Asymptomatic Carotid Stenosis: Cognitive Function and Plaque Correlates (ACCOF)

Unique Protocol ID: CARA-024-10S

NCT01353196

May 21, 2019

UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

Date: Thursday, January 10, 2019 2:56:25 PM Print Close

View: v2_Introduction Page

Introduction Page

1 * Abbreviated Title:
ACCOF Study

2 * Full Title:
Asymptomatic Carotid Stenosis: Cognitive Function and Plaque Correlates

3

* Select Type of Submission:
IRB Application

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:

ID: VIEW4DF8709A33C00
Name: v2_Introduction Page

View: v2_Research Team Information

Research Team Information

1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Brajesh Lal

1.1 * Does the Principal Investigator have a financial interest related to this research?
○ Yes ● **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Kimberlly Nordstrom

2.1 Does the Point of Contact have a financial interest related to this research?
○ Yes ● **No**

3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

Name	Edit Submission	cc on Email	Research Role	Has SFI?
Moira Dux	no	yes	Other	no
Vicki Gray	no	yes	Research Team Member	no
Amanda Hutchinson	yes	yes	Research Team Member	no
Laila Anthony	yes	yes	Study Coordinator	no
Siddhartha Sikdar	no	yes	Sub-Investigator	no

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

ID: VIEW4DF85C16F2800
Name: v2_Research Team Information

View: v2_Resources

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

1 * Describe the time that the Principal Investigator will devote to conducting and completing the research:
The PI will oversee recruitment of potential participants, collection and storage of study data, regulatory deadlines and data analysis. This will be accomplished primarily through a standing weekly meeting with research team members. The PI will also meet individually with the study coordinator weekly or as needed to discuss recruitment and any safety issues related to data collection.

2 * Describe the facilities where research procedures are conducted:
All patient's will be consented at the VA Medical Center. They will also complete neurocognitive testing, questionaires, and phlebotomy at the VA Medical Center. Participants will be escorted to the vascular lab at the University of Maryland Medical Center to complete imaging and walking and balance assesssments. Patient's recruited from the University of Maryland Medical Center will be escorted to the VA Medical Center for consenting, neurocognitive testing, questionaires, and phlebotomy.

For the purpose of the additional follow-up planned; patients will undergo ultrasound testing, physical function testing and questionnaires at the University of Maryland Medical Center vascular lab.

3 * Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:
All efforts will be made to ensure subjects are seen safely and efficiently. Reasonable time will be allotted for each subject to complete testing. All procedures will be conducted by trained professionals in the areas of phlebotomy, neuropsychology, and vascular imaging. The PI is available by phone and pager at all times.

4 * Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:
The PI will speak with all research team members to discuss the study (purpose and procedures) and their role within the study. A standard of practice document will be completed and placed in the research office outlining all procedures of the study. Protocol and study related topics are discussed regularly at a weekly ACCOF conference with all team members.

ID: VIEW4DF83CB976400
Name: v2_Resources

View: v2_Sites Where Research Activities Will Be Conducted

Sites Where Research Activities Will Be Conducted

1 * Is this study a:
- (●) **Multi-Site**
- ( ) Single Site

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?
( ) Yes (●) **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?
( ) Yes (●) **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date

There are no items to display

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)
( ) Yes (●) **No**

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)
( ) Yes ( ) No

6 * Institution(s) where the research activities will be performed:
VAMHCS
University of Maryland Medical System (Select below)

* UMMS Sites:
University of Maryland Medical Center

ID: VIEW4DF870DF2C000
Name: v2_Sites Where Research Activities Will Be Conducted

View: v2_Funding Information

Funding Information

1 * Indicate who is funding the study:
Federal

2 * What portion of the research is being funded? (Choose all that apply)
Staff
Other

3 Please discuss any additional information regarding funding below:
None

ID: VIEW4DF85DF452400
Name: v2_Funding Information

View: v2_DHHS Funded Study

DHHS Funded Study

You indicated that this is a Federally funded study.

1 * Is this study sponsored by a Department of Health and Human Services (DHHS) agency?
○ Yes ● **No**

2 If Yes, indicate the grant number(s):
- OR - Check here if the grant is not assigned a number. ☐

3 If Yes, upload all grant documents:

Name	Created	Modified Date

There are no items to display

ID: VIEW4DF87B9560800
Name: v2_DHHS Funded Study

View: v2_Federal Agency Sponsor Information

Federal Agency Sponsor Contact Information

You indicated that this is a Federally funded study.

1 * Agency Name:
Department of Veterans Affairs

* Address 1:
810 Vermont Avenue,NW

Address 2:

* City:
Washington DC

* State:
MD

* Zip Code:
20420

* Contact Person:
Miriam J. Smyth PhD

* Phone Number:
410 605 7000 Ext 6510

Grant Number 1 (if applicable):
CARA- 024-10S- OR - Check here if Grant 1 is not assigned a number. ☐

If Grant 1 has no number, please provide the following information:
Title of Grant 1:

PI of Grant 1:

Grant Number 2 (if applicable):
- OR - Check here if Grant 2 is not assigned a number. ☐

If Grant 2 has no number, please provide the following information:
Title of Grant 2:

PI of Grant 2:

Grant Number 3 (if applicable):
- OR - Check here if Grant 3 is not assigned a number ☐

If Grant 3 has no number, please provide the following information:
Title of Grant 3:

PI of Grant 3:

Grant Number 4 (if applicable):
- OR - Check here if Grant 4 is not assigned a number. ☐

If Grant 4 has no number, please provide the following information:
Title of Grant 4:

PI of Grant 4:

ID: VIEW4DF8584874400
Name: v2_Federal Agency Sponsor Information

View: v2_Research Protocol

Research Protocol

1 * Do you have a research protocol to upload?
No, I do not have a research protocol and will use the CICERO application to enter my study information

2 If Yes, upload the research protocol:

Name	Created	Modified Date
recruitment letter template UMMC.docx	7/1/2013 9:37 AM	7/1/2013 9:37 AM
ACCOF form 9 DSMB_10_2012.doc	10/16/2012 3:58 PM	10/16/2012 3:58 PM
ACCOF form 9 DSMB.doc	4/30/2012 12:24 PM	4/30/2012 12:24 PM
recruitment letter template stenosis.docx	4/9/2012 3:19 PM	4/26/2012 9:04 AM
recruitment letter template control.docx	4/9/2012 3:19 PM	4/9/2012 3:19 PM
ACCOF - revised 2-14-11	2/15/2011 10:14 AM	2/15/2011 10:14 AM

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

View: v2_Risk Level

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:
Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.

ID: VIEW4E02805225800
Name: v2_Risk Level

View: v2_Type of Research

Type of Research

1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):
Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).
Sample (Specimen) Collection and/or Analysis (including genetic analysis).

2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related

biomedical or behavioral outcomes.

● Yes ○ No

ID: VIEW4E0280569E000
Name: v2_Type of Research

View: v2_Lay Summary

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Carotid artey stenosis is a recognised cause of Stroke and/or TIAs(mini stroke). Under appreciated is the fact that the consequence of carotid stenosis may be a slow impairment in thinking, learning, memory and problem solving without evidence of stroke or TIAs.
The goal of this study is to measure the magnitude of cognitive impairment , its impact on the quality of life and its pathophysiology in patients with asymptomatic carotid stenosis.

**With regards to the planned additional follow-up, the goal is to assess how carotid-stenosis-induced cognitive impairment may or may not impact physical function.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

View: v2_Justification, Objective, & Research Design

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

The goal of this proposal is to perform a systematic, adequately powered study to measure the magnitude of cognitive impairment in asymptomatic carotid stenosis, its impact on quality of life, and its potential pathophysiological mechanisms. Information from this study will define an unsuspected morbidity of carotid stenosis and identify subsets of patients at risk for cognitive impairment. It will form the foundation for future studies on prevention, pre-emptive treatment, or rehabilitation of patients with carotid stenosis. It will also improve the selection of patients with carotid stenosis to decrease unnecessary revascularization procedures.

Specific Aim 1 will assess if patients with asymptomatic carotid stenosis differ in cognitive function compared to age-matched controls without carotid stenosis but with similar vascular risk profiles. We hypothesize that in patients with asymptomatic carotid stenosis □50% who survive stroke free for 2 years; the change in overall and domain-specific cognitive function will be significantly different compared to those without stenosis. The study will recruit 284 subjects and will detect a clinically significant difference in cognitive score with 90% power. We will use a novel battery of cognitive tests specifically developed to address the unique issues relating to carotid stenosis.

Specific Aim 2 will define plaque-morphometric, biologic, and hemodynamic characteristics that correlate with cognitive impairment in patients with asymptomatic carotid stenosis. We hypothesize that carotid plaque architecture, plaque composition, microembolic counts, serum pro-inflammatory markers, and cerebral hypoperfusion could each mediate cognitive decline over a 2-year
follow-up period. We will implement a novel clinical 3D B-mode ultrasound imaging technique developed to obtain reliable serial plaque measurements.

Specific Aim 3 will measure the impact of cognitive impairment on quality of life. We hypothesize that at 2 years, regardless of plaque features, cognitive impairment will correlate with a reduction in health-related quality of life measures.

Carotid artery plaques are known to cause stroke. Cognitive impairment is an insidious but poorly understood problem in patients with carotid plaques. Cognitive function describes how we perform mental processes such as thinking, learning and problem solving. Asymptomatic carotid plaques may affect □1 million veterans who may be at risk for cognitive impairment. In this study, we will uncover the extent of cognitive impairment in veterans with carotid stenosis who are currently labeled "asymptomatic". Programs to prevent or mitigate cognitive impairment will depend on identifying the mechanisms by which this occurs. We will use sophisticated 3D imaging techniques developed by our group to measure the structure and composition of plaques, number of particles breaking off from them, blood levels of chemicals that could disrupt them, and blood flow restriction to the brain from them. This will help identify patients at risk for cognitive impairment who may benefit from preventative measures and improve selection of patients to decrease unnecessary surgical procedures.

**With regards to the planned additional follow-up, the goal is to assess how carotid-stenosis-induced cognitive impairment may or may not impact physical function.

We hypothesize that participants with carotid stenosis will demonstrate impaired physical function at baseline, increased deterioration of physical function on follow-up evaluation, and reduced response to balance training.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

RESEARCH DESIGN & METHODS
This is a prospective longitudinal controlled single-center clinical study designed to measure the extent of cognitive impairment associated with asymptomatic carotid stenosis, potential mediators of impairment, and the functional impact of the resulting disability

Specific Aim 1 is to determine whether patients with asymptomatic carotid stenosis will differ in cognitive function compared to age-matched individuals without carotid stenosis but with similar vascular risk factors. The primary hypothesis is that in patients with asymptomatic carotid stenosis (≥50% diameter-reducing) who survive stroke-free for 2 years; the change in
overall and domain-specific cognitive function will be significantly different compared to those without stenosis.
The primary analysis of impact will be the overall and domain-specific cognitive change score at 2 years, with the initial score at recruitment serving as the baseline.

Patient recruitment
Eligible patients are defined as having asymptomatic ≥50% diameter reducing carotid stenosis. Asymptomatic status in patients will be confirmed by a history, physical examination, and numeric NIH Stroke Scale96 as defined in prior NIH carotid trials1-4. While asymptomatic patients with diameter stenosis ≥60% benefit from revascularization2, that benefit is reduced when compared to symptomatic patients1, 4. Most centers including

ours, follow the common practice of operating on symptomatic patients with stenosis, but only consider revascularization for asymptomatic patients when the stenosis is >80%45, 46. In this standard of care approach, asymptomatic patients with moderate carotid stenosis (50-80%) are treated medically and followed with annual screening studies to monitor for disease progression. Once a decision has been made that they do not require revascularization, these patients will be recruited to our proposed study. The decision as to whether a subject is appropriate to be followed with medical management alone will be made by the treating clinician in consultation with their patient. Participation in this study will not require any change in the standard clinical care that patients receive.

Patients recruited to this study will have an effective luminal diameter at the level of the maximal stenosis that is ≤50% of that of the distal normal internal carotid artery (i.e. ≥50% stenosis). This identification will most commonly be made by duplex sonography, but could be made by any other standard imaging modality namely MRI, angiography, or CT. Our center follows standardized ICAVL-approved (Inter-societal Commission for Accreditation of Vascular Laboratories100) Doppler velocity criteria to determine the degree of stenosis101; as has been done in previous NIH carotid trials1-4.

Exclusion criteria will be a previous stroke or TIA, severe medical illness that would interfere with evaluation of outcomes or reduce the likelihood of a 2-year follow-up, carotid occlusion, and patients scheduled for carotid revascularization procedures. We chose not to use a dementia-screening tool to exclude patients since false positives may be as high as 61%102

Exit/Endpoints: Patients will exit the study if they develop a stroke or TIA during follow-up, or if they undergo carotid revascularization; however, data accrued up to the exit point will be included for analysis (see statistical analysis section). Patients will be dropped from the study if the first 3D B-mode imaging assessment as part of the study indicates that their arterial diameter reduction is actually less than 40%.

Specific Aim 2 (a through d) is designed to identify the potential mechanisms of cognitive change in patients with asymptomatic carotid stenosis. Specifically, we will: 1) assess if carotid plaque architecture, plaque composition, microembolic counts, serum pro-inflammatory markers, and cerebral hypoperfusion hypothesized to be in the causal pathway of cognitive decline, could each independently predict a change in cognitive function and 2) assess if patients with asymptomatic carotid stenosis who develop cognitive impairment will differ in these factors compared with similar patients that remain unchanged over 2 years of follow-up. The specific factors that will be analyzed in this aim are: carotid plaque architecture (cross-sectional area, longitudinalsectional area, volume, lipid core volume, core distance from lumen); plaque tissue composition (percent distribution of hemorrhage, lipid, fibro-muscular tissue, and calcium); microembolic counts (on TCD); serum proinflammatory marker levels (hsCRP, MMP-9, IL-6); hemodynamic alteration (cerebrovascular reactivity);

Specific Aim 3 will determine the impact of cognitive impairment on quality of life measures (Short Form-36 and Frenchay activities index). We will test whether at 2 years, regardless of plaque features, cognitive impairment will correlate with a reduction in health-related quality of life scores.

**With regards to the planned additional follow-up, all subjects enrolled in the study will be eligible to participate. They will be contacted to come on ONE day for 2 hours to undergo carotid ultrasound testing, physical function testing, and to answer a questionnaire.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

Cognitive impairment is known to occur in patients with stroke from carotid stenosis [CS]. However, isolated cognitive impairment in CS patients without a stroke/TIA has not been looked for systematically, or reported in any detail. We have used our prior experience along with published information, to develop a battery of cognitive tests specifically for patients with CS. The methodology has been piloted and validated for clinical relevance and minimum important difference, MID. We will use this test battery in Aim 1 to compare cognitive function in patients with asymptomatic CS vs. control subjects with no stenosis. Plaque morphologic features are better predictors of future risk of rupture than degree of stenosis. Plaques remodel rapidly, and must be monitored serially. No studies of evolving non-invasive morphologic plaque features have been performed; nor have correlations been made with atheroembolic complications such as cognitive impairment. We have developed novel approaches that address each of these important considerations. In the first study of its kind, we will implement a sophisticated 3D B-mode imaging protocol for serial plaque assessments, and correlate these with cognitive changes over 2 years. Principal descriptors will be plaque architecture (cross & longitudinal sectional areas, volume, core volume, and distance from flow lumen), and composition (percent volumetric distribution of plaque tissues). Asymptomatic CS is associated with “silent” microembolization to the MCA, and “silent” cerebral microinfarctions; however, cognitive function is not routinely tested in these patients. Silent microinfarctions in otherwise healthy individuals are associated with cognitive impairment. Therefore, we will utilize TCD to determine the relationship between silent microembolization and cognitive impairment in our patients with CS. The potential role for hsCRP, MMP-9 and IL-6 in predicting risk for plaque rupture and cognitive impairment in asymptomatic CS patients has not been studied systematically in a longitudinal protocol. Strategies to utilize imaging and inflammatory markers in conjunction to improve risk-stratification have also not been explored. We will identify whether serum levels of hsCRP, IL-6 and MMP-9 in patients with CS correlate with cognitive impairment. Both chronic and acute cerebral hypoperfusion can cause cognitive impairment. We will determine the relationship between chronic cerebral hypoperfusion and cognitive function in patients with CS over the 2-year follow-up period of the study.

**With regards to the planned additional follow-up, there is no available information on the relationship between carotid-stenosis-induced cognitive impairment and physical function. There is data to suggest, however, that impaired cognition may lead to impaired physical function in patients without a carotid stenosis.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Carotid artery stenosis is a well-known cause of atheroembolic stroke. Stroke prevention in these patients has been the focus of intense investigation. Cognitive impairment is a more insidious but poorly understood outcome in patients with “asymptomatic” carotid stenosis who have not suffered a stroke. Cognitive function describes how a person produces and controls mental processes such as thinking, learning, and problem solving. It is an important outcome measure that affects patient well-being and their ability to live independent productive lies. It is well-known that cognitive impairment coexists in patients with stroke from carotid stenosis. However, isolated cognitive deficits in patients with asymptomatic carotid stenosis have not been looked for, and have therefore not been reported in any detail.
Asymptomatic carotid stenosis affects 2-12% of people. With 23.4 million veterans in the country, at least 1 million (4.3%) have asymptomatic carotid stenosis and are at risk for cognitive impairment. A subset analysis of the Cardiovascular Health Study found cognitive decline in 34% of 32 patients with asymptomatic carotid stenosis. In this proposal, we will define the extent of initial and progressive cognitive impairment in veterans with carotid stenosis who are currently labeled as “asymptomatic” in the absence of a focal neurologic deficit (stroke, transient ischemic attack). Programs to prevent, postpone, or mitigate cognitive impairment in patients with carotid stenosis will depend on the identification of mediators for cognitive impairment. Microembolic brain injury and cerebral hypoperfusion have been associated with cognitive impairment in elderly individuals. Therefore plaque architecture, plaque composition, microembolic counts, serum inflammatory markers, and cerebral hypoperfusion are likely mediators of impaired cognition in patients with asymptomatic carotid stenosis. As part of this proposal, we will identify the biological mechanisms by which carotid stenosis could result in cognitive impairment.
BACKGROUND AND SIGNIFICANCE
The magnitude, determinants,and functional impact of cognitive impairment associated with carotid stenosis have not been evaluated . In the first study of its kind, we

propose to systematically assess the magnitude of cognitive impairment
associated with carotid stenosis among veterans, in an appropriately powered analysis. Cognitive assessment in patients with carotid stenosis is challenging since there is no dedicated battery of tests for these patients. We have developed and tested a
novel cognitive battery and interpretation scheme that will address this issue. A detailed search for mediators
of cognitive impairment in this cohort will uncover potential avenues of investigation for prevention, preemptive
treatment, or rehabilitation that could mitigate the large expenditure incurred by the VA system for this
morbidity. While non-invasive imaging can identify morphologic features of ruptured plaques; characteristics of
pre-embolic unstable plaques have not been defined. This is the first study to test the novel hypothesis that carotid
plaque morphology will predict future cognitive impairment. We have developed a novel 3-dimensional Bmode
ultrasound imaging and post-processing methodology for serial non-invasive monitoring of carotid
plaque characteristics. We will also test the novel hypothesis that serum pro-inflammatory markers correlate
with cognitive impairment. In addition, we will measure embolic counts and cerebral blood flow to complete the
most comprehensive assessment of potential predictors of cognitive change in patients with carotid stenosis.
Finally, the study will establish the important principle that clinical outcome in carotid stenosis should be considered
more than just stroke.

**With regards to the planned additional follow-up, there is data to suggest that impaired cognition may lead to impaired physical function in patients without a carotid stenosis. This forms the rationale for our exploration of this relationship in our cohort.

ID: VIEW4E02805EA0C00
Name: v2_Justification, Objective, & Research Design

View: v2_Supporting Literature

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

The goal of this proposal is to perform a systematic, adequately powered study to measure the magnitude of cognitive impairment in asymptomatic carotid stenosis, its impact on quality of life, and its potential pathophysiological mechanisms. Information from this study will define an unsuspected morbidity of carotid stenosis and identify subsets of patients at risk for cognitive impairment. It will form the foundation for future studies on prevention, pre-emptive treatment, or rehabilitation of patients with carotid stenosis. It will also improve the selection of patients with carotid stenosis to decrease unnecessary revascularization procedures.
Specific Aim 1 will assess if patients with asymptomatic carotid stenosis differ in cognitive function compared to age-matched controls without carotid stenosis but with similar vascular risk profiles. We hypothesize that in patients with asymptomatic carotid stenosis ≥50% who survive stroke free for 2 years; the change in overall and domain-specific cognitive function will be significantly different compared to those without stenosis. The study will recruit 284 subjects and will detect a clinically significant difference in cognitive score with 90% power. We will use a novel battery of cognitive tests specifically developed to address the unique issues relating to carotid stenosis. Specific Aim 2 will define plaque-morphometric, biologic, and hemodynamic characteristics that correlate with cognitive impairment in patients with asymptomatic carotid stenosis. We hypothesize that carotid plaque architecture, plaque composition, microembolic counts, serum pro-inflammatory markers, and cerebral hypoperfusion could each mediate cognitive decline over a 2-year follow-up period. We will implement a novel clinical 3D B-mode ultrasound imaging technique developed to obtain reliable serial plaque measurements. Specific Aim 3 will measure the impact of cognitive impairment on quality of life. We hypothesize that at 2 years, regardless of plaque features, cognitive impairment will correlate with a reduction in health-related quality of life measures.

**With regards to the planned additional follow-up, there is data to suggest that impaired cognition may lead to impaired physical function in patients without a carotid stenosis. This forms the rationale for our exploration of this relationship in our cohort.

2 If available, upload your applicable literature search:

Name	Created	Modified Date
Tromso study	7/7/2010 11:41 AM	7/7/2010 11:41 AM
CREST REVIEW	7/7/2010 11:41 AM	7/7/2010 11:41 AM
Endarectomy for symptomatic carotid artery stenosis	7/7/2010 11:40 AM	7/7/2010 11:40 AM

3 * Provide a list of 3 keywords or search terms (1 per line) relevant to your research that would help potential participants find your study using search engines:

Keyword 1: Carotid

Keyword 2: Cognition

Keyword 3: Plaque

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

View: v2_Study Procedures

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

The schedule for major evaluation components is provided in Table II of the protocol page 32
The time required to obtain the information is provided in Table III of the protocol page 32.
To assess the stated endpoints, our study will establish for each patient, the baseline demographics, vascular risk factor profile, neurologic status (history, neurologic examination, NIHSS), cognitive function (cognitive function tests), plaque information (3D B-mode imaging), microembolic counts (TCD testing), inflammatory status (serum pro-inflammatory markers), perfusion status (cerebrovascular reactivity) and quality of life (SF36, Frenchay index). To assess change in status we will measure for each patient,

follow-up cognitive function, plaque information, microembolic counts, inflammatory status, perfusion status, and quality of life, at 1 and 2 years post-recruitment. The stenosis-free control subjects will undergo an ultrasound carotid assessment at baseline (to rule out stenosis), and assessments of cognitive function at baseline and at 1 and 2 years post-recruitment.

**With regards to the planned additional follow-up, participants will attend one session of approximately 2 hours duration.
Assessment of physical function including tests of balance and gait. Include the Berg Balance Scale-7 item (BBS), the Dynamic Gait Index-4 item (DGI), the Four Square Step Test and Short Physical Performance Battery. Questionnaires related to balance and walking function will include the Activities-specific Balance Confidence (ABC) Scale, Falls Efficacy Scale. Overall mental health will be assessed using the Mini-mental State Exam questionnaire and activity level will be assessed with the Physical Activity Scale for Elderly (PASE). Carotid Ultrasonography will be used to assess carotid artery blockage. This test is non-invasive and is being performed per clinical standard of care. Patients will remain comfortably recumbent on a stretcher during the testing period. It is extremely unusual for patients to experience any discomfort during the testing. Every effort will be made to explain the test and ensure patient comfort during testing.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

Cognitive function testing
Conduct of testing. In Specific Aim 1 the primary hypothesis is that in patients with asymptomatic carotid stenosis (≥50% diameter-reducing) who survive stroke-free for 2 years; change in overall and domain-specific cognitive function will be significantly different compared to those without stenosis (fig 1 and 3). The primary analysis of impact will be the overall and domain-specific cognitive change score at 2 years, with the initial score at recruitment serving as the baseline. Patients and control subjects will undergo a 50-minute neurocognitive battery at 3 time points: baseline, 1 year, and 2 years after recruitment. Baseline testing will take place within a few days of recruitment. Following the approach of our prelim data #3 for performing cognitive testing in a similar patient population, the battery will consist of 10 standardized neuropsychological tests for multiple cognitive domains selected on the basis of the NIH harmonization standards, our own preliminary data #3, and published experience in patients with carotid stenosis5-10, 31. All tests have published age-adjusted norms. All participants will undergo all 10 tests. The order of test administration will remain constant for baseline and follow-up evaluations. Tests will be conducted in a quiet room. The order of administration accommodates the delays required for recall intervals and minimizes stimuli interference in memory tasks.
Plaque architecture and composition
The architecture and composition of plaques may influence the risk and quantity of atheroembolization, and the nature and extent of microembolic cerebral injury (fig 1). Specific Aim 2a of our study will investigate whether cognitive impairment is mediated by plaque features that predispose it to rupture and atheroembolization. Specifically, we will test whether A) at 2 years, carotid plaque architecture and composition will independently predict a change in cognitive function and, B) at 2 years, patients with asymptomatic carotid stenosis who develop cognitive impairment will differ in these characteristics compared with similar patients that remain unchanged.
The primary analysis of impact will be plaque cross sectional area. Additional features assessed will be longitudinal sectional area, plaque volume, lipid core volume, distance of core from flow lumen, and tissue composition. These features will be measured by the novel 3D B-mode imaging methodology developed by the applicant, and will be obtained once at the time of recruitment and at 1 and 2 years of follow-up, in conjunction with their clinical visits to avoid additional trips for the patient.
3-D B-mode imaging protocol. The investigators have experience with and are aware of several complex non-clinical MRI protocols that afford good plaque imaging. However, these protocols require surface coils and prolonged imaging times in excess of 1 hour, which renders them inconvenient, impractical, and exorbitantly expensive in a clinical environment requiring repeated testing for plaque evolution. Ultrasound is readily available across the country in thousands of vascular laboratories, is inexpensive ($200-300/test), and high resolutions (250-400 μm) are achievable by modern 8-15 MHz array transducers since the carotid artery is superficially located. It is therefore ideally suited for clinical protocols requiring serial surveillance testing. Incorporation of 3D imaging to the B-mode protocol enhances the amount of information obtained, and quality of information received, while reducing observer variability and test-time. In our protocol, a balance has been reached between feasibility, time (less than 20 minutes), patient comfort, cost, and comprehensiveness. The proposed protocol will be immediately translatable to clinical practice. We will utilize our novel 3D ultrasound image capture and processing system to obtain the following plaque measurements
Measures of architecture (fig 19). Cross-sectional plaque area. Sequential cross sectional images will be obtained using the 3D image capture system described in prelim data #8. All images will be acquired with EKG gating and captured at end-diastole to allow consistent serial comparisons. The largest plaque area measurement at the region of maximum stenosis will be selected to be compared at each followup point. Longitudinal-sectional plaque area.
Sequential 3D images will be captured across the longitudinal plane and the largest plaque area in this plane will be measured and compared in serial examinations.
Plaque volume. Sequential cross sectional images will be reconstructed to obtain serial volumetric measures of the plaque. Lipid core volume. As described in prelim data #6, the lipid core can be identified in ultrasound images as a discrete hypoechoic area in the plaque. The volume of the hypoechoic region will be measured for serial comparisons.
Least distance of lipid core from flow-lumen. Since it is flanked by a hypoechoic lumen and an underlying lipid core, intervening plaque fibromuscular tissue between the two structures (a measure of plaque fibrous cap thickness) can be visualized by ultrasound111. A planimetry program based on intensity gradients and smoothness will be used to measure the least thickness.
Measures of composition. Tissue composition. We have described our approach to standardizing dynamic range, gain and gray map settings to enable normalization of grayscale images across ultrasound platforms (prelim data #7). 3D images will be acquired with this standardization so that valid segmentation processing can be performed on all the images to obtain information on percent composition of each tissue type (hemorrhage, lipid, fibromuscular tissue and calcium) as described in prelim data #5 and #6.
Microembolic counts
Our physiological hypothesis is also designed to investigate whether cognitive impairment is mediated by the number of cerebral microemboli detectable in the middle cerebral artery (fig 1). In Specific Aim 2b, microembolic counts will be correlated with cognitive function at baseline and at 1 & 2 years of follow-up. They will be obtained by a 1-hour transcranial Doppler (TCD) recording with digital filters set to identify solid microembolic particles.
TCD protocol. TCD monitoring of middle cerebral artery flow is currently the most sensitive and specific method for real-time, in-vivo detection of cerebral emboli. We have experience in TCD monitoring in patients with carotid stenosis (prelim data #9). All study examinations will be digitally recorded and audited with remeasurement of embolic counts to ensure accuracy of interpretation. Simultaneous bilateral TCD monitoring will be accomplished by trained vascular technologists for a total duration of 60 minutes. Testing will occur through transtemporal windows using a 2-2.5 MHz pulsed wave probe at an insonation depth of 48-58 mm (optimized for each patient). The velocity scale of the recording will be adjusted to 100-150 cm/s.
Serum pro-inflammatory markers
Another component of our physiological hypothesis will correlate levels of serum inflammatory markers with change in cognitive function (Specific Aim 2c) (fig 1). 20 ml of blood will be sampled from each patient to perform tests at baseline, 1 year and 2 year follow-ups.
Protocols. Serum samples will be stored at −80°C and analyzed in batches. Serum hsCRP concentrations will be measured using standard ELISA (United Biotech Inc., Mountain View, CA) per the manufacturer's instructions

and blinded to the clinical information. The assay has a minimum detectable concentration of 0.00035 mg/L. Cytokines (MMP-9 and IL-6) will be measured by standard ELISA (Bender MedSystems). We will use high sensitivity immunoassays to detect low serum concentrations of these molecules.
Functional tissue pulsatility imaging (fTPI) for hypoperfusion
While carotid flow-arrest and systemic hypotension are associated with cognitive dysfunction, it is not known whether cerebral hypoperfusion influences cognitive outcome in patients with carotid stenosis. The final component of our physiological hypothesis will investigate whether cognitive impairment is mediated by any cerebral hypoperfusion associated with the stenosis (fig 1). In this Specific Aim 2d, the primary analysis of impact will be a standard clinical cerebrovascular reactivity test in response to hyperventilation112 measured by functional tissue perfusion imaging (fTPI) as decribed by our group87. Measurements will be obtained once at the time of recruitment and at 1 and 2 years of follow-up.

**With regards to the planned additional follow-up, none of the proposed tests are being performed for diagnostic or treatment purposes.

3 * Describe the duration of an individual participant's participation in the study:
Duration of participation for subjects will be for 2 years following enrollment.
Due to enrollment still ongoing, participation will extend for another two visits after their 2 year follow-ups have been completed for already enrolled patients. Until all follow-up for all enrolled patients is complete, we will continue to see patients on a yearly basis and adminster cognitive functioning battery. Also, for patients who have already completed their follow-up, we will ask if they are agreeable to also submitting a blood sample for genetic testing and obtain that if they are willing to continue to be followed.

**With regards to the planned additional follow-up, subjects will be invited to participate in one additional follow-up visit that will be approximately two hours in duration.

4 * Describe the duration of the entire study:
Study timeline
Overall, the project will require approximately 4 years to complete; separated into four major activities. The first year will be devoted to planning, IRB application, and commencing data acquisition. We anticipate an early start to data collection since our center has an established recruitment and treatment infrastructure in place. The projected duration of patient recruitment is 2 years. Follow-up will begin immediately after recruitment, and those patients who entered as late as month 24 will be followed until conclusion of the trial.

**With regards to the planned additional follow-up, the entire duration of the study will be one year.

5 * Describe any additional participant requirements:
Original ACCOF protocol: Quality of life questionnaires will have to be completed by the participant.

**With regards to the planned additional follow-up, there will be no additional participant requirements other than those listed above in question 1.

ID: VIEW4E0280585B400
Name: v2_Study Procedures

View: v2_Sample Size and Data Analysis

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:
Statistical Analysis
Power Analysis. There are no data from carotid stenosis studies in the literature that used longitudinal change scores to evaluate cognition using the battery of tests proposed in this study. Therefore, in order to calculate the sample size needed, we used the raw data from our study which evaluated cognitive changes after carotid revascularization. As described in our prelim data #3, we utilized the raw scores from the cognitive tests to calculate composite change scores and standard deviations (SD) using the methodology proposed in this study. In a follow-up analysis (prelim data #4), we demonstrated that a composite change score of 0.41-0.7 resulted in >2 SD change in quality of life measures. Therefore, if our study is able to show a similar cognitive change, our results will have a clinically significant impact on our patients' quality of life.
We calculated power based on the conservative approaches of: A) establishing the detectable difference based on a t-test (rather than the mixed model which will allow incorporation of results from patients that are also lost to follow-up), and B) aiming to detect a difference in cognitive change score of 0.4 SD (rather than the 0.41 SD that defines the clinically important difference).
Based on these conservative assumptions, 142 controls and 142 patients would have the power to detect a change in cognitive score of 0.3 SDs with 80% power, and a change score of 0.3 SDs with 80% power (fig 20). As such, we have outstanding power to detect significant differences.

**With regards to the planned additional follow-up, the relationship being tested in our carotid stenosis patients is novel and therefore there is no direct sample size calculation possible. Indirect evidence in non-carotid stenosis patients shows a strong relationship that encourages us to believe that we will be able to identify or exclude the relationship based on our available cohort of approx 150 patients.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:
Specific Aim 1 of the study will assess whether in patients with asymptomatic carotid stenosis ≥50% who survive stroke-free for 2 years; change in overall and domain-specific cognitive function will be significantly different compared to those without stenosis. We will confirm the group distribution of demographic variables.
Additional analyses will be performed after correction for the age, education and mood status of patients. This hypothesis will be examined with analysis of covariance comparing the composite change scores for patients versus non-stenosed control groups at the 2-year time point after adjustment for the baseline cognitive function score. Although we anticipate the level of missing data due to missed visits to be modest, these analyses will be conducted using the mixed modeling approaches of Laird and Ware.

Specific Aim 2 (a through d) is designed to identify potential mechanisms of cognitive change in patients with asymptomatic carotid stenosis. We hypothesize that carotid plaque architecture, plaque composition, microembolic counts, serum pro-inflammatory markers, and cerebral hypoperfusion could each mediate cognitive decline. Within this aim, there are 2 hypotheses for each mechanism:

A) At 2 years, the features listed above will independently predict a change in cognitive function. The statistical approach for this aim will be identical to that of the hypothesis in specific aim 1. Associations with cognitive

change scores and plaque area, volume, composition, microembolic counts, serum pro-inflammatory marker levels and cerebrovascular reactivity will be assessed using the mixed models of Laird and Ware106. Power to detect associations of cognitive decline with each of these features can be estimated using the same approaches as for the hypothesis in aim 1. We have used the most conservative approach of dichotomizing these continuous variables at their median value – the actual analysis will be performed using the variables as continuous measures where the power will be greater. Using this very conservative approach for power calculations, the same detectable differences in change score of 0.4 SD with 90% power, and of 0. 3 SD with 80% power, are achievable.

B) At 2 years, patients with asymptomatic carotid stenosis who develop cognitive impairment will differ in these characteristics compared with similar patients that remain unchanged. The differential mean value for plaque area, volume, composition, microembolic counts, serum pro-inflammatory marker levels and cerebrovascular reactivity will be tested between the two groups using t-tests. The detectable difference for each of these factors is again very conservatively estimated to be the same differences of 0.4 SD with 90% power, and 0.3 SD with 80% power (now the SD of each of these factors). Such a small change relative to the SD of each of these factors is reasonable to define as being small enough to detect all “clinically important changes.”

Specific Aim 3 is designed to explore whether cognitive changes in patients with asymptomatic carotid stenosis correlate with changes in health-related quality of life. We hypothesize that at 2 years, regardless of plaque features, cognitive change will correlate with change in health-related quality of life measures.
For this aim, the principal outcome variables will be the change in quality of life measures (Frenchay and SF-36) between baseline and follow- up. The outcome event will be cognitive change score at the corresponding follow-up time point. Initially, the correlation between each quality of life change score and corresponding cognitive change score will be explored in a univariate fashion using t-tests. Subsequently, multivariate analysis will be used to determine the independent impact of altered cognition on quality of life after
controlling for additional patient variables such as age, gender, mood, medical co-morbidities, and degree of stenosis. Independent predictors of change in quality of life will be selected based on p≤0.05. With the sample size of 142, a correlation of 0.2 between
change in cognitive function and change in quality of life can be detected with 90% power, and a correlation of 0.18 can be detected with 80% power .

Potential difficulties and Alternate approaches/analyses:
Practice effect on cognitive testing. Since patients will be exposed to the same cognitive tests at different periods, scores may improve due to the “practice effect.” In this study, the practice effect is anticipated to be low since tests are being repeated at 1 year intervals (baseline, 1 year, and 2 years post-recruitment). Alternate test forms will be used wherever possible. Reliable change analyses will be used to determine if changes detected in the composite score, as well as on specific domain scores of interest exceed that which is expected based on repeated exposure to the measure, error variance, and maturation
.
Additional analysis of Aim 1 including patients with post-recruitment stroke. Based on prior randomized trials, it is anticipated that approximately 1-2% of our patients per year will suffer a stroke2. Separating primary cognitive deficits from poor performance on cognitive testing due to disability associated with stroke is difficult. Furthermore, patients that develop stroke during follow-up will require carotid revascularization with elimination of the stenosis per standard of care. That is why the proposed study will exclude such patients when evaluating cognitive outcome. This attrition has been accounted for in the power analysis, and will not affect our results. Moreover, for those unable to complete testing due to stroke, the statistical E-M algorithm (Laird and Ware106) will be used to provide an estimate of the mean score in the presence of the missing data. This statistical approach has been shown to produce unbiased estimates that are more precise than alternative approaches in the presence of data that are missing.
Additional analysis of Aim 1 comparing baseline cognition in the two groups. We feel that a major strength of the application is the longitudinal data collection and comparisons of change scores. This is statistically much more powerful than a simple cross-sectional comparison. However, we will have data on baseline cognitive scores for patients versus control subjects. In an additional analysis we will perform a simple comparison of these scores to measure differences at baseline in the two populations.

Additional analysis of Aim 2 focusing on correlations with stroke during follow-up. For the patients in the cohort that suffer a stroke during follow-up, we will have plaque architecture, plaque composition, microembolic count, pro-inflammatory marker, and perfusion information, prior to their stroke. We are aware of the fact that the focus of our study is not on stroke; furthermore, these 5 to 10 patients will be too few to derive statistically strong conclusions. However, we will analyze available data and report additional conclusions on plaque correlates of stroke, if the information is hypothesis-generating.

TCD microembolic counts. We are aware that automated emboli counts and classifications are subject to the effectiveness of signal filtering algorithms. Therefore filters will be programmed according to criteria validated in consensus documents70. As an added precaution, we will analyze all spectral recordings manually to confirm embolic counts.

Temporal consistency. We are aware that the significance of outcomes and interpretation of mechanisms may be influenced by differential temporal effects. While the primary statistical approach will be to evaluate change scores over 2 years; we will describe the temporal pattern of cognitive changes and assess if the hypotheses are temporally consistent at the 1-year time interval.

Vascular risk factor distribution. We realize that the control group will include patients with a heterogeneous mix of one or more vascular risk factors. It is likely that one risk factor may have a larger influence on cognitive function than another; or multiple risk factors together in a patient may influence cognition more than in a patient with one risk factor. However, in a study of this size with finite resources, it will not be possible to expand the control group to the large numbers required to study the effects of each risk factor alone and in various combinations. In any case, that is well beyond the focus of this investigation. We will closely monitor the control subjects to ensure no unusual heterogeneity of cognitive scores. If such is found, we will then focus on recruiting patients with limited (one or two) risk factors alone.

**With regards to the planned additional follow-up, we will perform standard correlation analyses between cognitive scores of the subjects obtained previously with physical function scores that we plan to obtain during the additional follow-up.

ID: VIEW4E02806052800
Name: v2_Sample Size and Data Analysis

View: v2_Sharing of Results

Sharing of Results

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject’s primary care physicians) and if

so, describe how it will be shared:
Study results will not be distributed to the participants. However, subjects can request a copy of their results for their records. Additionally, study data will not be added to the patient's chart. If abnormal findings are discovered, the PI will refer the subject to the appropriate clinical service and share relevant information with them. The PI will personally approve each subject request.

**With regards to the planned additional follow-up, we will follow the same approach as described in the original protocol.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

View: v2_Psychological/Behavioral/Educational Methods and Procedures

Psychological/Behavioral/Educational Methods & Procedures

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

1 * Select all behavioral methods and procedures which apply to this study:
Surveys/questionnaires
Neuropsychological or psychophysiological testing

ID: VIEW4E09416F57800
Name: v2_Psychological/Behavioral/Educational Methods and Procedures

View: v2_Surveys/Questionnaires

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:
Original ACCOF protocol
Summary of Neurocognitive Tests: 1.Trail Making Test A & B, 2.Animal naming test, 3.Digit Span, 4.Digit Symbol-Coding, 5.Boston Naming Test-short form, 6.Hopkins Verbal Learning Test, 7.COWA oral word association test, 8.Rey Figure copy, 9.Brief Visuospatial Memory Test, 10.Grooved pegboard ("affected hand"), Grooved pegboard ("unaffected hand"),

Quality of Life Questionnaires: 1. SF 36 , 2. FAI

** With regards to the planned additional follow-up, we will perform the following tests:
Assessments of physical activity: 1) ABC, 2) FES, 3) PASE, 4) SF12,
Assessments of cognitive Health: 1) MMSE

2 * Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
ACCOF Mini Mental State Exam.pdf	6/9/2017 9:04 AM	6/9/2017 9:04 AM
ACCOF SF12.doc	6/9/2017 9:03 AM	6/9/2017 9:03 AM
ACCOF PASE.doc	6/9/2017 9:03 AM	6/9/2017 9:03 AM
ACCOF FES.doc	6/9/2017 9:03 AM	6/9/2017 9:03 AM
ABC	6/9/2017 9:03 AM	6/9/2017 9:03 AM
Animal naming test (neurocognitive test)	8/9/2010 11:28 AM	8/9/2010 11:29 AM
Neurocognitive tests	8/5/2010 12:59 PM	8/5/2010 12:59 PM
Quality of Life forms	7/22/2010 2:48 PM	7/22/2010 2:48 PM

3 * What is the total length of time that each survey is expected to take?
Original ACCOF protocol: Neurocognitive Battery tests will take 50 mins of time to complete. Quality of life tests will take 15 mins to complete

** With regards to the planned additional follow-up: Assessments of physical activity will take 20 minutes to complete; Cognitive Health assessment will take 5 minutes to complete.

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)
○ Yes ● **No**

5 * Do any questions elicit information related to the potential for harm to self or others?
○ Yes ● **No**

5.1 If Yes, what procedures are in place to assure safety?
N/A

ID: VIEW4E09460F5EC00
Name: v2_Surveys/Questionnaires

View: v2_Testing

Testing

You indicated that this study involves neuropsychological or psychophysiological testing.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * List all of the tests to be used in the study, including both standardized and non-standardized assessments:
Original ACCOF protocol: 1. Trail making test A & B, 2. Animal naming test, 3. Digit span, 4.Digit symbol coding, 5. Boston Naming Test - short form, 6. Hopkins Verbal Learning Test, 7.COWA oral word association test, 8. Rey Figure Copy, 9.Brief Visuospatial Memory Test, 10. Grooved Pegboard (Affected hand), Grooved Pegboard (Unaffected Hand)

** With regards to the planned additional follow-up: 1) Timed Up and Go, 2)Four Square Step Test, 3) Berg Balance Scale, 4) Dynamic Gait Index, 5) Short Physical Performance Battery

2 * Describe procedures related to all testing:
Patients and control subjects will undergo a 50-minute neurocognitive battery at 3 time points: baseline, 1 year, and 2 years after recruitment. Baseline testing will take place within a few days of recruitment. Following the approach of our prelim data #3 for performing cognitive testing in a similar patient population, the battery will consist of 10 standardized neuropsychological tests for multiple cognitive domains selected on the basis of the NIH harmonization standards, our own preliminary data #3, and published experience in patients with carotid stenosis5-10, 31. All tests have published age-adjusted norms. All participants will undergo all 10 tests. The order of test administration will remain constant for baseline and follow-up evaluations. Tests will be conducted in a quiet room. The order of administration accommodates the delays required for recall intervals and minimizes stimuli interference in memory tasks.

**With regards to the planned additional follow-up, subjects will undergo balance and walking assessments. The Short Physical Performance Battery requires approximately 10 minutes. The BBS, DGI, TUG and FSST test takes an approximate 5 to 10 minutes each for a total estimated test time of 20 to 40 minutes.

3 * Upload relevant testing materials:

Name	Created	Modified Date
ACCOFSPPB_form.docx	6/9/2017 9:27 AM	6/9/2017 9:27 AM
ACCOF SHORT FORM Dynamic Gait Index.doc	6/9/2017 9:27 AM	6/9/2017 9:27 AM
ACCOF SHORT FORM Berg Balance Scale.docx	6/9/2017 9:27 AM	6/9/2017 9:27 AM
ACCOF Four Square Step Test.doc	6/9/2017 9:27 AM	6/9/2017 9:27 AM
ACCOF Data Form_Timed Up and Go.doc	6/9/2017 9:27 AM	6/9/2017 9:27 AM
Animal naming test (neurocognitive testing)	8/9/2010 11:31 AM	8/9/2010 11:31 AM
Neurocognitive tests	8/5/2010 1:05 PM	8/5/2010 1:05 PM

4 * What is the individual duration of each test and what is the entire duration of all tests?
Original ACCOF protocol: Neurocognitive tests will take 50 mins to complete

** With regards to the planned additional follow-up, the Short Physical Performance Battery requires approximately 10 minutes. The BBS, DGI, TUG and FSST test takes an approximate 5 to 10 minutes each for a total estimated test time of 20 to 40 minutes.

5 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)
○ Yes ● **No**

6 * Do any questions elicit information related to the potential for harm to self or others?
○ Yes ● **No**

6.1 If Yes, what procedures are in place to assure safety?
N/A

ID: VIEW4E0BC1E3C2800
Name: v2_Testing

View: v2_Sample Collection/Analysis

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

1 * What type of samples will be involved in this study? (Check all that apply)
Prospective (will be collected)

2 * Will genetic analysis/testing be done on any of the samples?
● **Yes** ○ No

3 * Will this study involve banking of samples (storing for future research use)?
● **Yes** ○ No

4 * What is the purpose of the sample collection and/or analysis?
The purpose is to correlate levels of serum inflammatory markers with change in cognitive function.

5 * Is there the possibility that cell lines will be developed with any of the samples?
○ Yes ● **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?
● **Yes** ○ No

6.1 If Yes, give name(s) and affiliation(s):
Subhradip Mukhopadhyay PhD
University of MD Medical Center
Center for Vascular and Inflammatory Diseases
800 W. Baltimore St.reet, Biopark 1 room 230, Baltimore MD 21201

7 * Will the sample material be sold or given to any third parties?
○ Yes ● **No**

7.1 If Yes, give name(s) and address(es):

ID: VIEW4E0E1A4B80000
Name: v2_Sample Collection/Analysis

View: v2_Prospective Samples

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

1 * What type of sample will be collected? (Check all that apply)
Blood

1.1 If Other, specify:

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:
4 teaspoons of blood at baseline, 1 year , and 2 year follow up visits.
4 teaspons of blood at one visit for genetic sample

3 * What type of samples will be collected? (Check all that apply)
Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study

3.1 If Other, specify:

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?
Samples are labeled with the date the sample was taken and a unique code specific to this study.

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
If the patient elects to withdraw, samples collected prior to withdraw will continue to be utilized. No further collections will be made after the date of withdraw.

8 * Will the samples be destroyed after the study is over?
○ Yes ● **No**

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.
Samples will be stored in the VA freezer for 2 years after completion of last follow up in order to allow time for complete analysis and publication. The samples will then be destroyed.

ID: VIEW4E0E257D60C00
Name: v2_Prospective Samples

View: v2_Genetics Research

Genetics Research

You indicated that genetic analysis/testing is being done on the samples.

1 * How would you classify your genetic study? (choose all that apply)
Pedigree Study (to discover the pattern of inheritance of a disease and to catalog the range of symptoms)
DNA diagnostic study (to develop techniques for determining the presence of specific DNA mutations or polymorphisms)

1.1 If Other, specify:

2 * Discuss the potential for psychological, social, and/or physical harm that could result from participation in this research. In your discussion, consider the following aspects: risks to privacy, confidentiality, insurablity, employability, immigration status, paternity status, educational opportunities, or social stigma.
There is no potential risk for psychological, social, and/or physical harm that could result from participation in this study. Samples will be kept in the VA basement freezer and will not be labeled with any PHI, but will be labeled with a unique subject marker. No samples will be used or disclosed for any other purpose other than the research study. No risk to insurability, employability, immigration status, paternity status, educational opportunities, or social stigma is present.

3 * Will subjects receive any information resulting from the genetic analysis?
○ Yes ● **No**

3.1 If Yes, describe the information that subjects will receive:
Please note: genetic analysis results should only be shared if the testing will be performed in a CLIA certified lab.

4 * Will participants be offered any type of genetic or educational counseling?
● **Yes** ○ No

4.1 If Yes, who will provide the education or counseling?
Education and counseling will be provided by Dr. Lal, the PI, or a study team member.

4.2 Under what conditions will education or counseling be provided?
Education and counseling will be provided in a private setting by a member of the study team.

5 * Is there the possibility that a family's pedigree will be presented or published?
○ Yes ● **No**

5.1 If Yes, describe how you will protect family members' confidentiality:

ID: VIEW4E0E7C50FBC00
Name: v2_Genetics Research

View: v2_Sample Banking

Sample Banking

You indicated that the study involves banking of samples (storing for future research use).

1 * Where will the sample(s) be banked? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number is was approved under.)
University of MD Medical Center,
Center for Vascular and Inflammatory Disease,
800 W. Baltimore Street, Biopark1 Room 230
Baltimore, MD 21201

2 * Does the banking institution have an approved policy for the distribution of samples?
● **Yes** ○ No

3 How long will the sample(s) be kept?

4 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

5 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

6 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
The sample it will be anonymized

7 * If the participant withdraws, explain how the data obtained from their sample(s) will be handled (e.g., will it be deleted?)
(Please note that data for FDA regulated research cannot be deleted):
Data from the sample will be anonymized.

ID: VIEW4E0E7E82B5800
Name: v2_Sample Banking

View: v2_Clinical Trial Registration

Clinical Trial Registration

You indicated on the "Type of Research" page that your study is a clinical trial.

1 * Does the UM Clinical Trials Registry policy require registration of this trial?
○ Yes ● **No**

2 * Has this trial been registered?
● **Yes** ○ No

ID: VIEW4E093BF078C00
Name: v2_Clinical Trial Registration

View: v2_Clinical Trial Registration Information

Clinical Trial Registration Information

You indicated that this clinical trial has been registered.

1 * Was this trial registered at www.clinicaltrials.gov?
● **Yes** ○ No

2 If no, was this trial registered on a site other than clinicaltrials.gov?
○ Yes ○ No

2.1 If Yes, specify the name of the other site:

2.2 Provide justification for registering this trial on this site:

3 * Registration Number
NCT01353196

ID: VIEW4E093BF1D0800
Name: v2_Clinical Trial Registration Information

View: v2_Participant Selection

Participant Selection

1 * How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? ***Screening includes determining potential participants' initial eligibility for and/or interest in a study.***
400

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? ***A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.***

Local - the number being enrolled at this site:
284

Worldwide - the number being enrolled total at all sites (including local enrollment):
284

3 * Gender:
Male
Female

4 * Age(s):
18 years and older (Adult)

5 * Race/Ethnicity:
All Races Included

6 * Language(s):
English

6.1 Specify Other:

7 * Are you excluding a specific population, sub-group, or class?
○ Yes ● **No**

7.1 If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

ID: VIEW4E0E519C1D000
Name: v2_Participant Selection

View: v2_Vulnerable Populations

Vulnerable Populations

1 * Will you be including ANY of the following Vulnerable Populations? (Select all that apply)
None of the above

You may not include any members of the above populations as subjects in your research unless you indicate this here.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

View: v2_Eligibility

Eligibility

1 * Do you have an existing Eligibility checklist(s) for this study?
● **Yes** ○ No

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
Inclusion Exclusion Criteria - control group	8/13/2010 12:37 PM	8/13/2010 12:37 PM

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Subject must have asymptomatic Carotid Stenosis greater than or equal to 50% Asymptomatic status being confirmed by history, physical examination and numeric NIH stroke scale
View	2	The carotid stenosis must be identified by duplex sonography or other imaging modalities e.g. MRI, Angiography or CT.
View	3	Doppler velocity criteria will be used to determine the degree of stenosis

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Previous stroke or TIA
View	2	Severe medical illness that would interfere with evaluation of outcomes or reduce the likelihood of two year follow up.
View	3	Patients scheduled for carotid revascularization procedure.
View	4	Carotid Occlusion

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00046810_18 v8-29-2013-1377782152656(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

View: v2_Recruitment

Recruitment

1 * Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):
Subjects will be recruited from the Vascular Clinic and the Vascular Lab from both the VA and University of Maryland Medical Center. The Vascular clinics have a substantial referral base and are currently following greater than 200 such patients who could be enrolled in the study immediately. Patients will be identified on presenting to the clinic with audible bruits or work up for other vascular conditions. Vascular surgery receives referrals from Cardiology, Neurology and Primary care. These patients undergo a diagnostic imaging study (Carotid duplex being the preferred screening modality). Patients who have a 50% or greater stenosis of the carotid artery and who are asymptomatic are eligible for enrollment in the study. In the standard of care approach asymptomatic patients with 50% - 80% stenosis are treated medically and followed with annual screenings to monitor for disease progression. Asypmtomatic patients with stenosis of greater than 80% are treated with revascularization. Once a decision has been made that these patients do not require revascularization, they will be introduced to the study and if they desire to participate, they will be enrolled.into the study.

** With regards to the planned additional follow-up, all subjects enrolled in ACCOF will be contacted directly to gauge their interest in participating. There is no script being used to recruit these subjects other than information contained in the informed consent.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study,

enter "N/A"):
The study purpose, procedures, risks and benefits will be explained to the patient. An evaluation to sign consent form will be used to determine the mental eligibilty of the consenting individual. If the subject answers more than one question incorrectly he will be disqualified.

** With regards to the planned additional follow-up, the same procedure will be followed.

3 * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)
Study Staff

3.1 If you are using a third party, specify Third Party Recruiters:

4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date

There are no items to display

ID: VIEW4E0BCAA0A6C00
Name: v2_Recruitment

View: v2_Advertising

Advertising

1 * Will you be using advertisements to recruit potential participants?
○ Yes ● **No**

ID: VIEW4E0BCCF811000
Name: v2_Advertising

View: v2_Research Related Risks

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1 * Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:
Original ACCOF protocol:
Risks to subjects
Human subjects' involvement and characteristics. This study will involve 142 adult patients with asymptomatic carotid artery stenosis, and 142 adult subjects without carotid stenosis but with one or more vascular risk factors (hypertension, diabetes, prior cardiovascular disease, or smoking). No patients with a prior stroke, pregnant women, prisoners or children will be included. The vulnerability of the study population will be limited to the fact that they are patients with a risk for stroke.
Patients eligible for the study will have asymptomatic ≥50% carotid stenosis. Asymptomatic status in all patients will be confirmed by a history, physical examination, and numeric NIH Stroke Scale1 as defined in prior NIH carotid trials2-4. While asymptomatic patients with diameter stenosis ≥60%3 benefit from revascularization, that benefit is reduced when compared to symptomatic patients with diameter stenosis ≥50%2, 5. Most centers including ours, follow the common practice which is to operate on symptomatic patients with ≥50% stenosis but only consider revascularization for asymptomatic patients when the stenosis is >80%3, 6-9. Asymptomatic patients with moderate carotid stenosis (50-80%) are treated medically and followed with annual screening studies to monitor for disease progression. Once a decision has been made that they do not require revascularization, these patients will be recruited to our proposed study. The decision as to whether a subject is appropriate to be followed with medical management alone will be made by the treating clinician in consultation with their patient. Participation in this study will not require any change in the standard clinical care that patients receive.
Patients recruited to this study will have an effective luminal diameter at the level of the maximal stenosis that is ≤50% of that of the distal normal internal carotid artery (i.e. ≥50% stenosis). This identification will most commonly be made by duplex sonography, but could be made by any other standard imaging modality namely MRA, angiography, or CTA. Our center follows standardized ICAVL-approved (Inter-societal Commission for Accreditation of Vascular Laboratories10) Doppler velocity criteria to determine the degree of stenosis11.
Patients ineligible for the study will be those with a previous stroke or transient ischemic attack (TIA), severe medical illness that would interfere with evaluation of outcomes or reduce the likelihood of a 2-year follow-up, carotid occlusion, and patients scheduled for carotid revascularization procedures.
Control subjects to be recruited will have no carotid arterial stenosis but will have one or more stroke risk factors. Inclusion criteria will be based on those utilized by the Framingham Study12 13and include: hypertension, defined as ≥160/95 recorded as the average of 2 measurements, or use of an antihypertensive drug; current smoking; diabetes mellitus defined as a random blood glucose of ≥126 mg/dL, a previous diagnosis of diabetes, or using hypoglycemic medication or insulin; and previous cardiovascular disease, including coronary heart disease, heart failure, atrial fibrillation, and peripheral arterial disease. Potential subjects with the risk factor/s will undergo duplex ultrasound (DUS) examination to confirm absence of carotid stenosis prior to recruitment to the study. While absence of carotid stenosis will be confirmed most commonly by DUS; alternate imaging modalities (MRA, CTA) if already performed on a patient during the course of their normal clinical management will be acceptable.

Potential risks. The current study does not influence the management of recruited patients. Once a decision has been made that they do not require revascularization, these patients will be recruited to our proposed study. The decision as to whether a subject is appropriate to be followed with medical management alone be made by the treating clinician in consultation with their patient. Participation in this study will not require any change in the standard clinical care that patients receive.
The specific procedures that patients will be subjected to as a result of enrollment in the study, and their potential risks are as follows. 1) Cognitive testing: there are no significant risks to the subjects, except for the psychological burden of being tested for 50 minutes. If at any time the patient reports uneasiness,or symptoms of depression the test will be discontinued and the patient will be given a break . Questionnaires and interviews will be conducted after adequate explanation and reassurance to allay anxiety or concern. If the patient continues to feel anxiety or distress the neuropsychologist will provide support and will offer a treatment referral to a clinical neuropsychologist if necessary.

If the tests reveals significant cognitive dysfunction the patient will be referred to the clinical neuropsychology service for further follow up and treatment.
2) duplex ultrasound of the carotid artery: this noninvasive test will be performed while lying down with minimal discomfort. It takes approximately 30 minutes. The electromagnetic fields used in this study are within federal guidelines, 3) transcranial Doppler microemboli monitoring is non-invasive and recordings will be made for 60 minutes, while the patient is lying down with minimal discomfort, 4) transcranial ultrasound measurement of cerebrovascular reactivity to CO2 a reactivity will be performed with the patient sitting comfortably and breathing medical grade 5% CO2 mixed with 95% O2 for 2-4 minutes; this is a standard clinical test performed routinely in the vascular laboratory. It is not associated with any known published complications. The patients' blood pressure will be monitored manually during the test, and 4) blood draw (approximately 20 ml) for serum pro-inflammatory markers. This will be accompanied by the same discomfort associated with any intravenous blood sample collection. While patients may decide to opt out of the study at any time- there are no specific alternatives to the tests described.
Adequacy of protection against risks
Recruitment and informed consent. Patients will be recruited in an outpatient setting by the Investigator, study coordinator, or other designated study personnel, after a decision has already been made to continue medical management for their carotid stenosis. Discussion with the patient about all risks and benefits of the study will take place only after that. Patients who wish to speak with their own physician will be encouraged to do so. They will be informed that they are at liberty to refuse participation or to withdraw at any time. Written informed consent will be obtained for all patients enrolled in the study.
Protection against risk. Since data collection for the study involves questionnaires, interviews, and noninvasive testing, there is minimal risk of bodily harm. Cognitive function questionnaires and interviews will be conducted after an adequate explanation and reassurance to allay any potential anxiety or concern during the testing. Every effort will be made to ensure patient comfort during the testing. Examination sessions can be adjusted to include breaks for any patient who appears fatigued or wishes to rest in the middle of the assessment. Ultrasonography and transcranial Doppler testing will be preceded with specific descriptions of the test. Patients will remain recumbent or sitting during the testing period. No IV lines will be required since the sequences do not require contrast injections. Serum inflammatory marker testing will require a venous blood draw. The procedure will be explained carefully and will be conducted according to standard of care.
Data security. The primary risk of concern is ensuring protection of patient health information. Every effort will be made to ensure confidentiality. As patients are enrolled, a tracking number will be assigned that will be used for labeling questionnaires, information gathered from interviews, and data obtained from the medical record. Records of all tests will be stored in research binders at a designated secure office in the clinical center, and in the password secured study computer database; both of which will contain only the tracking number and no information that can be used to identify the patient. This will effectively ensure confidentiality since all hard copies and electronic information will not contain names, medical record number, social security numbers, dates of birth, or any information that can be traced back to the patient.

** With regards to the planned additional follow-up:

There is an unlikely risk that subjects may fall and injure themselves during the walking and balance assessments. During these clinical balance and walking tests a safety belt will be applied and trained research staff will be with the subjects at all times.

There is a possible risk of feeling uncomfortable with some of the personal questions on questionnaires and screening tools. Questionnaires will be given by experienced research staff, subjects will be provided privacy during questionnaires and reminded that there is no right or wrong answer to minimize the chances of feeling uncomfortable answering questions.

There is a less likely risk of fatigue during tests. In order to reduce the chance of fatigue, regular rest periods will be both scheduled and/or provided as the subject needs.

The carotid ultrasound being performed is a standard clinical non-invasive procedure lasting approximately 20 minutes. It will be performed while lying down with minimal discomfort.

Loss of confidentiality will be minimized by storing data in a secure location, such as a locked office and cabinet. Electronic data will be password protected.

ID: VIEW4E1B52509F000
Name: v2_Research Related Risks

View: v2_Potential Benefits and Alternatives

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the potential direct benefit(s) to participants:
Potential benefits of the proposed research to the subjects and others
There will be no clear, direct benefit to the patient 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. However, the study could uncover hitherto unidentified morbidity in some patients. In the event that significant cognitive dysfunction is identified in a patient during the study, appropriate clinical referrals will be made for clinical cognitive assessment and intervention. We anticipate that knowledge gained from this study will provide additional treatment options for patients at risk for stroke from carotid stenosis to enhance their rate and completeness of recovery. Therefore, this study could potentially provide highly significant information by subjecting patients to the minimal risks of questionnaires and non-invasive testing.
Importance of knowledge to be gained

There is no direct benefit for participating in the follow-up sub-study.

2 * Describe the importance of the knowledge expected to result from the study:
As discussed in the body of the proposal, this project is intended to provide crucial knowledge about the contribution of cerebral microembolic injury to changing cognition during the natural history of carotid stenosis. Information on neurocognitive morbidity will uncover a currently un-diagnosed morbidity of carotid stenosis. Additionally, identification of subgroups of patients at increased risk for cognitive dysfunction will guide optimal treatment strategies in individual patients. The potential minor risks involved with the protocol are reasonable in relation to the research goals.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:
Potential benefits of the proposed research to the subjects and others
There will be no clear, direct benefit to the patient 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. However, the study could uncover hitherto unidentified morbidity in some patients. In the event that significant cognitive dysfunction is identified in a patient during the study, appropriate clinical referrals will be made for clinical cognitive assessment and intervention. We anticipate that knowledge gained from this study will provide additional treatment options for patients at risk for stroke from carotid stenosis to enhance their rate and completeness of recovery. Therefore, this study could potentially provide highly significant information by subjecting patients to the minimal risks of questionnaires and non-invasive testing.
Importance of knowledge to be gained

4 * Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.
Participation is voluntary and the alternative is not to participate.

ID: VIEW4E1B5251B0400
Name: v2_Potential Benefits and Alternatives

View: v2_Withdrawal of Participants

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 * Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:
Participants will be administratively withdrawn if they fail to comply with study procedures. This includes, coming for their baseline visit. Failing to come for their follow up appointments, or refusing to participate in all study procedures.

2 * Describe procedures for orderly termination:
Subjects will be contacted by telephone 3 times. If they refuse to come in or do not respond, their participation will be terminated and a note entered in their medical record and resaearch binder.

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:
Subjects will be notified either by phone or letter that they have been withdrawn from the research. All procedures will be stopped and no further data will be collected. All data already collected will be used for analysis.

ID: VIEW4E1B52531F800
Name: v2_Withdrawal of Participants

View: v2_Privacy of Participants

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 * Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***
All subjects will have privacy i.e the right to control access to themselves. Study interviews will be held by a member of the study team only.

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:
In a private setting. Consent will be obtained by the PI or his team in writing. The evaluation to sign consent form will be used to determine mental eligibilty of the consenting individual.

3 * Describe potential environmental stressors that may be associated with the research:
We do not identify any potential stressors with this research.

ID: VIEW4E1B525B87C00
Name: v2_Privacy of Participants

View: v2_Confidentiality of Data

Confidentiality of Data

1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?
Yes

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)
Paper data will be kept in secure area, in a locked filed cabinet, behind two closed doors at the VA Maryland Medical Center 6th floor room 6B133. Electronic data will be kept oin the VA network.

3 * How will such data be secured?
Behind two locked doors. All electronic patient data (CPRS) will be stored on the VA network behind the firewall and will not leave the VA. In case of theft, loss of data, or loss of storage media: unauthorized access of sensitive data or storage devices or nocompliance with security controls the VA privacy officer and ISO will be informed. VA sensitive information with patient identifiers will not leave the VA protected environment. Only the investigators, and members of the research team will have access to the links to de-identified information. Mobile storage devices will not be used. Original electronic VA patient data will be backed up regularly and stored securely within VA's protected environment

4 * Who will have access to research data?
Principal Investigator, subInvestigators and the research team.

5 * Will study data or test results be recorded in the participant's medical records?

○ Yes ● **No**

6 * Will any data be destroyed? ***(Please note that data for FDA regulated research and VA research cannot be deleted)***
○ Yes ● **No**

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

7 Do you plan to obtain a Certificate of Confidentiality?
○ Yes ● **No**

7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name	Created	Modified Date
There are no items to display		

8 * Discuss any other potential confidentiality issues related to this study:
There is a potential loss of confidentiality as a result of participation in the study. Personal health information obtained by the investigators as part of this research protocol will be shared by individuals mentioned in the consent form. It is possible that personal information could inadvertently be shared by others.
All records of the VA participants will be flagged in the VA CPRS system to indicate they are pariticipating in the study.

ID: VIEW4E1B5265E0400
Name: v2_Confidentiality of Data

View: v2_Monitoring Plan Selection

Monitoring Plan Selection

1 * Type of data safety monitoring plan for the study:
Data Safety Monitoring by an Individual

ID: VIEW4E1B00E30D400
Name: v2_Monitoring Plan Selection

View: v2_Monitoring Plan - Individual

Monitoring Plan - Individual

You indicated that the monitoring will be done by an Individual.

1 * Identify the individual who will be performing the safety monitoring:
. Brajesh K. Lal MD

2 * Describe this individual's role in relation to the protocol:
Principal Investigator

3 * What data will be reviewed?
Adverse Events
Enrollment Numbers
Patient Charts/Clinical Summaries
Laboratory Tests
Raw Data
Outcomes (Primary, Secondary)
Preliminary Analyses

3.1 If Other, specify:

4 * What will be the frequency of the review?
Bi-Annually

4.1 If Other, specify:

5 * Safety monitoring results will be reported to:
IRB

5.1 If Other, specify:

ID: VIEW4E1B026A2A400
Name: v2_Monitoring Plan - Individual

View: v2_Research Related Costs

Research-Related Costs

1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?
Yes

1.1 If Yes, check all that apply:
Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)

1.2 If No, who is responsible for payment?

2 * Who is responsible for the uncovered research-related costs?
There will be no uncovered research-related costs

2.1 If Other, specify:

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

ID: VIEW4E1B5D9641800
Name: v2_Research Related Costs

View: v2_Compensation for Research-Related Injury

Compensation for Research-Related Injury

1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?
○ Yes ● **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date
There are no items to display		

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?
○ Yes ● **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E1B629EEC000
Name: v2_Compensation for Research-Related Injury

View: v2_Payment to Participants

Payment to Participants

1 * Will participants receive payment (money, gift certificates, coupons, etc.) for their participation in this research?
● **Yes** ○ No

ID: VIEW4E1C52A5D7800
Name: v2_Payment to Participants

View: v2_Payment Detail

Payment Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) for their participation in this research.

1 * Payment to participants will be for: (check all that apply)
Travel
Parking
Time and effort

1.1 If Other, specify:

2 * What is the total dollar value of the payments over the duration of the study? ***Total payment(s) for participation in research of $600 or more is required to be reported on an IRS Form 1099.***
30.00

3 * Describe the timing and distrubution plan for the payment (schedule, means, etc.)?
** Subjects that participate in the additional follow-up testing will be compensated with a check in the amount of $30.00 that will be mailed directly to the subject. They will also be provided with a parking voucher that covers the cost of parking at any UMMC garage.

4 * Method(s) of payment to be Used:
Check

4.1 If Other, specify:

ID: VIEW4E1C54A6ACC00
Name: v2_Payment Detail

View: v2_HIPAA

HIPAA (Health Insurance Portability and Accountability Act)

1 * HIPAA applies to the University of Maryland School of Medicine, the University of Maryland School of Dentistry and the VA. Are you affiliated with, or will be accessing data from, any of these places? ● **Yes** ○ No

2 If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA? ● **Yes** ○ No

ID: VIEW4E1B0A2114400
Name: v2_HIPAA

View: v2_Protected Health Information

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

1 * Which PHI elements will be used or disclosed in this study? (Check all that apply)
Name
Address (if more specific than Zip Code)
Telephone numbers
Social Security numbers

2 * Why is the PHI necessary for this research?
If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits).
The patients will be identified through their vascular lab studies. The PHI indicated is necessary to screen potential subjects for eligibility and contact those subjects to determine their desire to participate. The last 4 of the patients SSN is required to identify the patients in the patient record system at the VA. At the University of Maryland, the unique medical record number (MRN) will be used. SSN will not be used.

3 * What is the source(s) of the PHI?
The PHI will be collected from the VA computerized patient record system (CPRS)

4 * Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).
Protected health information will be kept secure at all times and will not be reused or distributed to any outside parties.

5 * How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply:)
Obtain written authorization *(upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms")*
Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)

5.1 If you are using a limited data set (LDS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date

There are no items to display

ID: VIEW4E1B0A24AA400
Name: v2_Protected Health Information

View: v2_Waiver/Alteration of Authorization

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

1 * Provide rationale for how the research presents no more than minimal risk to the privacy of individuals:
Information collected is for recruitment purposes only. The study team has taken steps to ensure the security of all patient protected health information. All information will either be stored on encrypted computers of kept behind two locked doors at all times.

2 * Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:
Patient information will be stored on VA encrypted computers that are behind the VA firewall and password protected. Any paper information will be stored under two locks at all times at the VA research office 6B133.

3 * Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:
In accordance with RCS 10.1, VA data can't be destroyed.

4 * Why could the research not practicably be done without access to and use of this PHI?
Eligible patient's are defined as having a 50-70% percent stenosis of their carotid artery as verified by duplex ultrasound. Access to the patient's duplex study is required to determine eligibility.

5 * Why could the research not practicably be done without the waiver or alteration?
Without a HIPPA waiver we would be unable to identify eligible patient's and contact them regarding partcipation in the above mentioned study.

6 * Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?
● **Yes** ○ No

6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.
PHI will be utilized by the VA Maryland Health Care System.

ID: VIEW4E1B0A2896400
Name: v2_Waiver/Alteration of Authorization

View: v2_Informed Consent Process

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/A" to the questions below.

1 * Indicate the type(s) of consent that will be involved in this study: (check all that apply)
Request to Waive Consent/Parental Permission (Consent is not being obtained)
Written Consent Form

2 * Describe the Informed Consent process in detail:
After explaining the protocol to potentially eligible patients, they will be given the oppurtunity to consider entering into the study. If they decide to enroll in the study they will be asked to sign an informed consent form .
Evaluation to sign consent form will be utilized to evaluate the capacity for valid informed consent.
Inabilty to respond adequately to questions on the evaluation form will indicate that the potential subject is not a suitable candidate.
This is a minimal risk study.

3 * Confirm that the consent process will explain the following:
- The activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

● **Yes** ○ No

4 * Describe who will obtain Informed Consent:
The PI and his research team

5 * If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. *(Answer "N/A" if not obtaining consent from LARs)*
N/A

6 * Describe the setting for consent:
The protocol will be explained to potentially eligible subjects. If they make a decision to enroll in the study they will be asked to sign a consent form and the HIPAA Document.

7 * Describe the provisions for assessing participant understanding:
The evaluation to sign consent form will be used to assess mental eligibility for entry into the study.

8 * Describe the consideration for ongoing consent:
This is a two year follow up study. Ongoing consent may not be necessary.

ID: VIEW4E1C661D0AC00
Name: v2_Informed Consent Process

View: v2_Waiver/Alteration of Consent Process

Waiver or Alteration Consent Process

You indicated that a waiver/alteration of consent is requested.

1 * Explain why the research involves no more than minimal risks to the subjects:
This request for waiver of informed consent is for recruitment purposes only, as required by the VA for studies that also obtain a waiver of HIPAA authorization for recruitment purposes. We will view information to determine eligibility but no research procedures will be conducted until such time that the participant agrees to take part in the study and signs the informed consent document. The recruitment process involves no more than minimal risk to the individual.

2 * Explain why a waiver or alteration of the consent process would not adversely affect the rights and welfare of the subjects:
This waiver request is for recruitment purposes only as required by the VA. If it is determined that the individual would be eligible to take part in the study, they will be approached and given the opportunity to agree and sign the informed consent document or they can decline participation.

3 * Informed consent is always required unless there is reason to grant a waiver or alteration of the consent process. Explain why you cannot carry out the research unless you are granted a waiver or alteration of the consent process:
This waiver request is for recruitment purposes only as required by the VA. If it is determined that the individual would be eligible to take part in the study, they will be approached and given the opportunity to agree and sign the informed consent document or they can decline participation.

4 If the research involves using identifiable private information or identifiable biospecimens, please explain why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

5 In some cases there will be additional pertinent information during the study that should be given to the participating subjects. For those subjects who have not been given informed consent because there is a waiver or alteration of the consent process, explain how the subjects will receive this additional important information. If applicable, please explain why a subject would not receive additional pertinent information.
N/A. Individuals who would be eligible to take part in the study will be given the opportunity to agree and sign the informed consent document or to decline participation.

6 If you are requesting an alteration of the consent process please explain why this request is necessary for the conduct of the research study. Please identify specifically what is being altered or changed in the consent process.
N/A

ID: VIEW4E1C73B344800
Name: v2_Waiver/Alteration of Consent Process

View: v2_Consent Forms - Draft

Consent and HIPAA Authorization Forms - Draft

1 Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
ACCOF patient ICF 11-4-10	11/4/2010 8:37 AM	11/4/2010 8:37 AM
ACCOF VAMHCS Consent Stenosis 12_31_2014.doc	1/23/2015 11:09 AM	1/23/2015 11:09 AM
VA Consent Form CONTROL 9-4-12.doc	9/21/2012 8:36 AM	9/21/2012 8:36 AM
ACCOF VAMHCS Consent Control 12_31_2014.doc	1/23/2015 11:09 AM	1/23/2015 11:09 AM
ACCOF UMMC Consent Form Stenosis_8_12_13.doc	8/12/2013 11:25 AM	8/12/2013 11:25 AM
ACCOF control ICF 11-4-10	11/4/2010 8:37 AM	11/4/2010 8:37 AM
ACCOF UMMC Consent Form Stenosis 12_31_2014.doc	1/23/2015 11:08 AM	1/23/2015 11:08 AM
ACCOF UMMC Consent Form Follow-Up 6-13-17.docx	6/13/2017 10:51 AM	6/13/2017 10:51 AM
ACCOF UMMC Consent Form Control 12_31_2014.docx	1/23/2015 11:08 AM	1/23/2015 11:08 AM
ACCOF UMMC Consent Form Follow-Up 6-23-17 Revised.docx	6/23/2017 3:35 PM	6/23/2017 3:35 PM
ACCOF - Carotid Stenosis group 5-5-11	5/5/2011 9:18 AM	5/5/2011 9:18 AM
ACCOF VAMHCS Consent Template Stenosis 4_15_13.doc	4/15/2013 9:26 AM	4/15/2013 9:26 AM
ACCOF UMMC Consent Form Stenosis_Approved.doc	4/8/2013 9:00 AM	5/13/2013 9:10 AM
VA Consent Form STENOSIS Group 9-4-12.doc	9/21/2012 8:36 AM	9/21/2012 8:36 AM
ACCOF UMMC Consent Form Control_8_12_13.docx	8/12/2013 11:26 AM	8/12/2013 11:26 AM
ACCOF VAMHCS Consent Template Control 4_15_13.doc	4/15/2013 9:25 AM	4/15/2013 9:26 AM
ACCOF UMMC Consent Form Control_Approved.docx	4/8/2013 9:00 AM	5/13/2013 9:10 AM
ACCOF - Control Group 5-5-11	5/5/2011 9:19 AM	5/5/2011 9:19 AM
ACCOF VAMHCS Consent Form Follow-up 6-23-17 Revised.docx	6/23/2017 3:35 PM	6/23/2017 3:35 PM
ACCOF VAMHCS Consent Template Control 8_12_13.doc	8/12/2013 11:26 AM	8/21/2013 10:13 AM
ACCOF VAMHCS Consent Template Stenosis 8_12_13.doc	8/12/2013 11:26 AM	8/12/2013 11:26 AM
ACCOF VAMHCS Consent Form Follow-up 6-13-17.docx	6/13/2017 10:54 AM	6/13/2017 10:54 AM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

1A Archived Consent Forms:

Name	Created	Modified Date
There are no items to display		

2 Upload any HIPAA authorization forms here:

ACCOF UMMC HIPAA_Approved.doc	4/8/2013 8:53 AM	4/8/2013 8:53 AM
revised HIPAA doc Nov 2011	11/22/2011 3:19 PM	11/22/2011 3:19 PM

HIPAA document	10/29/2010 9:36 AM	10/29/2010 9:36 AM

Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates:
http://hrpo.umaryland.edu/researchers/consents.html

ID: VIEW4E1C7712D3000
Name: v2_Consent Forms - Draft

View: v2_Organization Review Requirements (other than IRB)

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

Vascular Surgery

If this information is incorrect, please notify the HRPO office.

2 **RSC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation? ○ Yes ● **No**

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer? ● **Yes** ○ No
-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required.

* Does the protocol involve in any way studies related to the prevention, treatment, diagnosis, or imaging of neoplastic diseases? ○ Yes ● **No**

5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient-oriented research. Click Here for more information.

Answer the following to determine if review by the GCRC may be required.

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? ○ Yes ● **No**

6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

* 6.1 - Will the research be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments)? ● **Yes** ○ No

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? ● **Yes** ○ No

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? ● **Yes** ○ No

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

ID: VIEW4E1AF91AB2400
Name: v2_Organization Review Requirements (other than IRB)

View: v2_Institutional Biosafety Committee Review Required

Institutional Biosafety Committee Review Required

1 **NOTE**: based on your answers to questions on a previous page (see below) review by the Institutional Biosafety Committee (IBC) is required. This will involve extra steps on your (study team) part. Clicking the Continue button will result in the system creating a blank IBC Submission form for you. You will be required to fill out and submit this IBC form before you will be able to submit the Protocol form. The IBC Submission workspace and form can be reached by clicking the appropriate button on the left hand side of the Protocol submission's workspace (web page) after exiting the Protocol form.

2 **Question** - answered on IBC RSC review requirements page:
3.1 Does the research involve human gene transfer? - OR - Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.
3.2 Does the research involve: a) the exposure of human subjects to pathogenic microorganisms, or b) the potential exposure of UMB research staff to infectious materials through the sampling or processing of materials from patients with known infectious disease or from environmental surfaces?
3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

Yes

If the answer to this question is wrong, an IBC submission is not required, use the Jump To menu or your browser's <

3 * **Confirm** - you have read the above information and understand that in addition to the IRB Protocol form, you will fill out and submit the IBC Submission form :
● **Yes** ○ No

ID: VIEW4E1AF91ED4C00
Name: v2_Institutional Biosafety Committee Review Required

View: v2_Use of Non-Veterans

VA-Specific Criteria

1 * What is the relevance of this research to the mission of VA and the Veteran population that it serves*?
Prevents morbidity from carotid disease in veterans

2 * Describe who will be enrolled in this study:
Veterans and Non-veterans will be enrolled in this study

2.1 * If non-veterans will be enrolled in this study, provide a description of non-veterans who will be enrolled (For example: community members, family members/caretakers of Veterans, clinicians/caregivers to Veterans, etc.):
Community members of an age and vascular risk factor range similar to that seen in veterans. Study is curently closed for recruitment

2.2 If non-veterans will be enrolled in this study, provide a substantive justification** for the enrollment of non-veterans in this research:
The PI determined there was an insufficient number of veterans to meet recruitment goals. To increase enrollment we have decided to recruit individuals from UMMC, the consent forms were written on the approved template and approved by the PI.

2.3 * If this is a VA-funded study, was the use of non-veterans discussed within your merit award proposal?
Yes

*

http://www.va.gov/about_va/mission.asp

VA Mission Statement
To fulfill President Lincoln's promise “To care for him who shall have borne the battle, and for his widow, and his orphan” by serving and honoring the men and women who are America’s Veterans.

VA Core Values
VA’s five core values underscore the obligations inherent in VA’s mission: Integrity, Commitment, Advocacy, Respect, and Excellence. The core values define “who we are,” our culture, and how we care for Veterans and eligible beneficiaries. Our values are more than just words – they affect outcomes in our daily interactions with Veterans and eligible beneficiaries and with each other. Taking the first letter of each word—Integrity, Commitment, Advocacy, Respect, Excellence—creates a powerful acronym, “I CARE,” that reminds each VA employee of the importance of their role in this Department. These core values come together as five promises we make as individuals and as an organization to those we serve.
Integrity: Act with high moral principle. Adhere to the highest professional standards. Maintain the trust and confidence of all with whom I engage.
Commitment: Work diligently to serve Veterans and other beneficiaries. Be driven by an earnest belief in VA’s mission. Fulfill my individual responsibilities and organizational responsibilities.
Advocacy: Be truly Veteran-centric by identifying, fully considering, and appropriately advancing the interests of Veterans and other beneficiaries.
Respect: Treat all those I serve and with whom I work with dignity and respect. Show respect to earn it.

Excellence: Strive for the highest quality and continuous improvement. Be thoughtful and decisive in leadership, accountable for my actions, willing to admit mistakes, and rigorous in correcting them.

**

a. Non-Veterans may be entered into a VA-approved research study that involves VA outpatient or VA hospital treatment (38 CFR 17.45, 17.92), but only when there are insufficient Veteran patients suitable for the study. The investigator must justify including non-Veterans and the IRB must review the justification and provide specific approval for recruitment of non-Veterans.
b. Non-Veterans may be recruited for studies that will generally benefit Veterans and their well-being but would not include Veterans as subjects. Examples include surveys of VA providers, studies involving Veterans' family members, or studies including active duty military personnel. Although active duty military personnel are not considered Veterans, they should be included in VA studies whenever appropriate.
---
e. Non-Veterans may not be entered into VA studies simply because a non-Veteran population is easily accessible to the investigator.

[VHA Handbook 1200.05 §24]

ID: VIEW4E1C7A737E800
Name: v2_Use of Non-Veterans

View: v2_VA Prohibited Research

VA Prohibited Research

1 * Is the research planned emergency research in subjects from whom consent can not be prospectively obtained?
○ Yes ● **No**

2 * Does the study involve fetuses?
○ Yes ● **No**

3 * Does the study involve in vitro fertilization?
○ Yes ● **No**

4 * Does the research involve work with embryonic stem cells?
○ Yes ● **No**

5 * Does the study involve children **AND** is greater than minimal risk?
○ Yes ● **No**

6 * Will recruitment phone calls involve asking veterans for their Social Security numbers?
○ Yes ● **No**

ID: VIEW4E1C8AF03A400
Name: v2_VA Prohibited Research

View: v2_Additional VA

Additional VA

1 * For data that is combined, which site is the "Data Coordinating Center"?

2 If VA data will be combined with non-VA data, describe when and how this will occur and where the combined data will be stored.

3 If the VAMHCS is the Local Coordinating Center holding the "combined data", how is the data collected? (This answer may overlap with Research Related Procedures. If so, please refer to that section.)

4 If the VAMHCS is the Local Coordinating Center holding the "combined data", how is the data received and combined with the UM data?

5 If the UM is the Coordinating Center holding the "combined data", will you only use the combined data set while not on VA time or will you obtain approval from VA ORD/Regional Counsel to do this as an "off-site" VA Research activity.

ID: VIEW8D5931EAC5B1E6E
Name: v2_Additional VA

View: v2_VA Review Required

VA Maryland Health Care System Review Required

1

Note: Based on the answers provided in your submission, this protocol qualifies as a VA study. Therefore, VAMHCS Research &Development (R&D) Committee approval (in addition to IRB approval) is required prior to engaging in any research activities. **Importantly, you must submit the protocol to the VAMHCS Research Service within 60 days of IRB approval.**

**Details related to the VA submission and approval processes are best obtained by calling or visiting the Baltimore VA Research Office (Fred Ivey @ 410-605-7000

x6582). Despite not being able to submit at VA until after IRB approval is obtained, we strongly encourage immediate consultation with the VA R&D service, allowing time for early familiarization with VA requirements and VA Service clearance for your proposed work.

VA Research Service **Forms** can be accessed using the following link:

https://www.maryland.va.gov/research/human/human_subject_forms.asp

**In addition to the post-IRB VA approval process referenced above, there are also VA-specific items that must be addressed before IRB review. Failure to address the two VA components listed below will prevent your protocol from even receiving a full IRB review.

1. **VA information security and privacy Officer (ISO-PO) Approval:** This must happen before the IRB will move your protocol to full-board review. The ISO-PO approval process is initiated by submitting an ISO-PO checklist (accessible through the VA Forms link above) to the Baltimore VA Research Service. Personnel from the VA Research Office will then work to get the required approval signatures, ensuring that the signed ISO-PO checklist is uploaded as a public comment to your protocol's History Log. Again, your protocol CANNOT move forward to full IRB review without a fully signed ISO-PO checklist in the History Log, so getting that item submitted to the VA Research Service as quickly as possible should be a top priority.

2. **Specification of Research Activity Locations:** VA policy mandates that locations of all research activities (including data coordination, data analysis, and data storage) be clearly specified within appropriate sections of the CICERO protocol and the VA Informed Consent Document. Please ensure that locations of all research activities are clearly specified throughout these documents before submitting the protocol to IRB. This is particularly important for "VA Collaborative Studies" (i.e. those studies involving research activities that occur at both VA and non-VA sites). However, all studies, be they collaborative or not, should make clear delineation of research activity locations and data locations an emphasis.

2 **Questions answered on 'Organizational Review Requirements' page**:

The research will be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments):	**Yes**
The research will utilize VA resources (e.g. equipment, funds, medical records, databases, tissues, etc.):	**Yes**
The research will be conducted on VA property, including space leased to and used by VA:	**Yes**

Questions answered on 'VA Prohibited Research' page:

The research is planned emergency research in subjects from whom consent can not be prospectively obtained:	**No**
The study involves fetuses:	**No**
The study involves in vitro fertilization:	**No**
The research involves work with embryonic stem cells:	**No**
The study involves children AND is greater than minimal risk:	**No**
Recruitment phone calls involve asking veterans for their Social Security numbers:	**No**

If the answers to these questions are wrong, use the Jump To menu to return to the 'Organization Review Requirements' page to change your answers.

3 * **Confirm** - You have read the above information and understand that in addition to this IRB application form (CICERO), you are required to send a submission to the VAMHCS R&D Committee **within 60 days of receiving IRB approval**.

● **Yes** ○ No

ID: VIEW4E1C8F0D7B000
Name: v2_VA Review Required

View: v2_Summary of Required Reviews (other than IRB)

Summary of Required Reviews (other than IRB)

1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission		
IBC Submission: ACCOF Study	Workspace	SmartForm

2 **Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	**Review Status**
Vascular Surgery	Complete

ID: VIEW4E1C8D9AE4000
Name: v2_Summary of Required Reviews (other than IRB)

View: v2_Additional Documents

Additional Documents

1 Upload all additional documents here:

Name	Created	Modified Date

Name	Created	Modified Date
citiCompletionReport_2018.pdf	6/23/2017 3:36 PM	6/23/2017 3:36 PM
Human Research-HIPAA201.pdf	6/23/2017 3:36 PM	6/23/2017 3:36 PM
Evaluation to Sign Consent Form Follow-up.docx	6/13/2017 10:59 AM	6/13/2017 10:59 AM
ACCOF form 9 DSMB_10_2014.doc	10/10/2014 9:11 AM	11/12/2014 3:18 PM
ACCOF form 9 DSMB_4_2014.doc	4/28/2014 2:17 PM	4/28/2014 2:17 PM
ACCOF form 9 DSMB_10_2013.doc	11/15/2013 12:59 PM	11/15/2013 12:59 PM
ACCOF form 9 DSMB_4_2013.doc	4/8/2013 12:25 PM	4/8/2013 12:25 PM
HIPPA Waiver Approval Letter	6/29/2012 12:34 PM	7/13/2012 11:58 AM
evaluation to sign consent form	8/9/2010 11:34 AM	8/9/2010 11:34 AM
VA document - Just in time documents compliance	8/9/2010 11:33 AM	8/9/2010 11:33 AM

ID: VIEW4E0962513A000
Name: v2_Additional Documents

View: v2_Final Page of Application

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
Vascular Surgery	Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission		
IBC Submission: ACCOF Study	Workspace	SmartForm

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation
By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- Obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

Click the "Finish" button and then click "Submit Application" in the submission Workspace.

ID: VIEW4E1B10C500000
Name: v2_Final Page of Application

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Moira Dux

2 Research Role:
Other

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will

automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a financial interest related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Several years of research experience and multiple publications. Was PI on a VA Career Development Award Study.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Vicki Gray

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a financial interest related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Gray is well versed on conducting and implementing research protocols and has vast knowledge and expertise in exercise physiology.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Amanda Hutchinson

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a financial interest related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Amanda Hutchinson has had 1 1/2 years of data collection and records maintenance and 4 years of data collection and records reconciliation oversight.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Laila Anthony

2 Research Role:
Study Coordinator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a financial interest related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
She has several years in conducting human research and has immense knowledge in research. She is detailed-oriented and well informed on research ethics. She is well informed on the knowledge of the local study.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Siddhartha Sikdar

2 Research Role:
Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a financial interest related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Bioengineer who has worked on several studies with multiple publications.