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PROTOCOL

STATIN NEUROPROTECTION AND CAROTID ENDARTERECTOMY: SAFETY, FEASIBILITY AND OUTCOMES"

An observational and randomized, placebo-controlled, 1,000-subject clinical trial of statin dose maximization prior to carotid endarterectomy to protect against early cognitive dysfunction

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PRECIS

Study Title

Statin Neuroprotection and Carotid Endarterectomy: Safety, Feasibility and Outcome (STANCE)

Objectives

The purpose of this study is to evaluate the safety, feasibility and outcome of administering three different statins at submaximal and maximal dose on early cognitive dysfunction (eCD) and delayed cognitive dysfunction (dCD). The primary study objectives are to:

1) Determine whether patients on a pre-existing sub-maximal dose of the three most commonly prescribed statins (simvastatin <40mg, atorvastatin <80mg, rosuvastatin

<20mg) experience a higher incidence of eCD and dCD than those randomized to 218 doses of pre-operative statin supplementation to the maximal dose (simvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 20 mg).

2) Determine whether approximately 2-18 doses of optimal statin supplementation is sufficient by comparing whether patients randomized to receiving statin supplementation each individually experience a higher incidence of eCD and dCD than those patients on a pre-existing maximal dose of the three most common statins, and whether statins that pass the blood-brain barrier better correlate with reduced eCD and dCD.
3) Determine whether patients on no pre-existing statin regimen exhibit less eCD and dCD when randomized to 2-18 doses of pre-operative maximal dose atorvastatin (80mg) compared to minimum dose atorvastatin 10mg.
4) Determine a dose-response relationship to these 3 statins by determining whether all patients at the time of surgery have less eCD and dCD if they are on: 1) simvastatin 40mg rather than on <40mg; 2) atorvastatin 80mg rather than on <80mg; and 3) rosuvastatin 20mg rather than on <20mg.

The secondary study objectives are to:

1) Determine whether a pre-operative statin regimen alters the prevalence of early mortality at Day 365 +/- 30.
2) Determine whether differences in eCD/dCD identified in Primary Objectives 1- 4 are associated with either:
    a. levels of, or peri-operative changes in, ESR/CRP, and/or
    b. changes in either activities of daily living (BLESSED) or cognition (TICS-M) in the year following randomization and surgery.

Design and Outcomes

This is a phase III study for patients with carotid artery stenosis designed to assess if maximizing statin doses for (2-18) prior to carotid endarterectomy (CEA) is neuroprotective. All patients undergoing this procedure and who can tolerate the statin regimen will be asked to participate in this multi-center study. If patients are already on a statin, then only patients on *atorvastatin, simvastatin,* or *rosuvastatin* will be recruited. Subject participants will be grouped to one of three arms as a function of their pre-existing statin regimen, or lack thereof. Throughout the term of the study, subject participants will be closely monitored for medication compliance as well tolerance and safety via phone calls and in person.

The randomization will be stratified by center, previous use of statin and in random blocks of 4 and 6.

We have defined our primary outcome on Z-scores based on the mean and standard deviation of cognitive testing change in scores of a surgical reference group before and after surgery (24h and approximately 30 days post-op OR when the patient returns for their post-CEA clinical visit). The cognitive testing was divided by cognitive domains and the patients were considered to have postoperative early cognitive dysfunction (eCD) based on two criteria to account for

both focal and global/ hemispheric deficits. Consequently, anyone with: (a) ≥2SD worse than reference group in two or more cognitive domains or (b) ≥1.5SD worse than the reference group in all cognitive domains tested will be considered a primary outcome. If the subjects experience stroke or TIA peri-operatively, they will be considered as having reached a secondary outcome in the study.

Interventions and Duration

Participant subjects who are already on the maximal statin dose of either atorvastatin (80 mg), simvastatin (40 mg or 20 mg + amlodipine) or rosuvastatin (20 mg) will remain on their current statin doses and will be part of our observational arm (ARM 1). The subjects that are currently on sub-maximal daily doses of the previously mentioned statins will be randomized to their current dose plus placebo or their current dose plus the necessary milligrams needed to bring them to the FDA approved maximal dose per day for their corresponding statin (ARM 2). Those subjects who are statin naïve, 30 days prior to enrollment, will be randomized to daily doses of either 10 mg of atorvastatin or 80 mg of atorvastatin (ARM 3).

We will stay in contact with the subjects via phone calls prior and post their CEA to assure study drug compliance and safety. We will also assess them prior to their CEA, 12-25 hours post-CEA for early cognitive dysfunction (eCD) and during their post-operative clinical visit (approximately at 30 days post-CEA) for delayed cognitive dysfunction (dCD). The final follow-up phone call will be one year after their CEA procedure.

Sample Size and Population

One thousand CEA patients, who fulfill the remaining inclusion criteria, will be enrolled in the study prior to their scheduled CEA. We will enroll these patients at various sites over a 5 year period in one of our three study arms. We estimate that we will assign: 225 participants who are already on maximal daily doses of one of the study statins (atorvastatin 80 mg or simvastatin 40 mg or rosuvastatin 20 mg) to the Observational Arm (ARM 1). We will randomize 675 participants that are on sub-maximal doses of statins to either remain at their current dose or be increased to the FDA approved maximal daily dose of their current statin (ARM 2). We will randomize 100 participants that are statin naïve to receive a daily dose of either 10 mg of atorvastatin or 80 mg of atorvastatin.

The reported expectations for this study have been delineated based on our past experience studying carotid endarterectomy patients. We expect pregnant women and women with childbearing potential will not be included in this study. The average age of our patient population is 72, and hence most female patients are well beyond their reproductive age.

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1 STUDY OBJECTIVES

1.1 Primary Objective

The purpose of this study is to evaluate the safety, feasibility and outcome of administering three different statins at submaximal and maximal dose on eCD and dCD. We hypothesize that a pre-operative statin regimen is protective against eCD (12-25h post-CEA) and dCD (30d), and early (365d) mortality. In addition, maximal doses may be essential in achieving optimal neuroprotection against eCD and dCD, with statins that pass the blood-brain barrier achieving similar effects at lower doses due to enhanced entry into the brain. In order to test this, our primary objectives will be:

1) Determine whether patients on a pre-existing sub-maximal dose of one of three most commonly prescribed statins (simvastatin <40mg, atorvastatin <80mg, rosuvastatin <20mg) experience a higher incidence of eCD and dCD than those randomized to 218 doses of pre-operative statin supplementation to the maximal FDA approved dose (simvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 20 mg).
2) Determine whether approximately 2-18 doses of maximal statin supplementation is sufficient by comparing whether patients randomized to receiving statin supplementation each individually experience a higher incidence of eCD and dCD than those patients on a pre-existing maximal dose of the three most common statins, and whether statins that pass the blood-brain barrier better correlate with reduced eCD and dCD.
3) Determine whether patients on no pre-existing statin regimen exhibit less eCD and dCD when randomized to 2-18 doses of pre-operative maximal dose of atorvastatin (80mg) compared to lower dose of atorvastatin (10mg).
4) Determine a dose-response relationship to these 3 statins by determining whether all patients at the time of surgery have less eCD and dCD if they are on: 1) simvastatin 40mg rather than on <40mg; 2) atorvastatin 80mg rather than on <80mg; and 3) rosuvastatin 20mg rather than on <20mg.

1.2 Secondary Objectives

1) To determine whether a pre-operative statin regimen alters the prevalence of early mortality at Day 365 +/- 30.
2) To determine whether differences in eCD/dCD identified in Primary Objectives 1- 4 are associated with either:
   a. levels of, or peri-operative changes in, ESR/CRP, and/or
   b. changes in either activities of daily living (BLESSED) or cognition (TICS-M) in the year following randomization and surgery.

2 BACKGROUND AND RATIONALE

2.1 Background on Cognitive Dysfunction, Statins, and CEA

High-grade extra-cranial carotid artery stenosis accounts for nearly 120,000 strokes annually in the USA (3) and many of these patients will undergo CEA surgery. CEA reduces the risk of

future stroke in this patient population by 55-65%, but its effectiveness is dependent on very low peri-operative morbidity. Recent improvements in the medical management of patients with asymptomatic stenosis have improved the outcome for un-operated patients to such a degree that some have even questioned whether the benefits of asymptomatic CEA still justify its risks even though the rate of peri-operative stroke has fallen precipitously over the same period to less than 1.5%. While this debate can only be settled by a large, massively expensive, clinical trial like the presently recruiting CREST-II, it is nevertheless critical that perioperative management continue to evolve if the neuroprotective effects of CEA are to be realized for not only asymptomatic, but symptomatic patients as well. Given that post-CEA stroke is so rare, investigators have increasingly looked to subtler forms of cerebral injury to inform treatment decisions, as well as, to improve procedural safety. Several groups have previously used neuropsychological tests to evaluate outcome after CEA (4-9). eCD affects up to 25% of patients undergoing CEA for those that were statin naive. Defined as a worsening in cognitive performance of ≥2 standard deviations (SD) on ≥2 cognitive domains – verbal memory, visuo-spatial organization, motor function, and executive action – or ≥1.5SD worse on >4 cognitive domains when compared to a surgical reference group at 24hrs. eCD is associated with marked elevations in tissue markers of cerebral injury (S100B) (10) (Figure 1) and is associated with earlier post-CEA mortality (2, 11, 12). This clinically significant, but occult, cerebral injury is 10 times more common than stroke and its mechanism appears to be similarly related to regional hypoperfusion and ischemia. We now have data that pre-operative statin use is not only associated with a reduction in perioperative clinical stroke, but a 50% reduction in eCD (Figure 2) (72). While no patient taking statins actually suffered a stroke, the rate of eCD varied dramatically among both statin type and dose. In fact, in looking at the incidence of eCD in those taking the two most commonly prescribed agents (80% of patients), simvastatin use was associated with significantly less eCD than atorvastatin at any dose (Figure 2) (76). This difference was observed at all doses with the exception of high dose atorvastatin (80mg), which provided similar neuroprotection as simvastatin (40mg). We also observed that statin use was associated with less risk of early mortality (12.5 years vs. 16.0 years; $\chi 2=6.5$, P=0.01) that appears to be completely related to its effect on eCD (Figure 3), supporting the contention that statins not only protect against injury, but may be involved in injury repair as has been shown previously in animals.

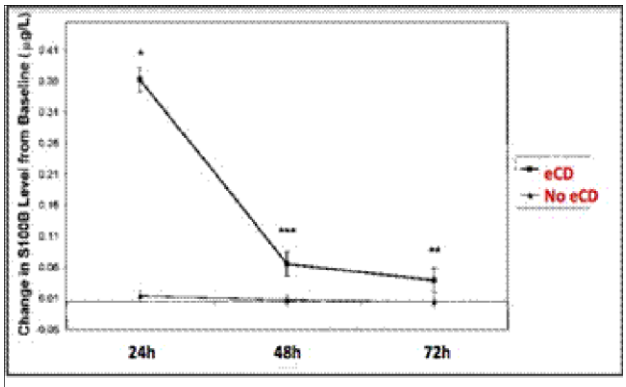


Figure 1. eCD & Elevations in S100B

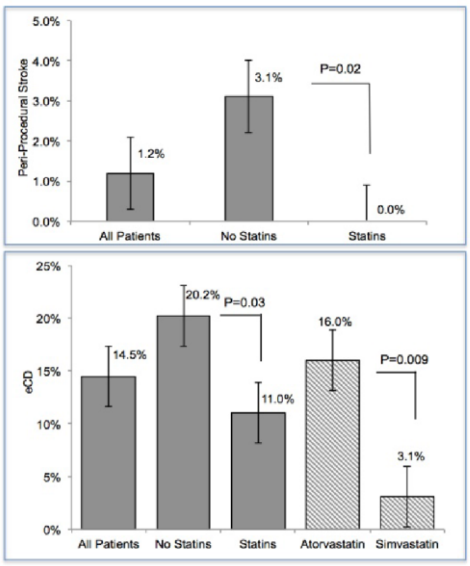
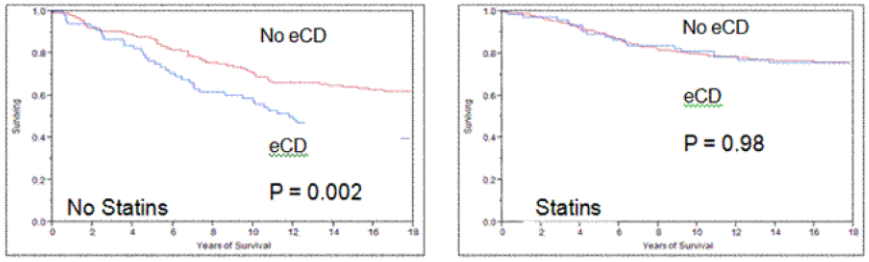


Figure 2: Pre-operative statin use is associated with less postop stroke (top) and eCD (bottom), and Simvastatin is associated with less than Atorvastatin (bottom, right)

As >50% of patients are on a sub-optimal statin regimen, it is imperative that we determine in a prospective randomized trial whether alteration of preoperative statin regimens leads to improved neurologic outcome, an even lower incidence of stroke, and possibly greater survival. In order to optimally design and conduct such a trial it is critical that we: 1) explore the safety and feasibility of altering statin regimen acutely (approximately 2 weeks) before CEA, 2) clearly establish the neuroprotective outcome of an acute alteration in statin regimen, and 3) determine if statins that pass the blood-brain barrier more easily are more efficacious. If we can do this, we will be well on our way to achieving our ultimate goal of better understanding statin neuroprotection in humans and determining the optimal statin treatment that affords the most neuroprotection in patients undergoing one of the most commonly performed procedures in the US.

Figure 3. Kaplan-Meier Analyses of Mortality.



2.1.1 Cognitive Dysfunction (early and delayed) in Patients Undergoing CEA

Prior to surgery, patients are evaluated with an extensive battery of neuropsychometric tests (NPTs) that evaluate verbal memory, visuo-spatial organization, motor, and executive action. Patients are administered general anesthesia or regional anesthesia and clamps are applied to the common, internal, and external carotid arteries. The cerebral hemisphere ipsilateral to the surgical side generally receives collateral blood flow from the anterior and posterior communicating arteries, or less commonly from a shunt placed from the common to the internal carotid artery below and above the respective clamps. It is hypothesized that eCD occurs as a result of regional hypoperfusion as a result of insufficient collateral flow. Evidence for this comes from the fact that patients without EEG changes during cross clamping of the carotid artery but with decreased middle cerebral artery flow velocities as measured by transcranial Doppler are more likely to exhibit these deficits (14). After the repair of the carotid is complete, reperfusion is established and flow to the hemisphere is restored to either pre-operative levels or levels somewhat higher. Patients are then awakened, allowed to recover from the effects of anesthesia, and re-evaluated within 24h of the CEA with a different version of the same battery of NPTs to guard against practice effect. The different version of the same battery at the followup time points (baseline, 24 hours and at 30 days), also allows us to determine individual, rather than group differences/changes, in neuropsychometric performance.

To further control for practice effect, and ensure that neither anesthesia or perioperative pain are creating the false appearance of diminished cognition, we have used a surgical reference group of patients undergoing lumbar micro-discectomy or 1-2 level laminectomy lasting <4 hours, without blood transfusion or intensive care unit stay. Based on the difference scores for both the CEA and surgical reference patients, we calculate Z-scores. To the degree that patients in CEA group have “practice effect”, we expect the same “practice effect” in the surgical reference group

except they should not have cognitive changes from surgery. Therefore, negative changes in the neuropsychometric performance on these tests are recorded and normalized to the changes in neuropsychometric performance in the surgical reference group. Patients are labeled as either injured or not based on their Z-scores. We use rigorous cutoffs for injury that are associated with serum evidence of cerebral tissue injury and which predict mortality. Preliminary evidence suggests that eCD (24h) and dCD (30d) as defined by these criteria are due to regional cerebral ischemia rather than microembolization (15-17). In the randomized study proposed below, we will only include age, pre-op IQ and education-level matched patients for the reference surgical population who have been similarly screened for MCI pre-op (see below) and delirium postop (see below). Since perioperative pain is a wellrecognized confounder of NPT, albeit rare after CEA, we plan, *as we have done in all our prior work*, to exclude from analysis for all reference patients with pain scores > 4 on the 11-point Numeric Pain Intensity scale. Scores ≤ 4 will be recorded and analyzed in the univariate and multivariate models planned for the specific Aims. (18)

2.1.2 Statins & Cognition

The impact of statins on baseline cognition remains controversial. A study by Hajjar et al. concluded that statins are associated with better cognitive outcomes in elderly populations (19). Similarly, there is evidence statins may also improve cognition (20) through multiple mechanisms, including their action on eNOS (21). While some have suggested that statins may have a deleterious effect on cognition (22, 23), one large literature review suggests otherwise (24), concluding that no significant cognitive impairment can be concluded. A review by Golomb et al. addresses many of the issues related to the deleterious effects of statin and specifically simvastatin therapy (25, 26). The PROSPER study was an observational study in which 5,804 were evaluated at six different time points using four neuropsychological performance tests (27). They concluded that there was neither benefit nor detriment to the cognition of patients on pravastatin. However, the jury is still out on whether the adverse effects are significant for a large percentage of patients or are just rare occurrences. Whatever the case, our previous work strongly suggests that simvastatin is more neuroprotective than atorvastatin in CEA patients (13). While we do not have sufficient numbers of patients to comment on the comparative efficacy of less commonly prescribed statins, it appears that the lipophilic and small molecule size of simvastatin, may make it more effective at penetrating the blood brain barrier than atorvastatin, which although lipophilic, is significantly larger. We have also identified two important demographic factors which independently increase the risk of eCD: age >75 years, and diabetes mellitus (28). Genetic polymorphisms may also confer increased risk with the possession of the ApoE-ε4 (29, 30) allele being the best characterized, but complement cascade (13), phosphodiesterase (31) polymorphisms perhaps playing a role as well. The consequences of eCD after CEA is significant, with a higher risk of early mortality, with statins appearing to attenuate this difference in mortality (2).

2.1.3 Statin Ischemic Neuroprotection in Humans: Case for Differential Protection

Statins have revolutionized the treatment of hypercholesterolemia and its consequences of stroke and coronary artery disease. Endres has reviewed the effect of statin administration on

the incidence of stroke (32). Surprisingly, while large clinical studies have demonstrated a reduction in the incidence of cerebrovascular events, hypercholesterolemia by itself is not an established risk factor for stroke (32). It is thought that the action of statins is through noncholesterol lowering pleiotropic effects (32-34). Treatment at stroke onset may be beneficial as well. A large meta-analysis which included 113,148 patients found that statin therapy at stroke onset improves functional outcome at 90 days (35). Statins (rosuvastatin and atorvastatin) have been shown to reduce infarct volume and improve functional outcome in murine focal ischemia reperfusion models (36), in part by upregulating eNOS (21, 34). While several statins have been shown to be neuroprotective (including simvastatin, atorvastatin, and rosuvastatin), comparative studies looking at the relative protection achieved with doses equivalent to low, medium and high doses in humans do not exist (34, 37). There are studies in humans, which have shown that statins not only reduce the risk of stroke, but their use is associated with better stroke outcomes. Yet there is no data on whether any individual statin at any particular dose is likely to be more neuroprotective (38, 39). Our data in asymptomatic CEA suggests that eCD is rare in patients taking simvastatin or pravastatin at any dose, rare in patients taking high dose (80mg) atorvastatin or high dose (20mg) lovastatin and quite substantial in patients taking low dose lovastatin (<20mg), low dose atorvastatin (<80mg) or rosuvastatin at any dose. Overall, <50% of statin users are taking what appears to be a neuroprotective dose.

2.1.4 Cognitive Decline After Stroke: Inflammatory Biomarkers and Hippocampal Volume

The purpose of this study is to evaluate the safety, feasibility and outcome of administering three different statins at submaximal and maximal dose on eCD and dCD. However, we think that one potential mechanism of protection may be attenuation of systemic inflammatory state by statin therapy. For that reason we propose to look at measures of acute and chronic inflammation as demonstrated in a recent study of first ever strokes by Kliper et al. (40). They found that post-stroke elevations in “erythrocyte sedimentation rate (ESR) remained unchanged in follow-up examinations, suggesting a chronic inflammatory background in some patients and that higher levels of ESR were associated with worse performance in cognitive tests, particularly memory scores, even after adjustment for confounders. Moreover, in a multivariate regression model, higher ESR values were related to reduced hippocampal volume, suggesting that chronic post-ischemic inflammation may contribute to cognitive impairment and that statin regimes that are most effective in addressing this may promote hippocampal health and neuropsychometric memory performance. In the present study, we plan to monitor chronic and acute inflammation in study patients using serum ESR and CRP levels along with the lipid levels at designated time points and correlate them with NPT performance as a secondary aim.

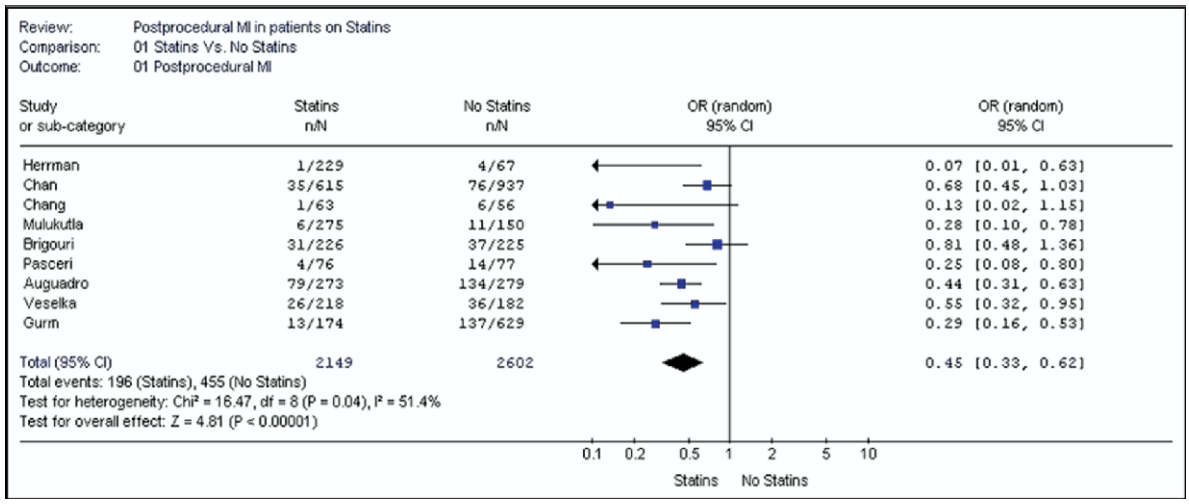
2.1.5 Delirium and Mild Cognitive Impairment as Confounders

Both pre-operative mild cognitive impairment (MCI), and post-operative delirium may be confounders in studies of per-procedural cognitive injury. Mild cognitive impairment (MCI) has been defined as “mental impairment beyond what is felt to be normal for age.”(41). There are non-amnestic as well as amnestic subtypes of MCI with impaired memory being a prominent component for some and executive function a prominent symptom for others(41, 42). The

Minimental state examination (MMSE), the Montreal Cognitive Assessment (MoCA) and the EightItem Informant Interview to Differentiate Aging and Dementia **(**AD8) have been used to screen for MCI (including eCD, dCD) (43,44, 69, 70, 72). However, since the MoCA has been found to be a more adequate tool than the MMSE to screen for mild cognitive impairment (75), we will use the MoCA and the AD8 to screen for MCI at baseline. We will identify patients with both subtypes of MCI (44). While the incidence of pre-operative MCI may be as high as 50% in our patient population(45), the effect of MCI on postoperative cognitive dysfunction, at least following analogous studies of on-pump coronary surgery seems very small (46). Nevertheless, we will screen patients for cognitive decline (AD8 ≥2) and the MoCA (≤25) prior to randomization.

Delirium is a syndrome consisting of a number of symptoms including an acute fluctuating disturbance in consciousness/attention, a change in cognition (memory deficit, disorientation, language disturbance), and a disruption in sleep-wake cycle. A considerable number of predisposing factors have been identified including: older age, cognitive impairment, cardiac failure, cerebrovascular disease, depression, sensory impairment, dehydration, malnutrition, and drug/alcohol dependence. Delirium can also be precipitated by metabolic disarray, medications, infection, and stress. While the incidence of delirium in patients undergoing some highly invasive vascular surgical procedures can be as high as 15%, the incidence in patients undergoing less invasive procedures such as asymptomatic carotid endarterectomy, appears to be no greater than 1.5%(47). Nevertheless, while less common than MCI, delirium, if present, can severely impact assessment of acute cognitive injury like eCD. Thus we will use the Confusion Assessment Method (CAM) to screen for it (48) in all CEA patients as well as all spine surgery controls, both at 24h and 30d. This instrument has been validated for use by nonpsychiatrists and can be performed in 5 minutes with high reliability. Nine questions are quickly addressed and if the patient has inattention (feature 2) that is acute in onset or fluctuating (feature 1) and either disorganized thinking (feature 3) or altered level of consciousness (feature 4) they will be considered delirious. Patients with delirium at any time point or MCI at study onset will be identified using the criteria outlined above, and these data will be analyzed in the univariate and multivariate models planned for the specific Aims.

Our preliminary data suggest the novel finding that cognitive performance can be used to identify a subtle form of cerebral injury, eCD and/or dCD with important clinical implications. Preventing this subtle injury with statins is a novel use of this class of drugs and identifying optimal dosing parameters and agents that are most protective, perhaps due to their lipophilicity/blood-brain barrier permeability, is equally unparalleled. The cerebral protective action of statins may be: 1) dose-, 2) time-, and 3) lipophilicity/blood barrier permeabilitydependent. It is unclear how long it is necessary to be on statin therapy for statins to be efficacious. However, the lipid lowering action of statins may be separate from the effect of statins to reduce eCD and dCD. This difference may be similar to the action of statins to reduce cardiac ischemia associated with percutaneous coronary intervention (PCI). As an example, a number of studies have demonstrated a reduction in peri-procedural non-Q-wave myocardial infarction in patients undergoing percutaneous coronary intervention (PCI) who were treated with a statin.(49-54) (59-54) Figure 1 shows the variability of these actions.(53)



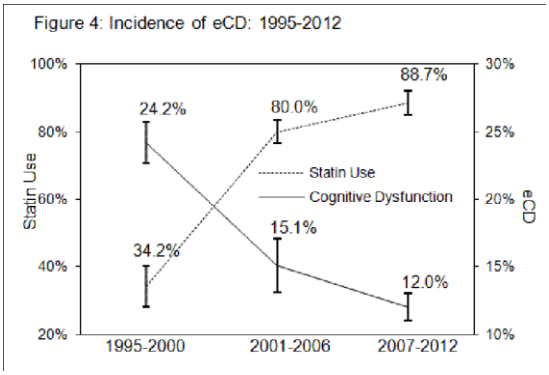
One study looked at different statins -- atorvastatin (29% of cases), pravastatin (29% of cases), simvastatin (39% of cases), and fluvastatin (3% of cases) – administered for a little as 3 days prior to PCI. (50) The protective action of these statins occurs prior to the lipid lowering action of these statins. Their actions may be as anti-inflammatory or anti-thrombotic, which are not associated with changes in lipid profiles. Because of this separation in time between functional and biochemical actions of statins, statin action may be separated in time between when a statin may be neuroprotective and when a statin changes the lipid profile.

This aspect of statin neuroprotection has never been explored in detail in humans. Less lipophilic statins than simvastatin may become effective at high concentrations, underscoring the importance of generating a putative dose-response curve. While about 90% of patients at Columbia University Medical Center are already on a statin, we have reason to believe that in more underserved (lower income, less educated) populations, such as those at Montefiore Medical Center in Bronx NY and the University of New York in Buffalo NY, a smaller percentage of patients will be on statins prior to enrollment, and those that are likely to be on diminished doses that preliminary data suggests are less neuroprotective (55). Thus, if we can demonstrate a benefit in the total population, we may also have identified a pre-op therapy that would be particularly important for underserved populations. A second potentially innovative aspect of the proposal concerns the surveillance of systemic inflammation in this population. If certain statin regimes protect against eCD and dCD, whether these regimes are associated with less (or marked changes in) systemic inflammation will be important mechanistic data regardless of the result.

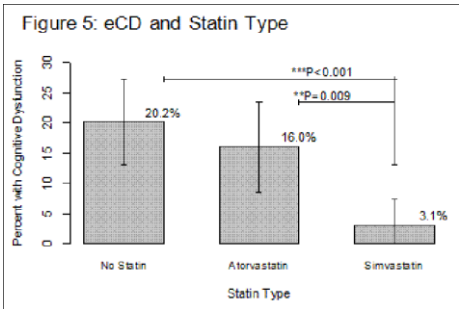
Our previous grant (R01 AG17604) was funded from July 1, 2003 to June 30, 2013. Over the 10 years the grant was funded, and the 15 years we have been studying patients having treatment for CEA, there has been a dramatic change in the incidence of eCD. We have investigated the reason(s) for this change. This analysis has been the primary outcome of this funding period. During our previous R01 grants, we enrolled 878 patients: 620 having CEA, 68 having CAS, and 190 reference patients having either “simple” spine surgery (155 patients) or coronary artery angiography or stenting (34). Of the 620 CEA patients, 559 had full neuropsychometric analysis completed pre- and post-operatively. Of these 559 patients, 231 were symptomatic patients undergoing CEA and 328 were asymptomatic. Symptomatic status refers to whether the patient

has a history of stroke or transient ischemic attack prior to surgery. We significantly surpassed our enrollment goals for all granting periods. All of the neuropsychometric data were analyzed, except for the data from 8 symptomatic and 4 asymptomatic patients because they experienced a peri-operative stroke. We utilized our reference population to account for practice effect and learning due to repeated neuropsychometric testing.

Performance was compared between patients having CEA and a reference group consisting of patients having "simple" spine surgery by testing them before, and 24h and 30 days after surgery (11, 12). We generated Z-scores based on the mean and standard deviation of the change scores of reference group before and after surgery within 24h and at 30 days. We subtracted the mean change scores from the reference patients from the change scores for patients having CEA and divided this difference by the standard deviation of the change scores of the reference patients to generate Z-scores for each test, for each patient. Similar to previous studies (56), the tests were grouped by cognitive domain and patients were considered to have postoperative eCD based on two criteria to account for both focal and global/ hemispheric deficits: (a) ≥2SD worse than reference group in two or more cognitive domains or (b) ≥1.5SD worse than the reference group in all cognitive domains tested.



We observed that the incidence of eCD has declined from 24.2% (1995-2000) to 12.0% (20072012) (Figure 4). We verified that the decrease in the incidence of eCD was not due to changes in patient characteristics by evaluating all of the common characteristics (age, gender, BMI, years of education, hypertension, diabetes mellitus, history of smoking, duration of cross-clamp, etc.), different surgeons (eight different surgeons provided care, 75.3% of the surgeries were performed by 3 surgeons), one anesthesiologist (Dr. Heyer) was involved in ~75% of the cases, and the 12 different clinical coordinators were all trained by the same neuropsychologist (Dr. Stern). The surgical technique, anesthetic management, and indications for CEA have remained constant at this institution, as previously described (11, 12, 15). The only factor that changed over this time period was statin use. Statin use increased from 34.2% to 88.7% (Figure 4). Of the 324 asymptomatic CEA patients with neuropsychometric testing, the pre-operative statin makeup was as follows: no statin (N=124), atorvastatin (N=94), simvastatin (N=66), fluvastatin (N=2), pravastatin (N=9), rosuvastatin (N=12), and lovastatin (N=17).



Although the incidence of peri-operative stroke was too low to comment on trends, asymptomatic patients taking statins had a significantly lower incidence of peri-operative stroke (0.0% vs. 3.1%, P=0.02) and exhibited significantly less eCD when taking statins (11.0% vs.

20.2%, P=0.03) than those not taking statins (2). Within the asymptomatic population, patients taking simvastatin exhibited significantly less eCD than those taking atorvastatin (3.0% vs. 16.0%, P=0.005) (Figure 5). There were no other significant pairwise differences in eCD among the other statin types (13). There were significant pairwise differences in HDL among statin types. HDL levels were higher in patients taking simvastatin compared to those taking atorvastatin (P<0.001). There were significant pairwise differences in LDL levels only between simvastatin and atorvastatin (P=0.003). However, there were no significant differences in triglycerides or total cholesterol levels among the statin types (13). Patients taking statins had significantly lower pre-operative monocyte counts than those not taking statins (7.0±2.0 vs. 8.2±2.1 x109/L, P<0.001) at the time of surgery. However, there were no differences in monocyte counts amongst the statin types. The central question that we hope to answer is whether statin neuroprotection depends on the type of statin (simvastatin, atorvastatin or rosuvastatin and/or lipophilic versus non-lipophilic) or dose of statin.

A similar decrease in eCD was also seen in symptomatic and asymptomatic patients not taking and taking statins, and if looked at when both groups are analyzed together (symptomatic and asymptomatic patients together): P= 0.04 (Asymptomatic), P= 0.19 (Symptomatic), and P= 0.015 (together).

2.1.6 Genetic Factors

We found that certain genetic polymorphisms of APOE, phosphodiesterase 4D, and complement were also associated with increased eCD (13, 29-31). For example, patients who have the polymorphism APOE-ε4 have an increased incidence of eCD. In patients with deleterious polymorphisms, eCD is also attenuated by the use of statins.

2.1.7 Mortality

We have investigated if early neurocognitive change, eCD, was predictive of other significant life events. We specifically looked at mortality as a function of the presence or absence of eCD and the interaction of statin use on mortality. Our hospital laboratory database links to the National Death Index for patient mortality information. We determined mortality information on all of our patients. In the 225 patients who had died, we obtained their date of death. Using Kaplan-Meier Analyses, we observed that those asymptomatic patients who were not taking statins who have eCD have a significantly increased risk of earlier mortality than those patients who did not have eCD. Median survival of CEA patients that exhibited eCD was 12.5 years compared with 16.5 years for patients without eCD (Log rank P=0.06), and five-year cumulative incidence survival proportions and 95% confidence intervals were 0.82 (0.76-0.89) and 0.86 (0.83-0.90), respectively. This difference is significantly attenuated with the use of statins (Figure 3). We have demonstrated that statins decrease the incidence of both stroke and eCD in asymptomatic CEA patients, eCD predicts a higher risk of early mortality compared to patients without eCD, and different gene polymorphisms have effects on the incidence of eCD through a variety of mechanisms. Additionally, we find that some statins work better than others to reduce eCD in asymptomatic patients, the efficacy of statins may be dose-dependent, and the effect of statins on asymptomatic patients having CEA is also present in patients having carotid artery stenting and endarterectomy for symptomatic stenosis.

2.2 Study Rationale

CEA reduces the risk of future stroke in this patient population by 55-65%, but its effectiveness is dependent on very low peri-operative morbidity, especially in patients presenting with asymptomatic disease. Recent improvements in the medical management of patients with asymptomatic stenosis have improved the outcome for un-operated patients to such a degree that some have even questioned whether the benefits of asymptomatic CEA still justify its risks. The rate of peri-operative stroke has fallen precipitously over the same period to less than 1.5%. It is critical that peri-operative management continue to evolve if the neuroprotective effects of CEA are to be realized for all CEA patients. Given that post-CEA stroke is so rare, investigators have increasingly looked to subtler, although more common, forms of cerebral injury to inform treatment decisions and improve procedural safety. eCD affects ~25% of patients undergoing CEA and ~15% of undergoing asymptomatic CEA. It is associated with marked elevations in tissue markers of cerebral injury (S100B) and is associated with earlier post-CEA mortality (1-3).

This clinically significant, but subtle, cerebral injury is 10 times more common than stroke and its mechanism appears to be similarly related to regional hypoperfusion and ischemia. We now have data that pre-operative statin use is not only associated with a reduction in peri-operative clinical stroke, but a 50% reduction in eCD (4). While no patient taking statins actually suffered a stroke, the rate of eCD varied dramatically among both statin type and dose. In fact, in looking at the incidence of eCD in those taking the two most commonly prescribed agents (80% of patients), simvastatin use was associated with significantly less eCD than atorvastatin(5).This difference was observed at all doses with the exception of high dose atorvastatin (80mg), which provided similar neuroprotection as high dose simvastatin (40mg). We also observed that statin use was associated with less risk of early mortality that appears to be completely related to its effect on eCD, supporting the contention that statins not only protect against injury, but may be involved in injury repair as has been shown previously in animals (6,7). As >50% of patients are on a lower dose statin regimen, it is imperative that we determine in a prospective randomized trial whether alteration/increase of preoperative statin regimens leads to improved neurologic outcome and an even lower incidence of stroke and possibly greater survival. In order to optimally design and conduct such a trial it is critical that we: 1) explore the safety and feasibility of altering statin regimen acutely (~2 weeks) before CEA, and 2) clearly establish the neuroprotective outcome of an acute alternation in statin regimen.

We think that in doing this, we will be well on our way to achieving our ultimate goal of better understanding statin neuroprotection in humans and determining the statin treatment that affords the most neuroprotection in patients undergoing one of the most commonly performed procedures in the US.

Additional support for the study rationale comes from the previous study with a cohort of asymptomatic CEA patients and regardless of statin dose or type, where it was found that ~20% of patients' not on statins had cognitive dysfunction compared to 11% of patients on statins.(72) This statistic alone leads us to believe that while a higher dose may be "more neuroprotective," any statin therapy at all will be beneficial to a patient undergoing CEA, and should become standard of care. Although we have evidence to demonstrate the efficacy of statin neuroprotection in CEA, the aim of this study is to reconfirm this and indicate that statin use

should be a standard of care preoperatively. We do not have a dose response curve and are guessing that a high dose is most beneficial. The purpose of this study is to show that. In addition, patients in the first arm of the study who are already on the high dose will be maintained, so no risk there. Patients in the second arm of the study, having already been started on statins, will just maintain the original regimen deemed appropriate by their prescribing physician or a higher, maximal dose, which we hope to demonstrate will reduce the incidence of cognitive dysfunction. Regardless of the randomization, they will be on a dose considered to be suitable for them and we believe they will experience sufficient neuroprotection peri-operatively. As for the third arm of this study, while we would have liked to randomize patients not already on a statin, to placebo or maximal high dose of atorvastatin, we think that providing a low dose may be sufficient. There is no evidence of the most effective dose of atorvastatin or any statin to provide increased benefit. These patients not already on statin therapy, will have ~2 week preoperative statin period which will afford significantly greater protection than going into CEA without any statin therapy. As no patients in this study will be entirely without statin therapy, we feel the benefit of a statin in general (versus no statin) greatly outweighs the issue of optimal (versus sub-optimal) dose.

2.2.1 Hypothesis

While there are several non-modifiable risk factors for eCD after CEA identified from previous research, including medically treated diabetes mellitus and the presence of the ApoE-ε4 genotype, we have only been able to identify one potentially neuroprotective factor, namely preoperative statin use. Consequently, we hypothesize that in CEA patients:

1) A pre-operative statin regimen is protective against eCD (12-25h) and dCD (30d); consequently, early (365d) mortality.

2) Maximal doses may be essential in achieving optimal neuroprotection against eCD and dCD, with lipophilic statins or those that pass the blood-brain barrier more easily achieve similar effects at lower doses.

3 STUDY DESIGN

This is a Phase 3, multicenter, observational (ARM 1), randomized and double-blind study (ARM 2 and ARM 3), and placebo-controlled (ARM 2), where 1,000 carotid stenosis outpatient participants will be assigned to a specific daily statin regimen of no fewer than 2 and no greater than 18 doses prior to their CEA.

We will include patients who are either statin naive, assuming no history of adverse experience with a statin, or on one of three types of statins: simvastatin, atorvastatin, or rosuvastatin. Patients will be enrolled, and based on their preexisting statin regimen, they will be grouped into one of three arms prior to CEA: ARM 1) Patients on a pre-existing maximal daily dose statin regimen will be observed, ARM 2) Patients on a pre-existing statin regimen at sub-maximal doses will be randomized to maintain their current dose plus placebo or current dose plus the necessary milligrams to reach maximal daily dose, and ARM 3) Patients who are on no preexisting statin regimen, statin naïve in the last 30 days, will be randomized to atorvastatin

10mg or atorvastatin 80mg for no fewer than 2 and no greater than 18 daily doses before their CEA (Figure 6).

As per the simvastatin drug insert, patients taking amlodipine (Norvasc) should not exceed 20 mg of simvastatin; therefore, we will only potentially increase any patient who is also on amlodipine to daily doses of 20 mg and not 40 mg. Consequently:

*If subject is on 40 mg simvastatin without amlodipine – they will be in ARM 1 (observational)
*If subject is on 40 mg simvastatin + amlodipine – they will be in ARM 1 (observational)
*If subject is on 20 mg simvastatin + amlodipine – they will be in ARM 1 (observational) *If subject is on < 40 mg of simvastatin without amlodipine, they will be in ARM 2 and potentially randomized to 40 mg of simvastatin daily.
*If subject is on < 20 mg of simvastatin + amlodipine, they will be in ARM 2 and potentially randomized ONLY to 20 mg of simvastatin daily not 40 mg.

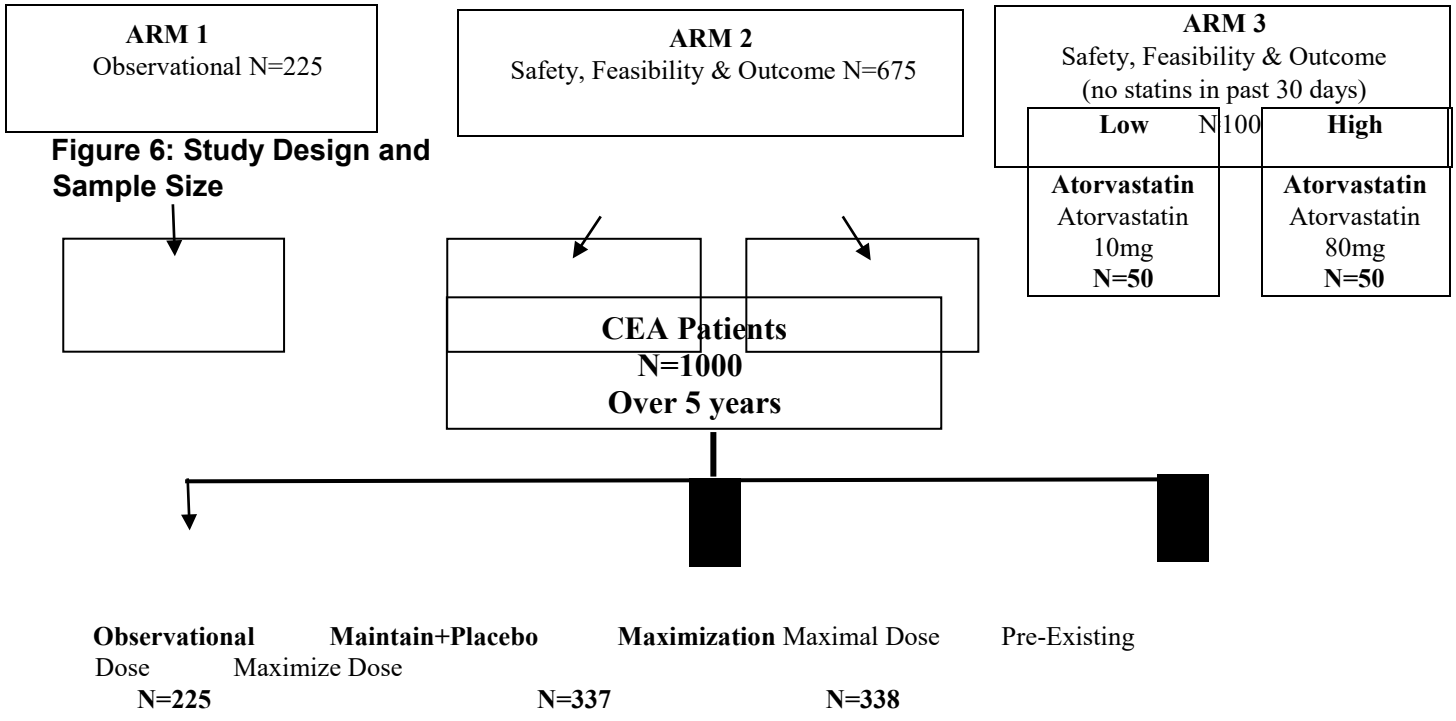


Figure 6: Study Design and Sample Size

All potential participants will be pre-screened for eligibility prior to offering them participation in the study. Once informed consent has been obtained, the final screening process to screen out those who may already have mild cognitive impairment (MCI) from the study will consist of the Montreal Cognitive Assessment (MoCA ≤25 = abnormal) and the Ascertain Dementia 8-item Informant Questionnaire (AD8 ≥2 = abnormal). If both assessments are not within normal ranges, these patients will not be randomized or assigned to the observational arm. Those with baseline MCI will be screened out from the study and not followed.

All of the potentially eligible subjects will be documented in the Study Screening Log (see Appendix III) and the logs will be collected monthly by the Central Coordinating Center at CUMC.

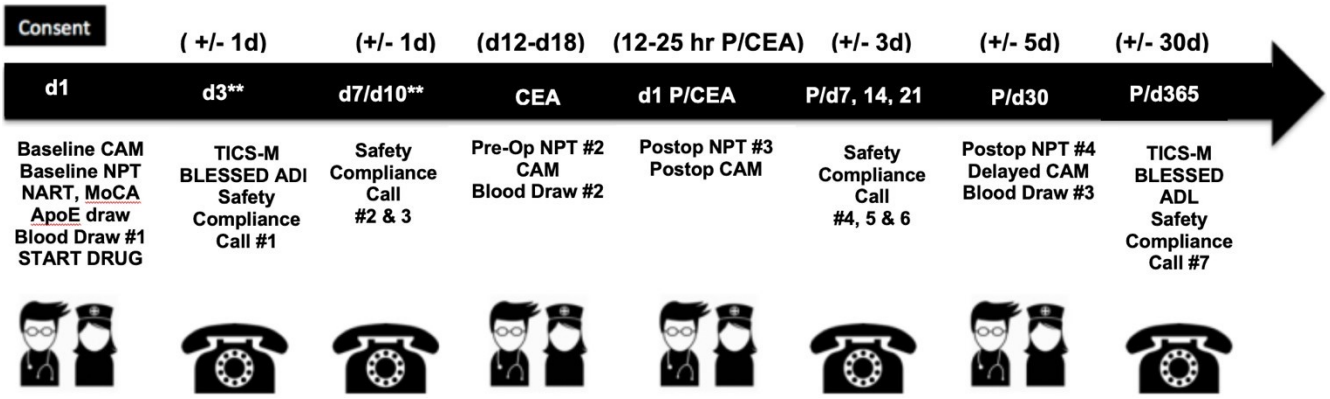
The randomization design is stratified by center, previous use of statin and in random blocks of 4 and 6. After the participant completes the screening process, ARM 2 and ARM 3 will be randomized using a centralized, secure web-based system created and managed by the Statistical Analysis Center (SAC) at the Mailman School of Public Health at Columbia University.

The study personnel will request the study drug from the site's Pharmacy/Research Pharmacy and provide the participant with the study drug instructions and corresponding amount of study drug capsules to take during their dosing period. The participants will self-administer the assigned daily doses of study statin and keep a Study Medication Compliance form (diary) of all doses taken, including their current statin doses, and the reasons for any missed dose(s) from enrollment to the day of their CEA. On the day of CEA, the remaining study drug capsules will be counted and the Study Drug Log will be collected to assess compliance.

The participant's statin therapy after their CEA will be determined by their attending or primary care doctors and not the study physicians. The study team will inform the participant and their attending doctors. Their primary care doctor will receive a letter informing them of their patient's study participation (see Appendix V PMD letter).

The study will evaluate if the changes in statin regimen prior to CEA are neuroprotective against eCD (12-25 hours post-CEA) and dCD (30 +/- 5 days post-CEA or day of their post-CEA clinical visit) with neuropsychometric tests. The neuropsychometric tests are designed to demonstrate general neuropsychological performance and not to be diagnostic of specific neuropsychiatric disorders. The average amount of time to complete the neuropsychometric battery is 30-45 minutes. Individual subject participation will conclude Day 365 +/- 30 days post-CEA to assess morbidity and mortality (Figure 7). Consequently, the individual subject participation will be one year post CEA and the overall study completion timeline will be five years of enrollment years plus one year follow up for the last participant enrolled to complete follow up.

Figure 7: Study Participation Timeline



** follow-up calls before CEA will be conducted only if not preceded by CEA

We have defined our primary outcome on Z-scores based on the mean and standard deviation of cognitive testing change in scores of a surgical reference group before and after surgery (1225h and approximately 30 days post-op). Consequently anyone with: (a) ≥2SD worse than reference group in two or more cognitive domains or (b) ≥1.5SD worse than the reference group in all cognitive domains tested will be considered a primary outcome.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

The subject participants must meet all of the inclusion criteria and not meet any exclusion criteria in order to be enrolled and assigned to an arm of this study.

4.1 Inclusion Criteria

1) Age ≥ 18 years of age.
2) Patient is currently on atorvastatin or simvastatin or rosuvastatin or statin naïve (no statins in the last 30 days).
3) The patient has unilateral or bilateral carotid artery stenosis that is considered severe (carotid artery diameter reduction ≥ 70%) as defined by any of these: a) Peak systolic velocity of at least 230 cm/s OR
   b) CTA showing ≥ 70% stenosis OR
   c) MRA showing ≥ 70% stenosis
4) The patient's attending doctor(s) (PMD, cardiologist, vascular/neurosurgeon) AND the patient have decided to proceed with a CEA to treat the patient's severe carotid stenosis.
5) The patient has no known circumstance or condition likely to preclude 1 year follow-up or adherence to the study protocol.
6) The patient is independent in their Activities of Daily Living at baseline (without cognitive, hearing or visual impairments which would impede NP testing). Walking impairments will not be a reason for exclusion.
7) Patient has the ability to provide informed consent.

4.2 Exclusion Criteria

1) Patient has underlying disease other than atherosclerosis (i.e. autoimmune disease, known active malignancy).

2) Patient has documented dementia or screens out based on abnormal Baseline MoCA (≤25) and AD8 (≥2).
3) Patient's life expectancy is < 12 months.
4) Patient has advanced renal failure (serum creatinine > 2.5 mg/dL)
5) Patient has evidence of severe congestive heart failure or has history of end-stage cardiovascular disease (e.g. CHF NYHA Class III or IV or unstable angina).
6) Patient has history of intolerance or allergic reaction to any statins (myotoxicity, hepatic dysfunction, rash, etc.) – unless they would be in the Observational Arm (Arm 1) and therefore will not be receiving any study drug.
7) Patient has received an investigational drug within 30 days.
8) Patient is pregnant or lactating.
9) Except those eligible for the Observational Arm who do not receive any study statin, patient who is currently taking any of the following which have been shown to interact with atorvastatin and/or simvastatin and/or rosuvastatin (as per current drug package inserts):
   *Cyclosporine;
   *HIV Protease Inhibitors/Antivirals (e.g. rotanavir or plus rotanavir, tipranavir, lopinavir, boceprevir, saquinavir, darunavir, fosamprenavir, nelfinavir, efavirenz/tenofobir, atazanavir, simeprevir);
   *Hep C Protease Inhibitor/Antivirals (e.g. telaprevir);
   *Antibiotics (i.e. cobicistat-containing products like Tybost, rifampin/rifampicin, clarithromycin, telithromycin, erythromycin);
   *Anti-fungals (i.e. itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole); *Gemfibrozil; Other Fenofibrates (e.g. Tricor, fibric acid);
   *Niacin > 1g/day or statins in combination with niacin (e.g. Vytorin, Simcor);
   *Colchicine;
   *Danazol;
   *Calcium Channel Blockers: Diltiazem, Varapamil;
   * Dronedarone;
   *Amiodarone;
   *Digoxin;
   *Ranolazine;
   *Nefazodone;
   *Warfarin/Coumadin;
   *Lomitapide;
   *Grapefruit juice (subject must be willing to avoid grapefruit juice).

4.3 Study Enrollment Procedures

All patients will be referred from primary care physicians, cardiologists, and neurologists to neurosurgeons, vascular surgeons, and cardiologists. We will enroll patients after they consult their respective surgical team, who will be providing their care and a decision has been made to proceed with a CEA. We will not be part of that decision-making process. Patients will be approached after giving permission to discuss the study with the research team and after the study team confirms that the potential subjects are able to provide informed consent. The potential participants are then informed about the study by either a study coordinator or physician, given

opportunity to ask questions, are offered participation, and if they agree, subsequently provide informed consent to participate in the study. All participants who consent will be given a copy of the informed consent form for their records and the original consent form will be filed in their study subject binder.

Typically, the study procedures post-consent will be conducted at the site; however, if necessary and at sites where home visits are permissible, the study visit and procedures can be conducted at the subject's home. If the home study visit includes a blood draw, these will be conducted by study personnel authorized to draw blood (e.g. physicians, nurse, phlebotomist, coordinators with phlebotomy training). The blood samples drawn for the study will be delivered to the study's corresponding laboratories ambiently (site's clinical laboratory for the CK, CBC with differential, lipid panel, CMP, ESR, C-RP and if the ApoE sample is also drawn during that home visit, then it will be hand delivered by CUMC study staff or shipped to CUMC-IGM Biobanking Core by the other sites as usual). The team will use appropriate safety equipment for the draw, disposal of equipment (sharp's container), and transport the blood sample in IATA approved Category B Ambient Shipping boxes, via private vehicles, until they are ready to be delivered to the site's clinical laboratory and/or ready to be shipped/delivered to CUMC-IGM Biobanking Core.

All potential subjects identified will be screened for eligibility and reasons for ineligibility or nonparticipation of eligible candidates will be documented in the Study Screening Log (see Appendix III). The Study Screening Log will be collected on a monthly basis from all sites documenting all subjects considered for participation in the study.

After consent, the participants will be screened for MCI. If they pass the screening tests, they will be randomized by the coordinator on a central, web-based system created and maintained by the Statistical Analysis Center (SAC) at the Mailman School of Public Health at Columbia University and considered enrolled. The randomization will be based on each patient's pre-existing statin regimen, each patient will be grouped into one of the three previously described arms after the screening process. The randomization design will be stratified by center, previous use of statin and in random blocks of 4 and 6.

4.3.1 Gender and Minority Issues.

Although we do not select patients on the basis of gender or race, we will make every effort to facilitate minority recruitment.

We think that at least 50% of the patients will be female, in line with the gender difference in prevalence of carotid artery stenosis. As per previous studies, the projected gender and ethnic distribution is 50% female, 80-85% white, 5% African American, 5% Hispanic/Latino, and 5% Asian/Pacific Islander/other. It must be noted that extra-cranial carotid disease tends to predominate in whites compared to other race-ethnic groups, in whom intracranial atherosclerosis is more common.

We anticipate that as a result of expanding to a multi-center trial, we will have more minority patients. Consequently, we will strive to provide a bilingual neurocognitive tester for our Spanishspeaking patients.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The study assigned statin dosing will be taken daily for no fewer than 2 and no greater than18 doses prior to the participant's CEA. If the encounter and enrollment happen prior to the 18 day timepoint and the patient cannot return to the study site prior to their CEA, then the subject will be given the study drug and begin taking it no greater than 18 days prior to their CEA. We will strive to enroll the subjects as early as possible so that they may receive as many doses (up to 18 doses) prior to CEA. The date of drug start will be noted in the Medication Compliance form (diary) and the eCRF upon enrollment. The safety follow-up phone calls will begin based on when the study drug is scheduled to start or upon enrollment for Arm 1. All of the participants in each arm will be provided with instructions in the Study Medication Compliance form where they will note each dose taken or the reason(s) for missing a dose. This includes logging in their current statin use for the observational/ maximal dose group (Arm 1) and the sub-maximal dose group (Arm 2). This form will be collected when the subject returns to the medical center for their CEA. The treatment arms are as follows:

ARM 1: Subjects already on **maximal daily doses** will continue to take their daily statin during the dosing period prior to CEA (atorvastatin 80 mg, simvastatin 40 mg with/without amlodipine or simvastatin 20 mg plus amlodipine, or rosuvastatin 20 mg). No additional drug will be dispensed to this group.

ARM 2: Subjects on **sub-maximal daily doses** (atorvastatin <80 mg or simvastatin <40 mg without amlodipine and <20 mg on amlodipine or rosuvastatin <20 mg) will continue to take their daily statin during the dosing period prior to CEA PLUS they will be given the corresponding study drug bottles of:

- **Atorvastatin vs Placebo (each active study capsule = 10 mg)**
  - 126 capsule count bottle
    - Coordinator will write on the label how many capsules the participants need to take when they take their statin drug each day (example: If subject is currently on 10 mg of atorvastatin, then they will need to add 7 capsules/day to potentially reach 80 mg of active drug.)

- **Simvastatin vs Placebo (each study capsule = 5 mg)**
  - 126 capsule count bottle
    - Coordinator will write on the label how many capsules they need to take when they take their statin drug each day (example: If subject is

on 5 mg of Simvastatin, then they will need to add 7 capsules/day to potentially reach 40 mg of active drug unless they are also on amlodipine and then they will only potentially be optimized to 20 mg for safety.)

- **Rosuvastatin vs Placebo (each study capsule = 5 mg)**
  - 54 capsule count bottle
    - Coordinator will write on the label how many capsules they need to take when they take their statin drug each day (example: If subject is on 5 mg of rosuvastatin, then they will need to add 3 capsules/day to potentially reach 20 mg of active drug)

ARM 3: Subjects that are statin naïve (no statins in the past 30 days) will be randomized to receive either 10 mg or 80 mg of atorvastatin during the dosing period.

- 18 capsule count bottle
- Subjects will take 1 (one) capsule/day

Patients who will be treated with invasive transcarotid artery revascularization (TCAR) procedures that use a special transcarotid neuro-protection system (NPS) will be excluded.

5.2 Handling of Study Interventions

Atorvastatin, simvastatin and rosuvastatin will be purchased and distributed to all the study sites through a private vendor, the Biomedical Research Institute of New Mexico (BRINM). BRINM is affiliated with the VA Cooperative Studies Program Clinical Research Pharmacy Center, and will provide the same pharmacy supply services previously managed by Columbia University's Research Pharmacy Department. For this blinded phase 3 study, drug or placebo will be provided in randomized, prepackaged bottles and shipped to all sites by BRINM.

The study drug will consist of the corresponding statin tablets over-encapsulated and back-filled with microcrystalline cellulose. The matching placebo capsules will be prepared using microcrystalline cellulose as the fill. Each dose will be self-administered daily prior to the participant's CEA. Doses will be prepared using capsule shells of the same capsule size and color within each dosing arm. The capsule sizes will be kept as small as possible in ARM 2 as they may have to take up to 7 capsules per day if they are on the lowest dose of atorvastatin or simvastatin upon randomization. For statin naïve participants in ARM 3, the capsule size for the group will be the same for both the 10 mg and the 80 mg dose per day. In ARM 3, the capsules will be larger in both arm options to accommodate the larger 80 mg pill inside the capsule. This group will only take 1 capsule per day and having the larger, but same size capsule between both options in this arm will maintain the blind.

Each bottle will be labeled with a blinded, study bottle number, dosing instruction, and other study specific information. The name of the participant and number of capsules to take per day will be written on the label by the study personnel.

BRINM will process the study medication in compliance with Certified Good Manufacturing Practices (cGMP), inspect the shipments, assign unique tracking ID number to each lot received/study drug bottles, store the medication in controlled (15˚C – 30˚C) limited access areas. Any temperature excursions will be communicated to the Central Coordinating Center at CUMC within one business day.

Investigators will not be involved in preparation or delivery of drug to maintain the blind. BRINM has prepared blinded and randomized drug supplies for several randomized trials. It will provide all pharmacy support for the study, including preparation of the randomization schedule, placebo and active statin drug supplies, monitoring of procedures for shipping drug to multiple sites, and documentation of drug handling and disposal of remaining study drug at its site.

Inventory will be monitored by BRINM to make sure that we maintain at least 3 bottles for each randomization option for any potential enrollment of subjects in ARM 2 and ARM 3. This will allow adequate inventory at each site for any potential randomization. Consequently, we will strive to maintain 24 bottles of study drug at each site [ARM 2 requires 6 study bottles for the atorvastatin group (3 placebo + 3 active drug for maximization); 6 study bottles for the simvastatin group (3 placebo + 3 active drug for maximization), and 6 study bottles for the rosuvastatin group (3 placebo + 3 active drug for maximization) while ARM 3 will require 3 bottles of 10 mg atorvastatin and 3 bottles of 80 mg atorvastatin.] Upon randomization of each subject, the study database will automatically send an email to BRINM to inform them of the bottle number used and the study option that needs to be replenished.

The study drug will be requested from the site's research pharmacy with a doctor's order, copy of 1st and signature page of the consent form, copy of the randomization page from the study website, site approved cover fax form, and in accordance with regulatory and pharmacy procedures. Study treatment is to be dispensed only to subjects enrolled in this study. Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Once study treatment is dispensed to a subject, it cannot be used for another. Study treatment bottles are only for the dosing period prior to CEA. None of the remaining capsules from one subject can be used for another subject.

The study pharmacist/investigator(s) must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (subject-by-subject accounting), and accounts for any study drug accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed at the site as per the pharmacy's destruction protocol. A written explanation is required for any discrepancies (Appendix IV).

No one will have access to unblinded treatment information on a regular basis other than the packaging pharmacy. All handling of study medication will take place using blinded bottle codes. It is not expected that serious adverse events will require revelation of treatment assignment, but the study web site will provide for online unblinding in emergencies. Revelation of treatment assignment will be available only to authorized users, who will be required to provide a clinical justification for unblinding. Each case of unblinding will be addressed by study personnel to

ensure access to unblinded treatment assignment information is limited, and that such incidents are limited to circumstances where it is necessary for the health of the patient.

5.3 Concomitant Interventions

A concomitant therapy is any drug or substance administered between time of informed consent to enroll and completion of assessments at Day 365 +/- 30 days post-CEA. The use of concomitant therapies or procedures must be recorded on the subject's Concomitant Medications and Adverse Events eCRFs, according to instructions for completion and data entry. All AEs following the administration of these therapies or procedures must be documented on the appropriate worksheet/eCRF, regardless of relatedness.

5.3.1 Allowed Interventions

Concomitant therapy with any of the following is allowed as long as the exclusion criteria described in Section 4.2 are observed:

- Medications necessary for treatment of AEs according to the discretion of the Investigator.
- Medications used in standard of care to treat CEA patients, cardiovascular risk factors, or other comorbid conditions.

5.3.2 Required Interventions

- The subjects must undergo their scheduled CEA in order to be eligible.

5.3.3 Prohibited Interventions

- During the dosing period, the subjects should not switch to other statins.
- Concomitant therapy with any investigational product is not allowed.
- Subjects will be screened for and asked not to concurrently take the following medications during the study dosing period prior to CEA:
  *Cyclosporine;
  *HIV Protease Inhibitors/Antivirals (e.g. rotanavir or plus rotanavir, tipranavir, lopinavir, boceprevir, saquinavir, darunavir, fosamprenavir, nelfinavir, efavirenz/tenofobir, atazanavir, simeprevir); *Hep C Protease Inhibitor/Antivirals (e.g. telaprevir);
  *Antibiotics (i.e. cobicistat-containing products like Tybost, rifampin/rifampicin, clarithromycin, telithromycin, erythromycin);
  *Anti-fungals (i.e. itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole);
  *Gemfibrozil; Other Fenofibrates (e.g. Tricor, fibric acid);
  *Niacin > 1g/day or statins in combination with niacin (e.g. Vytorin, Simcor); *Colchicine;
  *Danazol;

*Calcium Channel Blockers: Diltiazem, Varapamil;
* Dronedarone;
*Amiodarone;
*Digoxin;
*Ranolazine;
*Nefazodone;
*Warfarin/Coumadin;
*Lomitapide;
*Grapefruit juice (subject must be willing to avoid grapefruit juice)

5.4 Adherence Assessment

Subjects are expected to take at least 2 doses of the assigned statin doses prior to their CEA.

In order to assess study drug compliance/safety, we will call the subjects on follow up Day 3 (+/-1 day), Day 7 (+/-1 day), and Day 10 (+/- 1 day) if the day of CEA has not yet occurred. The pre-CEA follow ups done per patient will be determined by their date of CEA. If the date of CEA occurs on or before a scheduled pre-CEA follow up, then those follow ups will not be done. If the CEA is done on the day of a follow up, the Day of CEA follow up will include the BLESSED ADL. The absence of a follow up as a result of following CEA will not be considered a deviation from protocol. The safety follow-up phone calls will begin based on when the study drug is scheduled to start or upon enrollment for Arm 1. We will collect the study drug bottle once the patient is admitted for their CEA to count any remaining capsules and also collect the Study Medication Compliance form (diary) completed by the subject attesting they took the doses and noting the reason(s) any dose was not taken.

6 STUDY PROCEDURES

6.1 Schedule of Assessments

Procedure	STUDY DRUG TREATMENT PHASE				D2-D18	POST CEA FOLLOW UP PHASE					
	Baseline Dose 1	***Day 3** +/- 1d***	***Day 7** +/- 1d***	***Day 10** +/- 1d***	***CEA DAY***	***Day 1* (12-25 hours)***	***Day 7 (+/-3d)***	***Day 14 (+/-3d)***	***Day 21 (+/-3d)***	***Day 30 (+/-5d or PO Visit)***	***Day 365 (+/-30d)***
Informed Consent	X										
Randomization	X										
Study Drug given to subject along with # of capsules to take per dose in the Study Medication Compliance form	X										
Concomitant Medications	X	Any other time the subject states he/she has had a change in medication									
Vitals (height/weight/BP from chart)	X				X	X				X	
Demographics	X										
Education	X										

Medical History (chart/interview)	X	Any other time the subject states he/she has had a change in medical status									
Tobacco Use	X										
Substance Use	X										
CAM	X				X	X				X	
MoCA/AD8 Screening	X										
AMNART or WAT	X										
Neuropsychological Tests (NPT)	X				X	X				X	
TICS-M		X									X
BLESSED ADL		X									X
Safety Questionnaire (CALL)		X	X	X			X	X	X		X
Safety Questionnaire (IN-PERSON)					X	X				X	
Pill Count					X						
CEA Details					X						
Neurological Exam post CEA (chart)					SOC	SOC					
EKG (from chart)	SOC				SOC						
Shipped Lab: ApoE (1x only)	At enrollment or during hospitalization(shipped as ambient blood Monday-Thursday)										
Site Lab: Comprehensive Metabolic Panel	X				X					X	
Site Lab: CK	X				X					X	
Site Lab: Lipid Profile	X				X					X	
Site Lab: CBC with differential	X				X					X	
Site Lab: ESR (Sedimentation Rate)	X				X					X	
Site Lab: C-Reactive Protein	X				X					X	
Site Lab: Urine Pregnancy or Beta-HCG[A]	SOC as part of pre-op labs[A]										
Assess for Adverse Events (AEs)		X	X	X	X	X	X	X	X	X	X
Procedure	**STUDY DRUG TREATMENT PHASE**				**D2-D18**	**POST CEA FOLLOW UP PHASE**					
	Baseline Dose 1	***Day 3** +/- 1d***	***Day 7** +/- 1d***	***Day 10** +/- 1d***	***CEA DAY***	***Day 1* (12-25 hours)***	***Day 7 (+/-3d)***	***Day 14 (+/-3d)***	***Day 21 (+/-3d)***	***Day 30 (+/-5d or PO Visit)***	***Day 365 (+/-30d)***
Study Completion/Discontinuation	At the end of the subject's participation										

*After surgery ends ** follow-up calls before CEA will be conducted only if not preceded by CEA [A] Urine Pregnancy test or Beta-HCG will be measured only in women of child-bearing age. SOC: Standard of Care v. 1-30-2018

6.2 Description of Evaluations

6.2.1 Consenting Procedure

The site's IRB protocol approval will state who is designated to consent potential participants. Study doctors and coordinators approved by the site's IRB will be permitted to facilitate the informed consenting process. All investigators need to be certified, by examination, in Good Clinical Practices and the Protection of Human Subjects. This study will be approved by the Institutional Review Board of the Columbia University Medical Center, as the coordinating site, and the IRBs of the other local centers.

The potential subject participant will be identified by the surgical/clinical team via the planned consultation to discuss undergoing a carotid endarterectomy. The potential subject participant will be informed about the study, once the potential subject expresses interest in knowing more about the study, the study coordinator and/or doctor will approach the individual and give them the opportunity to participate in this clinical trial. A copy of the consent form will be provided to them, in English or Spanish (whichever is their preferred language), and then the study personnel will facilitate the understanding of the study purpose, procedures and timeline of participation to allow them to make an informed decision about whether or not to participate in this clinical investigation. The information provided will include:

- the purpose and rational of the study
- the clarification that this is an experimental process and not part of the current standard of care
- what their participation process and procedures will be during the study
- the duration of the study participation
- the expected risks and benefits
- the number of study participants expected and approved at the site and at other sites participating in this study
- understanding that they will not incur any additional costs to participate in this study
- clarification of whom they should contact if they experience any adverse reactions and also if they feel they have been harmed in any way due to their study participation
- discuss how confidentiality will be addressed and protected
- details of when a subject's participation may be screened out or considered an OUTCOME by the study investigator without regard to the subject's consent ○ If the MoCA (≤25 points) and the AD8 (≥2 points) - screen failure
    - If baseline laboratory results indicate existing hepatic or muscle abnormalities that would preclude potentially increasing or adding statins to their current medical regimen (CK >5x ULN and LFTs > 2X ULN) – screen failure ○ If the subjects experience stroke or TIA peri-operatively, they will be considered as having reached a secondary OUTCOME in the study.
- explanation that participation is voluntary and that refusal to participate will not create any loss of benefits to which they would have otherwise received:
    - Including the clarification that they can discontinue their participation at any time without affecting their clinical treatment or any other right or benefits to which he/she is otherwise entitled.
    - Details of procedures expected for an orderly termination of the study participation by the individual

Once the study has been explained, the potential subject participants will be asked if they have any questions and given adequate amount of time to ask questions and/or discuss the study with family and friends to decide whether they should participate.

This process will allow sufficient opportunity for the potential participants to provide voluntary, informed consent to participate (or not) and know that they can withdraw at any time without any undue influence or coercion. All participants who consent will be given a copy of the informed consent form for their records and the original consent form will be filed in their study subject binder.

Subjects must provide individual informed consent before any screening tests are performed. When a subject signs the Informed Consent Form (ICF), the subject is considered consented, but not enrolled until they pass the complete screening process for MCI and hepatic/muscle abnormalities (see 6.2.1).Then and only then will they be assigned/randomized to a study arm. The study personnel consenting the subject participant must also sign and date the ICF.

6.2.2 Screening Evaluation

The screening evaluations for MCI and hepatic and muscle testing will be completed after consent and prior to randomization in the study. The screening assessments must be completed prior to the subjects CEA such that the minimum of 2 doses (maximum of 18) are taken. The screening assessments are:

- MoCA
- AD8
- Laboratory (LFTs & CK)

All potential participants will be pre-screened for eligibility by reviewing patient chart and speaking with the patient regarding the inclusion/exclusion criteria prior to offering them participation and informed consent. The final screening process for participation will be after they have consented to participate in order to screen those who may already have mild cognitive impairment (MCI) from the study. The participants who provide informed consent will be screened for MCI by administering the MoCA (≤25 abnormal) and the AD8 questionnaire (≥2 abnormal). If both assessments are not within normal ranges, these patients will not be randomized or assigned to the observational arm. Those with baseline MCI will be screened out from the study and not followed.

- **MoCA (Montreal Cognitive Assessment):** The MoCA is a global cognitive screening test with favorable psychometric properties (69, 70); it has been shown to be more sensitive to executive impairment than the Mini-Mental State Examination (MMSE). (75) It screens 8 domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. The assessment takes approximately 10 minutes. The highest possible total score is 30 points, and the assessment is available in various languages, including Spanish.

- **AD8 (Eight-item Informant Interview to Differentiate Aging and Dementia):** A screening test in itself is insufficient to diagnose a dementing disorder. The AD8 is, however, quite sensitive to detecting early cognitive changes associated many common dementing illness including Alzheimer disease, vascular dementia, Lewy body dementia and frontotemporal dementia. (72) This will serve

as a preliminary screen for MCI by asking the patient if they have noted any memory loss in spite of having normal ADLs (65).

- **Laboratory Screening**: Blood Draw #1 will include testing for Liver Function Test (LFTs) and Creatine Kinase (CK). If the baseline laboratory results indicate existing hepatic or muscle abnormalities that would preclude potentially increasing or adding statins to their current medical regimen (CK >5X ULN and LFTs > 2X ULN), this will also constitute a screen failure and the subject will be informed and considered a screen failure.

Participating study sites are required to document all screened candidates considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion must be documented in the screening log (Appendix III) and the subject's file folder containing his signed consent form. The screening logs will be collected monthly by the Central Coordinating Center at CUMC.

6.2.3 Enrollment, Baseline, and Randomization

Enrollment

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject in accordance with local practice and regulations. Once the subject has provided informed consent and passed the screening process, then he/she will they be considered enrolled.

Baseline Assessments

The baseline assessments are to be obtained after screening and randomization, but before the subject is started on the study assigned statin. These include:

- AMNART for English-Speaking Subjects or WAT for Spanish-speaking subjects
- NPT #1 ○ Hopkins Verbal Learning Test (HVLT)
  - ○ Rey Complex Figure ○ Grooved Pegboard ○ Trails A & B
  - ○ Controlled Oral Word Association ○ Animal Naming
- CAM
- Blood Draw #1 ○ Comprehensive Metabolic Panel (includes LFTs) ○ CK
  - ○ Lipid Profile ○ CBC with differential ○ ESR (Sedimentation Rate) ○ C-Reactive Protein
- ApoE blood draw - Unlike other baseline assessments, the ApoE blood draw can be obtained at baseline or at any other time point during the subject's participation in the study.
- EKG from patient chart (e.g. part of pre-op testing)
- If applicable, Urine Pregnancy or Beta-HCGA (as part of pre-op testing)
- Demographics, Baseline Characteristics (handedness, education level, childbearing potential, tobacco/alcohol/substance use), medical history, and concomitant medications will be noted

Randomization

After subjects have passed the screening assessments, which should not take more than 15 minutes, the coordinator or other study personnel will either assign them to the Observational Arm (ARM 1) or randomize them within the arm corresponding to their current statin dosage status (ARM 2 and ARM 3). The randomization design will be stratified by center, previous use of statin and in random blocks of 4 and 6. The randomization process will be supported by the Statistical Analysis Center (SAC) at the Mailman School of Public Health at Columbia University. SAC will provide a central secure web-based randomization data system. All trials supported by the SAC employ central randomization that takes place in real-time. In other words, the patient's treatment assignment is made at the moment of randomization, based on probabilities calculated according to the randomization scheme, and communicated to the recruiting site via a central source (i.e. a secure web site).

Upon subject enrollment on the study website, the study drug start date will be noted for Arms 2 and 3. Those in the Observational/Maximal Dose group (Arm 1) will use a start date of the date of enrollment.

After randomization, the subject will complete the baseline assessments, the study drug will be requested and obtained from the site's research pharmacy and given to the subjects for self-administration on a daily basis as per protocol verbal and written instructions provided to each participant.

6.2.4 Neuropsychometric Evaluations

There will be four neuropsychometric battery of tests performed during the subject's participation in the study. Preoperative neuropsychometric tests will be used to evaluate patients pre- and post-operatively. The neuropsychometric tests are designed to demonstrate general neuropsychological performance and not to be diagnostic of specific neuropsychiatric disorders. The average amount of time to complete the neuropsychometric battery is around 45-60 minutes. There are three types of tests administered: (1) a general evaluation of mental status, (2) an evaluation of speed of mental processing, and (3) an evaluation of ability to learn using a list of words. They will be performed at enrollment, before surgery, one day after surgery (12-25 hours post-op for eCD) and at Day 30 +/- 5 days post CEA or day of their post-op clinical visit (dCD). eCD and dCD will be measured as significant change in neuropsychometric performance. Neuropsychometric performance will be determined by calculating Z-scores. In order to account for "practice effect" we will utilize a reference group of age matched patients having "simple spine" surgery. This group should be an effective reference group for the effect of anxiety, the trauma of surgery and the effect of medications on neuropsychometric performance. "Practice effect" arises because patients when repeatedly tested improve performance simply due to the effect of repetition.

The differences between NPT #1 administered upon enrollment and the other battery of neuropsychometric tests will be to consider the effects of changing the statin regimen approximately 2 weeks prior to CEA for arms 2 and 3. We will also review overall test changes, in all arms, from enrollment to Day of CEA (NPT#2).

The major cognitive domains the study is testing are:

- **Memory**
  - Verbal memory: **Hopkins Verbal Learning Test (HVLT):** Total Recall, Delayed Recall, and Recognition. The HVLT was developed for the brief assessment of verbal recall and recognition (58, 59). The test consists of three learning/free-recall trials followed by a yes/no recognition trial. Test stimuli are 12 words, four from each of three semantic categories. Subjects are asked to recall the words (Total Recall). The HVLT has six equivalent forms and takes less than 10 minutes to administer. These features make the HVLT particularly suited to time constrained repeated assessment (e.g., drug trials, tracking neurological recovery) HVLT has been shown to be stable over time (60). Visual Memory: Rey Complex Figure-Immediate Recall (61). The subject is asked to draw from memory the complex figure copied in the visuospatial task described below. The same standardized scoring system is used as for the copy task.

- **Constructive** ○ Visuospatial: **Rey Complex Figure Copy:** The subject is asked to copy the figure with all its detail properly located. A standardized scoring system, as described in Lezak (62), is used to score both the presence of specific design features and the accuracy of their location as well as the recall task.

- **Motor**
  - **Grooved Pegboard:** The subject places 25 notched-pegs into mirror image holes. The score is the time in seconds needed to complete this task. This test was selected because it combines both motor speed and dexterity with sensorimotor demands, making it sensitive to brain dysfunction. Because it is performed with both hands it can provide information about lateralization of brain dysfunction. This test was selected because it combines both motor speed and dexterity with sensorimotor demands, making it sensitive to brain dysfunction (56).

- **Executive** ○ **Trail Making Test, Part A** (63): The subject is asked to connect 25 numbered circles in ascending order with a single continuous line. The score is the time in seconds needed to perform this task. This speed-based task is a sensitive but relatively nonspecific indicator of brain dysfunction.
  - **Trail Making Test, Part B:** This test is similar to Trail Making Part A except that the 25 circles are numbered and lettered and the subject is asked to connect with a single line circles alternating between numbered and lettered sequences. The score is the time in seconds needed to perform this task. In addition to being a sensitive screening task, the alternation of letter and number sequences required by this task taps executive functions.
- **Language**
  - **Controlled Oral Word Association** (64a): The Controlled Word Association test will be administered. The patient is given 1 min to name as many words beginning with a particular letter as he/she can. This test is considered to be sensitive to frontal lobe damage.

  - **Animal Naming Test** to assess the verbal fluency of the individual and has been validated for testing MCI patients (64b).

In addition, we will also be testing for:

- **Pre-morbid Intelligence (pIQ) at Baseline Only** ○ As enhanced cognitive reserve may be a function of pre-morbid intelligence, we will administer the AMNART to all study and control patients who are English-speaking. If they are Spanish-speaking, please administer the WAT.

  Either measure should take 5 additional minutes.

- **Post-operative Delirium** ○ The Confusion Assessment Method (CAM) will be used to screen for post-operative delirium in CEA patients and surgical controls at one day post CEA (12-25 hours post-op) and Day 30 +/- 5 days post CEA or day of their post-CEA clinical visit (48). See Section 2.1.5.

The main neuropsychometric battery of tests (NPT#1 – NPT #4) will consist of:

- Hopkins Verbal Learning Test (HVLT)
- Rey Complex Figure
- Grooved Pegboard
- Trails A & B
- Controlled Oral Word Association
- Animal Naming

6.2.5 Follow-up Visits [based on study drug start date (Arms 2 & 3) or date of enrollment (Arm 1)]

Call Day 3 (+/- 1 day) if CEA does not occur before day 3: •
Safety Compliance Questionnaire (telephone)

- TICS-M
- BLESSED ADL
- Medical Status/Concomitant Medications (review & add/edit from baseline)
- Adverse Event Assessment

Call Day 7 and 10 (+/- 1 day), if CEA does not occur before day 7 and 10, respectively:

- Safety Compliance Questionnaire (telephone)
- Medical Status/Concomitant Medications (review & add/edit from prior visit)
- Adverse Event Assessment

Day of CEA: The subject can have their pre-CEA testing done the actual Day of CEA or up to 18 days after enrollment/start of their study drug. All of their post-CEA testing needs to be done the actual Day of CEA after the surgery has been completed:

- Safety Compliance Questionnaire (in person)
- Collection of Study Medication Compliance form
- Collect Study Drug bottle and complete PILL COUNT
- Vitals
- EKG from patient chart (only if this is clinically required as part of SOC)
- NPT #2 ○ Hopkins Verbal Learning Test (HVLT)

- Rey Complex Figure ○ Grooved Pegboard ○ Trails A & B
- Controlled Oral Word Association ○ Animal Naming

- CAM
- Blood Draw #2 ○ Comprehensive Metabolic Panel (includes LFTs) ○ CK
  - Lipid Profile ○ CBC with differential ○ ESR (Sedimentation Rate) ○ C-Reactive Protein
- Collect ApoE blood draw (if not collected at baseline)
- Medical Status/Concomitant Medications (review & add/edit from prior visit)
- Neurological Exam (Day of CEA post-op from chart)
- Adverse Event Assessment

<u>Day 1 Post CEA (12-25 hours post-op):</u>

- Safety Compliance Questionnaire (in person)
- Vitals
- NPT #3 ○ Hopkins Verbal Learning Test (HVLT)
  - Rey Complex Figure ○ Grooved Pegboard ○ Trails A & B
  - Controlled Oral Word Association ○ Animal Naming
- CAM
- Collect ApoE blood draw (if not collected at baseline)
- Medical Status/Concomitant Medications (review & add/edit from prior visit)
- Neurological Exam (post-op from chart)
- Adverse Event Assessment

<u>Call Day 7, 14, & 21 Post CEA (+/- 3 day):</u>

- Safety Compliance Questionnaire (telephone)
- Medical Status/Concomitant Medications (review & add/edit from prior visit)
- Adverse Event Assessment

<u>Day 30 Post CEA (+/-5 days) or Day of PO Visit:</u>

- Safety Compliance Questionnaire (in person)
- Vitals
- NPT #4 ○ Hopkins Verbal Learning Test (HVLT)

- Rey Complex Figure ○ Grooved Pegboard ○ Trails A & B
- Controlled Oral Word Association ○ Animal Naming

- CAM
- Blood Draw #3 ○ Comprehensive Metabolic Panel (includes LFTs) ○ CK
  - Lipid Profile ○ CBC with differential ○ ESR (Sedimentation Rate) ○ C-Reactive Protein
- Collect ApoE blood draw (if not collected at baseline)
- Medical Status/Concomitant Medications (review & add/edit from prior visit)
- Adverse Event Assessment

6.2.6 Completion/Final Evaluation

Call Day 365 (+/- 30 day):

- Safety Compliance Questionnaire (telephone)
- TICS-M
- BLESSED ADL
- Medical Status/Concomitant Medications (review & add/edit from prior visit)
- Adverse Event Assessment
- Upon completion of the study or at any time when subject discontinues his/her study participation**,** the coordinator will interview the participant to complete the study's Completion Form, Discontinuation Form or have reported their death as an SAE.

6.3 Local and Central Laboratory Procedures

The participants' three blood draws for Comprehensive Metabolic Panel (CMP), Creatine Kinase (CK), Lipid Profile, CBC with differential, Sedimentation Rate (ESR), C-Reactive Protein (CRP), and their corresponding laboratory tests will be analyzed at each site's institutional laboratory and the results will be recorded in the participant's medical record (source document).

The ApoE blood draw is different as it will only be taken once during the subject's study participation and will be analyzed centrally. Unlike other baseline assessments, this blood draw can be obtained at baseline or at any other timepoint during the subject's participation in the study.

The ApoE blood draw will be shipped to the Central Coordinating Center (CCC) at:

IGM Biobanking Core, CUMC
701 West 168th St., HHSC 1406 New
York, NY 10032
Attn: Colin Malone, Ph.D.
Tel: 212-305-1110

IGM Biobanking will be in charge of receiving ApoE blood samples, extracting the DNA and storing the biological specimens until they are ready to be tested for ApoE. IGM will use the Isolation of (high molecular weight) HMW genomic DNA from blood by using the salting out purification protocol which is a standard DNA isolation method.

The extracted DNA samples will be plated by IGM and sent to LGC Genomics for ApoE allele testing at:

LGC Genomics
Att: Jonathon Dunn
100 Cummings Center
Suite 420H
Beverly, Massachusetts 01915
978.338.6308 www.lgcgroup.com

LGC uses KASP genotyping chemistry on their own instrumentation to genotype samples. Briefly, they first perform a quality check on the customer DNA by using a serial dilution of the DNA and genotyping on internal quality control assays. Once passing QC, PCR plates in either 384 well or 1536 well format are prepared using an automated liquid handler (RepliKator) at the appropriate dilution from the testing and dried in an oven. They then apply the primer and PCR master mix on the dried down DNA using a semiautomated dispenser engine (Meridian). Once the reagents are added, the plates are sealed via a laser sealer (Fusion). PCR is performed using an automated water bath machine (Hydrocycler) using a touchdown procedure with denaturation temperature of 94 and annealing temperatures from 61 to 55 for the first 10 cycles and then 55 for an additional 26 cycles (there is no extension step). Fluorescence is measured using a plate reader (PheraStar, BMG Labtech). As they read the plates toward the end, but still within the exponential phase of PCR, they perform an additional 3 cycles of PCR and re-read the plates until clustering of the samples is complete. The clustering data is checked by experienced staff members and then second checked by a senior member of staff before being exported and results sent out. For the ApoE testing, they use two SNPs, rs429358 and rs7412.

7 SAFETY ASSESSMENTS

7.1 Clinical Risks

Patients will have clinical laboratory tests upon enrollment and a research coordinator or nurse will contact them 3 days after starting the study drug to verify the patient's complying with the statin regimen as well as to ask questions regarding their subjective experience of taking the study assigned statin regimen (if the CEA does not occur prior to day 3). If the CEA does happen prior to day 3, the Day of CEA Safety Questionnaire will verify compliance and ask about the subjects experience with the assigned statin regimen. Patients will be asked about a variety of symptoms associated, though rarely, with statin use. According to the FDA, the value of statins has been clearly established yet they also advise that statins,

including the ones which will be part of this study (i.e. simvastatin, atorvastatin and rosuvastatin) offer some rare, but potential risks to statin users:[1]

- Hepatic toxicity (indicator symptoms: elevated liver enzymes, bleeding or jaundice)
- Muscle toxicity (indicators symptoms: myalgia and arthralgia)
- Increased glucose levels

In addition, from clinical practice, we also know that statins may produce some minor gastrointestinal discomfort; however, these are minor and mostly tolerated as the benefit of statins tends to outweigh the minor stomach upsets they may produce in some individuals.

Patients randomized to maximize their statin regimen or randomized into the atorvastatin 80mg group are the only patients we anticipate having any risk of side effects.

If a patient reports subjective experiences of side effects, their statin regimen will be modified at the discretion of the caring physician. Although the randomization of the patient is compromised, we will continue to evaluate that patient and proceed with intention to treat principles. If the laboratory values the morning of surgery present with elevations in CK or LFT, their statin regimen will be modified at the discretion of the caring physician.

Other Potential Study Procedure Risks:

- Some people may feel uncomfortable taking cognitive tests.
- Slight pain and/or temporary discoloration of the skin after blood draws.
- Unlikely, but potential breach of confidentiality

7.2 Specification of Safety Parameters

7.2.1 Protection Against Clinical Risks

Protection against other statin drugs being given to the subject participants prior to CEA:

- A letter for the subject's Primary Medical Doctor will be prepared to avoid duplication of prescribed statin doses or unknown changes to their statin regimen (see Appendix VI).

- Although extremely rare in FDA approved statin doses, the risks associated with statin use such as myalgias, arthralgias, gastrointestinal distress, or elevation in blood sugar can occur in some individuals.[2] Consequently, consented participants will first have various laboratory tests and assessed for clinical symptoms to assure safety. The laboratory tests conducted at baseline, Day of CEA, Day 1 post CEA (12-25 hours post-op) and 30 +/- 5 days post CEA or Day of post-op clinical visit. These include: CBC w/differential, comprehensive metabolic panel (which includes blood glucose levels, creatinine, and Hepatic LFTs), CK, and a lipid profile to detect any physiologic symptoms associated with the statin intervention.

[1] (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm):

[2] (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm):

- Abnormal lab results at baseline: anyone with elevated CK (5x > ULN) or LFTs (2x > ULN) will not be asked to take the study drug. These subjects will screen out from the study, and their future statin regimen will be determined by their treating physician. The blood draw will not be done fasting; however, anyone with abnormally high and uncontrollable blood glucose levels will also be screened out. All of the results will be reported to the subject participants via phone and advised to address abnormal results will become part of their medical record.
- Abnormal lab results on Day of CEA, Day 1 post CEA (12-25 hours post-op) and/or Day 30 +/- 5 days post CEA (or Day of PO clinical visit): anyone with elevated CK and LFTs will be considered an AE. Anyone with CK 5x > ULN with symptoms or 10x > ULN without symptoms and/or LFTs 2x > ULN with symptoms or 3x > ULN without symptoms will be considered a Serious Adverse Event. Also, their statin regimen will be determined by their treating physician who will be made aware of the abnormal findings. The results will also be in the patient's medical records and available for the treating physicians to address. We will continue to follow them for the remainder of the study to assess for safety.

- We will report any abnormal laboratory values **not present at baseline** as adverse events. This will include abnormal laboratory values showing any potential acute kidney injury (AKI) defined as a serum creatinine increase of 50% from baseline within 7 days.[3]

- Clinical study assessments for statin intolerance will be done via phone using structured questionnaires to assess for safety/adverse events and compliance on:

    - Day 3 (+/-1d) if not preceded by CEA, 7 (+/- 1d) if not preceded by CEA, 10 (+/- 1d) if not preceded by CEA and Post-CEA: Day 7 (+/- 3d), Day14 (+/- 3d), Day 21 (+/- 3d), and Day 365 (+/- 30d)
- Clinical assessments for statin intolerance will be done in person while the patient is in the hospital for their CEA and during Day 30 +/- 5 days post-CEA or in-person the day of their post-CEA clinical visit.

- In addition, while the patient is in the hospital for the CEA, we will monitor the medical chart for any adverse events (clinical or laboratory based).

7.2.2 Protection Against Other Minor Procedure/Study Related Risks

- It is expected that some individuals may feel uncomfortable taking cognitive tests; consequently, we will make every effort to ensure subject participant comfort during their neurocognitive testing.
- There will be three blood draws which could potentially produce minimal pain, bruising or discomfort; however, blood draws will be conducted by trained professionals which will minimize any of the above mentioned risks
- Every effort will also be made to ensure the confidentiality of the subject participant, including the use of unique patient identifiers for the study forms, and database entry. The subject binders/data

[3] http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf

will be kept in a locked cabinet within a locked room which is only accessible to the study team. If any subject contact information is kept digitally, it will be kept in a password protected computer only accessible to authorized study personnel.

7.3 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

There are common and significant side effects of statins. The commonest are: headache, difficulty sleeping, flushing of the skin, muscle aches, tenderness, or weakness (myalgia), drowsiness, dizziness, nausea and/or vomiting, abdominal cramping and/or pain, bloating and/or gas, diarrhea, constipation, rash. In addition, statins also carry warnings that memory loss, mental confusion, high blood sugar, and type 2 diabetes are possible side effects. Patients can have elevations of liver transaminase levels. The most significant side effects are: myositis, elevated levels of CPK, or creatine kinase, and rhabdomyolysis. We will evaluate patients for all of these side-effects (73, 74). Guyton describes the risks of severe side-effects as very small (73). “The significant risks pertain to rhabdomyolysis and myopathy.” Rhabdomyolysis risk … is about 3 cases per 100,000 person-years. …. However, because only 4 cases have been defined thus far, there is no basis for assigning an occurrence rate other than “rare.” (74) Statin-attributable peripheral neuropathy incidence of 12 per 100,000 person-years or prevalence of 60 per 100,000 persons. Acute liver failure has occurred in statin users with a spontaneous reporting rate of 0.1 case per 100,000 person-years of treatment. Correction for underreporting might increase this rate to 0.5–1 case per 100,000 personyears, but this is approximately equal to the background rate of liver failure in the general population. There is no evidence that statins cause acute or chronic kidney damage.”

At the time that a patient is invited to enroll, we ask about side effects that the patient might have previously had associated with statins, and especially if the side effects occurred at higher doses. Patients will not be enrolled if they had any side effects at their current dose or at higher doses. Since the three statins we will be studying may also interact with other medications, changing either their pharmacokinetic or pharmacodynamics properties (3), we will record other medications and their dosages that patients are taking.
All patients enrolled will have lipid profiles, CBC w/Diff, and comprehensive metabolic panels (including creatinine, LFTs), and CK obtained at several time points to detect any physiologic symptoms associated with the statin intervention. At multiple time points, patients will have a research coordinator or nurse contact them to verify that the patient is complying with their statin regimen as well as to ask questions regarding their subjective experience of taking the statin regimen. Patients will be asked about a variety of symptoms associated, though rarely, with statin use, i.e., myalgias, gastrointestinal distress, arthralgia, etc. (Section 6 Schedule of Assessments).

Patients randomized to maximize their statin regimen or randomized into the atorvastatin 80mg group are the only patients we anticipate having a significant risk of side effects. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators study enrolled 4731 patients to be randomized to receive atorvastatin 80mg or placebo(4). The median follow up was 4.9 years. Except for elevations of the liver enzymes ALT and AST, there were no differences between the atorvastatin and placebo groups. Patients in arm 1 and randomized to placebo in arm 2 are at minimal, to no, risk, as their statin regimen will not be changed. Patients randomized to atorvastatin 10mg in arm 3 are at minimal risk of side effects, as they will be started on a new statin regimen, but at a very low dose of a slightly lipophilic statin.

In addition:

- During their CEA hospital stay, the electronic medical chart will be reviewed from admission to discharge and a copy of the admission and discharge notes will be printed for the subject binders and de-identified to be uploaded into the study database.
- The Central Coordinating Center (CCC) will also screen for AEs at all sites while reviewing the data entered and the de-identified Admission/Discharge notes each site must upload to the study database. All study data will be entered into the study database in a timely fashion, no later than 7 days after completion of the follow up unless a safety concern arises and then the report timing must be based on Section 7.6 Reporting Procedures.

7.4 Definition of Adverse Events

- **Adverse events (AE)** will be defined as any symptom, sign, clinically significant abnormal test result, disease, or syndrome occurring during the trial which was either not present at baseline, or if present, worsened during the trial, without any judgment about causality or relationship to the drug.

- **Serious Adverse Event (SAE):** An adverse event will be considered an SAE if it results in any of the following outcomes: death, life-threatening experience, requires or prolongs hospitalization, new significant disability, congenital anomaly or birth defects, or in the opinion of the investigator, other important medical event, whether or not considered related to the participation in the study or not.

- **Non-serious Events (NSAE):** are those adverse events that do not meet the criteria for an SAE, but are still unfavorable medical occurrences in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research.

- **Unexpected Adverse Event (UAE):** adverse AEs not expected from the study drugs being used in the study:
    - Not known side effects of this type of drug in the Package Insert for statins like those being used in the study (i.e. simvastatin, atorvastatin, and/or rosuvastatin).
        - Not listed at the specificity or severity previously observed.

- **Serious, Unexpected and Suspected Adverse Reaction (SUSAR):** serious adverse events that are unexpected and suspected to be related to the study drug must be reported within 15 days to the FDA. These must meet ALL of the following: ○ Serious (S) ○ Unexpected (U)
    - Suspected Adverse Reactions (SAR)

7.5 Reporting Procedures

All AEs will be reported by the local Principal Investigator or designee using the study NSAE/SAE form and based on the Common Terminology Criteria for Adverse Events (CTCAE v.4.03)[4] for language and severity

[4] CTCAE_4.03_2010-06-14_QuickReference_8.5x11 http://evs.nci.nih.gov/ftp1/CTCAE/About.html

grade criteria. Data regarding timing, seriousness, severity, expectedness, resolution, study drug action taken, if AE resulted in withdrawal from the study, and relationship to the drug along with a preliminary narrative summary will be entered in the NSAE/SAE form. The supporting documentation will also be included with the NSAE/SAE form. All of the AE information will also be entered and uploaded into the study database. The timing of adverse event reporting will correspond to the type of adverse event as noted below (i.e. NSAE, SAE, Unexpected, SUSAR). All semi-annual DSMB/Progress reports will contain details of all NSAEs and SAEs, including any unexpected events or suspected unexpected serious adverse reactions (SUSARs).

In addition to the CTCAE criteria, to screen for acute kidney injury (AKI), we will use the definition provided by the Kidney Diseases Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (vol 2, issue 1, March, 2012) which states that AKI can be defined by an increase from baseline in serum creatinine (SCr) by 50% within 7 days.[3]

The Independent Medical Monitor (IMM), Dr. Peter D. Angevine, will indicate to the Sponsor, Statistical Analysis Center (SAC), and DSMB through Dr. Luci Roberts/NIA officer whether there are any concerns after review of semi-annual reports. In addition, if the IMM determines that there are any concerns between semi-annual reports or after reviewing SAE reports, the IMM will also notify the Sponsor, SAC, and DSMB, and DSMB ISO through Dr. Roberts. A teleconference will be conducted with the IMM as needed.

7.5.1 Reporting of Non-Serious Adverse Events (NSAE)

NSAEs will be reported within 48 hours of discovery by the local investigative team to the Coordinating Center by entering the NSAE(s) into the study database. Available de-identified supporting documentation will be included by uploading it to the study database. If further documentation is to be obtained, it will also be uploaded to the study database.
All NSAEs at each site will be reported by the Local Principal Investigator or designee using the NSAE/SAE form. Unless unexpected and/or the events suggest the research places the participants or others at a greater risk of physical or psychological harm that was previously known, the NSAE information will be submitted to the DSMB and ISO/IMM during the semi-annual review. If the NSAE is unexpected and/or the events suggest the research places the participants or others at a greater risk of physical or psychological harm that was previously known, then it will be submitted to the IMM for review within 24 hours from receipt and reported to the IRB, OHRP, and NIA within 2 weeks of receiving the event. In addition, it will also be reported to the other participating sites for their IRB notification.

7.5.2 Reporting of Serious Adverse Events (SAE)

SAEs will be reported within 24 hours of discovery by the local investigative team to the Coordinating Center by entering the SAE(s) into the study database. Available de-identified supporting documentation will be uploaded to the study database. If further documentation is to be obtained, it will also be uploaded to the study database.

The database will email the IMM the list of SAE(s) for him to review and enter his findings within the study database. The database will compile SAEs for the semi-annual DSMB report unless the IMM deems it necessary for the DSMB to review the adverse event before the next semi-annual meeting.

All SAEs at each site will be reported by the Local Principal Investigator or designee using the NSAE/SAE form.

7.5.3 Reporting of Unexpected Serious Adverse Events/Problems (USAE and SUSAR)

All unexpected SAEs/Problems will be reported by the Local Principal Investigator or designee and within 24 hours of discovery to the Central Coordinating Center by entering them into the study database which will immediately trigger emails to Dr. Connolly (Central PI), Dr. Heyer (Central Co-PI), Dr. Angevine (IMM), and Rebeca Aragón García (Central Study Coordinator). Available de-identified supporting documentation will be uploaded to the study database. If further documentation is to be obtained, it will also be uploaded to the study database.

The Central Coordinating Center (CCC) will provide the NIA, DSMB Chair, DSMB ISO, Independent Medical Monitor (IMM), and CUMC IRB with the SAE form for the "unexpected event" and supporting documentation within 24 hours of its receipt at the Central Coordinating Center. We will provide any additional information requested and report to the FDA within 15 days. In addition, it will also be reported to the other participating sites for their IRB notification.

Furthermore, if the adverse event is serious, unexpected, and suspected to be associated with the study drug (SUSAR), it will be reported to the NIA, DSMB ISO/IMM, and CUMC IRB within 24 hours of discovery and to the other participating sites so that they can report it to their respective IRBs.

7.6 Follow-up for Adverse Events

Any adverse event that is ongoing when the subject completes or discontinues the study will be followed by the Investigator(s) until the event has resolved, stabilized, or returned to baseline status. The resolution date should be noted on the case report form of the corresponding AE and in the study database.

7.7 Safety Monitoring

As soon as the site's Principal Investigators become aware of any SAEs, their team must submit corresponding AE reports to the CCC. The CCC will inform the ISO/IMM and DSMB as noted in our DSMP, section 1.2.2 Adverse Event Reporting. The DSMB will meet twice a year, by teleconference call to review study progress, data quality, and participant's safety.

Safety reports will be sent to the DSMB/ISO/IMM twice a year and will include a detailed analysis of study progress, data and safety issues.

The Principal Investigator (PI) at each site will be responsible for ensuring participants' safety on a daily basis. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

In addition, we will require that all of the subject's case report form data to be entered into the study database (eCRFs) within 7 days of generating the data along with any pertinent source documentation, all items scanned per visit and uploaded to the study database. The uploaded documents will be reviewed by the CCC Multisite Coordinator, Rebeca Aragón García, against the data entered in the study database to

assure for completeness and accuracy of the data in real time. Any queries or concerns will be forwarded to the CCC Principal Investigator, Dr. E. Sander Connolly, and as formal queries to each site's coordinator with copy to the corresponding site's Principal Investigator.

Once the subject participant is admitted for the CEA procedure, a de-identified copy of the hospital admission and discharge notes will also be uploaded to the study database and the CCC Multisite Coordinator will review these for adverse events.

Any queries which arise from receipt of the subject data or hospital notes will allow for continuous data and safety monitoring in real time and not just in preparation for DSMB meetings.

The prevalent errors/omissions/queries found through these monitoring reviews will also be addressed generically during our monthly multi-site team calls as part of our continuing study personnel training.

The payment for subject enrollment and participation will be linked to the timely entering of subject data (within 7 days) after each study visit and submission of the corresponding source documentation to the study database. This will ensure our ability to continuously monitor each site for safety, completeness and accuracy of the study data.

Dr. Connolly and/or his representative will also visit each study site, virtually or in-person, weekly for the first 6 months after their site initiation visit (SIV) and then monthly to insure protocol procedures are followed clearly, consistently, and while keeping patient safety forefront.

There will also be monthly conference calls with all of the sites to make sure that any concerns or questions are addressed and shared with the whole study team. Further visits will be on an as needed basis if a site shows a pattern of study violations and/or have procedural errors that show they need to receive booster training or further study monitoring.

In addition, the data center (SAC) will design the database to evaluate, validate and monitor trial data as part of an ongoing process. The initial validation takes place as early as possible in the data collection process, including real-time validation for range checks, limits on categorical variable entry, checks for completion and consistency, etc. Further error checking, including validation for completeness, is performed when data is posted. Since some errors (in changes over time, and consistency between different forms or scales) cannot be detected on initial data entry, validation checks are performed daily. All data errors and queries are processed promptly. Regular reports to investigators and coordinating centers on accrued data identify unusual or unexpected data points and request that they be confirmed or corrected.

7.7.1 Adjudication of Adverse Events

Prior to DSMB bi-annual meetings, the IMM will review the SAE forms and supporting documentation for all SAEs.

The IMM and the DSMB will make a final determination as to diagnosis, seriousness, expectedness, severity, resolution, and relationship to study drug, based on available narrative summary and supporting documentation. The IMM may request additional information as needed, and the Sponsor will request the

information from the site. If the IMM determines that the treatment assignment of the subject is needed, this information will be provided by the SAC.

The IMM will complete a confirmation (Adverse Event Review form), indicating agreement or disagreement with any of the items in the SAE form. Final adjudicated SAE review forms will be entered into the study database.

8 INTERVENTION DISCONTINUATION

The study treatment doses will be stopped for any of the following reasons:

- The subject experiences a hypersensitivity or suspected allergic reaction to study treatment
- Subject consent for participation is withdrawn
- The subject experiences a medical emergency that necessitates discontinuation of study treatment
- The subject experiences a medical emergency that necessitates unblinding of the subject's treatment assignment
- At the discretion of the Principal Investigator or the Sponsor for other medical reasons

The reason for discontinuation of study treatment must be recorded in the subject's study worksheets and entered in the study database eCRF. For all subjects who discontinue study treatment, safety data will be collected at subsequent follow up visits until Day 365 +/- 30 days visit (except for those that have withdrawn their consent).

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

For all analyses, the primary outcome will be derived from changes in test scores between enrollment and the morning of surgery (baseline), Day 1 post CEA (12-25 h post-op) (eCD) and Day 30 +/- 5 days after CEA or Day of Post-Operative clinical visit (dCD). Neuropsychometric assessment at baseline, will allow screening for MCI and determining if there is a change in cognitive performance from recruitment to operative day due to statin alteration. The intention to treat principle will be used for all analyses. All of the analyses will be performed in two general ways. 1) Significant neurocognitive change for both CEA will be defined compared to an appropriate reference group frequency matched for age, education level, pIQ, and type of anesthetic or sedation. Significant eCD will be defined as performance: (1) ≥2SD worse than reference group in two or more cognitive domains or (2) ≥1.5SD worse than the reference group in all cognitive domains tested.

The following data will be kept for patients having CEA: demographic and risk factor variables (age, gender, race, a history of hypertension, diabetes, level of glycosylated hemoglobin, previous myocardial infarction, previous CEA, ApoE genotype, pre-morbid IQ, MCI), degree of carotid stenosis, all additional cerebrovascular workup (i.e. Intracranial MRA, SPECT scanning, angiography, etc.), previous surgeries/anesthetics, laboratory values, all standing medication names (statin usage), doses, and

durations, and all neurologic and neuropsychological scores. Data will also be kept on the results of the delirium screen and the post-operative pain scores.
In general, for the continuous variables, a two-sample Student's t-test will be used for comparing means between the two groups, patients with eCD or dCD and those without eCD or dCD. Non-normally distributed variables will be transformed to improve distributional characteristics. In particular, neuropsychometric test scores will be subjected to a square root transform that yields values that are approximately normally distributed and provide analytic results using parametric tests that are similar to those obtained by non-parametric analysis of the untransformed values. Non-parametric techniques will be used for any variables for which suitable transformations cannot be found. Dichotomous variables will be analyzed using a $\chi 2$ test. Multiple linear and logistic regression models will be used to adjust for the risk factors that are out of balance ($p < 0.10$) between groups. Logistic regression analysis will be used to determine whether any demographic or risk factors other than statin regime significantly affects outcome. Since post-operative pain >4 adversely effects performance, change scores for each test will be obtained using the patients in the reference group, with average pain scores less than 4 as the cutoff value (18).

Missing Data

When data are missing completely at random (MCAR), i.e. when the probability that an outcome is missing does not depend on any outcomes, statistical inference based on completely observed data is valid. If data are missing at random (MAR), i.e. when the probability that an outcome is missing depends on the observed outcomes (such as observed outcome at baseline), inference based on complete data is not valid. We will first check whether the data are MCAR by fitting logistic models for missing data indicators. For example, at the end of the study, the dependent logistic variable is the indicator of whether neuropsychometric test is missing, and the explanatory variables are the outcome at baseline. An insignificant test of the global null hypothesis will confirm MCAR. Assuming the data are not MCAR, we will attempt to obtain bias-corrected estimates under MAR, and we will conduct sensitivity analyses under "non-ignorable missingness".

Interpretation of Results

We anticipate that patients, who are on a sub-maximal statin regimen, will experience more eCD and dCD than patients on a pre-existing maximal statin regimen or randomized to a maximal statin regimen. We anticipate that patients who are randomized to atorvastatin 10mg will experience more eCD and dCD than patients randomized to atorvastatin 80mg. We anticipate that simvastatin will provide more neuroprotection than atorvastatin or rosuvastatin measured by lower incidences of eCD and dCD at comparable statin doses for lipid lowering. Conclusions regarding the arm of statin naïve patients may be somewhat underpowered depending on the number of statin naïve patients we see. Results will be interpreted with according caution. We expect the randomized nature of the trial to randomly distribute patients with regard to age, diabetes, educational level, pIQ, MCI, perioperative delirium and ApoE-e4, but now have accounted for these in the statistical plan and also include long-term outcomes out to a year as well. Post-hoc assessments will also examine whether the primary findings regarding eCD and dCD apply to subgroups of patients but these analyses will be viewed as hypothesis generating only.

9.2 Sample Size and Randomization

Power Analysis

All of the aims will use logistic regression with presence of eCD as the response variable as the primary statistical analysis. A separate independent analysis for dCD will also be performed. Power calculations used data simulations (1000 simulations for each) with power=0.8, $\alpha=0.05$, and expected rates of eCD

based on existing preliminary data. For the comparison between subjects in arm 1 with a maximal dose (N=225) and those in arm 2 beginning with a sub-maximal dose and increasing to a maximal dose (N=338), the estimated minimum detectable effect size corresponds to a 65% reduction in eCD in the former cohort vs. the latter. For the comparison in between subjects in arm 2 beginning with a sub-maximal dose and increasing to a maximal dose (N=338) and those staying at the sub-maximal dose (N=337), the estimated minimum detectable effect size corresponds to a 46.7% reduction in eCD in the former cohort vs. the latter. For the comparison between subjects in arm 3 with 80 mg of atorvastatin (N=50) and those with 10 mg of atorvastatin (N=338), the estimated minimum detectable effect size corresponds to a 91.3% reduction in eCD in the former cohort vs. the latter.

Rationale for Sample Sizes

As per the power analysis above, the 1000 targeted patient enrollment is reasonable considering the aims of this study. We anticipate approximately 350 patients will be scheduled for CEA per year from the six participating institutions (Columbia-Presbyterian, St. Luke's Roosevelt, Cornell University, Valley Hospital, Montefiore Medical Center, and Buffalo Medical Center). Approximately 80% are anticipated to be asymptomatic, leaving 280 per year.

Expecting an approximate 75% recruitment rate, 210 eligible asymptomatic patients will be enrolled each year from the six sites. Over five years, this rate allows for 1000±50 patients to be enrolled. Based on our previous R01 grant, we estimate that a) 225 patients will already be on a pre-existing maximal statin regimen of simvastatin, atorvastatin, or rosuvastatin, b) 675 patients will be on a sub-maximal statin regimen of simvastatin, atorvastatin, or rosuvastatin, and c) 100 patients will be on no pre-existing statin regimen.

For the comparison between subjects in arm 1 with a maximal dose (N=225) and those in arm 2 beginning with a sub-maximal dose and increasing to a maximal dose (N=338), the estimated minimum detectable effect size corresponds to a 65% reduction in eCD in the former cohort vs. the latter. For the comparison in between subjects in arm 2 beginning with a sub-maximal dose and increasing to a maximal dose (N=338) and those staying at the submaximal dose (N=337), the estimated minimum detectable effect size corresponds to a 46.7% reduction in eCD in the former cohort vs. the latter. For the comparison between subjects in arm 3 with 80 mg of atorvastatin (N=50) and those with 10 mg of atorvastatin (N=338), the estimated minimum detectable effect size corresponds to a 91.3% reduction in eCD in the former cohort vs. the latter.

9.2.1 Treatment Assignment Procedures

The randomization design will be stratified by center, previous use of statin and in random blocks of 4 and 6. The randomization process will be supported by the Statistical Analysis Center (SAC) at the Mailman School of Public Health at Columbia University. SAC will provide a central secure web-based randomization data system. All trials supported by the SAC employ central randomization that takes place in real-time. In other words, the patient's treatment assignment is made at the moment of randomization, based on probabilities calculated according to the randomization scheme, and communicated to the recruiting site via a central source (i.e. a secure web site).

- Patients on maximum dose of one of the three statins will be maintained on that dose (ARM 1). This arm will contain 225 participants.

- Those patients on submaximal doses of the 3 study statins will be randomized to their current dose plus placebo or their current dose plus the additional milligrams necessary to bring to raise them to the maximal daily dose of simvastatin (40 mg) or atorvastatin (80 mg) or rosuvastatin (20 mg) depending on which statin they are already on, (ARM 2). There will be 337 participants maintained at their current dose and 338 raised to the maximum dose of their statins.

- If patients are statin naïve, then they will be randomized to either atorvastatin 10 mg or 80 mg daily (ARM 3). ARM 3 will be have 50 participants in each arm.

The randomization will be performed automatically by the web-based data system. No one will have access to unblinded treatment information on a regular basis other than the packaging pharmacy. All handling of study medication will take place using blinded bottle codes. It is not expected that serious adverse events will require revelation of treatment assignment, but the study web site will provide for online unblinding in emergencies. Revelation of treatment assignment will be available only to authorized users, who will be required to provide a clinical justification for unblinding. Each case of unblinding will be addressed by study personnel to ensure access to unblinded treatment assignment information is limited, and that such incidents are limited to circumstances where it is necessary for the health of the patient.

9.3 Interim analyses and Stopping Rules

The objectives of interim monitoring are to 1) monitor for evidence of toxicity, 2) track participant accrual rates, 3) track study participant adherence to the prescribed medication, and to 4) monitor the primary outcome for early evidence of efficacy, harm or futility. To accomplish this, summaries of data quality, accrual, adherence, and distribution of baseline factors, toxicity, study endpoints and other analyses as requested will be prepared for review by the Data Safety Monitoring Committee (DSMB).
The primary outcome of the trial, changes in test scores between enrollment and the morning of surgery (baseline), Day 1 post CEA (12-25 h post-op) (eCD) and Day 30 +/- 5 days after CEA or Day of PO clinical visit (dCD), is the basis for formal interim analysis plan that follows.

One interim analysis and one final analysis are planned for ARM 2 of the trial, for a total of 2 analyses. These analyses will be performed when 0.66 and 1.0 fraction of the total number of participants in ARM 2 will have finished the approximately 30 day post-CEA assessment. Since ARM 2 will have a maximum sample size of 675 participants, we will have approximately 446 participants accrued and evaluated at approximately 30 days post-surgery at the time of the interim analysis.

We will use the Lan-DeMets approach, implementing an O'Brien-Fleming-type spending function that allots most of the type I error to the final look [Lan, K.K.G.; DeMets, D.L. Discrete sequential boundaries for clinical trials. Biometrika 1983, 70(3), 659-663]. The resulting alpha critical values to be used for each analysis are 0.0116 at the interim analysis, 0.05 at the final analysis.

The judgment by the DSMB and the NIA as to whether to continue the study will be based on the results of the interim analyses of the study's primary endpoint as well as other factors such as toxicity, adherence, secondary outcome measures, and development of any new external scientific evidence with regard to treatment with statins.

(The final study analysis of all arms (1-3) will be completed upon the conclusion of the study.)

9.4 Outcomes

We have defined our primary outcome on Z-scores based on the mean and standard deviation of cognitive testing change in scores of a surgical reference group before and after surgery (12-25h and 30 days postop/ Day of PO clinical visit).

The cognitive testing has been divided by cognitive domains and the patients are considered to have postoperative early cognitive dysfunction (eCD) based on two criteria to account for both focal and global/hemispheric deficits. Consequently anyone with:

(a) ≥2SD worse than reference group in two or more cognitive domains or
(b) ≥1.5SD worse than the reference group in all cognitive domains tested will be considered a primary outcome.

If the subjects experience stroke or TIA peri-operatively, they will be considered as having reached a secondary OUTCOME in the study.

9.5 Data Analyses

For all analyses, the primary outcome will be derived from changes in test scores between the day before or morning of surgery (baseline) and the final time point Day 1 post CEA (12-25h post-op). The intention to treat principle will be used for all analyses. All of the analyses will be performed in two general ways. 1) Significant neurocognitive change for both CEA will be defined compared to an appropriate reference group frequency matched for age and type of anesthetic or sedation. Significant eCD will be defined as performance: (1) 2SD worse performance in two or more cognitive domains or (2) 1.5SD worse performance in all cognitive domains.

The following data will be kept for patients having CEA: demographic and risk factor variables (age, gender, race, a history of hypertension, diabetes, level of glycosylated hemoglobin, previous myocardial infarction, and previous CEA), degree of carotid stenosis, all additional cerebrovascular workup (i.e. Intracranial MRA, SPECT scanning, angiography, etc.), laboratory values, all standing medication names, doses, and durations, and all neurologic and neuropsychological scores. In general, for the continuous variables, a two-sample Student's t-test will be used for comparing means between the two groups, patients with eCD and those without eCD. Non-normally distributed variables will be transformed to improve distributional characteristics. In particular, neuropsychometric test scores will be subjected to a square root transform that yields values that are approximately normally distributed and provide analytic results using parametric tests that are similar to those obtained by non-parametric analysis of the untransformed values. Non-parametric techniques will be used for any variables for which suitable transformations cannot be found. Dichotomous variables will be analyzed using a 2 test. Multiple linear and logistic regression models will be used to adjust for the risk factors that are out of balance ($p < 0.10$)

between groups. Logistic regression analysis will be used to determine whether any demographic or risk factors other than CEA significantly affects outcome. Post-operative pain >4 adversely effects performance, for this reason, change scores for each test will be obtained using the patients in the reference group. The cutoff value for pain scores is 4. When data are missing completely at random (MCAR), i.e. when the probability that an outcome is missing does not depend on any outcomes, statistical inference based on completely observed data is valid. If data are missing at random (MAR), i.e. when the probability that an outcome is missing depends on the observed outcomes (such as observed outcome at baseline), inference based on complete data is not valid. All of the aims will use logistic regression with presence of eCD as the response variable as the primary statistical analysis. No patients will be enrolled for reference group study. We have previously collected data for the reference group. Z-scores in the past have been generated based on this surgical reference group's performance to account for practice effect, trauma of surgery, general anesthesia, and the overnight hospital stay experience. The surgical reference group was composed of age- and sex-matched patients 60 years of age undergoing lumbar level laminectomy or microdiscectomy on 2 levels without fusion, no tumor/cyst, or blood loss necessitating transfusion. These patients experience similar surgical and anesthetic times as well as a similar general anesthetic. The mean difference score of the surgical reference group has typically been subtracted from the difference score for the CEA patient and then divided by the standard deviation (SD) of the surgical reference group ([Difference CEA – Mean Difference Reference]/SD Reference) to generate Z-scores.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms (eCRFs)

The Central Coordinating Committee has created the study worksheets that have been transformed into electronic case report forms (eCRFs) based on the current objectives and hypothesis described in this protocol. The eCRFs must be printed from the study database and submitted for individual site IRB approval.

The data sources collected for the eCRFs (including study worksheets) must be kept secure in individual subject binders, reviewed and signed by site Principal Investigator, entered into the study database(eCRFs), scanned/uploaded to the study database, (see 10.2 Data Management) and made available for study monitoring by the Sponsor and/or corresponding regulatory agencies.

10.2 Data Management

All patient information will be coded. Coding involves the replacement of direct patient identifier from data sets with a linking code by which the data remain identifiable. For linking purposes, we use study specific codes, rather than medical record numbers, social security numbers, or other easily decoded combinations of initials and birth dates. Access to the linking files will be restricted to authorized study personnel and regulatory agencies.

The data will be collected and stored on an encrypted, password-protected multi-user system created and maintained by the Statistical Analysis Center (SAC) at the Mailman School of Public Health at Columbia University. The data management infrastructure created for the trial, and will be responsible for creating

the database where to store and upload the eCRF data and for reporting results to the Data & Safety Monitoring Board (DSMB). All subject research data will be coded with subject ID number. All laboratory and clinical information obtained from this research will be maintained in locked offices and will be accessible only to the main investigators of this project. The electronic database used during the trial is secure and password protected. This web-based system, developed at the SAC, ensures confidentiality and data integrity through the use of a secure server; password protected access, and encrypted data. Specifically, the browser-based front end of the system uses 128 bit Secure Sockets Layer (SSL) technology to ensure that users are properly authenticated to the server and all data exchange occurs in an encrypted fashion. High level of security will be actively maintained. Subjects' information will not be discussed in any form in the presence of other subjects or non-study personnel. Subjects will only be referred to by their subject unique ID number in all study documents. Specimens will be coded using the subject ID number only. For every research participant, relevant clinical information is documented on electronic case report forms and source documents and stored in the secure electronic database or in a double locked area. All study records will be maintained for 7 years. The unique study ID will be generated by the data management system (via the web interface) when a patient enrolls in the study. PHI will be strictly limited to those items essential to the operation of the trial and the specified analyses (dates of diagnosis, dates of treatment, etc.) Clinicians and other personnel involved with patient recruitment, treatment and follow-up will obviously have access to both patient identifiers and the trial data, including the subject ID. Typically, a subject binder/folder is created for each participant, which contains source documents and other information collected for the trial, including subject ID. It is the responsibility of the clinical team to store these folders in a secure place and ensure that they are available only to authorized personnel. Trial personnel not involved in patient contact, including data staff and statisticians, will not have access to identifying information. All trial data, including the subject ID, will be stored on the SAC's secure database servers. The SAC's data systems have been approved for the collection of clinical research data by CUMC IT Security.

In addition, the data center (SAC) will design the database to evaluate, validate and monitor trial data as part of an ongoing process. The initial validation takes place as early as possible in the data collection process, including real-time validation for range checks, limits on categorical variable entry, checks for completion and consistency, etc. Further error checking, including validation for completeness, is performed when data is posted. Since some errors (in changes over time, and consistency between different forms or scales) cannot be detected on initial data entry, validation checks are performed daily. All data errors and queries are processed promptly. Regular reports to investigators and coordinating centers on accrued data identify unusual or unexpected data points and request that they be confirmed or corrected.

10.3 Quality Assurance

10.3.1 Training

During the site initiation visit (SIV), members of the CCC will train the site's study members on the study protocol and procedures. Dr. Connolly and/or his representative will also visit each study site, virtually or inperson, weekly for the first 6 months after their site initiation visit (SIV) and then monthly to insure protocol procedures are followed clearly, consistently, and while keeping patient safety forefront. There will also be monthly conference calls with all of the sites to make sure that any concerns or questions are addressed and shared with the whole study team. Further visits will be on an as needed basis if a site

shows a pattern of study violations and/or have procedural errors that show the need to receive booster training or further study monitoring.

In addition, the study team's neuropsychologist, Dr. Stern and/or Dr. Caccappolo, will conduct the initial training for the neuropsychometric measures for study staff that will administer these tests (i.e. coordinators). They will test and certify the study members and additional training will be provided via conference/video calls and on-site visits as needed.

The initial protocol training will be supplemented by teaching moments provided during the Monthly Conference Call with all study sites.

10.3.2 Protocol Deviations

Any study protocol deviation/violation must be documented in the subject binder, submitted to site's IRB (as per their rules and regulations) and the CCC team for review (see Appendix V). Some of the protocol deviations will also provide a metric for identifying sites that may need further training.

10.3.3 Monitoring

All study sites must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. The Central Coordinating Center Monitors (Dr. E. S. Connolly, Dr. E.J. Heyer and Rebeca Aragón García) will visit the sites at regular intervals during the study and after the study has completed, as appropriate. During these visits, study worksheets, eCRFs/database entry and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

In addition, because it is required that all of the subject's case report form data not just be entered but also uploaded to the study database in a timely fashion along with any pertinent source documentation, the uploaded documents (i.e. worksheets, admission notes, etc.) will be reviewed by the CCC Multisite Coordinator, Rebeca Aragón García, against the data entered in the study database to assure for completeness and accuracy of the data in real time. Any queries or concerns will be forwarded to the CCC Principal Investigator, Dr. E. Sander Connolly, and as formal queries to each site's coordinator with copy to the corresponding site's Principal Investigator.

Once the subject participant is admitted for the CEA procedure, a de-identified copy of the hospital admission and discharge notes will also be uploaded to the study database and the CCC Multisite Coordinator will review these for adverse events.

Any queries which arise from receipt of the worksheets, eCRFs or hospital notes will allow for continuous data and safety monitoring in real time and not just in preparation for DSMB meetings.

The prevalent errors/omissions/queries found through these monitoring reviews will also be addressed generically during our monthly multi-site team calls as part of our continuing study personnel training.

The payment for subject enrollment and participation will be linked to the timely entering of subject data after each study visit and submission of corresponding source documentation to the study database. This will promote our timely ability to continuously monitor each site for safety, completeness and accuracy of the study data.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents (Appendix II) and any subsequent modifications will be reviewed and approved by the IRB at Columbia University Medical Center who is responsible for oversight of the study at CUMC. They will also review the individual IRB approval for the other sites that are part of this multisite study.

11.2 Informed Consent Forms

The potential subject participant will be identified by the surgical/clinical team via the planned consultation to discuss undergoing a carotid endarterectomy within. The potential subject participant will be informed about the study, once the potential subject expresses interest in knowing more about the study, the study coordinator and/or doctor will approach the individual and give them the opportunity to participate in this clinical trial. A copy of the consent form will be provided to them, in English or Spanish (whichever is their preferred language), and then the study personnel will facilitate the understanding of the study purpose, procedures and timeline of participation to allow them to make an informed decision about whether or not to participate in this clinical investigation. The information provided will include:

- the purpose and rational of the study
- the clarification that this is an experimental process and not part of the current standard of care
- what their participation process and procedures will be during the study
- the duration of the study participation
- the expected risks and benefits
- the number of study participants expected and approved at the site and at other sites participating in this study
- understanding that they will not incur any additional costs to participate in this study
- clarification of whom they should contact if they experience any adverse reactions and also if they feel they have been harmed in any way due to their study participation
- discuss how confidentiality will be addressed and protected

- details of when a subject's participation may be screened out or considered an OUTCOME by the study investigator without regard to the subject's consent ○ If the MoCA (≤25 points) and the AD8 (≥2 points) - screen failure
    - If baseline laboratory results indicate existing hepatic or muscle abnormalities that would preclude potentially increasing or adding statins to their current medical regimen (CK >5x ULN and LFTs > 2X ULN) – screen failure ○ If the subjects experience stroke or TIA peri-operatively, they will be considered as having reached an OUTCOME in the study.
- explanation that participation is voluntary and that refusal to participate will not create any loss of benefits to which they would have otherwise received:
    - Including the clarification that they can discontinue their participation at any time without affecting their clinical treatment or any other right or benefits to which he/she is otherwise entitled. ○ Details of procedures expected for an orderly termination of the study participation by the individual

Once the study has been explained, the potential subject participants will be asked if they have any questions and given adequate amount of time to ask questions and/or discuss the study with family and friends to decide whether they should participate.
This process will allow sufficient opportunity for the potential participants to provide voluntary, informed consent to participate (or not) and know that they can withdraw at any time without any undue influence or coercion. All participants who consent will be given a copy of the informed consent form for their records and the original consent form will be filed in their study subject binder.

Subjects must provide individual informed consent before any screening tests are performed. When a subject signs the Informed Consent Form (ICF), the subject is considered consented, but not enrolled until they pass the complete screening process for MCI and hepatic/muscle abnormalities (see 6.2.1).Then and only then will they be assigned to a study arm.

In a separate consent form, the participants will be given the opportunity to allow the surplus blood samples obtained from the study to be used in Future Research. This is not required to participate in the main study. If they agree, their surplus samples will be stored at CUMC for future research use. If they do not consent to Future Research, any remaining samples will be destroyed after the study analysis have been completed.

11.3 Participant Confidentiality

All patient information will be coded. Coding involves the replacement of direct patient identifier from data sets with a linking code by which the data remain identifiable. For linking purposes, we use study specific codes, rather than medical record numbers, social security numbers, or other easily decoded combinations of initials and birth dates. The STANCE Subject Code List (Appendix VIII) will be recorded and maintain the subject code-name linking log for their site. Access to the linking files will be restricted to authorized personnel, which will include:

- The National Institute of Health/National Institute of Aging (NIH/NIA, the funding sponsor of this study)
- Institutional Review Board (IRB)
- Members of the study research team at Columbia University Medical Center and members of the study research team at the local sites for participants of the corresponding sites (for safety monitoring purposes)
- Columbia University medical staff, and New York Presbyterian Hospital staff providing treatment for CUMC participants and the local sites' medical staff for participants from the corresponding sites, if necessary
- The Office of Human Research Protections ('OHRP')
- The U.S. Food and Drug Administration (FDA)
- Other regulatory agencies

The data will be collected and stored on an encrypted, password-protected multi-user system. The Statistical Analysis Center (SAC) at the Mailman School of Public Health at Columbia University will create the data management infrastructure for the trial, and will be responsible for creating the electronic database to enter study data and for reporting results to the Data & Safety Monitoring Board (DSMB). All subject research data will be coded with subject ID number. All laboratory and clinical information obtained from this research will be maintained in locked offices and will be accessible only to the main investigators of this project. The electronic database used during the trial is secure and password protected. This webbased system, developed at the SAC, ensures confidentiality and data integrity through the use of a secure server; password protected access, and encrypted data. Specifically, the browser-based front end of the system uses 128 bit Secure Sockets Layer (SSL) technology to ensure that users are properly authenticated to the server and all data exchange occurs in an encrypted fashion. High level of security will be actively maintained. Subjects' information will not be discussed in any form in the presence of other subjects or non-study personnel. Subjects will only be referred to by their subject unique ID number in all study documents. Specimens will be coded using the subject ID number only. For every research participant, relevant clinical information is documented on electronic case report forms and source documents and stored in the secure electronic database or in a double locked area. All study records will be maintained for 7 years. The unique study ID will be generated by the data management system (via the web interface) when a patient enrolls in the study. PHI will be strictly limited to those items essential to the operation of the trial and the specified analyses (dates of diagnosis, dates of treatment, etc.) Clinicians and other personnel involved with patient recruitment, treatment and follow-up will obviously have access to both patient identifiers and the trial data, including the subject ID. Typically, a subject binder/folder is created for each participant, which contains source documents and other information collected for the trial, including subject ID. It is the responsibility of the clinical team to store these folders in a secure place and ensure that they are available only to authorized personnel. Trial personnel not involved in patient contact, including data staff and statisticians, will not have access to identifying information. All trial data, including the subject ID, will be stored on the SAC's secure database servers. The SAC's data systems have been approved for the collection of clinical research data by CUMC IT Security.

11.3.1 Protection while data being collected

Before the data is coded, the subject binders will be kept in a locked cabinet within a locked office to which only the coordinator and approved study personnel have the keys. In addition, any subject contact

information/PHI, if kept digitally, will be kept on an encrypted and password protected computer managed by the study coordinator.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

Unless altered by the DSMB, the end of study will be when the last subject completes his/her last study visit (approximately one year from their CEA) or final collection of data.

12 ETHICAL CONSIDERATIONS

Investigators must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations. The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

12.1 DECLARATION OF HELSINKI

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

12.2 ETHICS/IRB COMMITTEE

All site Investigators must obtain IRB approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Site Investigators make any changes to the ICF, the Sponsor must approve the changes before the ICF is submitted to their IRB. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant IRB and the Sponsor. It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.
The Sponsor must receive a letter documenting IRB approval for each site, which specifically identifies the protocol and ICF, prior to the initiation of the study activities. Protocol amendments will be subject to the same requirements as the original protocol.
A progress report must be submitted to the IRB at required intervals and not less than annually.
At the completion or termination of the study, the investigational site must submit a close-out letter to the IRB and provide proof to Sponsor.

12.3 SUBJECT INFORMATION AND CONSENT

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject in accordance with local practice and regulations, and authorization to enroll is provided according to the site's local IRB/EC guidelines and requirements for acute clinical trials or by another process compliant with applicable national laws and regulations and IRB/EC requirements. The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject or the subject's representative and according to local IRB/EC guidelines or by another process compliant with applicable national laws and regulations and IRB/EC requirements.

A copy of the ICF, signed and dated by the subject according to local IRB/EC must be given to the subject. Each consent form should contain an authorization allowing the Principal Investigator(s) and Sponsor to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law. The signed consent form will be retained with the study records.

12.4 SUBJECT DATA PROTECTION

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization - HIPAA). The subject will not be identified by name in the study database or in any study reports, and these reports will be used for research purposes only. The Sponsor, its partners and designees, IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential. In addition to using SAC which has been certified as a secure website, we will keep subject contact information and any other subject PHI in a locked cabinet within a locked office and in an encrypted and password protected CUMC desktop.

12.5 COMPENSATION FOR INJURY

In the event of an injury resulting from a subject's participation in this study, you should seek appropriate medical care and inform the study doctor. In the event of an emergency you should go to an emergency room.

If you are injured or harmed as a result of participating in the study and receive medical care through the New York-Presbyterian Hospital (NYPH), a Columbia doctor, or any other health provider, you will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance.

Columbia University and New York-Presbyterian Hospital (NYPH) are not offering to provide you the drug/device after the termination of the study or to pay you for pain, worry, lost income, the cost of your medical care or non-medical care costs that might occur as a result of your taking part in this study. However, you do not waive any of your legal rights in signing this form.

12.6 CONFLICT OF INTEREST

The Investigators should address any potential conflicts of interest (e.g., financial interest in

Study drug manufacturer, distributor) with the subject before the subject makes a decision to participate in the study.

12.7. REGISTRATION OF STUDY AND DISCLOSURE OF STUDY RESULTS

The Sponsor has registered the study and will register the post study results regardless of outcome on www.clinicaltrials.gov, a publicly accessible website, in accordance with the applicable laws and regulations.

13 COMMITTEES

The Central Coordinating Center Executive Committee will meet via conference call/video once per month to discuss the progress of the study. The members are:

- Dr. Connolly, MD, FACS • Dr. Heyer, MD, Ph.D
- Yaakov Stern, Ph.D.
- Elise Caccappolo, Ph.D.
- Richard Buchsbaum
- Emilia Bagiella, Ph.D
- Brandon Christophe (multisite coordinator)
- Rebeca Aragón García, B.S.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

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16 SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Statin Neuroprotection and Carotid Endarterectomy: Safety, Feasibility and Outcomes" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

APPENDICES:

Appendix I: Schedule of Assessments

Procedure	STUDY DRUG TREATMENT PHASE				D2-D18	POST CEA FOLLOW UP PHASE					
	Baseline Dose 1	*Day 3** +/- 1d*	*Day 7** +/- 1d*	*Day 10** +/- 1d*	*CEA DAY*	*Day 1* (12-25 hours)*	*Day 7 (+/-3d)*	*Day 14 (+/-3d)*	*Day 21 (+/-3d)*	*Day 30 (+/-5d or PO Visit)*	*Day 365 (+/-30d)*
Informed Consent	X										
Randomization	X										
Study Drug given to subject along with # of capsules to take per dose in the Study Medication Compliance form	X										
Concomitant Medications	X	Any other time the subject states he/she has had a change in medication									
Vitals (height/weight/BP from chart)	X				X	X				X	
Demographics	X										
Education	X										
Medical History (chart/interview)	X	Any other time the subject states he/she has had a change in medical status									
Tobacco Use	X										
Substance Use	X										
CAM	X				X	X				X	

MoCA/AD8 Screening	X										
AMNART or WAT	X										
Neuropsychological Tests (NPT)	X				X	X				X	
TICS-M		X									X
BLESSED ADL		X									X
Safety Questionnaire (CALL)		X	X	X			X	X	X		X
Safety Questionnaire (IN-PERSON)					X	X				X	
Pill Count					X						
CEA Details					X						
Neurological Exam post CEA (chart)					SOC	SOC					
EKG (from chart)	SOC				SOC						
Shipped Lab: ApoE (1x only)	At enrollment or during hospitalization(shipped as ambient blood Monday-Thursday)										
Site Lab: Comprehensive Metabolic Panel	X				X					X	
Site Lab: CK	X				X					X	
Site Lab: Lipid Profile	X				X					X	
Site Lab: CBC with differential	X				X					X	
Site Lab: ESR (Sedimentation Rate)	X				X					X	
Site Lab: C-Reactive Protein	X				X					X	
Site Lab: Urine Pregnancy or Beta-HCG[A]	SOC as part of pre-op labs[A]										
Assess for Adverse Events (AEs)		X	X	X	X	X	X	X	X	X	X
Study Completion/Discontinuation	At the end of the subject's participation										

*After surgery ends ** follow-up calls before CEA will be conducted only if not preceded by CEA [A] Urine Pregnancy test or Beta-HCG will be measured only in women of child-bearing age. SOC: Standard of Care

Appendix II: Study Screening Log

STANCE Screening Log

Site: ____________________________

Investigator: ____________________________

Screening Number	Gender	Screening Date	Screening Status (use codes below)	Consent Obtained	Enrolled	IF NOT ELIGIBLE, indicate reason(s) from codes below	Study ID # (if Enrolled) Site-Subject Ex. 01-001	Date Enrolled
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy
☐☐☐☐	☐ M ☐ F	/ / mm/dd/yyyy	☐ 1 ☐ 2 ☐ 3 ☐ 4 ________	☐ Yes ☐ No	☐ Yes ☐ No	☐ 1 ☐ 2 ☐ 3 ________		/ / mm/dd/yyyy

Screen Status Codes:

1-Eligible
2-Eligible, declined participation
3-Not Eligible
4- Other, specify in space provided

If not eligible, Reason:

1-Inclusion # (specify)
2-Exclusion # (specify)
3-Other (specify)

StANCE Screening Log Version 1 – December, 2016 *Page 1 of _____*

- **Appendix III: Study Drug Accountability Log**

PAGE NO.

STANCE Trial –
Study Drug Accountability Record

Name of Institution:	Protocol Number: CUMC AAAM2407 /
Drug Name: (atorvastatin, simvastatin, rosuvastatin v. placebo)	Dose Form and Strength: capsules atorvastatin 80 mg vs. placebo; simvastatin 40 mg vs. placebo; rosuvastatin 20 mg vs placebo; atorvastatin 10 mg vs. atorvastatin 80 mg
Protocol Title: Statin Neuroprotection and Carotid Endarterectomy: Safety, Feasibility and Outcome (STANCE)	Dispensing Area: Research Pharmacy
Investigator Name:	Investigator or site Number

Line No.	Date	Participant's ID No.	ARM 2 or 3	Quantity Dispensed Or Received (128-128-64 capsules)	Bottle Number	Rcpt / Disp Recorded By		Date Returned	Qty Return (capsules)	Qty Destroyed (capsules)	Date Destroyed	Recorder's Initials
1.												
2.												
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17.												

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- **Appendix IV: Protocol Deviation Log (for subject binders)**

STANCE Trial Protocol Deviations Log

Site Number: _____	Visit Date: __ __ / __ __ / 2 0 __ __ (m m d d y y y y)
Pt_ID: _____	

Did this participant have any protocol deviations? ☐ Yes ☐ No

Description of Protocol Deviation:	Deviation Category*	Deviation Code**	Date Deviation Occurred: (mm/dd/yyyy)	Date IRB Notified (if applicable):	Principal Investigator's Signature	Date Signed (mm/dd/yyyy)

STANCE Protocol Deviations Page ____ of _____ Version 1.0

***DEVIATION CATEGORIES:**
A. Safety
B. Informed Consent
C. Eligibility
D. Protocol implementation
E. Other, specify in log

**DEVIATION CODES: Numbers listed by the sample protocol deviations

Safety (Category A)
1. Not reporting an SAE within 24 hours
2. Laboratory tests not done
3. AE/SAE is not reported to IRB
4. Other, specify in log

Informed Consent (Category B)
5. Failure to obtain informed consent
6. Consent form used was not current IRB-approved version
7. Consent form does not include updates or information required by IRB
8. Consent form missing
9. Consent form not signed and dated by participant
10. Consent form does not contain all required signatures
11. Other, specify in log

Eligibility (Category C)
12. Participant did not meet eligibility criterion
13. Randomization of an ineligible participant
14. Participant randomized prior to completing Baseline Assessment, etc.
15. Randomization and/or treatment of participant prior to IRB approval of protocol
16. Other, specify in log

Protocol implementation (Category D)
17. Failure to keep IRB approval up to date

18. Participant receives wrong treatment
19. Participant seen outside visit window
20. Use of unallowable concomitant treatments
21. Prescribed dosing outside protocol guidelines
22. Missed assessment
23. Missed visit
24. Other, specify in log

- **Appendix V: Primary Medical Doctor Letter:**

Statin Neuroprotection and Carotid Endarterectomy: Safety, Feasibility and Outcomes" (STANCE)
Columbia University Medical Center
Department of Neurological Surgery
P&S 630 West 168 Street, 5-462
New York, New York 10032

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

[date]

RE: [name]

Dear Doctor [name of PMD]: DOB: [DOB]

This letter is to inform you that your patient has elected to take part in a research study entitled, Statin Neuroprotection and Carotid Endarterectomy: Safety, Feasibility and Outcomes" (STANCE). The study is sponsored by the National Institutes of Aging (NCT02850081) and is being conducted at multiple sites in the US including Columbia University Medical Center.

This is a phase III study for asymptomatic patients with carotid artery stenosis designed to assess if maximizing statin doses for approximately two weeks (12-18 days) prior to carotid endarterectomy (CEA) is neuroprotective. Patients who are already on the maximal statin dose of either atorvastatin (80 mg), simvastatin (40 mg) or rosuvastatin (20 mg) will remain on their current doses and will be part of our observational arm. The patients that are currently on sub-maximal daily doses of the previously mentioned statins will be randomized to either 1) their current dose plus placebo or 2) their current dose plus the necessary milligrams needed to bring them to the FDA approved maximal dose per day for their corresponding statin. Those patients who are statin naïve, 30 days prior to enrollment, will be randomized to daily doses of either 1) 10 mg of atorvastatin or 2) 80 mg of atorvastatin.

We will stay in contact with Mr./Mrs. _____ via phone calls prior to the CEA to assure study drug compliance and safety. We will also assess him/her prior to the CEA, 12-25 hours post-CEA, and during their post-operative clinical visit (approximately at 30 days post-CEA) for early cognitive dysfunction (eCD). The final follow-up phone call will be one year after their CEA procedure.

We have attached a copy of your patient's study consent form. We ask that you not alter your patient's assigned statin dose unless it is clinically necessary. If you do change their dose prior to their CEA, please let us know. After their CEA, Mr./Mrs._____ will be prescribed statins as per the standard of care for post-CEA patients by their treating physician and will not receive any further study drugs.

If you have questions, please do not hesitate to contact our Study Clinical Coordinator, [name of coordinator] at [contact number] or one of us.

Sincerely yours,

[Contact Information for Principal Investigator at Site]

- **Appendix VI: Delegation of Authority Log**

STANCE TRIAL

SITE PERSONNEL SIGNATURES &DELEGATED RESPONSIBILITIES LOG

Study Site:

NAME (PRINT OR TYPE)	SIGNATURE	INITIALS	STUDY ROLE (i.e. Site PI, Study physician, sub-investigators, Study Coordinator, Research Pharmacy, etc)	DELEGATED RESPONSIBILITIES* (list all that apply A-I)	DATES (involved in STUDY) (mm/dd/yyyy)	PI Initials/Date (mm/dd/yyyy)
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	
					Start: ____ Stop: ____	

Delegated Responsibilities:

A = Make eligibility decisions B = Obtain informed consent C = Rx Study Drug from Research Pharmacy
D = CRF completion/correction E = Baseline/follow-up evaluations F = Evaluate and monitor for adverse events
G = Pick up Study Drug Res Pharmacy H = Query resolution I = Maintain Regulatory Binder
J = Train Study Sites in NP measures K = Monitor Study Sites L = Research Pharmacy at Site M=Other: _____

Version date: 1/20/2017 Page ___ of ___

Appendix VII: Subject Code List

STANCE Trial Subject Code List

Investigator Name:	Protocol: Statin Neuroprotection and Carotid Endarterectomy: Safety, Feasibility and Outcomes" (STANCE)	Site Number:

Subject ID	Subject Name	Subject Initials

- This log is for site use only, as it contains protected health information (PHI). Protect the confidentiality of this log accordingly.
- Number each page and maintain this log securely and separate from research records.

STANCE _ Code-Subject List

Page _____ of _____

Check if final page of log: ☐