16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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**APPENDIX**

<b>Version</b>	<b>Date</b>	<b>Significant Revisions</b>