0 RESPONSE TO REVIEWERS

This grant is a revision of application number 1 R01 NS062835-01, entitled "Platelet-Oriented Inhibition in New TIA (POINT) Trial." We appreciate the many positive comments from the reviewers. The call for a large-scale trial of acute stroke prevention after TIA has grown progressively louder [1-7] and we have addressed the remaining constructive suggestions of the reviewers. Changes in the revised application, demarcated with a line in the right-hand margin, include:

1. We have solidified involvement of the NETT Network, which will contribute 69 of its sites.
2. We have identified all 150 sites interested in participating, with another 80 ready and committed.
3. Additional data from FASTER and EXPRESS clarifies that the current trial is feasible and important.
4. The findings of PRoFESS clarify that dipyridamole need not have a role in the trial.
5. The $ABCD^2$ score is now used as an entry criterion, with a reduction in necessary sample size.
6. Data management has been moved to the NETT Statistics and Data Management Center (SDMC) at the Medical University of South Carolina to reduce potential conflicts of interest.
7. The roles of the steering and executive committees have been enhanced.
8. Cost-effectiveness and cognitive outcomes have been dropped.
9. The definition of vascular death has been clarified and hemorrhagic stroke has been dropped from the primary composite outcome measure, while hemorrhagic events have been more clearly defined.
10. Sample size calculations now include consideration of crossovers and the planned survival analysis, and account for possibly lower event rates due to better control of risk factors.
11. The clopidogrel load will be 600 mg (instead of 300) and drug will be restarted (without a load) after CEA.
12. The plan for recruitment of minorities is explicitly defined, and a data monitoring plan is included.
13. A detailed Statistical Analysis Plan, Data Management Plan, and CRFs have been added.
14. The budget now explicitly includes the CRC and is more carefully justified.
15. Dr. Easton is moving to San Francisco and his role in the trial is clearly delineated.
16. Specific issues raised by individual reviewers have been addressed in the response below and in the grant.

<u>In response to the summary of discussion, we note the following:</u>

0.1. Ability of Dr. Easton to manage from Rhode Island the day-to-day operations of the UCSF center in Dr. Johnston's absence. Dr. Easton is moving to San Francisco and will be joining Dr. Johnston at UCSF, where he will have a faculty position. Without the responsibility of chairing a department, he will have ample time to devote to the trial. His role is now clearly defined (Section 4.3, Leadership Plan).

0.2. Ability to meet recruitment goals by relying solely on the CRC for recruitment given the somewhat ambitious timeline. Start-up time has increased while sample size has increased and number of active sites kept constant (Section 4.2), so target recruitment rates have decreased to 0.6 subjects/site/month. Also, we have now identified 230 total sites that are interested in participating: 75 original sites selected based on validated recruitment metrics, 16 NETT hubs and 53 of their spokes (with some overlap with the original target sites), and an additional 56 sites identified solely through the CRC. The original sites were carefully selected based on validated metrics, which we have now extended to the other sites (Section 3.6). The NETT sites were rigorously vetted through the R01 mechanism in order to be a part of the Network, and therefore, they have the infrastructure to do clinical trials and will be productive. The CRC sites are less proven but our data suggest several are likely to be excellent recruiters. For the trial, we plan to invite 200 sites initially, with an estimated 175 contracts (NETT spokes do not require separate contracts), of which we assume 150 will result in productive sites. The additional 30 sites will remain on call to replace poorly performing sites, along with previously identified internationally sites with expressed interest (Section 3.7, Appendices IC and ID).

0.3. Clarity of some of the eligibility criteria. They are now more clearly specified and new criteria have been added, as suggested by the reviewer comments (Section 4.7, Table 4.2).

0.4. Independence of the safety monitors. The safety monitors are now based in Michigan and have no reporting relationship to the PI.

0.5. Safeguarding access to data. The data will now be managed by the NETT SDMC, which will also generate blinded and unblinded interim analyses for the DSMB. Thus, the PI and clinical coordinating center will be distant from the data.

0.6. The need for a more substantial role for the steering and executive committees. We have added additional members to both committees (Appendix IB) and have increased the frequency of meetings and clarified that changes in the protocol will require approval of these committees (Leadership Plan).

0.7. Although the rationale for the proposed trial is bolstered by the data from the FASTER study that showed a non-significant reduction in the 90 day risk of stroke from 11% to 7% with clopidogrel, several troubling aspects of that study and how they impact the present proposal are not critically discussed by the investigators. We have asked the FASTER investigators to clarify these issues and they have provided a letter (Appendix IH). We remind the reviewers that this was a small study and that it should not be over-interpreted. In terms of the specific issues raised by the reviewers:

a. The lack of effectiveness in statin treated patients: In Table 5 from the original paper [8], it can be seen that there is a 26% RRR in stroke with clopidogrel among those randomized to simvastatin. Though the risk reduction for their secondary efficacy outcome (stroke, myocardial infarction, and vascular death) was only 9% for clopidogrel among those taking simvastatin, the difference in these two measures was caused by two events and should not be over-interpreted in this small study. Also, many studies, including large randomized trials, have not shown a difference in efficacy of clopidogrel among those taking a statin [9-15]. The confidence intervals of effect size from FASTER are very wide. We have not used the FASTER results to estimate our effect size; rather, we are searching for a minimal effect that would change clinical practice and justify expense and inconvenience of use (clarified in Section 4.18). We have added an analysis to compare effects on and off statins (Section 4.15.2) but we will be encouraging statin use in the trial (Section 5.5.2).

b. A bias in favor of the clopidogrel treated groups (lower hypertension, lower carotid disease, lower cardiac cause of stroke): All these differences were small and non-significant. Cardiac cause and a history of hypertension have not generally been associated with an increased risk of stroke after TIA [16, 17]. Though large-artery mechanism has [18, 19], groups were similar for this characteristic: 46 patients in the clopidogrel group and 48 in those receiving its placebo.

c. The need to increase the FASTER time window from 12 (as proposed in this study) to 24h due to poor recruitment: From Michael Hill, Co-PI of the FASTER trial, "The statin issue was relevant, we think, in recruitment. We surveyed sites and this was the dominant reason for excluding patients [ie, that it was possible to randomize to not receiving a statin]. The proportion of exclusions for this reason rose throughout the course of the study. Increasing to a 24h window did not change the recruitment curve. Issues in recruitment for us included interruption of drug supply due to factors beyond our control. However, the recruitment curve was, on average fairly smooth throughout the course of the study." This explanation was also provided in a published letter [20]. If we delayed recruitment to 24 hours, we would be expected to reduce event rates by at least 25%. Just as it is important and feasible to enroll stroke patients in a narrow time window, we believe a similar approach is justified in TIA.

0.8. Likewise, the results of other recent TIA trials (EXPRESS, SOS TIA) suggesting that early intervention alone may reduce recurrent ischemic event rates by 70% or more are not considered. In particular, the effect of early blood pressure control and early carotid endarterectomy (CEA) should be addressed, given the strong impact of these factors on recurrent stroke risk.

For SOS TIA [21], the absence of a control group prevents assessment of the possibility that low-risk patients were referred to the study, and $ABCD^2$ score would not be expected to fully capture the risk of those referred given its limitations, as lucidly discussed in an editorial by Kernan and Schindler [3]. These authors also discuss the unlikelihood that the interventions in SOS TIA or in EXPRESS [22] could produce a combined 80% relative risk reduction (RRR). The delay in assessment in SOS TIA would also be expected to significantly reduce event rates, since patients referred but not seen, perhaps because of a new stroke, were not enrolled in the study.

Peter Rothwell was kind enough to generate new data from EXPRESS for this grant submission. Similar to SOS, patients in EXPRESS were evaluated from the time of their first evaluation, which was often delayed. When the data were re-analyzed based on time from symptom onset, event rates rose to 11% in Phase 2, similar to those reported in meta-analyses of other observational studies and in FASTER. We also asked him to evaluate the impact of various treatments on 90-day stroke risk in his cohorts, adjusting for the components of the $ABCD^2$ score. He found the following OR (95% CI): clopidogrel-aspirin vs. aspirin, OR 0.65, 95% CI 0.18-2.33; statin use 1.05, 0.32-3.48; and antihypertensive use 0.85, 0.27-2.67. Thus, there was no major impact of early statin or antihypertensive use, though there was some suggestion (nonsignificant) of an impact for clopidogrel-aspirin, providing yet more justification to proceed with POINT. Dr. Rothwell has provided a letter acknowledging these analyses and the need for a trial (Appendix IG).

Early carotid intervention could not account for reduction in event rates in these studies. Overall, carotid intervention occurred in only 5.9% of TIA patients in SOS TIA with a median delay of 6 days [21]

and in 5.4% in Phase 2 of EXPRESS with 40% occurring within 7 days [22]. Not only are rates of endarterectomy low, but timing would have meant that most new strokes expected would not have been preventable.

The results of PRoFESS argue that early initiation of antihypertensive therapy is unlikely to have a major impact on stroke risk after TIA [23].

The FASTER trial had entry criteria similar to those we propose but allowing more delayed entry (to 24 hours after a TIA or minor stroke) [8]. Many other aspects of care were optimized. Nonetheless, those randomized to aspirin alone had an 11% risk of stroke at 90 days, similar to the rate we have projected even though they included some patients at lower risk (longer delay and no use of an $ABCD^2$ criterion).

We are confident that some new studies will report low stroke rates after TIA while others show higher rates but we doubt very much that there is substantial systematic reduction in stroke risk, and use of the $ABCD^2$ score in this trial should reduce the impact of subject selection in the ultimate stroke risk.

0.9. Data from the PRoFESS study when available should also be integrated into the design... PRoFESS did not demonstrate a benefit of dipyridamole-aspirin over clopidogrel alone [24]. Furthermore, dipyridamole-aspirin was associated with an increased risk of intracranial hemorrhage. Thus, we will not permit use of dipyridamole in the trial. This will reduce heterogeneity.

0.10. The reason for the investigators' decision of not applying their own $ABCD^2$ rule to the identification of patients for enrollment in this study was very unclear to some of the reviewers... We have added back the inclusion criterion $ABCD^2$ score >3. This permits a reduction in sample size (18% reduction) and will likely increase the impact of therapy excluding those less likely to have true TIAs.

0.11. Reviewers also felt that the cost-effective analysis study was not well justified. This has been dropped and the per-patient reimbursement has been dropped.

0.12. The definition of vascular death in the proposal was thought to be very heterogeneous and reviewers suggested that the investigators provide a detailed justification of the safety (especially bleeding) markers. Additionally, a stronger justification should be provided for combining ischemic and hemorrhagic stroke in the composite primary outcome. We have sharpened the definition of vascular death (now ischemic vascular death) and added additional justification of the bleeding outcomes (Sections 4.12.2 and 4.13). The primary outcome of the trial will be new ischemic vascular events (ischemic stroke, myocardial infarction, or ischemic vascular death) and we will combine this with major hemorrhage (not just intracranial hemorrhage) as a secondary outcome for those who also want an outcome measure that includes all major expected efficacy and safety events. Major and minor hemorrhage will be tracked and reported using the definitions established in PRoFESS, allowing easy comparison with prior studies (Section 4.12.2).

0.13. On a comparatively minor note, some reviewers also suggested that the investigators might consider: providing a stronger rationale for not allowing CEA patients to resume therapy: The protocol now specifies that medications should be resumed after CEA.

And for cognitive assessment during follow-up: This has been dropped to simplify the protocol.

Including provision for cross over from placebo to clopidogrel in the sample size calculations as this might more accurately reflect clinical practice: This is now included in the sample size calculation, which also accounts for crossovers in the opposite direction (Sect 4.18, Appendix IIA & B).

Faster inhibition of platelet aggregation: Given recent data from the lab and trials, we have altered the loading dose to 600 mg of clopidogrel (Section 2.3.2).

The effect of a lower event rate in the aspirin with placebo treatment group: This is now explicitly discussed in Section 4.18.1. We have powered the trial so that even if event rates are 22% lower than anticipated, we will have 80% power to find the effect size we have specified.

0.14 Other topics now covered to address specific reviewer comments: Ethics of randomizing to aspirin when taking aspirin at the time of the TIA (Sections 3.4, 4.21.3); experience of the PI running multicenter clinical trials (Section 4.3 and Leadership Plan); the data safety and monitoring plan, which seems to have been misplaced when the grant was uploaded, has been added back (4.19, Appendix IIIC); hemorrhage events and their monitoring and adjudication are now explicitly defined (4.12.2, 4.19, Appx IIIC); the potential impact of ischemia vs. hemorrhage on long-term patient outcomes is discussed (2.3.3), a published meta-analysis has been added clarifying that the RRR we are powered to detect is likely conservative (2.3.3); potential collaboration with FASTER II is discussed (2.6, 4.21.4); extension of start-up period and explanation of timeline (4.2); survey clarifying current use of clopidogrel-aspirin, comfort with randomization to aspirin alone, and timing of carotid imaging and endarterectomy (3.4 and 3.5).

1 SPECIFIC AIMS

Transient ischemic attacks (TIA) are common, with an estimated 250,000-350,000 occurring each year in the US, an incidence about 30-40% that of stroke. Rapid recovery of cerebral ischemia is a defining characteristic of TIA and distinguishes it from completed stroke. This recovery defines a distinct pathophysiologic feature that generally indicates the presence of previously ischemic tissue still at risk: a characteristic that may be responsible for greater instability. In fact, numerous studies have shown that short-term risk of stroke is high after TIA, particularly in the first few days, even in patients treated with aspirin, the current standard of care. Antithrombotic therapy may play a distinct role in this acute pathophysiology. Effective therapies in those with TIA could significantly reduce the overall burden of stroke if initiated immediately. However, no large-scale trial has evaluated an acute intervention in patients with TIA.

Platelet aggregation is an important contributing factor in cerebral ischemia, as in other forms of ischemia. Antiplatelet agents reduce the risk of ischemic stroke in a variety of settings with distinct pathophysiologies (e.g., atrial fibrillation, small-vessel stroke, and large-vessel atherothrombosis). Aspirin given to patients with a history of stroke or TIA reduces subsequent risk of stroke. Furthermore, aspirin initiated as an acute intervention after stroke reduces risk of death and recurrent stroke. Trials of clopidogrel in combination with aspirin after stroke/TIA suggest that the combination reduces risk of stroke but increases risk of major hemorrhage. However, the risk of thrombosis is extremely high in the acute period after TIA and risk of hemorrhage is expected to be lower than after a completed stroke, so the combination may be particularly effective and relatively safe in this setting. Even more compelling, clopidogrel combined with aspirin reduced the 90-day risk of stroke by 36% compared to aspirin alone in a pilot trial of 392 patients treated acutely after minor stroke or TIA, and it was well tolerated. Clopidogrel also has advantages in being oral, without major side effects other than hemorrhage, and it will be inexpensive by trial completion. Nonetheless, antiplatelet therapy has never been tested in a pivotal trial as an acute intervention after TIA, a setting with distinct pathophysiology that may favor the use of this class of agents.

We are proposing the Platelet-Oriented Inhibition in New TIA (POINT) trial. The **Primary Specific Aim** of this randomized, double-blind, multicenter clinical trial is to determine whether clopidogrel 75 mg/day by mouth after a loading dose of 600 mg is effective in improving survival free from **major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death)** at 90 days when initiated within 12 hours of TIA onset in patients receiving aspirin 50-325 mg/day.

Several secondary analyses will be performed, including as treated analysis and evaluations of the impact of therapy on risk of the composite of major ischemic vascular events or major hemorrhage, and on risk of major systemic or intracranial hemorrhage separately. Additional tertiary/exploratory analyses will include evaluation of the impact of therapy on: 1) ischemic stroke, 2) hemorrhagic stroke, 3) all-cause death, and 4) new handicap as measured by a change in Rankin Scale score. The impact of therapy on the composite outcome will also be evaluated in specific patient groups (e.g., African Americans, those previously taking aspirin, those with imaging evidence of new infarction).

The **primary null hypothesis** in this study is:

> In patients with TIA treated with aspirin 50-325 mg/day, there is no difference in 90-day rates of survival free from major ischemic vascular events in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared to placebo when therapy is initiated within 12 hours of onset.

We plan to enroll 4150 patients at 150 centers over 4 years. We will work with the NINDS Neurological Emergencies Treatment Trials (NETT) Network, which will be responsible for statistical support, data management and all oversight of NETT sites, and with the NINDS Clinical Research Collaboration (CRC), which will be responsible for site management of all non-NETT sites. There are few conditions as common and ominous as TIA for which no pivotal randomized trial has been performed. In fact, it is startling that proposing such a trial remains highly innovative given the obvious need in this area.

2 BACKGROUND AND SIGNIFICANCE

TIA is a unique and important type of cerebral ischemia characterized by substantial instability, in which acute treatment is potentially highly consequential and has never been properly studied. Currently, the treatment choice ranges from immediate hospitalization and initiation of intravenous antiplatelet agents or heparin to outpatient evaluation and treatment with aspirin. TIAs are not simply mini-strokes and they are not minor events. We will justify these statements, postulate a pathophysiology, and rationalize a trial for a promising treatment strategy that has already been well vetted in a pilot trial.

In 2001, we first submitted a proposal for a randomized trial similar to that described here. That proposal was extensively modified based on reviewer comments but did not receive funding after two resubmissions. One major concern was that the drug company holding the patent to clopidogrel was a more appropriate sponsor. Thus, we submitted a similar proposal to the manufacturers of clopidogrel, who funded the trial. That trial (CASTIA) was initiated, with many of the 240 sites already receiving IRB approval, but cancelled in 2006 before any patients were enrolled after a generic clopidogrel was introduced into the market. The patent for clopidogrel will expire in 2012, so the manufacturer is no longer interested in investing in new indications.

Beyond the issue of the appropriate sponsor, there were three other concerns raised in final review of our NIH proposal that have now been addressed. First, there was concern that the risk of stroke after TIA may not be as high as our preliminary studies demonstrated. Now there are a large number of studies from many centers showing a very high risk of stroke after TIA (Section 2.2). Second, there was concern about the potential impact on stroke risk of clopidogrel when combined with aspirin. We now have results from a pilot randomized trial that suggests the impact of clopidogrel may be substantial. This is supported by several trials of clopidogrel used in conjunction with aspirin that have shown a greater benefit when the drug is initiated acutely after an ischemic event. Although long-term trials of clopidogrel with aspirin initiated well after a stroke or TIA (MATCH and CHARISMA) have shown that a reduction in risk of ischemic stroke is balanced with an increased risk of major hemorrhage, there are strong trends toward efficacy in the subsets of patients treated early, as shown below (Section 2.3.3). Third, the reviewers felt that a 90-day outcome was more congruent with our goal to prevent very early risk (we had proposed 180-day outcomes previously). We have modified this proposal so that the primary and secondary outcomes will be evaluated at 90 days. Since this reduces the event rate, the sample size is somewhat larger.

Given the many years of planning, revision, discussions, and modifications with involvement of a multitude of international experts, we feel the trial design is very well vetted and that the timing is optimal.

2.1 TIA Incidence

TIAs are common [25], and are often harbingers of disabling strokes. In the Framingham Study, the incidence of TIA was 86 per 100,000 person-years [26], corresponding to approximately 250,000 cases per year in the US. The incidence was 68 per 100,000 in Rochester, MN, which corresponded to a rate 41% of the incidence of stroke in this predomintly white population [25]; applying the relative incidence of TIA to the US incidence of stroke (based on a multiracial population) [27, 28], this corresponds to approximately 308,000 TIAs per year in the US. Recently, the Greater Cincinnati/Northern Kentucky Stroke Study reported a first TIA incidence of 75 per 100,000 among blacks and 55 per 100,000 among whites [29]; based on their analysis, they project that 240,000 TIAs occur and are diagnosed each year in the US [30]. In an analysis from National Hospital Ambulatory Care Survey: Emergency Department Survey 1992-2001, there were a projected 300,000 emergency-department visits/year for evaluation of TIA in the US [31]. In our cohort studies in California, we find that an equal number of TIAs are diagnosed outside the emergency department in outpatient clinics. Thus, approximately 250,000-350,000 TIAs are diagnosed each year in the US. Given median survival of more than 8 years [32], there are approximately 2.4 million TIA survivors. In a national survey we performed, one in fifteen of those over 65 years old reported a history of TIA [33], which is equivalent to a prevalence of 2.3 million in older Americans. Based on the prevalence of undiagnosed transient neurological events, the true incidence of TIA may be twice as high as the rates of diagnosis [33]. Based on our review of the National Inpatient Sample for 1997-2003, there were an average of 200,000 hospital admissions for TIA each year, with annual charges climbing quickly in the period to $2.6 billion in 2003.

2.2 Short-Term Prognosis

TIAs are ominous, carrying a substantial short-term risk of stroke, hospitalization for cardiovascular events, and death. Numerous studies have also shown that the short-term risk of stroke is particularly high, with most studies finding risks as high as 27% within 90 days after a TIA. These studies have recently been summarized in three systematic reviews, which have confirmed the extremely high rates and have noted that studies with

cases identified in the emergency department and with systematic follow-up have demonstrated particularly high rates [2, 34, 35].

Risk is particularly high in the first few days after TIA, with the majority of studies finding that one-quarter to one-half of the strokes that occur within 3 months of the onset of the TIA occur within the first 2 days [16, 30, 36-40]. For example, studies in Northern California and Oxfordshire (see Sections 3.1, 3.2, and Appendix IA2) found the risk of stroke in the first 24 hours after TIA to be 4%,[16, 41] about twice the risk of myocardial infarction or death in patients presenting with acute coronary syndromes (about 2% at 24 hours) [42]. This risk of stroke was over 50 times that expected in a cohort of similar age [3, 11], and the risk of cardiac events was 7 times greater [12]. The vast majority of strokes were fatal or disabling, requiring prolonged hospitalization. Most TIA patients were treated with aspirin (68%), and 92% were treated with an antiplatelet agent or anticoagulation. Stroke risk remained elevated in those treated with aspirin (10%) or with anticoagulation (14%). These findings underscore the need for prompt evaluation and treatment of patients with symptoms of ischemia, and show that current therapy is ineffective.

Table 2.1. Short-term stroke risk after TIA and after stroke

		Publication Year	N	Delay (days)	Stroke Risk	Projected 90-Day Stroke Risk*
Rochester, Minnesota [43]	Population-based cohort study	1973	198	0	10%/3 m	10%
London, UK [44]	Cohort study	1981	117	0	29%/ 6 m	27%
Iowa City, Iowa [45]	Cohort study	1985	74	1	6.8%/6 d	13%
Iowa City, Iowa [46]	Pilot trial (placebo group)	1989	55	2	9.1%/6 d	16%
Oxfordshire, UK [41, 47]	Population-based cohort study	1990	209	0	12%/1 m	15%
Northern California [16]	Cohort study	2000	1707	0	10.6%/3 m	11%
Oxfordshire, UK [48]	Population-based cohort study	2004	87	0	17.3/3 m	17%
NASCET [38]	Randomized trial (med therapy)	2004	603	0	20.1%/3 m	20%
Nueces County, Texas [37]	Population-based study	2004	612	0	4.03%/3 m	4%
Alberta, Canada [39]	Population-based cohort study	2004	2285	1	9.5%/3 m	10%
Ontario, Canada [36]	Cohort study	2004	265	0	6%/3 m	6%
Southwest Germany[49]	Population-based cohort study	2004	1150	0	13%/6 m	11%
Cincinnati, OH [30]	Population-based cohort study	2005	927	0	14.6%/3m	15%
Scotland, UK [50]	Cohort study	2005	205	0	7%/1m	11%
Northern Portugal [51]	Population-based cohort study	2006	141	0	12.8%/7d	17%
Athens, Greece [52]	Cohort study	2006	226	0	9.7%/1 m	13%
Barcelona, Spain [53]	Cohort study	2007	345	0	4.9%/7 d	9%
Northern California [17]	Cohort study (ED)	2007	1069	0	10%/3 m	10%
Northern California [17]	Cohort study (clinic)	2007	962	2	6%/3 m	10%
Oxfordshire [17]	Population-based cohort study	2007	545	0	9%/ 3 m	9%
Oxfordshire [17]	Cohort study (clinic)	2007	315	0	7%/ 3m	7%
AVERAGE						**11%**

Two recent studies, SOS-TIA [21] and EXPRESS [22], have suggested that event rates may be lower with aggressive secondary prevention. However, both studies had design features that makes comparison with larger studies and the target population of our trial problematic, as discussed in editorials [1, 3, 7, 54, 55] and detailed in the introduction to this resubmission (Section 0.8). Additional analysis from the EXPRESS study suggests that only patient selection, timing of follow-up initiation, and the use of clopidogrel-aspirin could account for the drop in event rates in this cohort study with historical controls (Section 0.8). Thus, event rates in a trial are expected to be high, even with optimal therapy.

The short-term risk of ischemic stroke after a completed ischemic stroke appears to be lower, with 10 studies reporting 3-month risks ranging from 4% to 8% [44, 56-69]. Three studies have directly compared short-term risk of subsequent ischemic stroke between TIA and stroke. In patients with hemispheric ischemia enrolled in the NASCET trial, the 90-day risk of stroke was 20.1% in the 603 with index TIA and 2.3% in those with an index ischemic stroke [69]. Similarly, an observational study of consecutive patients found greater 6-month risk of stroke after TIA (29%) than after completed stroke (7%) [44]. A population-based study from Rochester, MN, also found that short-term stroke risk was greater after TIA (10%) than after ischemic stroke

(7%), but the difference was smaller in this study [70]. Together these studies suggest that risk of stroke is greater after TIA than after a completed stroke.

Risk of cardiac events is also elevated after TIA. In one large study, 2.6% were hospitalized for major cardiovascular events (myocardial infarction, unstable angina, or ventricular arrhythmia) within 90 days.[71] Over the course of 5 or more years nearly equal numbers of patients with TIA will have myocardial infarction or sudden cardiac death as will have a cerebral infarction.[72]

2.2 Underlying Pathophysiology of TIA

The extent of early improvement after presentation with acute cerebral ischemia may be associated with risk of subsequent stroke because rapid recovery may indicate a distinct, unstable pathophysiology in some instances [73-78]. Rapid recovery is an indicator of return of normal function in a previously ischemic territory, often due to return in blood flow. The previously ischemic tissue remains at risk. When in-situ thrombosis at a ruptured atherosclerotic plaque is responsible for the initial ischemic event, a rapid recovery may signify resolution of the thrombosis. However, the plaque may remain highly thrombogenic, thereby elevating the risk of a subsequent ischemic event. Contrarily, if the ruptured plaque leads to a completed stroke in the distal vascular territory, additional thrombosis will generally be asymptomatic; the situation is more stable and risk of new stroke is lower. Thus, an elevated risk of deterioration would be anticipated after rapid recovery, suggesting reversal of ischemia, compared to after an ischemic event with no rapid recovery.

Supporting this concept, in one study of 50 patients who improved spontaneously within 6 hours of symptom onset, several of whom had TIAs, deterioration within 24 hours occurred in 16% and was associated with initial occlusion or stenosis of intracranial vessels [73]. Similarly, in an analysis of the NINDS tPA trial data, deterioration following initial improvement occurred in 13% of enrollees overall (occurring within 24 hours in 74% of these) and was attributed to reocclusion of a vessel in 73% [74]. Both these studies included patients receiving tPA, but rates were similar regardless of whether tPA was given. We have performed four additional studies that are reviewed below (Section 3.3), all of which confirm a higher risk of stroke when early recovery occurs [75-78].

We postulate that the pathophysiology of TIAs is analogous to that of acute coronary syndromes (i.e., unstable angina and non-Q-wave myocardial infarction) in which thrombosis and thrombolysis are acutely active and protracted [79]. Similarly, cerebral ischemia that acutely recovers may be a marker for ongoing thrombosis-thrombolysis, whereas major ischemia that persists may be a result of a largely completed thrombosis that is not amenable to acute antiplatelet therapy [66, 77, 78, 80]. Aggressive, early antiplatelet therapy with combinations of agents is highly effective in acute coronary syndromes [81-84]. We hypothesize the same will be true for the major events of TIA that we will study

2.3 Potential Therapies

There are few established, effective therapies for stroke prevention after TIA. Other than aspirin, the only approved therapy for acute cerebral ischemia, intravenous tPA, is explicitly contraindicated in patients with TIA [80]. Physicians, fully aware of the impotence of current therapy, are frustrated by their inability to improve outcomes after TIA. This has contributed to substantial practice variability in TIA management [85]. Clearly, an effective secondary prevention strategy after TIA is required. We hypothesize that very early treatment with clopidogrel in conjunction with aspirin treatment will substantially reduce the risk of recurrent ischemia.

Platelet activation and aggregation are important processes in most ischemic strokes, regardless of underlying etiology. Platelet thrombi contribute to small vessel strokes, large vessel thombosis and embolism, and cardiac embolism [86, 87]. Inhibiting platelets reduces risk of ischemic stroke from all these major etiologies [88, 89] and also reduces risk of ischemic cardiac complications in those at high risk [88]. In all these settings, the benefits of oral antiplatelet agents, including aspirin and clopidogrel, have exceeded an increase in risk of major hemorrhage. Thus, antiplatelet agents appear to have wide effectiveness in those at high risk of cerebral and cardiovascular ischemia.

The benefits of platelet inhibition may be greatest in the acute period. Platelets are activated dramatically and transiently in patients with acute cerebral ischemia, both from TIA and from ischemic stroke [90, 91], coincident with a period of greater risk for recurrence and progressive thrombosis [92, 93]. Antiplatelet therapy with clopidogrel added to aspirin in patients with acute cerebral ischemia blunts platelet activation compared to aspirin alone [94], reduces micro-embolic signals [95], and tends to reduce clinical ischemic events during the days after a stroke or TIA. New data from the FASTER pilot trial [8] supports the safety and potential efficacy of clopidogrel-aspirin in reducing stroke risk in the short-term after TIA or minor stroke (Section 2.3.3).

2.3.1 Aspirin

Aspirin has been a mainstay for long-term prevention of vascular events after stroke, and reduces the incidence of stroke, myocardial infarction, and vascular death by 22% [96]. Aspirin appears to be effective in reducing risk of small vessel strokes, large vessel atherothrombosis, and in atrial fibrillation [88].

In patients presenting acutely with stroke, aspirin also improves outcomes, but the effect is modest and is reduced by a small increased risk of intracerebral hemorrhage. The CAST and IST studies, each enrolling about 20,000, found that acute treatment with aspirin after ischemic stroke reduced the risk of recurrent ischemic stroke by 30% (an absolute change of 0.7%) with a small increase in intracranial hemorrhage (25% relative and 0.2% absolute increase) over 2-4 weeks of treatment [64, 65, 89]. The overall benefit of acute treatment with aspirin was present in those with and without atrial fibrillation and with and without a lacunar syndrome [89]. Thus, aspirin has become the standard of care in the acute treatment of patients with stroke. The optimum dose of aspirin continues to be vigorously argued, but is probably in the range of 50-325 mg/day [97]. Aspirin is also considered standard therapy in TIA, with clopidogrel and aspirin-dipyridamole acceptable alternatives, but none has been tested as acute therapy in this setting [97-99]. In planning a prior trial in acute TIA, international experts agreed that aspirin should be given to all patients but they could not agree on a specific dose within the range of 50-325 mg/day recommended in published consensus guidelines.

2.3.2 Clopidogrel

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation by blocking the ADP receptor [100, 101], a mechanism independent of the thromboxane-mediated pathway inhibited by aspirin. In the CAPRIE trial, clopidogrel 75 mg/day reduced long-term risk of stroke, myocardial infarction, or vascular death by 8.7% relative to aspirin in patients with vascular disease, without increasing risk of hemorrhage or other major side effects [102]. The trial was not designed to evaluate clopidogrel as an acute therapy, and no trial has evaluated the efficacy of clopidogrel after TIA.

Clopidogrel may be useful as an acute intervention after vascular events. With a loading dose of 600 mg, clopidogrel produces platelet inhibition faster than 300 mg, with greater inhibition at 3 and 4 hours after administration and 600 mg is more likely to be effective in those with clopidogrel resistance [103, 104]. It has been shown to be safe in multiple trials of acute coronary syndrome, with new increase in bleeding events compared to lower loading doses even when used in combination with other potent antithrombotics, and it has become the de facto standard for comparison with new antiplatelet agents [105-108].

2.3.3 Combination Clopidogrel-Aspirin

Clopidogrel has been studied in combination with aspirin in several trials of vascular disease, including two that included patients with stroke or TIA. Although results from these trials have not supported long-term use of clopidogrel after stroke/TIA, the drug has never been tested as an acute therapy in this population and the trials support that it may be more beneficial and particularly safe after TIA. It is also a logical agent to test because it is cheap (soon to go off patent), has well established, favorable pharmacodynamics and safety profile, and is delivered conveniently in the outpatient setting.

Aspirin and clopidogrel synergistically antagonize platelet aggregation [102, 109-111], and combined, may provide added benefit in stroke prevention. Aspirin and clopidogrel are used together after coronary, carotid, and intracranial stenting, and appear to be well tolerated [112, 113]. Evidence supporting clopidogrel also comes from cardiac trials, non-acute stroke/TIA trials, and most importantly, from an acute pilot trial of TIA and minor stroke, as reviewed below.

Cardiac Trials: The CURE trial of patients with acute coronary syndromes, also taking aspirin found that clopidogrel 75 mg/day after a loading dose of 300 mg reduced the risk of stroke, myocardial infarction, and vascular death by 20% at 3-12 month follow-up, and the effect was apparent in the first 10 days [81]. Myocardial infarction and vascular death accounted for the vast majority of events in this trial. There was a small increase in risk of major hemorrhage but no difference in life-threatening hemorrhage. In the CREDO study, clopidogrel also reduced the 1-year risk of cardiovascular events by 27% among those treated with aspirin undergoing percutaneous coronary intervention [114]. An early benefit was seen only in those who received a loading dose of clopidogrel $\geq$6 hours before the procedure, reinforcing the importance of an initial loading dose when ischemic events may occur within hours. There was a 1% absolute increase in risk of major bleeding at 28 days, but most of this was associated with procedures such as bypass surgery. Thus, clopidogrel reduces ischemic events in patients treated acutely after coronary ischemia or prior to

percutaneous coronary intervention.

Non-Acute Stroke/TIA Trials: The MATCH (Management of atherothrombosis with clopidogrel in high-risk patients with recent TIA or ischemic stroke) trial was a secondary stroke prevention trial that enrolled 7599 patients, mostly in Europe [115]. This study compared aspirin plus clopidogrel to clopidogrel. The majority of patients (79%) enrolled suffered a prior stroke, rather than TIA. The overall trial was negative, with a small insignificant 1% absolute benefit in terms of reduced risk of ischemic events balanced by a 1% but significant absolute increased risk of major hemorrhage. In subgroup analysis, however, there was a trend toward greater benefit in those treated sooner after the qualifying stroke or TIA, with a 17% RRR in those treated within 7 days. The CHARISMA trial randomized patients with vascular disease, who are treated with aspirin 75-162 mg/day, to clopidogrel 75 mg or placebo [116]. Similar to MATCH, the trial was negative with a small reduction in ischemic events balanced with a small significant increase in severe hemorrhages. However, also similar to MATCH, there was greater benefit in patients treated sooner after a clinical qualifying event (including stroke and TIA). In unpublished analysis of the 4320 patients enrolled in CHARISMA after TIA or stroke, a study involving Drs. Johnston and Easton (reviewed here to maintain continuity), the RRR of stroke with clopidogrel was 26% in those randomized within 30 days of the event and 17% in those randomized later, again suggesting that patients treated early are more likely to benefit (submitted manuscript, Appendix IA1). There was no increased risk of hemorrhage in those treated within 30 days or later among those randomized after stroke or TIA. In the PRoFESS trial, patients were initially randomized to clopidogrel combined with aspirin in one arm of the trial but this was changed to clopidogrel alone 8 months into the study after publication of the MATCH trial results and events on this combination have not been reported [24].

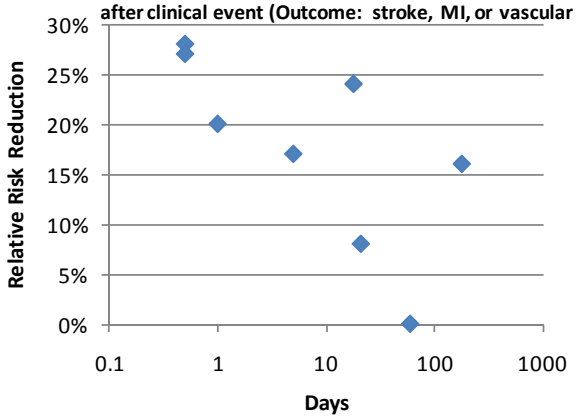
Pilot Acute TIA/Stroke Trials: FASTER was a pilot trial based in Canada and run by collaborators in the design of this trial (including Drs. Kennedy and Hill) [8]. It evaluated clopidogrel (300 mg load and 75 mg/day afterwards) and simvastatin in a factorial design on a background of aspirin in patients presenting within 24 hours of a TIA or minor stroke. The main principal motivating the trial was the recognition of the high frequency of poor outcomes in patients presenting with acute cerebral ischemia who are not candidates for thrombolysis. The trial enrolled 392 patients from 18 centers over 30 months (0.73 patients/site/month, with slow recruitment attributed to the requirement to randomize to statins). The risk of stroke (ischemic or hemorrhagic) at 90 days was 11% in those treated with aspirin alone and 7% in those treated with clopidogrel and aspirin, a non-significant 36% RRR in this pilot trial (p=0.19). There were two intracranial hemorrhages, both in patients treated with clopidogrel-aspirin; one occurred in a patient with minor stroke and uncontrolled blood pressure and the other occurred in a patient with TIA but details are uncertain. These hemorrhages were included in the primary outcome and did not overwhelm the benefit. The trial serves as an excellent pilot for the proposed trial, reconfirming a high risk of stroke in patients with TIA and minor stroke and suggesting that a large effect size is possible. Working together with the FASTER team, we will capitalize on their experience and aspects of design and implementation.

Details of the FASTER data are provided in Section 0.7 and in a letter provided by the investigators (Appendix IH)

Another pilot double-blind, placebo-controlled trial, CARESS, evaluated the impact of clopidogrel-aspirin vs. aspirin alone on presence of TCD micro-embolic signals in 107 patients with recently symptomatic carotid stenosis [95]. At 7 days, 44% on the combination and 73% on aspirin alone had persistent micro-embolic signals (p=0.005), suggestive of a reduction in ongoing thrombo-embolism. There were more strokes and TIAs in the aspirin-only group (11 vs. 4) but the difference was not significant.

Clopidogrel/Aspirin: Conclusions: The FASTER pilot trial provides strong support for POINT, but other negative trials of clopidogrel-aspirin also support testing it in the acute setting, where relative risk reduction

Figure 2.1 Impact of clopidogrel-aspirin vs. either alone based on timing of enrollment after clinical event (Outcome: stroke, MI, or vascular death)



Trial	Days	RRR
CHARISMA	18	24%
CHARISMA	180	16%
MATCH	5	17%
MATCH	21	8%
MATCH	60	0%
FASTER	0.5	28%
CURE	1	20%
CREDO	0.5	27%

have been consistently high in a number of trials from a variety of clinical settings (Figure 2.1). Taken together, they suggest that the combination clopidogrel-aspirin may be particularly effective early after acute ischemia, when the risk of recurrent ischemia is particularly high and platelet aggregation likely to be highly relevant. Of course, the risk of hemorrhagic conversion is also high in patients with acute infarction. However, patients with TIA have minimal or no infarction, so their risk of hemorrhage may be more similar to those with cardiac disease than to those with completed strokes that are disabling enough to meet entry criteria in prior trials [117]. In fact, the risk of brain hemorrhage is lower after less debilitating stroke [118, 119]. For example, in the TOAST study, risk of serious brain bleeding with danaparoid was 14% in those with an NIH Stroke Scale score >15 and only 0.5% in those with less severe stroke [118]. In the FASTER trial, intracranial and serious extracranial hemorrhage were rare, were concentrated in the group presenting with stroke rather than TIA, and did not overwhelm a benefit in reduced ischemic events. Though there was an excess of mild and moderate extracranial and asymptomatic hemorrhage with clopidogrel in FASTER, these events were all transient while strokes produced permanent injury that was disability in 35% [J. Kennedy, personal communication], which is lower than the disability rate published in prior cohort studies (eg, 85% of strokes in our study were disabling with 21% fatal [16]). Thus, hemorrhage risk with the combination of aspirin and clopidogrel should be relatively low after TIA and less consequential than the expected avoidance of ischemic events.

In a meta-analysis of results from FASTER, CHARISMA, CARESS, and MATCH for patients enrolled within 24 hours of onset of TIA or stroke, there was a RRR of 34% with clopidogrel-aspirin vs. aspirin alone for the composite outcome measure of stroke, TIA, acute coronary syndrome, and all-cause death [8], providing further evidence that the impact of clopidogrel-aspirin may be substantial in the acute period.

2.3.4 Dipyridamole

Two trials have demonstrated the efficacy of dipyridamole in preventing stroke recurrence: ESPRIT [120] and ESPS-II [121]. Both tested dipyridamole combined with aspirin and found it superior to aspirin alone. Neither trial evaluated the acute period after a stroke or TIA (median time to enrollment was >1 month), so safety and efficacy during this time period is unknown.

The PROFESS trial randomized patients with ischemic stroke to clopidogrel or aspirin/extended-release dipyridamole [24]. Enrollment occurred up to 90 days after the most recent ischemic event, with 40% enrolled within 10 days. Recurrent stroke occurred in 9.0% of patients treated with dipyridamole-aspirin and in 8.8% of patients treated with clopidogrel during a mean 2.5-year follow-up. Major hemorrhage and intracranial hemorrhage were more common in the group receiving dipyridamole-aspirin. Given these findings, and a greater risk of early headache with dipyridamole, many practitioners have limited its use. Guidelines do not reflect PRoFESS findings at this point [98, 99].

2.4 Potential Impact of a Trial

Effective prevention of subsequent stroke in patients with TIA would significantly reduce the overall stroke incidence and its associated economic burden [122]. We applied methods we previously used to value results of prior NINDS-sponsored trials [123] to estimate the potential impact of this planned trial. Based on the short-term risk of stroke in our pilot cohort study (Section 3.1) [16], approximately 30,000 strokes occur each year in the US within 90 days after a TIA. A therapy that reduces stroke risk by 22% in the first 90 days after TIA would reduce the burden of stroke by 6,600 each year if it could be given to all patients with TIA, with an annual cost savings of approximately $567,000,000, based on an average direct cost of $86,000 per stroke inflated to 2004 dollars [124, 125] and a net cost of treatment of approximately $100. Modeling the impact on quality of life using a Markov model, the benefit in preventing a stroke would translate on average to a gain of 1.4 quality-adjusted life years. Even if only 20% of patients with TIA could be treated with the study agent, the impact would still be large, with prevention of 1320 strokes per year, cost savings of $113,000,000, and gain of 1850 quality-adjusted life-years (equivalent to an additional $79,000,000 in benefit). (Based on our preliminary data, we anticipate that >80% of patients with TIA seen in the ED will meet inclusion criteria, and approximately half of patients with TIA are diagnosed in EDs [29]; thus, an estimate of 20% treatment rate is conservative.) The projected 10-year net societal benefit (discounted) would then be estimated at $1.7 billion, using the methods for assessing trial impact that we previously developed and assuming a 23% relative risk reduction.

Based on our previous analysis of the impact of NINDS-sponsored trials, it is unusual for a trial to result in cost savings, as is anticipated here [123]. Also, the net 10-year societal benefit estimated here is comparable to some of the most important trials in the NINDS portfolio of past years. For the investment to be considered “break-even”, there would need to be only a 2% chance that it would show a benefit of clopidogrel given the

cost of the trial.

An agent that reduced risk of stroke and cardiovascular events by 23% after TIA would have a number needed to treat of 28 to prevent one event in 3 months among the patients targeted for this study. If the agent were used in all patients with TIA, the number needed to treat would be 40. These numbers are relatively favorable compared to most secondary prevention strategies, particularly when the short length of follow-up is considered.

2.5 Advantages of a TIA Acute Treatment Trial

Secondary prevention of stroke after TIA is an excellent model for testing a new antiplatelet drug in combination with aspirin, and may be a great model for testing other interventions aimed at preventing acute ischemia. Using TIA rather than completed stroke as the index event for a secondary prevention trial has several advantages:

1. Patients with rapidly improving deficits are not candidates for thrombolysis with the initial event and are currently excluded from the majority of clinical trials. A study of TIA would not conflict with aggressive acute therapy and other clinical trials at most centers, improving enrollment. In fact, patients enrolled in this trial would still be eligible for ongoing trials such as IRIS (Section 2.6).
2. Rates of recurrent events are higher than after completed stroke, dramatically improving efficiency and reducing necessary follow-up time. A follow-up period of 3 month reduces the costs per patient enrolled and produces results more rapidly.
3. Risk of intracranial hemorrhage is lower because cerebral infarction is generally minimal or absent.
4. In many centers TIA is treated in the outpatient setting, making an outpatient regimen with limited monitoring particularly desirable.
5. Studying stroke prevention after TIA may lead to more efficient testing of stroke prevention in other settings. Given the high risk of ischemia and lower risk of hemorrhage after TIA, a drug that fails to prove effective in reducing stroke risk after TIA is less likely to be of benefit after stroke.

2.6 On-going Clinical Trials: Overlap

The Secondary Prevention for Small Subcortical Strokes (SPS3) Pilot study is completed [126] and a phase III trial has recruited about 70% of target enrollment. This study will evaluate the benefit of clopidogrel on risk of stroke in patients with small subcortical strokes taking aspirin; TIA is excluded. This important study is designed to evaluate benefit in chronic use (enrollment allowed up to 6 months after stroke) and will include only those with this specific subtype of stroke. Though small vessel ischemia may account for some TIAs, it is not currently possible to distinguish this subgroup of TIA patients. Results of SPS3 are not likely to affect enrollment or interest in POINT given these differences.

The POINT trial also should not impact recruitment for other ongoing NINDS-sponsored trials. IRIS allows recruitment out to 6 months after a clinical event, so patients be enrolled in IRIS after POINT follow-up is complete, and only 10% of current IRIS enrollees have had TIA as a qualifying event. ALIAS excludes TIAs. POINT excludes patients in whom carotid stenosis >50% could be an explanation for the TIA, so there should be limited overlap with CREST. Finally, WARCEF allows delayed recruitment and is limited to those with congestive heart failure, which should be a small subset in our trial. No other large-scale trials of patients with acute TIA are ongoing. Thus, there should be little competition for patients.

The FASTER II trial is planned and is similar to POINT. It is planned to involve Canada and Western Europe. If it is funded, there will be no overlap in sites and we will attempt a meta-analysis, as described below in Section 4.21.4.

3 PRELIMINARY STUDIES

During the past 12 years, we have performed a large number of studies that serve as background for this trial. Many were designed to address issues raised in proposing this trial. These include studies assessing the prevalence and community knowledge of TIA [127], establishing the high risk of stroke and cardiovascular events after TIA [16, 17, 71], identifying risk factors for stroke and other adverse events [16, 17, 71, 128, 129], defining the importance of early neurological recovery in identifying instability [75-78], evaluating current patterns of antithrombotic prescription and other aspects of care after TIA [85, 130-132], identifying predictors of site recruitment in randomized stroke/TIA trials [133], confirming ability to recruit to an acute TIA trial, creating metrics to evaluate the potential impact of clinical trials so that the planned trial can be evaluated in this light [123], and confirming the safety of clopidogrel-aspirin-dipyridamole in combination. Numerous reviews and editorials have also been written clarifying the urgency of treatment for TIA and the inadequacy of current therapies [98, 134-139]. Due to space constraints, published preliminary work is only reviewed very selectively and briefly, some in Section 2 and the rest below, and reviewers are invited to go to the appropriate citations for additional information.

3.1 Risk of Stroke and Cardiovascular Events is High after Acute TIA

In a series of studies, we have documented that the risk of stroke is very high in the days to months after a TIA. These results have been confirmed in multiple studies from other institutions, as reviewed in Table 2.1. The first of our studies on this topic was the Emergency Department TIA Study, a cohort study of 1707 patients diagnosed with TIA by emergency physicians at one of 16 hospitals in the Kaiser-Permanente Northern California (KPNC) medical care plan 1997-1998 [16]. Over 90% of patients arrived within 12 hours of symptom onset and 92% received an antithrombotic medication at emergency-department discharge. A total of 180 strokes occurred within 90 days of the index TIA, with an overall 90-day stroke risk of 10.5% (95% CI 9.1% - 12.0%). Hospitalization for myocardial infarction occurred in 1.4% (n=24) during the first 90 days. The 90-day risk of vascular death was 2.3% (n=40), with most deaths attributable to stroke. For the composite outcome of stroke, myocardial infarction, and vascular death, the 90-day risk was 13.0% (n=221). One third of events occurred in the first 24 hours, 50% occurred within the first 5 days, and 73% within the first month.

To validate findings from the pilot study of TIA evaluated in the emergency department, we performed a cohort study of all 976 patients in KPNC who were given a diagnosis of TIA in urgent care clinics 1997-1998 [17]. The median delay between symptom onset and first evaluation was 24 hours and 161 (17%) were considered unlikely to represent TIA on neurologist review. Even so, the 90-day stroke risk in this cohort was 6.2%, and 1.9% were hospitalized with a cardiovascular event. Overall, the risk of stroke, cardiovascular event, or vascular death was 7.9%. Among the 560 judged to have true TIA first seen within 24 hours of onset, the 90-day risk was 8.4% for stroke and 10.0% for the composite outcome, very similar to results from the emergency-department cohort.

Similarly, another validation cohort of 1069 patients diagnosed by KPNC emergency-department physicians 1998-1999 was developed [17]. Similar to the first cohort, the 90-day stroke risk was 10.2%, with another 2% experiencing vascular death or MI but not stroke. Combining the two emergency department cohorts (n=2776), the overall 90-day stroke risk was 10.3%, with 12.1% experiencing stroke, MI, or vascular death. Among the group of patients targeted for this trial and treated with aspirin, the risk of the planned composite outcome measure (stroke, MI, or vascular death) was 14% at 90-days. The overall stroke risk seen in these cohorts is consistent with many prior studies (Table 2.1). Even in recent studies, such as FASTER, during which greater vigilance to secondary prevention is likely, event rates are equally high.

There has been concern that the diagnosis of TIA is variable and unreliable. We found that over 90% of patients with TIA diagnosed by emergency physicians had the diagnosis confirmed when a neurologist reviewed it. More importantly, the high risks of stroke have been documented in cases identified by non-neurologists so the true incidence of stroke in a population with confirmed TIA is higher. Some symptom complexes are associated with particularly low risk of stroke, and this may help to identify a population with true TIA and more likely to benefit from aggressive treatment.

3.2 Predictors of Stroke Risk after TIA

There are several clinical and imaging factors that are associated with risk of stroke after TIA. The most extensively validated factors are the clinical elements that have come to constitute the $ABCD^2$ score. Five simple independent risk factors for stroke within the 90 days after a TIA were identified in the original cohort study [16]: age≥60 years, diabetes, duration ≥10 min, speech impairment, and weakness. These risk factors were confirmed in two independent cohorts from California [17], four cohorts from Oxford [17], and in another

cohort in Greece [140]. In a meta-analysis combining two cohorts from California and Oxford and validating a new model in four remaining cohorts from the two regions, the $ABCD^2$ score was created [17]. It includes all the elements of the original score and adds a couple of additional modifications. The score is created by summing points for each of several independent risk factors: age≥60 years (1), blood pressure ≥ 140/90 mmHg (1), clinical symptoms of unilateral weakness (2) or speech impairment without weakness (1), duration 10-59 min (1) or ≥60 minutes, and diabetes (1). Stroke risk was strongly associated with total score, with 90-day stroke risks ranging from 20% with a score of 6-7 to <1% with a score of 0-1.

The ABCD and $ABCD^2$ scores have now been independently validated by other groups, as well [18, 140-142]. Having such a score available and well validated will allow us to select the subgroup at highest risk of stroke, which increases power and focuses the trial on those most likely to benefit, in whom a potentially elevated risk of hemorrhage is easily justified. Selecting those with $ABCD^2$ scores >3 increases the expected event rate from 12.1% to 15.3% at 90 days while excluding only 30% of otherwise eligible cases, in whom the risk of outcome events is only 4.3%.

Perhaps not surprisingly, patients with isolated numbness, visual changes, or dizziness/vertigo, who constituted 16% of those diagnosed with TIA, were at low risk of stroke [129]. In the combined emergency department cohorts, the 90-day risk of stroke was 2% in the 451 patients with these isolated symptoms. This group of patients was also less likely to have a final diagnosis of TIA after expert review ($p<0.005$). A lower risk of stroke has been confirmed by other groups in patients with isolated dizziness [143], isolated visual symptoms [144], and isolated numbness [Rothwell P, personal communication].

3.3 Importance of Recovery: Risk of Stroke after Recovery in the NINDS tPA and TOAST Trials

We obtained data from four randomized trials—the NINDS tPA trial [80], TOAST [66], GAIN [78], and ASTIN [77]—to determine whether acute recovery was associated with a high risk of subsequent neurological deterioration due to causes other than intracranial hemorrhage. Results of these four analyses were all very similar. In brief, patients with greater initial recovery after presenting with cerebral ischemia were at greater risk of subsequent neurological deterioration attributable to ischemia. For patients with complete recovery at 24 hours, constituting a TIA subgroup, the risk was particularly high; for example, in the NINDS tPA study those with complete resolution at 24 hours had a 30% risk of subsequent deterioration compared to a 10% risk for those with no or less initial recovery ($p=0.001$). Risk was intermediate for those with partial initial recovery compared to no recovery. This provides additional confirmation of the hypothesis that TIA and lesser degrees of acute ischemic recovery represent a distinct pathophysiological characteristic associated with greater instability and risk of deterioration attributable to new ischemia.

3.4 Current Utilization of Antithrombotics After TIA

Background usage of antithrombotic medications after TIA may impact event rates and could inform appropriate selection of comparators. To estimate background utilization, we evaluated usage of antithrombotic medications after TIA in three populations: KPNC, the Coverdell Registry for California (CASPR, Johnston PI), and the Ethos Registry. In the KPNC ED cohort, the vast majority of patients (92%) were treated with an antithrombotic medication, most commonly aspirin (68%). The 90-day risk of the composite outcome was not significantly lower in those taking aspirin compared to others (12% vs. 15%, $p=0.11$). (Similarly, there was no difference in stroke risk between those taking a cholesterol-lowering agent ($n=152$) compared to others (13% vs. 13%, $p=0.94$), as was also seen in the FASTER pilot trial [8])

Among 174 patients with acute TIA in the 11 hospitals of the California Coverdell Registry [130], 153 (88%) were treated with an antithrombotic agent, of which 37% were treated with aspirin alone, 9% treated with clopidogrel alone, and 14% with clopidogrel combined with aspirin. Among 5090 with TIA in the 71 hospitals in the Ethos Registry 2001-2006, which is a nationwide quality improvement stroke and TIA registry [131], 4767 (94%) were discharged on an antithrombotic agent, of which 31% were treated with aspirin alone, 12% with clopidogrel, and 23% with clopidogrel combined with aspirin [132]. Combination clopidogrel-aspirin use decreased after publication of the MATCH trial, but remained at 17% in 2005. Data are not yet available about use of dipyridamole after the PRoFESS trial results were reported in May 2008, but use was expected to decrease.

At the suggestion of a reviewer, we polled our sites as to current practices in patients with TIA. Of 75 sites contacted, 57 provided complete responses to the survey. For patients with acute TIA, sites reported acute use of clopidogrel in combination with aspirin (among patients without stents) always (7 sites, 12%), often (3 sites, 5%), sometimes (15 sites, 26%), rarely (19 sites, 33%), and never (14 sites, 25%). Sites estimated that 50% of subjects are taking an antiplatelet agent at the time of the TIA but only 7% said they would be

uncomfortable randomizing such patients into the POINT trial (with the risk of receiving aspirin alone).

Thus, antithrombotic medications are commonly prescribed after TIA and current estimates of event rates are already impacted by this frequent use. Aspirin is most frequently prescribed but clopidogrel combined with aspirin is used frequently. Described rates of stroke after TIA incorporate baseline single-agent and duel-agent usage, and aspirin is an appropriate background therapy based on current patterns of usage (as well as on data from trials).

3.5 Carotid Imaging and Endarterectomy in POINT Participating Centers

Average percentages of patients presenting acutely with TIA receiving carotid imaging were 31% within 6 hours, 85% within 24 hours, and 98% within 1 week. Endarterectomy is typically performed 8 days after a TIA in appropriate candidates and can be performed as soon as 2.5 days on average. Thus, most sites perform carotid imaging rapidly already and could exclude patients with high-grade stenosis, and follow-up would be limited if we elected to include those with carotid stenoses.

3.6 Recruitment in Stroke Trials

Due to widespread problems of NINDS-sponsored trials in recruiting patients at target rates, we performed a series of analyses to try to define standard rates of patient recruitment in stroke/TIA trials and to identify predictors of sites that perform particularly well. In a systematic review that included 32 stroke trials, the average recruitment rate was 0.8 subjects per center per month (range 0.08 to 3.7) [133]. The primary study entry criteria that predicted reduced recruitment rate were the maximum allowable time from stroke to study enrollment (P=0.002) and the exclusion of mild strokes (P=0.009). Trials with a treatment window >6 hours had approximately double the recruitment rates of trials that used treatment windows $\leq$6 hours (1.03 versus 0.52 patients per center per month). Trials with broad inclusion criteria and those of safer drugs also recruited more quickly. Given the broad inclusion criteria of the proposed trial but the lower incidence of acute TIA diagnosis than ischemic stroke in the emergency department, we estimate that a rate of 0.75 subjects/site/month is realistic.

In an unpublished extension of this study, we created and validated an index of predicted recruitment rates for individual sites. With a database of over 500 variables and nearly 985 sites, we used generalized estimating equations to model average normalized recruitment rates for sites based on their performance in a series of stroke trials. These models were created without including recruitment to the four most recent large-scale trials and results of the modeled expected rates of recruitment were compared to actual recruitment in the most recent trials. We found several predictors of higher than average site recruitment rate, including institutional volume, performance in prior similar trials, and ongoing competing trials at the site. These were combined into indices that were normalized into z scores, and 95% confidence intervals were estimated from model uncertainty and from the completeness of available data (since some data are missing for nearly all sites). These indices were than validated using information on recruitment from four recent large-scale trials that were not part of the initial model. The recruitment indices were strongly associated with actual recruitment in this retrospective validation ($p<0.001$ by weighted linear regression).

This method was then applied to the sites selected for this trial. To generate the metric, site recruitment is normalized to average recruitment for each trial in which the site participated. The median of these normalized scores is then taken as the recruitment metric. This is calculated separately for acute therapy trials, which are expected to mimic POINT, with an average index of 1.12 among the sites with adequate data (including NETT spokes, which will be contributing cases in concert with a contracted HUB). However, since our model largely depends on performance in past trials, we also invited through the NINDS Clinical Research Collaboration (CRC), sites whose expected performance could not be modeled so as to increase the community of physicians participating in simple trials, such as this.

3.7 POINT Participating Centers

We have now have identified a total of 230 sites with confirmed interest in participation, including 75 original sites selected based on validated recruitment metrics (Section 3.6), 16 NETT hubs and 53 of their spokes (with some overlap with the original target sites), and an additional 56 sites identified solely through the CRC. The original sites were carefully selected based on validated metrics, which have been extended to the new sites when possible (Appendix IC). The NETT sites were rigorously vetted through the R01 mechanism in order to be a part of the Network and are expected to be productive. The CRC sites are less proven but our data suggests several are likely to be excellent recruiters, and including them will add to the list of sites regularly participating in trials. We will select sites from this list with a goal of recruiting and maintain 150 active sites.

Table 3.1 Characteristics of Sites Committing to Participation

Participating Centers	174 (+56 solely from CRC)
Recent Stroke/TIA Trial Participation	
Average Number of Trial Collaborations	8.5
Average Percentage of Patients Retained to Complete Follow-up	95.3%
Total Goal Recruitment in Prior Stroke/TIA Studies	12138
Actual Recruitment in Prior Stroke/TIA Studies	11724
Portion of Studies in Which Goal Recruitment Was Met or Exceeded	74%
Recruitment index, acute trials (ratio of actual to expected in prior trials	1.12
Annual Acute TIAs Treated	11347
Total Anticipated Recruitment for POINT over 4 y (for 150 active sties, target=3800 w/ others from CRC)	15084

Through the last 8 years, we have recruited sites for two prior similar trials: ATARI and, more recently, CASTIA (a cancelled industry-sponsored trial of TIA/minor stroke that we lead in 2006). Characteristics of 246 non-US sites that had agreed to participate in the CASTIA trial and had attended an initial face-to-face investigators' meeting are provided in Appendix ID. We have not listed these as sites for the POINT trial (and have not re-contacted them) because prior NIH reviewers were concerned about the complexity of handling international sites. We propose that selected sites from this list be recruited to join the trial if recruitment is slow. Resources have been set aside in the budget to replace slow-recruiting sites quickly.

The combined experience of the centers selected for participation is substantial, and they have performed well in prior stroke trials (Table 3.1). The anticipated enrollment from these centers is 83% greater than target rates. These centers have tended to underestimate actual recruitment when asked to set goals for prior stroke studies, so anticipated enrollment is likely realistic.

3.7.1 Prospective Eligibility Log

Nineteen sites volunteered to maintain prospective logs of potential candidates for the trial, which demonstrates great commitment to the study (Appendix IE). There were no apparent differences between sites that volunteered and others. Due to delays in receiving local IRB approvals, six sites recorded data for fewer months. Each site was asked to provide information about patient demographics, duration of symptoms and other characteristics of the qualifying event, timing from symptom onset to first evaluation, and presence of any exclusion criteria (Table 4.6). Patients were considered eligible if they met all inclusion criteria (Table 4.5), did not have an exclusion criterion, and were first evaluated within 10 hours of symptom onset. The most common reasons for exclusion were failure to obtain evaluation within 10 hours and fewer than three risk factors for stroke.

Table 3.2: Results of Prospective Log of Potential Enrollees

Participating Sites	23
Projected Enrollment	240
Identified Candidates	472
Sites meeting/exceeding goal	100%
Age, years; mean (range)	68 (19-100)
Female	54%
Ethnicity	
Non-Hispanic, white	60%
African American	10%
Hispanic	4%
Asian	2%
Other/Unknown	24%
Delay, hour; mean (range)	5.5 (0.1-9.5)

The identified number of eligible candidates exceeded projected enrollment of the sites (Table 3.2; Appendix IE). Even if only 60% of eligible candidates were approached and agreed to participate, sites would have met enrollment goals. Furthermore, projecting to all sites, only 25% of eligible candidates would need to be enrolled if this level of performance is reproduced at all sites. With education of emergency department staff, the number of potential candidates would be expected to increase. Thus, this prospective evaluation of enrollment suggests that projections for completion are realistic and are probably very conservative.

4 RESEARCH DESIGN AND METHODS

4.1 Study Design Overview

The primary null hypothesis of this randomized, double-blind multicenter clinical trial is, in patients with TIA treated with aspirin 50-325 mg/day, there is no difference in the event-free survival at 90 days in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared to placebo when therapy is initiated within 12 hours of onset . We define the event to be a composite outcome—ischemic stroke, myocardial infarction, or ischemic vascular death.

Patients with high-risk TIA (defined as an $ABCD^2$ score >3) who can be treated within 12 hours of symptom onset (thus requiring resolution of symptoms within 12 hours of onset) will be enrolled. Subjects will be randomized to receive clopidogrel 600 mg loading dose then 75 mg/day for the duration of the study, or to receive matching placebo. All subjects will receive aspirin 50-325 mg/day with the dose determined by the treating physician. Concomitant use of dipyridamole will be prohibited. Subjects will be followed for 90 days and risks of the composite outcome—ischemic stroke, myocardial infarction, and ischemic vascular death—will be compared in the treatment groups. The trial will be completed in 5 years, with 4,150 subjects recruited from 150 centers in the US in partnership with the NINDS Neurological Emergencies Treatment Trials (NETT) Network and the Clinical Research Collaboration (CRC). Recruitment will occur over 48 months, with a goal rate of 0.75 patients/site/month, which is reasonable based on our prior studies of recruitment, on the recruitment rate in the pilot trial, and on the expectations and past achievements of identified centers. From the perspective of the sites, the trial will be simple. A total of 530 primary outcome events is anticipated.

To increase efficiency, the duration of follow-up will be brief so that event rates are high throughout the period of study. We have chosen a composite outcome measure to fully reflect the potential benefits of treatment and to reduce the necessary sample size. In a secondary analysis, we will combine the composite outcome with major hemorrhage to capture anticipated life-changing risks and benefits in a single measure.

4.2 Study Time Table

We requested a 7-year funding period but there is currently no mechanism for applying funds over periods longer than 5 years (per Scott Janis). Thus, we have been asked to create a 5-year budget and recruitment plan. Initiation may take longer and recruitment could possibly require more time, as it has for the vast majority of other NINDS-sponsored stroke trials (see www.strokecenter.org for details) [145-150]. We have extended the study initiation period, taken steps to secure drug supply, obtained an IND waiver from the FDA, have identified a surfeit of interested sites and discussed budgets, which will be non-negotiable, and have many back up sites to bring on line. Thus, we remain optimistic about meeting milestones.

Pre-enrollment Study Initiation	9 months
Recruitment and Follow-up	45 months
Completion of Follow-up	3 months
Data Analysis and Publication	3 months
Total Duration	60 months

4.3 Organizational Structure and Communication Flow

The trial will be a partnership between the Clinical Coordinator Center (CCC) based in the UCSF Stroke Sciences Group (SSG), and the NINDS NETT Network, which will be responsible for data management and oversight of NETT sites, and the CRC, which will manage the non-NETT sites. Details of the trial leadership, management, and communications are provided in the Leadership Plan and a detailed scope of work is provided in Appendix IIA.

The UCSF SSG, directed by Dr. Johnston, involves 30 faculty and staff with expertise in study design, epidemiology, biostatistics, nursing, and study coordination. It has coordinated multicenter observational studies and clinical trials for the last decade, including QUISP (SC Johnston, PI: a CDC-sponsored group-randomized trial of a quality improvement intervention to improve secondary prevention after stroke that involved 4500 patients treated at 14 hospitals, NCT00328640) and MAPS (SC Johnston, PI: an industry-sponsored trial evaluating a new coiling technique for aneurysm treatment involving 630 patients treated at 50 sites internationally, NCT00396981). In addition, the SSG designed and coordinated the CASTIA trial, similar in design to that proposed here, which was cancelled after 240 worldwide investigators signed on (due to a threat in the patent-life of clopidogrel). The group has also managed several multicenter cohort studies, including the CARAT study [151], TIA studies described in Section 3, and the Coverdell Pilot Stroke Registry for California [152, 153]. Dr. Johnston has been the PI for all these projects; thus, he has experience leading

international multicenter clinical trials. Dr. J. Donald Easton has vast experience working on complex multicenter stroke trials and will serve as co-PI.

As a trial of a neurological emergency, POINT is well suited for involvement of the NETT. Most subjects will likely be identified in the emergency department. The NETT includes 17 "hub" institutions, each with at least three "spoke" hospitals that work together to recruit patients into simple trials of acute neurological diseases. The NETT Steering Committee independently recognized the importance of an acute TIA treatment trial and later came to the POINT investigators as a natural way to address this common clinical question. The NETT provides a proven data management system, highly motivated sites with the needed infrastructure already in place, many standard operating procedures, a superb site management team, and site monitoring expertise.

POINT is also well suited for the CRC, which will help increase the efficiency of the study and ensure high quality and timely performance, as the CRC contractor has for many past NIH and industry trials. The NINDS CRC is an important resource for identification, training, and oversight of community collaborating neurologists. The NINDS CRC has over 650 physicians registered from 45 states. The EMMES Corporation is the current contractor for the NINDS CRC Operations Center. For the past 30 years, EMMES has devoted its efforts exclusively to providing biostatistical, epidemiological, data management, computer systems development and support, as well as organizational and logistical support for clinical research, including multi-protocol and multi-site domestic and international clinical research projects. Accordingly, EMMES' organization, staff, facilities, and work methods have been developed solely for the purpose of supporting clinical research programs. EMMES has supported Coordinating Center activities for government, industry and foundation clients. A listing of projects currently supported by EMMES' 270 employees, is provided in Appendix IIC.

4.4 Selection of Sites

As discussed above, 231 sites interested in participating in the trial have been identified and have provided information about their past experience and targeted recruitment (Section 3.7, Appendix IC). We plan to invite 200 sites initially, with an estimated 175 contracts (NETT spokes do not require separate contracts), of which we assume 150 will lead to productive sites. The additional 31 sites will remain on call to replace poorly performing sites (Appendices IC and ID).

We plan to replace poorly performing sites quickly, adding a new site whenever one fails to recruit a patient after 3 months or when a site fails to get IRB and contract approval after 6 months. Thus, we have set aside funding to bring in a total of 200 sites, providing start-up funding only to sites that recruit at least one subject. If we need to involve other countries, we have a listing of international sites we previously approached that have expressed interest in participating in an acute TIA treatment trial (Section 3.7, Appendix ID).

4.5 Site Training, Certification, and Update

Both the NETT and the CRC have already provided training to their sites in Good Clinical Practice Guidelines and in outcome assessments. Online modules for training new sites are also available.

Prior to initiation of patient enrollment, Site Investigators and Coordinators will attend either a face-to-face or an on-line Investigators Meeting conducted by staff members from the CCC who have substantial experience in this regard, with assistance from both the NETT and the CRC. At this meeting, the patient selection criteria and follow-up procedures will be reviewed. Case studies illustrating potential problems in adhering to study protocol and blinding will be discussed. Case vignettes will be used to confirm comprehension of major elements of study enrollment (including appropriate thresholds for TIA diagnosis), treatment protocols, and follow-up. Additional training modules will include one for the Modified Rankin Scale. Successful completion of the training program and confirmation of approval from the local Institutional Review Board for human research will be required before a site is certified to enroll patients. The meeting will be video-recorded, along with slide presentations, and a Web-based training module will be created to train investigators who cannot make the initial meeting. Web-based meetings, with the PI and key staff available to address questions, will occur intermittently. Certification of competence will be obtainable on the Web.

The CCC, with assistance from the NETT and CRC, will finalize a detailed operations manual for all visits and procedures. The operations manual will be clear, well organized, thorough and detailed, as we created for the similar CASTIA trial. It will serve as a guide for training of clinical center personnel and will be updated periodically throughout the study, as needed. The Table of Contents from the operations manual of POINT is included in Appendix IIIE and CRFs are in Appendix IIID. As in our other studies, we will implement a system for the clinical centers to call, fax, or e-mail any procedural questions regarding the study to the CCC. The CCC will formulate answers in consultation with the Operations Committee, and will periodically distribute to

the participating centers a set of frequently asked questions and answers. These questions and answers will be available on the study website, and can be searched by topic. Intermittently, the answers to questions will be incorporated into operations manual revisions.

The NETT will conduct site visits for its sites and the CRC will manage the non-NETT sites. Each site will be visited at least once during the first two years of the trial and as needed, if questions about data quality or problems with recruitment arise. Based on experience with prior clinical trials, this is an important step to identify any divergence from protocols, to answer questions, to share solutions, to encourage more rapid enrollment, and to recognize excellence.

4.6 Contact Schedule and Measurements

Patient encounters will include screening, randomization, telephone follow-up, and a final visit. Visits for clinical events may also occur. Measurements to be taken at these encounters are listed in Table 4.1. Details of the visits are provided in the sections that follow.

Table 4.1 Contact Schedule and Measurements

Measurements	Screening/ Baseline	Randomization Day 0	Phone F/U Day 7+/-2	In Person FU Day 90+/-14	Event Visit	End of Study
Screen Failure Log	x					
Enrollment/ Demographics	x					
Inclusion/Exclusion Criteria	x					
Prior Medications	x					
Consent	x					
TIA Symptoms	x					
Medical History	x					
Vital Signs	x			x	x	
CT/MRI Scan	x*				x*	
Complete Blood Count	x*				x*	
ECG	x*				x*	
Modified Rankin Scale	x			x	x	
NIH Stroke Scale	x			x	x	
Randomization		x				
Adverse Events			x	x	x	
Concurrent Medications			x	x	x	
Stroke-Free questionnaire (QVSFS)			x	x		
Study Drug Compliance			x	x	x	
End of Study						x

*Part of standard evaluation; cost not covered by study.

4.7 Subject Identification and Eligibility

Potential subjects will be identified by neurologists and local emergency department and clinic staff in conjunction with study personnel. As we have done with other studies, the UCSF CCC will produce an engaging study brochure that can be tailored and used by the clinical centers in the recruitment of participants. Such brochures are effective in communicating to potential participants the importance of participation and in reminding them about the key goals and requirements of the study.

An electrocardiogram (ECG) will be required to rule out atrial fibrillation. A head CT or MRI scan will be required to rule out hemorrhage, vascular malformation, tumor, or abscess. (Patients with acute infarction but no symptoms are enrollable, consistent with the classical definition of TIA.) Local physicians will be responsible for interpretation. Since ECG and head imaging are recommended for all patients presenting with TIA and stroke [98, 99], the study will not cover these costs. A screen failure log will be completed for all patients who are screened but not randomized into the study. These screen failure logs will be useful in determining whether specific groups of patients are under-represented in the study, to confirm participation of sites, and to determine the most common reasons for failure to randomize.

Those meeting the eligibility criteria (Table 4.2) will be invited to participate. Patients already taking aspirin or another antiplatelet agent may be randomized at the discretion of the treating physician, as is consistent with current ASA guidelines [99]. Consent will be obtained directly from the subject prior to enrollment. Since neurological deficits will have resolved at the time of enrollment, consent from a responsible family member or legal surrogate should not be necessary.

4.8 Baseline Evaluation

The baseline evaluation will include patient demographic information, symptoms of the index event, prior medications, past medical history, family history, cigarette and alcohol use, vital signs, and a pretreatment Rankin Score. Results of head imaging, CBC, and ECG will be recorded using standardized instruments (Appendix IIID). Urgent carotid artery imaging will be encouraged but not required. If further diagnostic studies are performed, such as cardiac echo or cervicocerebral MRA, results will be recorded.

4.9 Randomization

The NETT statisticians will develop a randomization scheme (Section 4.18.1 and Appendix IIIA) that will be incorporated into the WebDCU™ system, a web-enabled clinical trials management system that was developed by the NETT Statistics and Data Management Center (SDMC) at MUSC. It has been internally validated and used in numerous large multicenter trials (Section 4.17, Appendix IIB). This system will allow Clinical Sites to perform subject randomization around the clock, 7 days a week. First, a study participant's eligibility is determined by site personnel prior to accessing the Randomization Module in WebDCU™. Qualified users then access the Randomization Interface and perform the following steps to affirm the eligibility of the participant and to randomize the participant into the trial: (1) complete a demographic information form, and (2) complete the protocol-specific eligibility checklist. If the Randomization Interface finds the participant to be eligible based on the information provided, a randomization number and a confirmatory e-mail are generated. CCC staff will be available at all times to answer investigators' questions about inclusion criteria or to resolve other problems that may arise.

The randomization number will correspond to the number on a study medication packet. The study medication packet will contain a label which has the treatment assignment (clopidogrel or placebo) concealed by a scratchable material, similar to that used in lottery tickets. This will allow investigators to unblind themselves, should it become necessary. Prior to giving the packet to the subject, the unadulterated label must be affixed to the subject's study folder at the clinical site so that it can be monitored at a later date.

Table 4.2 Inclusion/Exclusion Criteria

Inclusion Criteria
Neurologic deficit (exam finding or symptom unconfirmable on exam) attributed to focal brain ischemia, with complete resolution of the deficit within 12 hours of symptom onset.
Ability to randomize within 12 hours of symptom onset.
$ABCD^2$ score >3
Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess, that could explain symptoms or contraindicate therapy.
Exclusion Criteria
TIA with residual symptoms 12 hours after onset.
Stroke after the index event but before enrollment.
Symptoms of TIA limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo.
Gastrointestinal bleed or major surgery within 3 months.
History of intracranial hemorrhage.
Known carotid artery stenosis $\geq$50% that could be responsible for symptoms.
Clear indication for anticoagulation anticipated during the study period (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, antiphospholipid antibody syndrome, hypercoagulable state).
Qualifying TIA induced by angiography or surgery.
Severe non-cardiovascular comorbidity with life expectancy < 3 months.
Contraindication to clopidogrel or aspirin.
-Known allergy
-Severe renal or hepatic insufficiency
-Hemostatic disorder or systemic bleeding
-History of hemostatic disorder or systemic bleeding
-History of thrombocytopenia or neutropenia
-History of drug-induced hematologic or hepatic abnormalities
-Low white blood cell (<2 $x10^9$/l) or platelet count (<100 $x10^9$/l).
Anticipated requirement for long-term nonstudy antiplatelet drugs, or NSAIDs affecting platelet function.
Inability to swallow medications.
Unavailability for follow-up.
Inability to provide informed consent.
Other neurological conditions that would complicate assessment of outcomes during follow-up.
Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
Currently receiving an investigational drug.

4.10 Treatment Protocols

After randomization, subjects will be given a medication packet containing their study drug for the duration of the trial. The study coordinator must ensure that the number on the medication packet given to the subject is the same as the randomization number issued by WebDCU™.

Antiplatelet and anticoagulant agents other than aspirin will be discontinued prior to randomization. Subjects randomized to clopidogrel will receive clopidogrel 600 mg (8 tablets), and will be given a blister-pack containing a 90-day supply of clopidogrel 75 mg, with instructions to take one tablet each day. Those not randomized to clopidogrel will receive eight tablets of an identical appearing placebo, and will be given blister packs with placebo-clopidogrel and instructions to take one tablet each day. All patients will also take 50-325 mg of open-label aspirin daily; the dose will be determined by the treating physician. Use of extended-release or regular dipyridamole will be prohibited. If temporary interruption of study medication is required for surgery or other therapy, the subject's regimen will be resumed when it is considered safe by the subject's neurologist or primary care physician. Study medications will be restarted after carotid endarterectomy (Section 4.20.3). If a clear indication for anticoagulation is revealed during the 90-day study period (atrial fibrillation, for example), study medications will be stopped and anticoagulation will be initiated; subsequent events will be included in

the primary analysis.

Patients will be provided with a pocket card describing the study protocol, identifying the participating center investigator and coordinator with contact numbers, and the CCC contact number.

4.10.1 Risk Factor Evaluation and Management

To provide optimal care for study subjects and to reduce variability in management, treating clinicians will be encouraged to follow standard recommendations on evaluation and management of risk factors. These recommendations are based on published consensus guidelines [97-99], and a summary of key recommendations is provided in the Human Subjects Section, 5.5.2.

4.11 Description of Blinding System and Emergency Unblinding Procedure

The placebo for clopidogrel will be identical in appearance and taste. Minor side effects are unusual with the medication [102], so we do not anticipate that subjects or clinicians will be able to differentiate the placebo from the active drug. Standard laboratory tests cannot detect the effects of clopidogrel.

Medication packets will be coded with unique randomization numbers. The dataset linking the randomization number to the actual treatment (clopidogrel or placebo) will be generated and maintained at the NETT-SDMC. The electronic file that contains partially unblinded treatment assignment (e.g., A=clopidogrel, B=placebo) will only be accessed by one statistician (Dr. Yeatts) when preparing unblinded (closed) reports for the DSMB and the blinded (open) performance reports for the committees and for newsletters. The statistician at the CCC (Dr. Glidden) will be given access only to the locked dataset for final data analyses.

Unblinding is likely to be rare in the study. There are no data suggesting that taking clopidogrel is a contraindication to thrombolytic therapy. A major hemorrhagic event may result in the discontinuation of study medications, but knowledge of treatment assignment is unlikely to change therapy for these patients [154], and therefore, unblinding is likely to be unnecessary. However, in case of an emergency need for unblinding of a particular subject, the clinical site PI or his/her designee can scratch the cover material off the randomization label that was included with the subject's study medication packets and placed in the subject's study folder at the clinical site. Site monitors ensure that these labels are properly stored (with the respective subject's study folder) and remain blinded unless a life-threatening situation occurs such that unblinding becomes necessary.

In the event of either an accidental or deliberate unblinding, the clinical site individual who was unblinded must personally call the CCC emergency phone number to report the event. The CCC will maintain a log of these unblinding events on a restricted-access page of the WebDCU™.

4.12 Follow-up

4.12.1 Outcomes

The Site Coordinator will contact patients by telephone (or in person) at 7 days. A review of events (for possible stroke, TIA, or MI), neurological examination, and assessment of Modified Rankin Scale score will be performed at 90 days and after any possible endpoint. A screen for stroke-free status questionnaire [155], adapted to include TIA, will be administered at follow-up contacts. A follow-up evaluation will be scheduled whenever patient contact suggests that an outcome may have occurred. A listing of data collected during follow-up is included in Table 4.1. Outcomes, concomitant medications, and all adverse events will be recorded on standardized and tested instruments (Appendix IIID). Head imaging with CT or MRI will be required to document stroke and after any suspected TIA. ECG and cardiac enzyme will be required to document myocardial infarction. Appropriate laboratory testing will be required for documentation of systemic hemorrhage or other systemic complications. Autopsy will be encouraged when cause of death is unclear. Case report forms will be submitted online within 7 days of an event. Study medications will be stopped at the time an endpoint is documented.

4.12.2 Definitions of Clinical Outcomes

Ischemic stroke: An acute focal infarction of the brain or retina associated with neurological symptoms persisting more than 24 hours or of lesser duration but with death or documentation of acute brain infarction. Criteria: (1) rapid onset of a focal neurological deficit that lasts $\geq$24 hours and is not attributable to a nonischemic etiology (not associated with brain infection, trauma, or tumor, seizure, severe metabolic disease, or degenerative neurological disease); or, (2) rapid onset of a focal neurological deficit with associated acute ischemic changes in the brain seen on an imaging study.

TIA (as outcome): A neurological deficit of sudden onset, resolving completely within 24 hours attributed to focal brain ischemia without evidence of associated acute focal infarction of the brain. Criteria: (1) rapid

onset of a focal neurological deficit that lasts <24 hours and is not attributable to a nonischemic etiology (not associated with brain infection, trauma, or tumor, seizure, severe metabolic disease, or degenerative neurological disease); AND, (2) absence of lesions on acute brain imaging that are consistent with acute ischemia and could account for symptoms.

Intracranial Hemorrhage: An acute extravasation of blood into the brain parenchyma, subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: (1) Evidence of hemorrhage in the brain parenchyma, subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy; AND (2) focal neurological deficit or other symptoms (eg, headache, meningismus) attributable to the hemorrhage. We will distinguish intracerebral from other forms of hemorrhage.

Myocardial infarction: Evidence of myocardial injury attributable to ischemia from coronary artery disease. Criteria: The diagnosis of MI will be based on an algorithm developed for the HERS study that takes into account 3 categories of clinical information from the acute event: ischemic symptoms, ECG abnormalities, and elevated cardiac enzyme levels [156, 157]. The diagnosis will also be made if there was evidence of acute MI at autopsy.

Major hemorrhage (life threatening or non-life-threatening): A hemorrhagic event that resulted in clinically significant disability, symptomatic intracranial hemorrhage, intraocular bleeding causing loss of vision, the need for a transfusion of two or more units of red cells or the equivalent amount of whole blood, or the need for hospitalization [24]. Life-threatening hemorrhagic events will be defined as those that are fatal or require use of intravenous inotropic medication to maintain blood pressure, surgical intervention, or transfusion of four or more units of red cells or the equivalent amount of whole blood. Non-life-threatening hemorrhagic events will be defined as those classified as major hemorrhagic events but not as life-threatening.

Minor hemorrhage: All hemorrhagic events leading to interruption of therapy but not classifiable as major hemorrhagic events [24]. This may include bleeding events related to surgical procedures but not those related to accidental trauma.

Other treatment-related complication (serious or non-serious): Alteration in liver, renal, or hematological function or an allergic response that could be due to study medications. Criteria: Systemic dysfunction that is considered by the treating physician possibly related to study medications. Serious complications are those that require hospitalization or medication discontinuation; others are non-serious.

Ischemic vascular death: Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, or bowel or limb infarction. Criteria: Death most likely attributable to an ischemic etiology on adjudication of medical records including imaging and autopsy, when available.

4.12.3 Adherence

Adherence will be discussed during telephone interviews with the Site Coordinator. For clopidogrel and its placebo, remaining pills in the blister pack will be counted at the 90-day visit, and this will serve as the primary measure of adherence. Those taking more than 80% of the tablets will be considered adherent.

Adherence for patients randomized at each site will be monitored on a regular basis using reports generated automatically in the WebDCU™ system. The sites identified for the study have reported adherence rates of about 95% in prior stroke trials. However, if there are systematic problems with adherence at a particular site, the NETT and CRC will know this rapidly and will contact the site to identify possible solutions.

Concomitant medications will also be noted at follow-up visits.

4.12.4 Final Visit

At the final visit, the study physician will discuss options for antiplatelet therapy. Unless the subject's treating neurologist or primary care physician has a particular preference for one of the proven antiplatelet medications, clopidogrel 75 mg will be prescribed for patients who can afford clopidogrel or have medical coverage for it. For others, aspirin 81 mg will be prescribed. The physician will confirm that a high-dose, high-potency statin is also prescribed [158] and that blood pressure and diabetes are well controlled. Diet, exercise, and appropriate action in the event of stroke will also be discussed.

4.13 Rationale for Combined Outcome Measure

The primary outcome measure will be the composite of ischemic stroke, myocardial infarction, or ischemic vascular death. This composite outcome was chosen in order to isolate major clinical events that may be beneficially affected by clopidogrel. Each element of the composite outcome is life altering and is likely to

influence a clinician's decision about whether to employ a therapy. Antiplatelet therapy has been shown to reduce risk of stroke, MI, and ischemic vascular death in other studies. We prefer to include pulmonary embolism in our definition of ischemic vascular death to allow easier interpretation of this category of events and because the expected number of these events is extremely low. Major hemorrhagic events, including intracranial hemorrhage, will be evaluated separately to allow direct comparison of risks and benefits (and to prevent the common error of double-counting hemorrhages when interpreting trial results that incorporate hemorrhage into the primary outcome). In a secondary analysis, we will combine the primary outcome measure with major hemorrhage (intracranial and major systemic).

4.14 Rationale for 90-Day Study Duration

POINT is an acute intervention trial that will provide data unique from prior and on-going long-term secondary prevention trials. We had previously chosen a 6-month study period to evaluate acute and subacute impacts. However, prior reviewers thought that a 90-day trial was more consistent with our goals to establish acute treatments for TIA. Also, the results of the MATCH and CHARISMA trials suggest that most of the benefit of combination clopidogrel-aspirin is acute and that an increased risk of hemorrhage counter-balances long-term benefits in reduction in vascular events beyond the acute period, at least in a broader population with vascular disease**. We are not trying to revisit the long-term, non-acute studies already performed: The benefits of clopidogrel-aspirin are not worth the risk in long-term follow-up**. A short-duration trial will be simpler, will still capture the vast majority of events expected in the first year, and will provide an answer sooner.

One could argue that 30-day follow-up would be adequate since the majority of events will occur during this time frame and more data are available on the use of combined aspirin-clopidogrel afterwards. However, when we discussed this issue with clinicians, they preferred a longer duration study because the 90-day follow-up period is a standard in the field and delayed cross-over in event rates could be missed. We also note that there is little advantage of a shorter duration follow-up in trial performance. It would require an increase in sample size (approximately 15% increase), costs would not decrease significantly given the fixed number of follow-up visits, and additional losses to follow-up are not expected to have an important impact during the 30-90 day period. Thus, we have elected to follow patients for 90 days.

4.15 Rationale for Secondary Outcomes and Analyses

4.15.1 Main Secondary Outcomes and Analyses

Primary Composite Outcome Measure in a Per-Protocol Population: Although we expect that protocol violations and medication non-adherence will be rare, we will perform an as-treated analysis, as is expected in most clinical trials.

Main safety outcomes, intracranial, major, and minor hemorrhage: The risk of major hemorrhage may influence a clinician's threshold for using the studied treatments. Though reversible manifestations of hemorrhage are not likely to be as important to patients and clinicians compared to those incorporated in the primary composite outcome, their risk may alter the decision to treat in specific instances.

Secondary Composite Outcome Measure of ischemic stroke, MI, ischemic vascular death, major hemorrhage: This measure will incorporate potential benefits in terms of reduction in ischemic events with potential risks in terms of increased major hemorrhage.

4.15.2 Tertiary/Exploratory Outcomes and Analyses

Tertiary Composite Outcome Measure of ischemic stroke, TIA, MI, or ischemic vascular death: In FASTER and CHARISMA, there was a substantial impact of clopidogrel on recurrent TIA. TIA is not included in the primary outcome measure because its diagnosis is less reliable and its impact less than other components, but recurrent TIA does increase resource utilization and is frightening to patients. Based on results from the pilot cohort studies, we anticipate a 24% event rate for this composite outcome (Section 4.18.2).

Ischemic stroke: We anticipate that ischemic stroke will be the most common outcome of the trial, and the therapy has been chosen specifically to reduce its risk. If ischemic stroke is reduced with treatment but other elements of the composite outcome are unchanged or increased, implications for further studies will be different.

Intracranial hemorrhage: An increase in hemorrhagic stroke with treatment may have different implications in terms of appropriate dosing in future studies. Furthermore, if therapies become available to reduce risk of hemorrhage, it will be important to know whether TIA is an appropriate condition for their study and use.

<u>The following measures will be evaluated comparing treatment and safety in those with and without the defined characteristic, and testing for an interaction:</u>

Treatment effect in those previously taking aspirin: In WARSS, the risk of recurrent stroke was greater in those with a history of stroke who presented with an index stroke while taking aspirin, whether the patient was treated with aspirin or warfarin [159]. In the KPNC ED TIA study, the risk of the composite outcome was 14% in the third of patients previously taking aspirin compared to 12% in those not taking an antithrombotic medication at presentation (p=0.30). For those previously taking aspirin who are to be included in POINT, the 90-day risk is projected to be 18%. "Aspirin failure" may be a setting in which the addition of clopidogrel is particularly effective.

Treatment effects in women: Some studies have shown smaller reductions in cardiovascular events in women taking aspirin compared to men [160] while others have not [64, 65]. In women, ticlopidine was more effective relative to aspirin [161].

Treatment effects in African-Americans: Overall rates of stroke are two-fold higher in African Americans compared to whites [27, 162, 163]. The distributions of stroke subtypes and risk factors are different in African Americans [164, 165]. Few studies have evaluated the influence of ethnicity on response to stroke prophylaxis. Given ethnic differences in stroke and the absence of data, it is important to determine whether African Americans respond differently to the study medications.

Treatment effects in those taking statins: Some concerns about decreased efficacy and increased hemorrhage with clopidogrel in those taking statins remain, although large-scale trials have not confirmed an effect [9-15]. Nonetheless, further data on this question would be reassuring.

Primary outcome and intracranial hemorrhage in those with and without imaging evidence of infarction on head imaging: Some patients with transient symptoms but imaging evidence of acute infarction will be included. They appear to be at greater risk of subsequent ischemic stroke [19, 128, 166, 167] and may be at greater risk of intracranial hemorrhage. To evaluate this possibility, we will compare risk of the primary composite outcome and of intracranial hemorrhage in the subgroups with and without new ischemia on the initial head CT or MRI.

4.16 Adjudication of Outcomes and Complications

Outcomes will be detected by the Participating Centers during follow-up evaluations. The Participating Centers will be responsible for compiling an event packet, comprised of the hospital discharge summary and other relevant documents, and will send the packet to the coordinating center. All outcomes will be reviewed by the Adjudications Committee consisting of two independent groups of reviewers (the neurologists and the cardiologists/internists groups), with two independent reviews each and a third reviewer resolving disagreements. Neurologists will review all potential stroke outcomes (and classify cause by the TOAST criteria), and cardiologists/internists will review possible myocardial infarctions, and both groups will review possible ischemic vascular deaths and major hemorrhages.

The CCC has extensive experience with adjudication of a variety of cardiovascular outcomes and deaths, and is accustomed to coordinating the process.

4.17 Overview of Data Collection and Management

Data management will be handled by the NETT-SDMC which is housed in the Department of Biostatistics, Bioinformatics and Epidemiology at the Medical University of South Carolina (MUSC). All activities will be conducted in coordination with the study co-PIs, the NETT-CCC, the CRC, and the clinical sites. Details of are provided in the Data Collection and Management Plan in Appendix IIIB.

The entire study will be conducted using an electronic data acquisition method where all clinical data on randomized subjects will be data entered by the clinical site personnel via the study website interface. The data will be managed (including data queries) by the SDMC using the WebDCU™ system. This electronic data management system is currently used for several federally-funded multicenter studies including NINDS-funded projects such as the NETT Network (1 U01 NS059041) and the ALIAS and IMS III trials (U01 NS054630-01), an NIMH project (R01MH69887-01) and an NIDDK project (1R01DK074739-01). This user-friendly web-based database system, developed and validated by the SDMC, will be used for subject randomization, data entry, data validation, project progress monitoring, subject tracking, drug shipment tracking, user customizable report generation and secure data transfer.

The data validation procedure will be implemented in two stages. First, the automated data checks will flag items that fail a rule and the rule violation message will appear on the data entry screen at the time of data entry. The Study Coordinator at a clinical site will see these rule violations and will be requested to address it. His/her choices are to: (1) correct the entry immediately; (2) correct the entry at a later time; or (3) if the entered data is confirmed to be correct, dismiss the rule by checking off on that option provided by the

WebDCU™ system. Any changes made in the website will have a full audit trail. Secondly, for some checks that are more complicated, additional consistency checks will periodically be run after data entry occurs at the clinical site. All data items that fail the programmed consistency checks will be queried via the data clarification request (DCR) process initiated by SDMC data managers. Site monitors will also be able to generate DCRs when discrepancies are found during source to database verification. The DCRs will be generated, communicated to the clinical sites, and resolved on the secure study website.

Table 4.3. Assumptions and specifications used to calculate sample size

Proportion with events at 90 days in placebo (aspirin) group	15.24%
Relative risk with addition of clopidogrel	0.77
Delay between symptom onset and enrollment	12 hour
Loss to follow-up at 90 days (from FASTER)	2%
Crossovers at 90 days (from FASTER, non-event related)	12%
Impact of crossover on events	29%
Inflation factor for crossovers and losses if events at 90 days	31%
Modeled inflation factor to account for crossovers/losses	5.0%
Power	0.90
Alpha (2-sided)	0.05

In addition to the study database, the SDMC will provide the clinical site staff access (via password) to a standard set of web-enabled tools, including subject visit calendar, subject accrual status, case report form completion status, and outstanding DCR status pertaining to their respective clinical sites. Furthermore, all approved study materials, such as the protocol, informed consent template and Manual of Procedures, will be housed on the website to ensure that the clinical sites always have access to the most current trial documents.

Backup tapes of data collected on the WebDCU™ system will be generated on a daily basis and full-verified backups will be performed every Friday. The tapes, which are in current rotation, will be stored off site in the department IT manager's fire box. Once a backup tape has been filled or one month of active duty has passed, the tape will be archived off-site with a data storage vendor for long-term storage. The SDMC's software (logical) security policy has three main components: (1) antiviral protection with McAfee Enterprise Edition to POINT all servers and workstations from infection with virus definitions updated on a daily basis; (2) restricted access with password policies; and (3) two levels of firewall protection – MUSC firewall protection between the University and outside computer systems and the SDMC firewall on web servers with limited access. Furthermore, the WebDCU™ system uses SSL encryption methods that allow a secured Internet transfer. All transmission of data will be compliant with the standards set forth in the Health Insurance Portability and Accountability Act (HIPAA).

4.18 Statistical Issues

A detailed Statistical Analysis Plan is included in Appendix IIIA. We briefly describe the randomization scheme, sample size calculations, and analysis plan below.

4.18.1 Randomization Scheme

Randomization will be implemented centrally via the WebDCU™ system. In order to maintain the 1:1 treatment assignment balance throughout the study because of the planned interim safety and efficacy analyses, we propose to use the minimization+biased coin approach [168]. This is similar to stratified randomization but on the subject level. The covariable to "stratify" on is the clinical site.

4.18.2 Sample Size Estimates

Primary Null Hypothesis

In patients with high-risk TIA treated with aspirin 50-325 mg/day, there is no difference in the event-free survival at the 90-day follow-up in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared to placebo when therapy is initiated within 12 hours of onset. The event is a composite outcome consisting of ischemic stroke, myocardial infarction, or ischemic vascular death.

The minimum necessary sample size in the trial is established by the requirement to detect the smallest expected, clinically meaningful treatment difference comparing the treatment with placebo. A relative risk reduction of 23% is the smallest difference we feel is of clinical importance. With a sample size of **4,150 patients** (rounded up from 4,142), we will have 90% power to detect a relative risk reduction of 23% with a two-sided alpha of 0.05, 12% total medication crossovers and 2% losses to follow-up (Table 4.3). The sample size was estimated based on the ratio of the hazard rates of the two arms assuming an exponential survival distribution (hazard rate 16.5% in placebo group and 12.4% with clopidogrel), with inflation to account for two interim analysis for efficacy at equal intervals using O'Brien and Fleming stopping boundaries, and 12% crossovers and 2% losses to follow-up, as seen in FASTER [8]. Most events will occur early in the follow-up

period and hence a smaller fraction of events will be lost and a smaller total correction in sample size is required (5.0%, as explained below and detailed in Appendix IIIB.

Risk of outcome in placebo (aspirin only) group-. To reduce the necessary sample size and reduce the likelihood that episodes due to causes other than cerebral ischemia are included while still opening up the trial to the vast majority of patients with acute TIA, we have selected inclusion criteria that will result in a higher event rate in enrolled patients. Using data from the pilot cohort studies of natural history (Section 3.1) [16, 17], we evaluated the risk of the composite outcome during 90-day follow-up. In Table 4.4, several potential entry criteria are displayed to illustrate the consequences of each. Based on these calculations, we selected an entry criterion of an $ABCD^2$ score >3 is an excellent compromise between percentage eligible (69%) and overall risk. The 90-day risk of the composite outcome in this group is 15.24% among those treated with aspirin, excluding events that occurred with 12 hours of symptom onset. As discussed in Section 3.1, this event rate is similar in both emergency department cohorts and in a separate clinic cohort. Other potential criteria based on the $ABCD^2$ score are also shown in Table 4.4 for comparison [17].

As discussed in Sections 0.8, 2.2, and 3.1, we suspect that the event rate in the cohort studies is representative of results of the participating centers. Our pilot study was performed in a health maintenance organization, and care at academic medical centers may be more aggressive, particularly given our efforts to standardize and optimize medical therapy, so event rates in the trial could be lower than those projected. However, 92% of patients in the pilot study were treated with a secondary prophylactic medication and the event rates used for power analyses were based on the sample receiving aspirin. Also, there was no suggestion of benefit with lipid-lowering medications in the pilot trial [8] or in a secondary analysis of EXPRESS (Section 0.8). Furthermore, 5.6% of the spells called TIA in the pilot study were judged unlikely to represent true TIA when reviewed by a neurologist; event rates are expected to be higher with more careful exclusion of non-ischemic events, as expected in the trial. We anticipate that more careful diagnosis will counter-balance any reductions in event rates due to improved care (the Hawthorne effect) or a more compliant patient population (volunteer bias) [169]. Finally, earlier enrollment, exclusion of minor stroke, and use of the $ABCD^2$ score are expected to result in higher event rates compared to FASTER, which had a composite event rate of 12% [8]. In that trial, statins had no impact on outcome. Therefore, we anticipate that projected event rates are accurate. Nonetheless, we have chosen a sample size that will allow 80% power to detect a difference even if event rates are 23% lower than projected; that is, even if event rates are 11.8% in the control group, lower than those seen in FASTER, we will have 80% power to see an effect and we are studying a population that is at much higher risk of stroke.

Table 4.4 Sample size calculations for various entry criteria, based on the pilot cohort studies.*

			90-Day Risks*			Required Sample Size: 90% Power		Required Sample Size: 80% Power	
Potential Entry Criteria	**No.**	**%TIAs meeting criteria**	**Isch Stroke**	**CV/death****	**Stroke/CV/ Death**	**No drop outs**	**w/ cross, LTFU**	**No drop outs**	**w/ cross, LTFU**
All TIA	2776	100%	10.20%	1.84%	12.04%	5162	5420	3867	4060
Excluding low-likelihood	2325	84%	11.77%	2.15%	13.92%	4383	4602	3279	3443
$ABCD^2$ score									
>2	2182	79%	12.18%	1.98%	14.16%	4293	4508	3208	3368
>3	1907	69%	13.39%	1.85%	15.24%	3944	4142	2951	3099
>4	1361	49%	15.32%	1.92%	17.24%	3421	3592	2556	2684
>5	737	27%	17.33%	1.94%	19.27%	2991	3141	2240	2352

*Event rates account for aspirin use and 12 hour delay in treatment. **Excludes patients who also had stroke within 90 days

Minimum clinically significant relative risk reduction-. Sample size is based on the desire to detect a 23% relative risk reduction (or equivalently, a 25% reduction in the hazard rate assuming an exponential survival distribution). This level was selected because it represents a minimal change to dramatically change practice (not because we think it is the true underlying effect). With this relative risk reduction, treatment of 28 patients with TIA (regardless of other risk factors) would be expected to result in one fewer catastrophic event—ischemic stroke, myocardial infarction, or ischemic vascular death—over 3 months, based on the pilot study results (Section 3.1). This effect is likely to be considered clinically important by treating physicians; this level of benefit is greater than that of aspirin in secondary prevention after stroke, and aspirin is widely accepted and utilized in this setting. Given prior safety results (Section 2.3), we do not anticipate excess intracerebral or life-

threatening hemorrhage with clopidogrel in patients with TIA, particularly given the short duration of treatment but we are searching for a slightly greater RRR at account for a possible effect on hemorrhage risk. Though clopidogrel is more costly than aspirin, the cost of clopidogrel will decline rapidly after 2012 when generics become available, and the use of clopidogrel would be expected to be cost saving at a 23% RRR (Section 2.4). Finally, with our sample size, we will have 80% power to detect a 19% RRR.

As discussed in Section 2.3, we anticipate that clopidogrel will reduce risk of the composite outcome—ischemic stroke, myocardial infarction, and ischemic vascular death—independent of aspirin. The relative risk reduction (RRR) of clopidogrel compared to placebo demonstrated in the FASTER pilot trial was 28% (for the composite), but confidence intervals were broad given its small size [8]. Other estimates of RRR can be obtained from subgroup analyses of trials with broader entry criteria, though these include subgroups (esp, stroke) that we don't anticipate will respond as well, and treat patients for long periods of time, when the risk of drug remains and benefit is likely lower. In the CHARISMA trial, patients with stroke/TIA treated with clopidogrel-aspirin within 30 days of stroke or TIA had a 24% RRR compared to aspirin alone. In the MATCH trial, a RRR of 17% was demonstrated in patients treated within 7 days of stroke or TIA for aspirin-clopidogrel compared to clopidogrel alone [115]. Based on these prior studies, we suspect the actual RRR will be greater than 23%.

Delay between symptom onset and enrollment-. Strokes may occur before randomization due to delays in enrollment. For this sample size calculation, patients with events occurring within 12 hours of TIA symptom onset were eliminated from the analysis of event rates since many of these patients would not have been enrolled and treated before the outcome occurred.

Losses to follow-up/non-adherence-. Based on the results of the FASTER trial, we estimated that 3% of patients would be lost to follow-up and 12% would crossover to the other treatment group for a reason other than an outcome event (eg, intolerance, non-adherence, desire or need to take active drug) [8]. The follow-up in the trial is very brief, the CRC contractor has consistently achieved 95% follow-up rates in trials of much longer duration, and NETT sites have similarly been carefully vetted and are proven. Furthermore, the average follow-up to trial completion of the included centers was over 95% in recent stroke trials. Most importantly, though, the majority of outcomes are expected to occur during the first few days of the study, when losses are expected to be minimal. For example, discontinuation of medications for carotid endarterectomy would be expected to occur at least several days after enrollment, at which time more than 50% of outcomes would have been expected to occur.

To estimate the impact of a 2% loss-to-follow-up rate and 12% crossover rate at 90 days on expected events in the trial, we conservatively inflated necessary event requirements by 29% due to crossovers per the methods described by Piantadosi (Clinical Trials, p 175-6) and simulated expected event rates given this inflation factor while modeling losses and crossovers as occurring evenly throughout the 90 day follow-up (see Appendix IIIB for the model). Expected events were calculated based on the actual occurrence of events in the TIA cohorts identified in the emergency department (Section 3.1) [16, 17]. Given the very high early risk of events, a small percentage of losses would be expected during the period of greatest risk so the impact of losses and crossovers is much more modest than would be expected with an even distribution of risk. In the model, a 5.0% inflation of sample size was required to produce the same number of events with 12% crossovers and 2% losses, and we have adjusted our sample size estimates accordingly.

Power and alpha-. **Given the uncertainty in the assumptions used to predict effect size and event rates, we have chosen a sample size to provide 90% power. With this sample, we will have 80% power to detect a relative risk reduction of 19%. Further, we will have 80% power if the event rate is 23% lower than projected or early losses to follow-up are 4-times more frequent than anticipated**. **Power curves are shown in the Statistical Analysis Plan (Appendix IIIA).**

4.18.3 Secondary Outcomes

A number of other secondary outcomes will be evaluated, including risk of ischemic stroke, hemorrhagic stroke, and major hemorrhage (hemorrhagic stroke, transfusion, or life-threatening blood loss). The influence of gender and ethnicity will be evaluated in subgroup analyses. Using data from the pilot cohort study (Section 3.1) [16, 17] and the ethnic distribution of patients with TIA treated at participating centers, we calculated the power to detect a 22% RRR (relative risk [RR] 0.78) with either therapy compared to its placebo and the largest detectable RR with 80% power for a two-sided alpha=0.05. (SAP, Appendix IIIA).

4.18.4 **Statistical Analyses**

Primary Outcomes

The primary analysis will be intention to treat, with inclusion and treatment group defined at the randomization assignment. Missing values will remain missing and patients will be censored at their last follow-up assessment (time of clinical event, end of study, or last visit prior to loss to follow-up); based on projected loss rates, we expect only 5 subjects to be lost at 7 days and 70 subjects to lost at 90 days, so the problem is relatively minor. We will report Kaplan-Meier estimates of the cumulative risk of an event—stroke (ischemic or hemorrhagic), myocardial infarction, and vascular death—during maximum 90-day follow-up, with hazards ratios and 95% CI calculated using Cox proportional hazards methods (to provide an estimate of treatment effect) and the log-rank test to evaluate the treatment effect. This approach is being taken to maximize the time dependent information in the trial while still acknowledging the ease of interpretation of risks. The overall Type I error for the primary analysis will consider two-sided alpha=0.05 significant.

The number of interim evaluations of the primary outcome data will be determined by the DSMB, but we propose interim evaluations when 1/3 and 2/3 of study endpoints have been observed. We anticipate a total of approximately 530 events. We plan to adopt the O'Brien-Fleming stopping rules [170, 171].

Secondary Outcome Events

The analysis strategy outlined for the primary outcome will be used for most of the secondary analyses. We propose to test each secondary outcome event at the two-sided alpha of 0.05, recognizing the dangers of inflating the type I error probabilities. However, we view these as exploratory hypotheses that may or may not support the results of the primary analysis.

4.19 Data and Safety Monitoring Procedure and Plan

An external **Data Safety and Monitoring Board (DSMB),** comprised of at least five members who are not involved or affiliated with the trial, will be appointed by and report to the NINDS. Open and closed reports will be prepared by the NETT-SDMC statisticians. The committee will meet every 6 months with additional meetings scheduled as they require.

Three **Clinician Safety Monitors**, who are based at the NETT Coordinating Center at the University of Michigan, will review safety data on SAEs and specified AEs as it becomes available to the CCC, including adjudicating whether events are serious, related to the study drug, or unexpected. Two monitors will review each event with a third adjudicating any disagreements. The monitors will also review potential differential trends of pre-specified AEs and SAEs. The safety data will be made available to the monitors on the WebDCU™ to allow real-time access, review and reporting. The monitors will report to the DSMB and may advise convening an early meeting if rates of SAEs are excessive in one treatment group over the other. Once the safety monitors have finished their review of a SAE, an automatic email notification will be sent to the sites notifying them of the event. The sites can then log on to WebDCU™, print a blinded report of the SAE, and send it to their IRB in accordance with local IRB requirements. This study has received an IND waiver from the FDA.

4.19.1 Interim Analyses and Stopping Rules

Unacceptable Safety Profile. The DSMB will be asked to use judgment to weigh evidence of efficacy and rates of adverse events. The committee will meet at least every 6 months, as outlined in NINDS guidelines, to assure patient safety; additional interim analyses may be requested by the DSMB.

An early formal safety evaluation is recommended when 500 patients have completed 90-day follow-up (250 in each treatment arm; able to detect significantly a 5% absolute increase in hemorrhage risk). During this evaluation, detailed information about complications will be presented to the DSMB. If rates of serious adverse events are judged to be excessive relative to potential benefits, enrollment will be discontinued. Since frequency, severity, and distribution of adverse events, as well as early evidence of benefit, are all likely to affect the decision to discontinue a treatment arm, establishing strict criteria for stopping *a priori* is imprudent; rather, careful judgment of the DSMB will be required (see Draft DSMB Charter, Appendix IIIC).

Superiority or Inferiority Established Prematurely. The number of interim evaluations of the primary outcome data will be determined by the DSMB, but we are proposing interim evaluations when 1/3 and 2/3

of study endpoints have been observed. We anticipate 530 events and would propose interim analyses after approximately 177 and 353 endpoints. In the determination of whether to stop enrollment for premature detection of benefit or harm, we suggest an O'Brien-Fleming type rule [170, 171].

4.20 Potential Problems and Plans to Address Them

4.20.1 Low or High Patient Recruitment

Most of the centers selected for this study have proven ability to enroll a large number of patients into acute treatment trials of stroke and TIA, and have been chosen from a large number of interested centers. It is unusual for a study this size to identify all sites in advance. The estimated rate of enrollment is 2.3-fold times that required to complete enrollment on time, so the estimate of time to completion is conservative. Furthermore, a large subgroup of sites has prospectively identified potential enrollees at a rate 1.7 fold times that projected for enrolling patients (Section 3.2.1). However, we will be including sites recruited by the CRC with less experience doing clinical trials in order to increase the larger pool of capable sites for stroke/TIA trials. Several proven strategies to encourage enrollment will be employed including: 1) real-time daily monitoring of enrollment so that the CCC, CRC, NETT, and sites are aware of under-enrollment immediately, 2) newsletter and on-line reports comparing centers to support a competitive spirit, 3) site visits, 4) adequate per-patient reimbursement, and 5) a simple enrollment and follow-up protocol. Furthermore, we will eliminate sites that fail to enroll patients rapidly, and replace them with others, chosen from a list of alternate sites, which have been high enrollers in prior stroke trials and have already expressed interest in participating (Appendix ID). We have set aside funding to recruit an additional 50 sites into the trial if necessary. Given the past performance of these sites, projected enrollment 2.3-fold faster than target, and excellent performance on the prospective logs, we anticipate completing enrollment early. However, we do not consider inclusion of this number of sites excessive since the cost of including more centers is much less than costs associated with failure to complete the trial on time, a common problem with recent stroke trials.

4.20.2 TIA Is Difficult to Diagnosis

TIAs are sometimes difficult to diagnose, and even neurologists may disagree on the diagnosis when faced with the same patient [172, 173]. Thus, some patients who may not have had a true TIA could be included in the study, and thereby placed at unnecessary risk of complications from the treatments studied. However, even in a population defined by an emergency physician diagnosis of TIA, the risk of stroke is extremely high, so current levels of misdiagnosis are not obscuring a very high early risk. To reduce this problem even further, inclusion criteria require that patients have symptoms that are more specific for TIA and are associated with a greater risk of subsequent stroke [16, 17, 129]. By enhancing the specificity of the diagnosis of the treating physician, we will eliminate some conditions other than TIA and allow identification of a group in whom intervention is clearly justified. Furthermore, since completely accurate diagnosis of TIA is not possible in clinical practice, it is appropriate to study the group that would be treated in actual practice: Findings must be generalized to this group.

4.20.3 Interruption of Therapy

Some patients may undergo carotid endarterectomy. In the pilot study (Section 3.1) [16], only 12 of 1707 patients had an endarterectomy performed within 90 days of the TIA. Although the likelihood of endarterectomy may be greater in the trial due to the nature of centers included in the study, we do not anticipate that more than 3% of patients will require endarterectomy during the study period. This rate has also been confirmed in more recent studies, such as EXPRESS and FASTER [8, 22]. Furthermore, since the greatest risk of adverse events is in the first few days after a TIA, much of the anticipated treatment effect is expected before an endarterectomy is likely to be scheduled. When endarterectomy is planned, study medications will be stopped 5 days before. Treatment will be resumed after surgery, when deemed safe by the treating physicians. Treatment assignments will not be revealed, and these patients will be analyzed as randomized.

For other invasive procedures that should not be delayed until the end of the study period, medications will be stopped 5 days before and will be resumed when considered safe by the treating physicians. Treatment assignments will not be revealed, and these patients will be analyzed as randomized.

For patients with an established clinical indication for anticoagulation during the study period (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, antiphospholipid antibody syndrome, hypercoagulable state), study drug will be stopped and the patient will be followed until

study completion.

These protocols are designed to reflect potential usage of the tested medications in actual practice, where the presence of a carotid stenosis will likely be unknown at the time a treatment decision is made at least in some cases, and where the treatment could influence results of the procedure.

4.20.4 Thrombolysis

Aspirin alone is not considered a contraindication to tPA use [174], and was not associated with hemorrhage risk in the NINDS trial [175]. There are no data documenting the safety of tPA for ischemic stroke in patients taking clopidogrel alone or clopidogrel and aspirin, but there are suggestions from case reports and the laboratory that tPA may actually be more effective and no riskier when clopidogrel and aspirin are on board [176]. Even so, some physicians may not be comfortable administering tPA to patients who may be taking clopidogrel and aspirin, and those unable to receive tPA for ischemic strokes may be left with more severe deficits.

We suspect that the number of patients excluded from receiving tPA because of the study will be small. Even in academic centers, only 4% of patients with acute ischemic stroke receive tPA [177]. Although we anticipate that rates of usage would be higher in patients presenting after TIA since they would be better informed about the benefits of seeking treatment rapidly, it seems unlikely that more than 10% of ischemic strokes patients would be candidates for tPA if not on treatment.

Although we will not discourage use of tPA in study participants regardless of randomization, assignment to clopidogrel will be revealed immediately for all potential thrombolysis candidates whenever requested by the treating physician. Thus, if there is no benefit to clopidogrel, we estimate that fewer than 30 patients in the study would be unable to receive tPA for an ischemic stroke because of assignment to clopidogrel (2600 randomized to clopidogrel, 309 with ischemic stroke, 10% arriving in time for tPA). If clopidogrel reduces relative risk of stroke by only 10%, the same number of strokes would be entirely prevented. The trade off appears justified and underlines the potential benefits of prevention strategies.

4.21 Questions Relevant to the POINT Application

4.21.1 Why should the NIH sponsor this study rather than the pharmaceutical industry?

We have already attempted to work with industry and a trial called CASTIA was actually funded and initiated with Dr. Johnston PI. The trial was cancelled due to business concerns from a patent infringement lawsuit and introduction of a generic. By the time a trial could be completed now, there would be few years left under the clopidogrel patent, which is due to expire in 2012. Sponsorship by industry simply is not possible, even with our prior herculean (sisyphusian?) efforts.

There are other antithrombotic agents available or in development that may be even more effective than clopidogrel. In fact, we have had discussions with several companies about performing such a trial (eg, Johnson & Johnson, Daichi-Sankyo, Pfizer, Portola, Fibrogen, Paion, Lilly). However, all the agents they are developing will be very expensive. Waiting for another antithrombotic agent from industry is less desirable because the benefit to society would be blunted because of much higher drug costs [123, 178]. If clopidogrel is effective, it will raise the bar higher for more expensive agents.

4.21.2 Are preparations and preliminary data adequate to justify proceeding to a Phase III trial?

We believe it is time for a phase III trial for several reasons. First, the natural history of TIA has been clearly defined in a large number of diverse populations. Second, a pilot trial of patients with acute TIA or minor stroke has suggested that the combination of clopidogrel-aspirin is safe relative to aspirin alone and demonstrated that the actual treatment effect could be large. Third, clopidogrel-aspirin has been found previously to be relatively safe in other studies of patients with stroke, and TIA is likely to be an even safer setting. Fourth, there are strong data from subgroup analyses of several trials supporting the potential benefit of clopidogrel combined with aspirin when therapy is initiated soon after an ischemic event. Fifth, our participating centers have proven ability to enroll a large number of acute stroke patients into trials, have frequently met or exceeded enrollment goals, and have projected inclusion of 110% more patients than would be required to meet study goals. Sixth, the UCSF CCC, NINDS NETT, and NINDS CRC are highly experienced and complement each other; they have the staff and systems already in place to complete preparations for enrollment, to train participating centers and insure goals are met, and to gather and maintain accurate and complete data. Seventh, a large subgroup of the sites in a prospective study has shown that the projected enrollment rates are realistic.

4.21.3 Is it ethical to randomize someone on aspirin at the time of the TIA to continue only on aspirin?

Current AHA guidelines on secondary prevention of stroke and TIA state, "For patients who have an ischemic cerebrovascular event while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well studied in patients who have had an event while receiving aspirin [99]." Given the lack of evidence that changing from aspirin to another agent is beneficially in this setting, it is perhaps not surprising that only four of the sites have raised concern about this issue in our survey (Section 3.4).

4.21.4 Why not work together with the FASTER II investigators?

We have worked closely with the FASTER investigators in designing the two trials and in considering a close collaboration, and their leadership is included in our Executive and Steering Committees. Funding of FASTER II is uncertain. Thus, it would be unwise to hinge our trial on their efforts. If they are funded, we plan to perform a meta-analysis, but it will also be useful to have two trials, each with different study populations thus increasing the generalizability of findings (Appendix IH).

4.21.5 What is innovative about this grant?

After 8 years promoting this trial concept, it hardly seems innovative. Yet, still, this is the first pivotal trial to recognize TIA as an acute disease and to test urgent therapeutic interventions in this setting. TIA has previously been excluded from therapeutic trials of acute interventions, and in prevention trials, enrollments have been delayed by days to months after the original event. Since the risk of stroke after TIA is greatest in the first few days, this trial is the first to appropriately target those at greatest risk.

Establishing TIA as an emergency and identifying an effective acute therapy would dramatically alter the way that TIA management is conceptualized. Currently, there is not general acceptance that TIA is an emergency [85, 179]. This is primarily because there are no established effective acute treatments. POINT could change this, and this would represent a major conceptual innovation.

5 HUMAN SUBJECTS

During the course of the trial, 150 sites will enroll 4150 patients with TIA. Before enrolling patients into the study, all collaborating sites will obtain approval from local Institutional Review Boards (IRBs), which will have access to all study documentation and educational materials.

5.1 Study Population

Most enrolled patients will be elderly (mean age 72 years with 78% older than 60 years in the pilot study), with about an equal number of males and females (53% were female in the pilot study). Neurological impairment at the time of enrollment is expected to be minimal since the deficits prompting diagnosis will have largely resolved. Vascular risk factors, including diabetes, hypertension, and coronary artery disease, are expected to be common [16].

Pregnant women will be excluded from the study because the risk of clopidogrel is unestablished in this population, and this drug may increase risk to the fetus. No other vulnerable population will be excluded from the study.

5.2 Research Material

Patient demographic characteristics, clinical data, cognitive assessments, and quality-of-life assessments will be recorded as part of the trial.

5.3 Recruitment and Consent

Emergency-department physicians and neurologists at participating centers will identify potential subjects for the study. If patients are agreeable, study investigators will be informed about potential subjects, and will explain face-to-face the study purpose, protocol, risks, and potential benefits. Only study investigators will obtain consent for the study.

Written consent from the participant will be required. The consent form will clearly document in lay language all aspects of the study protocol, risks, benefits, and contact information; it will be approved by the IRB at UCSF and by the participating center. Patients will be given a copy of the consent form.

For those unable to provide consent, a legal guardian may serve as a surrogate, although we suspect this will be extremely rare since we are enrolling patients who have recovered from their neurological impairment. For children, the child will assent and the legal guardian will be required to consent.

5.4 Potential Risks

The greatest risks to subject health are the study medication, clopidogrel, when combined with aspirin. These agents have not been tested specifically after TIA, so rates of hemorrhage must be estimated from studies of stroke and acute coronary syndromes.

All patients in the study will receive aspirin. The benefits of aspirin outweigh its small excess risk of systemic and intracranial hemorrhage [64, 65].

Clopidogrel in combination with aspirin is likely to be associated with a small excess risk of major systemic hemorrhage (estimated at 1% for the study period) but no increased risk of life-threatening or intracranial hemorrhage [81, 116, 180]. Clopidogrel is also associated with a very small risk of thrombotic thrombocytopenic purpura [181], probably less than 1 per 100,000.

Loss of privacy due to additional contact from investigators not involved directly in patient care is another potential risk. We may seek funding for a long-term follow-up study, as well, with additional threat to privacy. There is also a small risk of loss of confidentiality.

5.5 Protection/ Minimization of Risk

The greatest risk to patient health is hemorrhage due to the study drugs. To reduce this risk, subjects will be monitored carefully during the study. Medications will be stopped if bleeding or other major complications occur and before any elective procedure. To mitigate potential risk of dipyridamole, we will discourage dipyridamole use in the first month after randomization and we will ask the DSMB to monitor events in this group separately.

Three clinicians will monitor safety by reviewing adverse event and endpoint reports throughout the trial. If adverse events are excessive, they may request an early meeting of the DSMB. A formal early evaluation of safety is planned when 500 patients have been followed through 6 months. In addition, the DSMB will monitor hemorrhagic and other complications every 6 months, and more frequently if necessary. If excess hemorrhage outweighs potential benefit, enrollment will be stopped by the DSMB.

To protect privacy, the schedule of contacts and visits will be included in the consent form, so that those wishing to preserve privacy can exclude themselves from participation.

To protect confidentiality, the study database that contains unique identifiers will be maintained on a single computer hard drive. An additional copy will be stored on CD, and a third copy will be maintained in a safety deposit box. Only key study personnel will be allowed access to the database with unique identifiers. The working database will include a patient ID that will not be linked to unique identifiers.

5.5.1 Management of SAEs

WebDCU has an integrated web-based serious adverse event (SAE) module that provides the mechanism by which adverse events are reported, reviewed, and identified as serious or non-serious. SAEs will then be made available to the appropriate CCC staff and the designated Medical Monitors for review. Reviews are performed on-line. Access restrictions are designed to allow only designated individuals read/write access to the SAE review form while providing clinical site staff read access. Integration of the medical monitoring functionality into the data entry system facilitates rapid review and reporting of events to the DSMB and regulatory bodies.

5.5.2 Risk Factor Evaluation and Management

To provide optimal care for study subjects and to reduce variability in management, treating clinicians will be encouraged to follow standard recommendations on evaluation and management of risk factors. These recommendations are based on published consensus guidelines [97-99], which will be detailed in the operations manual. Key recommendations are outlined below.

<u>Evaluation</u>

- An ECG, a complete blood count, prothrombin time, partial thromboplastin time, electrolytes, glucose, and head CT or MRI should be performed prior to study entry.
- Carotid imaging should be performed as soon as possible, preferably prior to study entry. An ultrasound, CT angiography, or MR angiography suggesting a stenosis greater than 50% should be followed by additional carotid imaging to confirm the degree of stenosis.
- Fasting cholesterol panel, a measure of glucose tolerance, erythrocyte sedimentation rate, and syphilis serology should be considered.
- Cardiac monitoring on a telemetry ward or by Holter monitor should be considered in those in whom there is concern for arrhythmia.
- Transthoracic or transesophageal echocardiography should be considered in those with a history of cardiac disease, an ECG suggestive of myocardial ischemia, or an abnormal cardiac exam.
- Screening for hypercoagulable state should be considered in those with no apparent risk factors for stroke.

<u>Management</u>

- Hypertension should be treated to maintain systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg; for those with diabetes, blood pressure should be maintained <130/85 mmHg.
- Counseling and treatment to assist with smoking cessation should be offered.
- Cardiac disease should be managed appropriately in consultation with a cardiologist.
- Alcoholism should be treated through formal cessation programs.
- High-dose, high-potency statin (eg, atorvastatin 80 mg daily) in all patients unless LDL is < 70 mg/dL.
- Tight control of diabetes is recommended to maintain fasting blood glucose levels < 126 mg/dL.
- Physical activity should be encouraged (>30 min for <u>≥</u>3 days/week).
- Patients with atrial fibrillation or an obvious cardiac source of embolus should be discontinued from study medications and treated with anticoagulation unless there is a contraindication.
- Patients with an internal carotid artery stenosis 70-99% that may have been responsible for the index event should be considered for urgent endarterectomy.
- Patients with an internal carotid artery stenosis 50-69% that may have been responsible for the index event should be considered for endarterectomy if risks of surgery are considered minimal.

5.6 Potential Benefits

The risk of ischemic events after TIA is very high. Reduction of absolute risk of ischemic events by only 1% is likely to outweigh the risks of hemorrhage. Based on prior studies, we estimate that the absolute reduction in risk of stroke, myocardial infarction, and vascular death will be at least 3% with clopidogrel (Section 4.18). Thus, we hypothesize that the benefits of treatment will outweigh the risks.

Information from this trial is likely to benefit a large number of patients, regardless of the trial outcome. If the trial demonstrates a protective effect, clopidogrel should reduce the risk of stroke in patients with TIA. If the trial is negative, physicians will reduce the use of these agents after TIA—a setting in which combination therapy is already being used (Section 3.4)—thus potentially reducing risk to patients and reducing cost to society.

5.7 Ethical and Consent Issues

As discussed above (Sections 2.3, 3.5, and 4.18), we do not anticipate a major increase in the risk of intracerebral hemorrhage with clopidogrel after TIA. In addition, we anticipate that any increase in risk of hemorrhage will be outweighed by the benefit in reducing ischemic events (estimated absolute risk reduction of 3% even including hemorrhagic stroke).

Subjects who are taking aspirin at the time of the initial TIA could be randomized to placebo, thus receiving only aspirin. Some have proposed altering the antiplatelet agent if a TIA occurs on aspirin [161, 182]. However, no clinical studies support this recommendation [97-99], so we are not withholding standard therapy from patients who are randomized to placebo.

5.8 Inclusion of Women and Minorities

Race-ethnic distribution was considered in selecting participating centers, with the goal of obtaining at least a 20% distribution of African Americans. The ethnic distribution of the trial was projected by multiplying a site's anticipated enrollment with its ethnic distribution of stroke/TIA patients. Gender distribution was projected from the pilot cohort study [16]. The overall gender-ethnic distribution anticipated in the trial (Table 5.1) suggests that African Americans and Hispanics, and both genders, will be well represented. This should permit planned secondary analyses in African Americans and women (Section 4.18.2).

Recruitment rates of women and minorities will be carefully monitored during the trial. Sites recruiting more subjects in under-represented groups will be further encouraged and sites failing to do so may be asked to halt recruitment in order to obtain by the end of the study, final numbers of women, African Americans, and Latinos within 20% of the goals below. Near the end of the study, it may be necessary to stop recruitment of all but those underrepresented groups, but we suspect that careful vigilence will prevent this.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Platelet-Oriented Inhibition in New TIA (POINT) Trial

Total Planned Enrollment: 4150

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	209	185	394
Not Hispanic or Latino	1990	1766	3756
Ethnic Category: Total of All Subjects *	2199	1951	4150
Racial Categories			
American Indian/Alaska Native	22	19	41
Asian	66	59	125
Native Hawaiian or Other Pacific Islander	17	16	33
Black or African American	499	443	942
White	1595	1414	3009
Racial Categories: Total of All Subjects *	2199	1951	4150

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

5.9 Inclusion of Children

Children will not be excluded from this study. However, TIA is extremely rare in children: The youngest patient with a TIA in the pilot cohort study was 22 years old. Therefore, it will not be possible to include an adequate number of children in the trial to evaluate outcomes in this group separately.

All site principal investigators have experience treating children, either as neurologists or as emergency-department physicians. Assent will be obtained from the child and consent will come from the legal guardian.

8 LEADERSHIP PLAN

The trial will be directed by the **Principal Investigator**, S. Claiborne Johnston, MD, PhD, who will have ultimate responsibility for all activities and products of the trial, and will oversee all functions (Figure 8.1). The Associate PI, J. Donald Easton, MD, will assist with trial oversight and will substitute for the PI as necessary, serving as Co-Principal Investigator. In addition, Dr. Easton will have a major responsibility for trial recruitment by regular monitoring, encouraging investigators through regular written and telephone communication, and, as necessary, making visits to sites to educate and stimulate interest and involvement (e.g., in Emergency and Neurology Department Grand Rounds and faculty and resident conferences). Investigator motivation and buy-in by all potential recruiters at the sites will be the goal. Recommendations will be made and pursued at the sites to involve the local media and advocacy and patient groups. This will enhance a collaborative study environment.

The trial will take advantage of the proven skills of three major entities: the UCSF CCC, the NINDS NETT Network, and the NINDS CRC. Each of these has distinct and well defined functions that have already been worked out in several meetings. The CCC has collaborated with multiple organizations including sponsors, CROs, and AROs and is confident that communication flow will remain smooth. Although the organization may seem complicated, it will bring together the key assets of multiple groups and may serve as a model to improve performance of future trials. The division of responsibilities is shown in Appendix IIA.

The **Operations Committee (OC)**, chaired by Dr. Johnston, will oversee the entire performance of the trial. The OC will meet every week, with members outside San Francisco joining by videoconference. The OC will include Drs. Johnston, Easton, Glidden, the project coordinator (Mary Farrant, RN, MBA), the CRC director (Anne Lindblad, PhD), and the NETT director (Bill Barsan, MD) and administrative director (Valerie Stevenson).

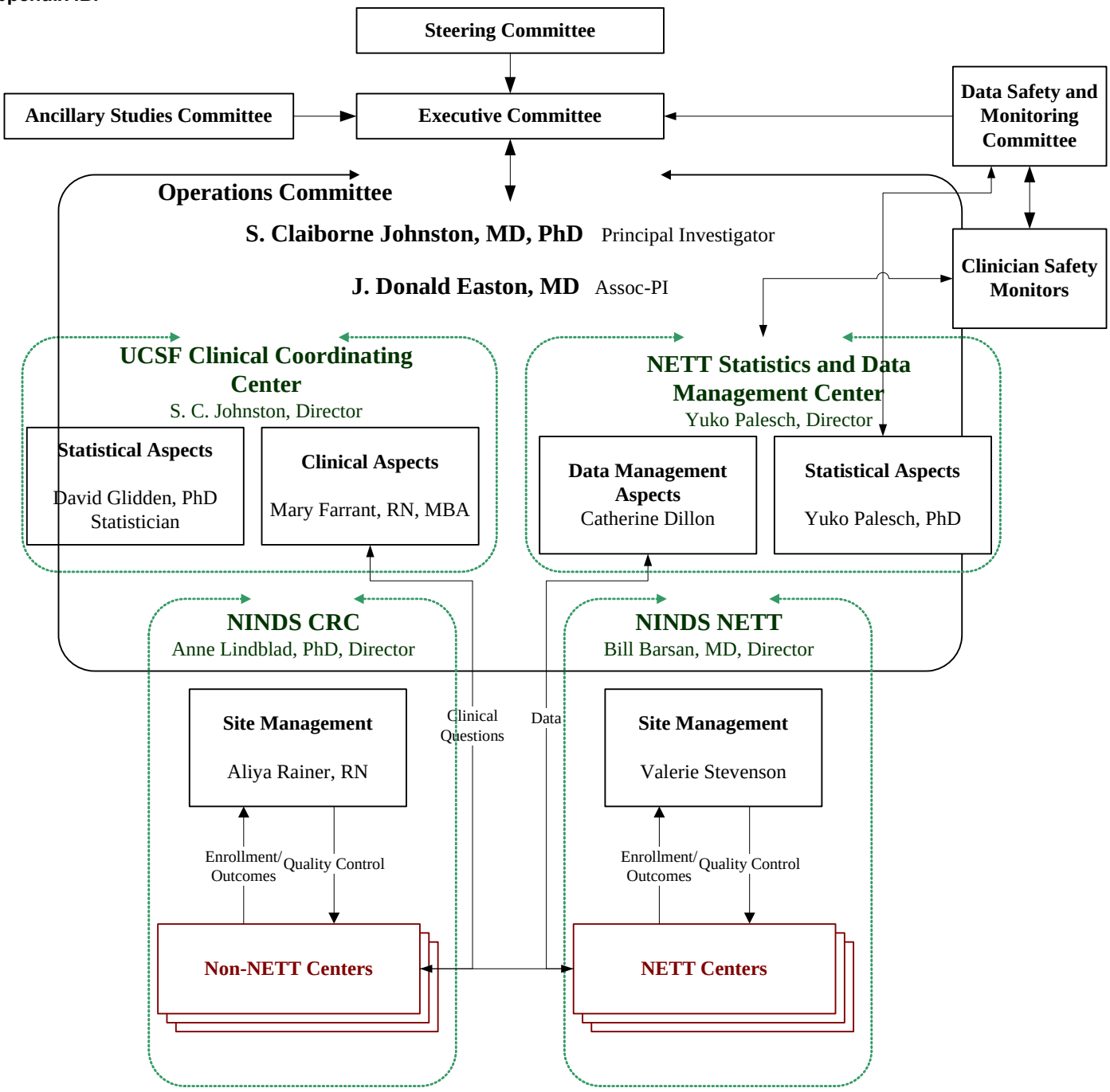
Overall trial administration and management will occur through the **Clinical Coordinating Center (CCC), as part of the University of California Stroke Sciences Group (UCSF SSG)**, directed by Dr. Johnston, whose capabilities are described above (Section 4.3). Dr. Johnston has led multicenter clinical trials previously, funded by the CDC and industry, and brings leadership that is unusual for most applicants for multicenter trials at NINDS.

The CCC will manage the overall performance and leadership functions of the trial, and will oversee the clinical aspects. It will provide clinical training to the sites, and produce newsletters and other correspondence. It will arrange all leadership meetings and oversee publications and applications for ancillary studies. Its statisticians will oversee finalization of the statistical analysis plan, in consultation with the NETT SDMC, and will produce the final analysis of the trial and any subsequent analyses.

The NETT, through its SDMC, will provide statistical support and data management services, including reports to the DSMB and medical safety monitoring, shielding the CCC from access to unblinded data during performance of the trial. The NETT SDMC will also produce performance reports of the sites, which will be communicated to the CCC and site monitors. At the end of the trial, the SDMC will clean the data and produce a final locked data set to the CCC and participate in the final analysis.

The NETT and CRC will each manage all aspects of the sites that they bring to the trial. They will negotiate contracts (from fixed templates and with nonnegotiable reimbursement). They will be responsible for data enquires not addressable directly on the online system, for recruitment problems, and site monitoring. Issues identified will be discussed with the OC through routine conference calls. Sites will be visited at least once at the beginning and end of the study and more often if needed for cause. The NINDS CRC will obtain central IRB approval for the study within two months of protocol finalization.

Figure 8.1 The administrative structure and communications flow for the trial. Members of the committees are listed in Appendix IB.



Mary Farrant, RN, MBA, the project coordinator, will be responsible for clinical oversight of the participating centers. Together with the Drs. Johnston and Easton, she will respond to all clinical and policy questions, and will ensure eligibility criteria are met and that treatment protocols are followed. She will coordinate, and oversee communications of the study, with the assistance of existing web-based technologies, and will handle all initial requests from the sites for unblinding.

David Glidden, PhD, from the Division of Biostatistics at UCSF, will direct CCC statistical analyses. Dr. Glidden will be responsible for the final statistical analysis plan and final data analysis. He will be responsible for the randomization protocol, in collaboration with Dr. Palesch from the NETT SDMC, which will be implemented through the NETT data management system.

The **Executive Committee** is the major advisory committee for the trial. The committee will meet yearly in person and by telephone conference monthly and as necessary, and will assist the Operations Committee with all major decisions regarding the study. Members will receive reports from all other committees on a regular

basis and will monitor the overall performance of the study and participating sites. The committee will supervise analysis and publication of primary results and subsequent analyses.

The larger **Steering Committee** will include a number of experts in stroke care and research, as well as representatives of top performing community and academic sites, and will meet quarterly to advise the Steering Committee and Principal Investigator to assure excellence in the performance of the trial. Members will assist in the recruitment of active and dedicated centers. Between annual meetings, the committee may be convened by teleconference to advise on extraordinary issues. A majority vote of a quorum of the Steering Committee will be required for protocol changes.

The **Ancillary Studies Committee** will oversee evaluation of proposals for subgroup analyses and other studies derived from the cohort developed in the clinical trial, which will require funding outside this grant. This committee will assure that all such studies are hypothesis driven and methodologically robust. Recommendations of the Ancillary Studies Committee will be forwarded to the Executive Committee for final approval.

An **Adjudications Committee** will include six members—three neurologists and three cardiologists/ internists—to assure timely adjudication of each endpoint by three independent reviewers. (See Section 4.16 for details of adjudication procedures).

Three **Clinician Safety Monitors** located at the NETT coordinating center will review safety data as it becomes available.

An external **Data Safety and Monitoring Board (DSMB),** is described in Section 4.19 and Appendix IIIC.

A **Quality Control Committee** will include the Study Coordinator, the Quality Assurance Coordinator, the Data Management Director, and six site coordinators. This committee will review and improve processes for assuring accurate and complete data in the study. It will meet each month by teleconference during the first 6 months of enrollment, and every other month for the duration of patient enrollment.

Pharmaceutical industry representatives have not been involved with the trial design and will not participate routinely in the execution of the trial or presentation of the results. Data will be controlled by the Executive Committee, which will review requests for access and specific analyses. Monitoring during the trial will be dictated by safety and scientific concerns rather than regulatory requirements. Sanofi-Aventis and Bristol-Myers Squibb have agreed to contribute clopidogrel and its placebo at no cost and with no restrictions (Appendix IF).

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9 CONSORTIUM/CONTRACTUAL ARRANGEMENTS

NETT Coordinating Center (U. Michigan)
The NETT provides a large number of ready sites on line to do acute neurological studies. The coordination of NETT is already sponsored by the NINDS but study specific costs are not. The relationship with the NETT has been secured with a contractual arrangement.

NETT Statistics and Data Monitoring Center (Medical University of South Carolina)
The NETT SDMC has a long, proven track record in supporting multicenter trials with its automated online data management system and through expert statistical support. The relationship with the NETT SDMC has been secured with a contractual arrangement.

NINDS Clinical Research Collaboration (EMMES Corporation)
The NINDS CRC contracted EMMES to create a large network of clinical neurologists available to participate in large simple trials. Though the NINDS provides support for the network, this contract is due for renewal in 2 years and may not cover the full costs of overseeing the CRC sites that will take part in this trial. Please understand that the sites participating in the trial that are not currently part of the NETT have agreed to join the CRC. The relationship with the CRC has been secured with a contractual arrangement.

Participating Sites
There will be 150 sites enrolling patients in the study. Patient enrollment will require the efforts of a site principal investigator and a research coordinator. The start-up costs and per-patient enrollment estimates have been based on discussions with potential enrolling sites and estimation of the required hours for screening and visits. Details of these costs are described in the budget justification. The NINDS CRC and NETT will enter into a contract with UCSF to provide capitation and core funding to the participating sites. This will be a strictly pass through arrangement. The NINDS CRC and NETT will be responsible for entering into letter agreements for study conduct and payment with the sites. A sample letter Agreement is provided as Appendix IID.