Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial

Study Protocol

Supported by
The National Institute of Neurological Disorders and Stroke (NINDS)

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Protocol Version 6.0

NCT00991029
EudraCT 2013-001185-41

INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol Version (6.0) dated (30NOV2016)

I have read this protocol and agree to adhere to the requirements.

I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study, applicable laws, regulations, international standards, and ethical and safety considerations, including 21 CFR Parts 50, 54 and 56, International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines, and Institutional Review Board (IRB) or Ethics Committee (EC) requirements.

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Clinical Site Date

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Site Principal Investigator Signature Date

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Site Principal Investigator Printed Name Date

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Country Coordinator Signature	Date
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Country Coordinator Printed Name	Date

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POINT PROTOCOL SYNOPSIS

Title:	**P**latelet-**O**riented **I**nhibition in **N**ew **T**IA and minor ischemic stroke (POINT) Trial, a randomized, double-blind, multicenter clinical trial
Primary Objective:	To determine whether clopidogrel 75 mg/day by mouth after a loading dose of 600 mg of clopidogrel is effective in preventing major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days when subjects are randomized within 12 hours of time last known free of new ischemic symptoms in patients receiving aspirin 50-325 mg/day (with a dose of 150-200 mg daily for 5 days followed by 75-100 mg daily strongly recommended).
Study Design:	A prospective, randomized, double-blind, multicenter trial with the primary null hypothesis that, in patients with TIA or minor ischemic stroke 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 subjects are randomized within 12 hours of time last known free of new ischemic symptoms.
Patient Population:	Patients 18 years of age or older with high-risk TIA (defined as an $ABCD^2$ score $\geq$ 4) or minor ischemic stroke (with NIHSS $\leq$3) who can be randomized within 12 hours of time last known free of new ischemic symptoms will be enrolled.

Inclusion/Exclusion Criteria:	**Inclusion Criteria**
	• Neurologic deficit (based on history or exam) attributed to focal brain ischemia and EITHER:
	  ○ **High risk TIA**: Complete resolution of the deficit at the time of randomization AND $ABCD^2$ score $\geq$4
	  Or
	  ○ **Minor ischemic stroke**: residual deficit with NIHSS $\leq$3 at the time of randomization
	• Ability to randomize within 12 hours of time last known free of new ischemic symptoms.
	• Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess, that could explain symptoms or contraindicate therapy.
	• Ability to tolerate aspirin at a dose of 50-325 mg/day.

Exclusion Criteria

- Age <18 years.
- TIA symptoms limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo.
- In the judgment of the treating physician, a candidate for thrombolysis, endarterectomy or endovascular intervention, unless the subject declines both endarterectomy and endovascular intervention at the time of evaluation for eligibility.
- Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to index event.
- Gastrointestinal bleed or major surgery within 3 months prior to index event.
- History of nontraumatic intracranial hemorrhage.
- Clear indication for anticoagulation (e.g., warfarin, heparin) anticipated during the study period (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, antiphospholipid antibody syndrome, hypercoagulable state).
- Qualifying ischemic event induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy <3 months.
- Contraindication to clopidogrel or aspirin:
  - Known allergy
  - Severe renal (serum creatinine >2 mg/dL or 176.8umol/L) or hepatic insufficiency (prior or concurrent diagnosis, with INR>1.5, or any resultant complication, such as variceal bleeding, encephalopathy, or icterus)
  - Hemostatic disorder or systemic bleeding in the past 3 months
  - Current thrombocytopenia (platelet count <100 $x10^9$/l) or neutropenia/granulocytopenia (<1 $x10^9$/l)
  - History of drug-induced hematologic or hepatic abnormalities
- Anticipated requirement for long-term (>7 day) non-study antiplatelet drugs (e.g., dipyridamole, clopidogrel,

ticlopidine), or NSAIDs affecting platelet function (such as prior vascular stent or arthritis).

- Not willing or able to discontinue prohibited concomitant medications.
- Inability to swallow medications.
- At risk for pregnancy: premenopausal or post menopausal woman within 12 months of last menses without a negative pregnancy test or not committing to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence).
- Unavailability for follow-up.
- Signed and dated informed consent not obtained from patient.
- Other neurological conditions that would complicate assessment of outcomes during follow-up.
- Ongoing treatment in another study of an investigational therapy that may potentially interact with study drug, or treatment in such a study within the last 7 days.
- Previously enrolled in the POINT study.

Randomization:

Subjects will be randomized 1:1 (clopidogrel: placebo), controlling for clinical center. A study participant's eligibility will be determined by site personnel prior to accessing the Randomization Module in the WebDCU™, a web-enabled clinical trials management system that was developed by the Neurological Emergencies Treatment Trials (NETT) Statistics and Data Management Center (SDMC) at Medical University of South Carolina (MUSC).

Qualified users will access the Randomization Interface and complete a protocol-specific eligibility checklist. If the Randomization Interface finds the patient to be eligible based on the information provided, a randomization number and a confirmatory email will be generated.

Primary Endpoint:

Composite endpoint of new ischemic vascular events: ischemic stroke, myocardial infarction or ischemic vascular death at 90 days.

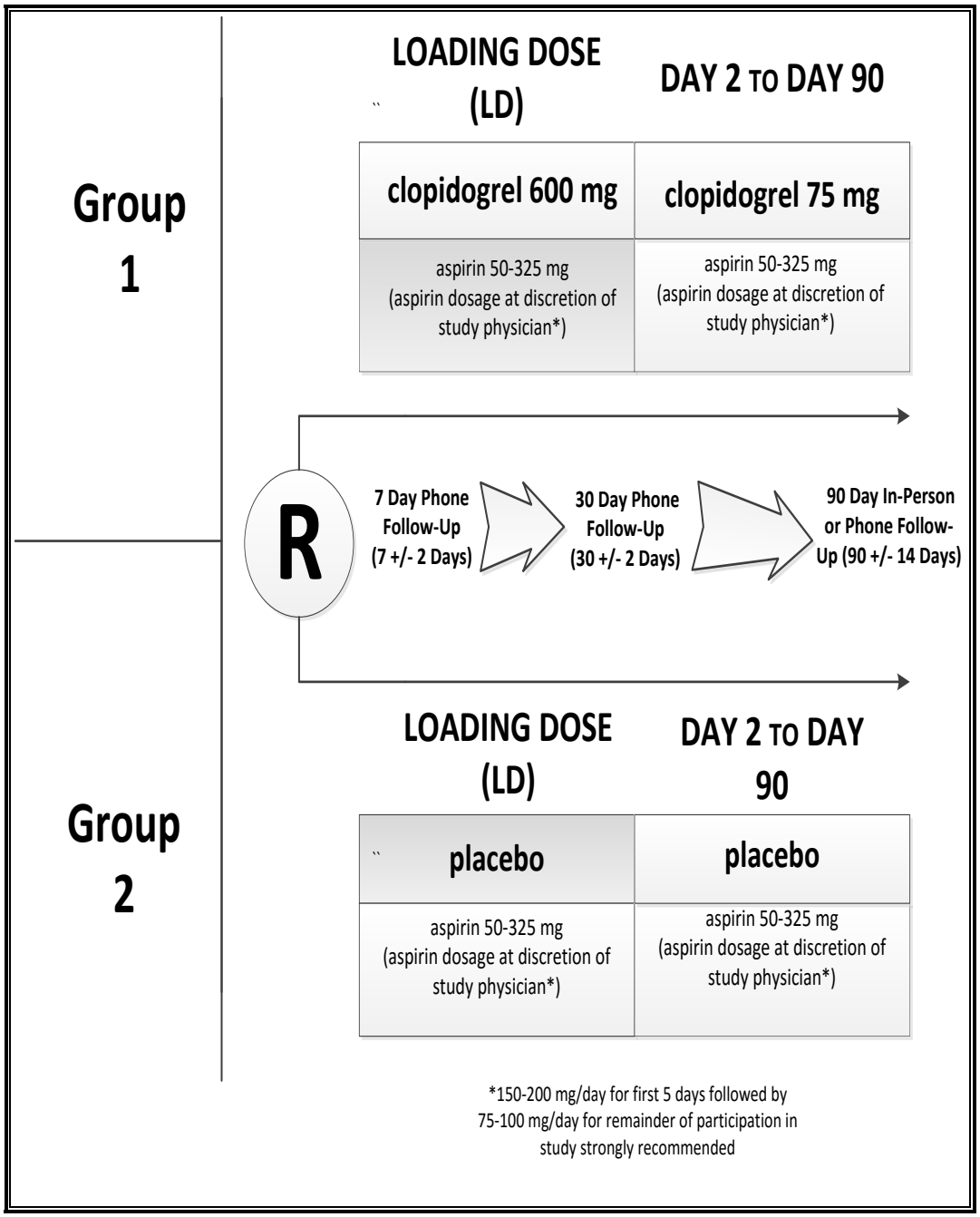
Study Duration for Each Subject:

Each subject is followed for 90 days from randomization; the trial will be completed in 7 years.

Number of Centers:	Up to a total of 350 investigational sites in partnership with the NINDS NETT Network and the POINT Clinical Research Collaboration (CRC).
Sample Size:	Total sample size for the study is 5,840 subjects.
Primary Statistical Analysis:	The primary efficacy hypothesis is tested with the log-rank test of the equality of survival curves. The log-rank statistic is tested at the two-sided alpha level of 0.05.
Ancillary Biomarkers Study:	Participants who consent to the POINT Trial will be asked to consent to an optional ancillary study consisting of a one-time venous blood sample of approximately 10mL collected at the time of enrollment in the trial.

1 STUDY FLOWCHARTS

1.1 Graphical Study Design



1.2 Schedule of Activities and Assessments

Contact Schedule and Measurements

Measurements	Screening	Baseline/ Randomization	Phone F/U Day 7 +/-2	Phone F/U Day 30[◎]	Phone or In-Person F/U Day 90 +/- 14[†]	Event Visit***	End of Study
Screen Failure Log	x						
Eligibility Form		x					
Consent (including optional study)		x					
Randomization Form		x					
Enrollment/ Demographics		x					
ABCD[2] Score		x					
Modified Rankin Scale (mRS)					x	x	
NIH Stroke Scale		x			x	x	x
Medical History		x					
Prior Medications		x					
Index TIA/Minor Stroke Symptoms		x					
Vital Signs		x					
Blood Sample (optional)		x*[2]					
Head CT/MRI Scan		x*			x*	x*	
ECG		x*			x*	x*	
Carotid Imaging		x*[1]			x*[1]	x*	
Stroke-Free Questionnaire: QVSFS			x	(x)	x	x	
Morisky Questionnaire			x	(x)	x	x	
Concomitant Medications Form			x		x	x	
SAE/Clinical Outcome Reporting			x		x	x	
Study Drug Compliance				(x)			x
Final Diagnosis		x					
End of Study Form							x
Protocol Violation	x	x	x		x	x	x

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

** As needed (visit can occur more than once).

*** Event Visits for MI can be completed by telephone.

† Preferably as soon as possible after the completion of 90 days.

[1] Encouraged as part of best practices but not required for study entry or at 90 days. If performed, record results on CRF.

[2] Blood sample obtained with subject's consent for optional ancillary study

Θ No study data collected.

Note: Certain follow-up assessments, such as the mRS and QVSFS, by telemedicine are acceptable.

2 BACKGROUND AND SIGNIFICANCE

A transient ischemic attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Restricted diffusion on an MRI at the appropriate site to explain the transient dysfunction indicated acute infarction and qualifies the transient event as an ischemic stroke. An ischemic stroke is a cerebral infarction. In POINT, eligibility is limited to brain TIAs and to minor ischemic strokes (with a National Institutes of Health Stroke Scale [NIHSS] score $\leq$3).

TIAs 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. The same is true for patients with minor ischemic strokes. The distinction between minor ischemic stroke and TIA is unimportant in terms of prognosis. Both groups are at high short-term risk for new ischemic stroke. The newly proposed definition of TIA already complicates the distinction between TIA and stroke, and the trial will ultimately promote a more unified view of these syndromes. In fact, numerous studies have shown that short-term risk of stroke is high after TIA and minor ischemic stroke, 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 these patients.

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.

TIA is a unique, 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.

2.1 TIA Incidence

TIAs are common, and are often harbingers of disabling strokes.

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, 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]. Studies in Northern California and Oxfordshire 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]. See Table 2.1.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 of limited benefit.

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%**

Recent results from the OXVASC cohort study and from the FASTER pilot trial suggest that minor ischemic stroke carries a similar high risk of subsequent stroke as TIA. In fact, event rates were higher for patients with minor ischemic stroke enrolled in the FASTER trial.

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]

2.3 Underlying Pathophysiology of TIA and Minor Ischemic Stroke

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.

The pathophysiology of TIAs and those with rapid but incomplete improvement in ischemia (as characterizes the majority of those with minor ischemic stroke arriving acutely) 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], and it is hypothesized that the same will be true for the major events of TIA studied here.

2.4 Potential Therapies

There are few established, effective therapies for stroke prevention after TIA or minor ischemic stroke. Other than aspirin, the only approved therapy for acute cerebral ischemia, intravenous tPA, is explicitly contraindicated in patients with TIA and is generally considered inappropriate in those with minor ischemic stroke [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. It is hypothesized 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).

Usman et al. report metanalyses of 13 studies comparing mean bleeding frequencies for aspirin (≤325 mg/day), clopidogrel, anticoagulants (warfarin and other vitamin K antagonists), aspirin plus clopidogrel, and aspirin plus extended-release dipyridamole (ER-DP). Total bleeding occurred at mean rates of 4.8% with aspirin (≤325 mg/day) alone, 2.9% with clopidogrel alone, 3.6% with aspirin plus ER-DP, 10.1% with aspirin plus clopidogrel, and 16.8% with anticoagulation. Major bleeding occurred at mean rates of 1% with aspirin (≤325 mg/day) alone, 0.85% with clopidogrel, 0.93% with aspirin plus ER-DP, 1.7% with aspirin plus clopidogrel, and 2.5% with anticoagulation. In conclusion, the combination of aspirin and clopidogrel is associated with significantly greater bleeding than either aspirin (≤325 mg/day) or clopidogrel alone. Aspirin plus ER-DP has a greater bleeding rate than clopidogrel but a lower rate than aspirin (≤325 mg/day) alone. [186]

2.4.1 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. However, given recent American College of Cardiology guidelines and potential safety issues with clopidogrel use, it is reasonable to strongly recommend lower doses of aspirin. An initial dose of 150-200 mg/day for 5 days (per the CAST trial) followed by 75-100 mg/day will be strongly recommended.

2.4.2 Clopidogrel

Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation by blocking the P2Y12 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 (ACS), with no 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].

In January 2009, the FDA released a report from MedWatch, the FDA Safety Information and Adverse Event Reporting Program regarding clopidogrel (Plavix®), notifying healthcare professionals that "the makers of Plavix have agreed to work with the FDA to conduct studies to obtain additional information that will allow a better understanding and characterization of the effects of genetic factors and all other drugs (especially the proton pump inhibitors (PPIs)) on the effectiveness of clopidogrel. FDA is aware of published reports that clopidogrel (marketed as Plavix®) is less effective in some patients than it is in others. Differences in effectiveness may be due to genetic differences in the way the body metabolizes clopidogrel or that using certain other drugs with clopidogrel can interfere with how the body metabolizes clopidogrel." In March 2010, a black box warning was added to the label for clopidogrel: "Reduced effectiveness in patients who are poor metabolizers of the drug – that some patients do not convert Plavix to its active form as well as other patients. These patients may not get the same benefit from Plavix and are known as poor metabolizers."

Some writers have advocated genotyping patients prior to initiating clopidogrel therapy to determine if they carry a reduced-function gene variant (primarily the CYP2C19*2 polymorphism) because these carriers appear to have an excess risk of cardiovascular events and mortality on clopidogrel. Studies do not address cerebrovascular disease. This issue remains controversial and caused the American College of Cardiology Foundation/American Heart Association on June 28, 2010 to issue a Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning" stating, "Overall, however, the evidence is insufficient to recommend routine genetic or platelet-function testing at the present." [183] Also, in an important study regarding this matter, it was concluded that CYP2C19 loss-of-function variants do not modify the efficacy and safety of clopidogrel [184].

2.4.3 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 [115,116]. 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 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. 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].

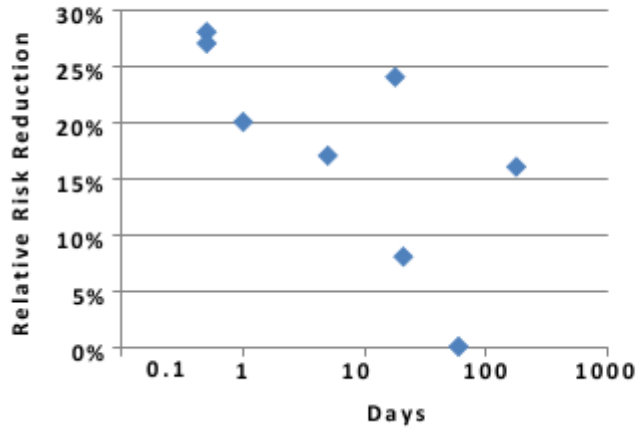
Pilot Acute TIA/Stroke Trials: FASTER was a pilot trial based in Canada and run by collaborators who participated in the design of this trial [8]. It evaluated clopidogrel (300 mg load and 75 mg/day afterwards) and simvastatin in a factorial design on a background of aspirin in patients presenting within 24 hours of a TIA or minor stroke. The main principle 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 no 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.

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 reductions 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 of 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].

Fig. 2.1 Impact of clopidigrel-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%

In the FASTER trial, intracranial and serious extracranial hemorrhages 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 disabling in 35% [J. Kennedy, personal communication], which is lower than the disability rate published in prior cohort studies (e.g., 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.

CHANCE (Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled trial conducted at 114 centers in China. 5170 patients were randomly assigned within 24 hours after the onset of minor ischemic stroke or high-risk TIA to clopidogrel plus aspirin vs. aspirin alone for 21 days, followed by clopidogrel vs. aspirin for the subsequent 69 days.

The primary outcome, ischemic or hemorrhagic stroke (ischemic or hemorrhagic) occurred in 8.2% in the clopidogrel-aspirin arm, and 11.7% in the aspirin arm, a significant hazards reduction, with no increase in major hemorrhage.[185] The result supports that more intense antiplatelet therapy is beneficial and superior to aspirin alone in this patient population. Whether this is generalizable to non-Chinese populations is unknown.

The POINT DSMB reviewed the accrued data in POINT, the CHANCE results and the opinion of a Bioethics Committee engaged by the National Institute of Neurological Disorders and Stroke (NINDS) to assess the ethics of continuing POINT in light of the CHANCE results. Following that review, the DSMB approved a modification to the informed consent to address the CHANCE results, and recommended POINT proceed as planned.

2.4.4 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].

2.5 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.

2.6 Preliminary Studies

During the past 12 years, a large number of studies that serve as background for this trial have been performed. 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, 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]. 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.

A series of studies 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 these 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, a cohort study of all 976 patients in KPNC who were given a diagnosis of TIA in urgent care clinics 1997-1998 was performed [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.

There has been concern that the diagnosis of TIA is variable and unreliable. It was 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.

2.6.1 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 minutes, 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 minutes (1) or ≥ 60 minutes (2), 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 selection of 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 ≥ 4 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%.

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].

2.6.2 Importance of Recovery: Risk of Stroke after Recovery in NINDS tPA, TOAST Trials

Data from four randomized trials—the NINDS tPA trial [80], TOAST [66], GAIN [78], and ASTIN [77]—was obtained 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 (with complete recovery) and lesser degrees of acute ischemic recovery represent a distinct pathophysiological characteristic associated with greater instability and risk of deterioration attributable to new ischemia.

2.6.3 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, usage of antithrombotic medications after TIA in three populations was evaluated: 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.

Sites were polled 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 dual-agent usage, and aspirin is an appropriate background therapy based on current patterns of usage (as well as on data from trials).

3 STUDY OBJECTIVES

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 **ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death)** at 90 days when subjects are randomized within 12 hours of time last known free of new ischemic symptoms in patients receiving aspirin 50-325 mg/day.

3.1 Secondary

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 (primary outcome plus 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/disability. The impact of therapy on the composite outcome will also be evaluated in specific subject groups (e.g., African Americans, those previously taking aspirin, those with index TIA vs. minor ischemic stroke).

4 STUDY DESIGN AND MANAGEMENT OVERVIEW

4.1 Study Design Overview

The primary null hypothesis of this randomized, double-blind multicenter clinical trial is, in patients with TIA or minor ischemic stroke 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 subjects are randomized within 12 hours of time last known free of new ischemic symptoms. The primary outcome event is defined as a composite outcome—ischemic stroke, myocardial infarction, or ischemic vascular death.

Patients with high-risk TIA (defined as an $ABCD^2$ score ≥ 4) or minor ischemic stroke (defined as an NIHSS ≤ 3), who can be randomized within 12 hours of time last known free from new ischemic symptoms will be enrolled. Subjects will be randomized to receive a 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; an aspirin dose of 150-200 mg daily x 5 days, followed by 75-100 mg daily will be strongly recommended. 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 7 years, with 5,840 subjects recruited from 350 centers in partnership with the NINDS Neurological Emergencies Treatment Trials (NETT) Network and the POINT Clinical Research Collaboration (CRC). Recruitment will occur over 90 months, with a goal rate of 0.40 subjects per site per month for U.S. sites, and 0.47 subjects per site per month for sites outside the U.S., which is based on prior studies of recruitment, on the recruitment rate in the pilot FASTER 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. A composite outcome measure has been chosen to fully reflect the potential benefits of treatment and to reduce the necessary sample size. In a secondary analysis, the composite outcome will be combined with major hemorrhage to capture anticipated life-changing risks and benefits in a single measure.

4.2 Study Milestones

A 7 year budget and recruitment plan have been created; key study milestones below.

STUDY MILESTONES	
Pre-enrollment Study Initiation	9 months
Recruitment and Follow-up	90 months
Completion of Follow-up	3 months
Data Analysis and Publication	6 months
Total Duration	**108 months**

4.3 Organizational Structure and Communication Flow

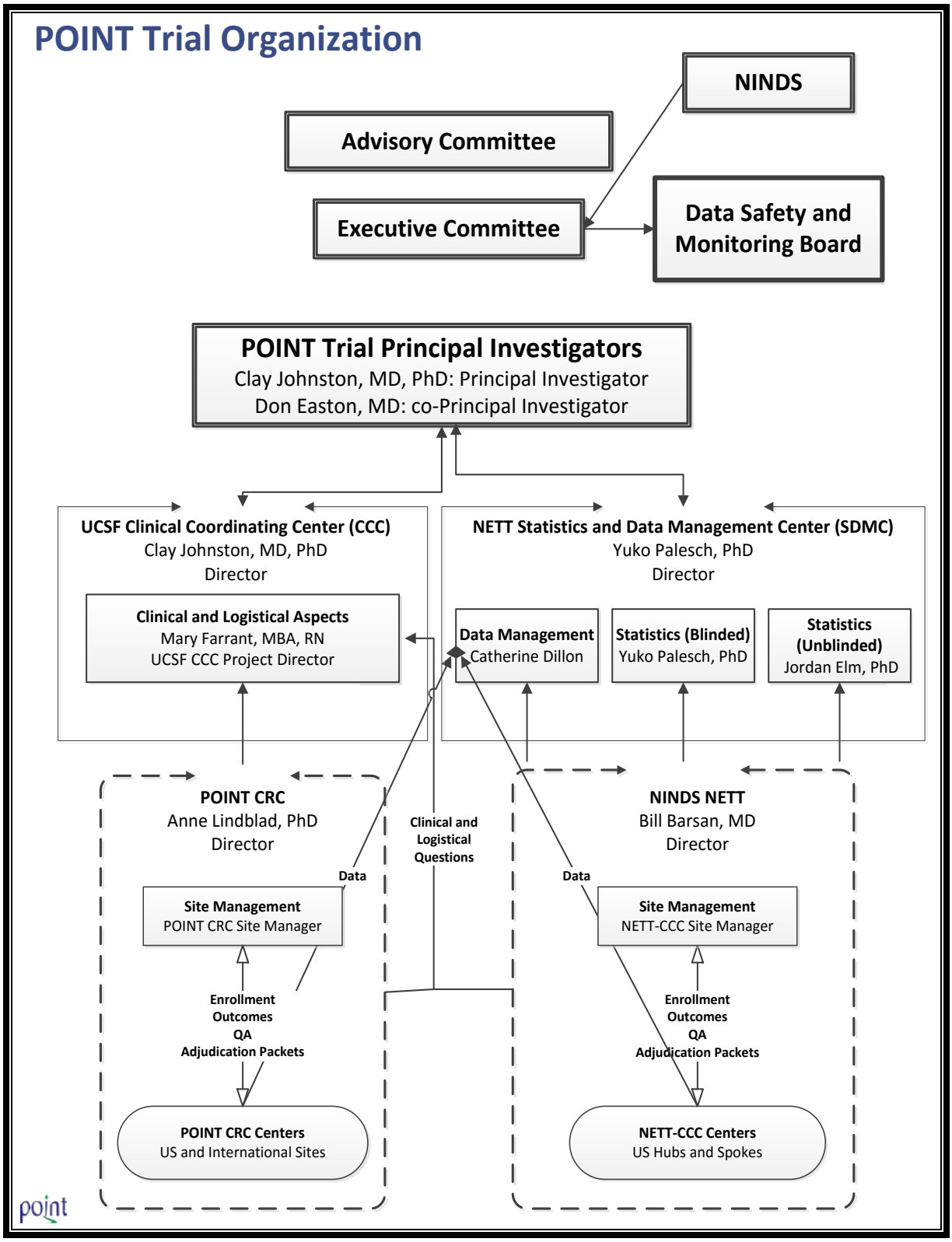
The trial management is a partnership of the UCSF Clinical Coordinating Center (UCSF CCC) based in the Stroke Sciences Group (SSG), the NINDS NETT Network, which will be responsible for data management and oversight of NETT sites, and the POINT CRC, which will manage the non-NETT sites, including the sites outside the United States. Details of the trial leadership, management, and communications are provided in the Manual of Procedures.

The UCSF SSG 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.

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 approximately three "Spoke" hospitals that work together to recruit patients into simple trials of acute neurological diseases.

POINT is well suited for CRC physicians due to its simple design and compelling question that should attract a wide breadth of neurologists treating acute stroke in the community. The CRC has over 1,100 physicians registered from 47 states. Use of central basic research training and a central Institutional Review Board (IRB) facilitates research participation of physicians who practice in a community setting. The CRC has experience activating sites over a short period of time.

Point Trial Organization



4.3.1 Trial Organization

The trial will be directed by the Principal Investigator, who will have ultimate responsibility for all activities and products of the trial, and will oversee all functions. The Co-Principal Investigator will assist with trial oversight and will substitute for the PI as necessary. The trial will take advantage of the proven skills of three major entities: the UCSF CCC, the NINDS NETT Network, and the POINT CRC.

The NINDS NETT, through its Statistical and Data Management Center (SDMC), will provide statistical support and data management services, including reports to the DSMB and Clinician Event Coordinator, and shielding the UCSF CCC, NETT-CCC and POINT CRC from access to unblinded data during the performance of the trial. The Director of the NETT SDMC will be responsible for the randomization protocol, final statistical analysis plan and final data analysis.

The Operations Committee (OC), chaired by the Principal Investigator, will oversee the entire performance of the trial. The OC will meet every week, with members outside San Francisco joining by teleconference. Membership of the OC is provided in the Manual of Procedures.

Sanofi has agreed to contribute clopidogrel and its placebo at no cost and with no restrictions through May 2016. From May 2016 forward, additional supplies of study drug will be provided by Sharp Clinical Services, Inc.

4.4 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 some outcome assessments (e.g., NIHSS, modified Rankin Scale). Online modules for training new sites are also available.

Prior to initiation of subject enrollment, Site Investigators and Coordinators will complete online training programs and their certifications. In these training modules, the subject selection criteria and follow-up procedures will be reviewed. Case studies illustrating potential problems in adhering to study protocol and blinding will be discussed.

All investigators must complete the following training modules, and receive certification:

- Study procedures
- Primer on the diagnosis of TIA and its mimics
- Use of the $ABCD^2$ score
- POINT eligibility
- Modified Rankin Scale
- NIHSS

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 subjects. 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.

A detailed Manual of Procedures will serve as the primary document describing all study related procedures. It will serve as a guide for training of clinical site personnel and will be updated periodically throughout the study, as needed. A system will be implemented for the clinical sites to call

or e-mail any procedural questions regarding the study. The UCSF CCC will formulate answers in consultation with the Operations Committee, and will periodically distribute to the participating centers a set of frequently asked questions (FAQ) and answers. These questions and answers will also be available on the POINT Resources and Training page under FAQs and can be searched by topic. Intermittently, the answers to questions will be incorporated into Manual of Procedures revisions.

The NETT will manage and conduct site visits for its sites and the CRC will manage and conduct site visits for the non-NETT sites. Each site will be visited at least once during the trial, and as needed if questions about data quality or problems with recruitment arise, or there is a concern about noncompliance requiring specific or systemic corrective actions.

4.5 Contact Schedule and Measurements

Subject encounters will include screening, randomization, telephone follow-up, and a final telephone or in-person visit. In addition, event visits are to occur whenever subject contact suggests that possible stroke, TIA or MI may have occurred. Stroke and TIA events can be evaluated via telemedicine when necessary. Event visits for MI may be conducted over the telephone. Event visits are conducted as needed and can be done more than once for the same subject. Measurements to be taken at these encounters are listed in Section 1.2, Schedule of Activities and Assessments. Details of the visits are provided in the Study Procedures section (Section 9).

Refer to the Manual of Procedures and Data Collection Guidelines for more specific details on how/when to submit Case Report Forms for events.

4.6 Outcomes

The primary outcome of the trial is a composite outcome: ischemic stroke, myocardial infarction, and ischemic vascular death. The primary safety outcome is major hemorrhage. Additional efficacy and safety outcomes also will be assessed. All components of the primary and safety outcomes will be adjudicated.

4.6.1 Definitions of Clinical Outcomes/Serious Adverse Events

Ischemic stroke: An acute focal infarction of the brain or retina (and does not include anterior ischemic optic neuropathy (AION)).

Criteria:

1) Rapid onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or
2) Rapid worsening of an existing focal neurological deficit that is judged by the Investigator to be attributable to a new infarction. Criteria for symptoms attributable to new infarction *may* include symptoms that persist and are judged by the investigator to be attributable to new infarction, imaging evidence of infarction, or no evidence of a non-ischemic etiology.

TIA: A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain.

Criteria: Rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease).

Symptomatic hemorrhagic transformation of an ischemic stroke: Any extravascular blood within an area of known acute/subacute infarction which is judged to be nontraumatic, and responsible for neurologic symptoms. To be considered symptomatic, the hemorrhagic transformation must be judged to be partially responsible for the subject's clinical neurologic presentation (i.e., the area of infarction is not adequate to explain the neurologic deficit, or a secondary neurologic deterioration occurred corresponding to the timing of hemorrhagic transformation.)

Criteria (must meet both of the following):

1) Imaging evidence (by CT or MR) of extravascular blood within the area of infarction.
2) Symptoms judged to be related to the hemorrhagic transformation. Scenarios which may be judged as symptomatic: (i), If blood is already present on imaging at presentation, symptoms are out of proportion to what would be expected for the size and location of the infarct at presentation; (ii) Clinical deterioration, defined by an increase of 4 points or more in the score on the NIHSS or leading to death, occurring after the initial ischemic event, and identified as the result of the hemorrhagic transformation; or (iii) Mass effect secondary to the hemorrhagic transformation causing symptoms.

Asymptomatic hemorrhagic transformation of an ischemic stroke: Any extravascular blood within an area of known acute/subacute infarct, judged to be nontraumatic, without any related neurologic symptoms.

Criteria (must meet both of the following)

1) Imaging evidence (by CT or MR) of extravascular blood within the area of infarct.
2) No symptoms related to the hemorrhagic transformation.

Symptomatic intracerebral hemorrhage: Any extravascular blood in the brain parenchyma, judged to be nontraumatic, and not in the area of an acute/subacute ischemic infarct, associated with and identified as the predominant cause of new neurologic symptoms (including headache) or death. In the case of a mixed intracranial hemorrhage (Intracerebral Hemorrhage (ICH), Subarachnoid Hemorrhage (SAH), Subdural Hemorrhage (SDH) and/or Intraventricular Hemorrhage (IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician. For example, if a subject has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: Evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy, which is not in the same territory of an underlying acute or subacute ischemic stroke, and is judged to be associated with any new neurologic symptoms (including headache) or leading to death.

Asymptomatic intracerebral hemorrhage: An acute extravasation of blood into the brain parenchyma, judged to be nontraumatic, and not in an area of an acute/subacute ischemic infarct, without associated neurologic symptoms or leading to death. In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician.

For example, if a subject has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: Evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy, which is not in the same territory of an underlying acute or subacute ischemic stroke, and is not judged to be associated with any new neurologic symptoms or leading to death.

Other symptomatic intracranial hemorrhage: Any extravascular blood within the cranium judged to be nontraumatic, and the predominant cause of the clinical deterioration or that led to death. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, subdural space or intraventricular space with associated symptoms (including headache). In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician.

For example, if a subject has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: Evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy.

Other asymptomatic intracranial hemorrhage: An acute extravasation of blood into the subarachnoid space, epidural space, subdural space or intraventricular space without associated symptoms, and judged to be nontraumatic. In the case of a mixed intracranial hemorrhage (ICH, SAH, SDH and/or IVH), the event should be classified according to the primary site of hemorrhage by the judgment of the clinician. For example, if a subject has a large ICH with a small amount of SAH, and the ICH is felt to be the primary site of bleeding, this should be classified as ICH.

Criteria: Evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy.

Myocardial infarction <u>with</u> coronary revascularization: Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, treated with coronary revascularization, such as angioplasty/stenting or coronary artery bypass graft (CABG), within 14 days.

Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.

Myocardial infarction <u>without</u> coronary revascularization: Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, not treated with coronary revascularization within 14 days.

Criteria: The diagnosis of MI will be based on an algorithm developed from the Universal Definition of Myocardial Infarction (Circulation 2007 116:2634-2653) that takes into account 5 categories of clinical information from the acute event: rise and/or fall of cardiac biomarkers, ECG abnormalities, clinical setting, imaging evidence, and pathology.

Coronary revascularization without myocardial infarction: A procedure to improve coronary blood flow for documented coronary artery disease, but with no documentation of new post-randomization myocardial infarction.

Criteria: Documented coronary angioplasty, stenting, or bypass surgery for demonstrated or presumed coronary artery disease.

Major hemorrhage other than intracranial hemorrhage (life-threatening or non-life-threatening): A hemorrhagic event, judged to be nontraumatic, that results in 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 or prolongation of existing hospitalization [24]. This may include bleeding events related to surgical procedures but not those related to accidental trauma. Life-threatening hemorrhagic events will be defined as those that are fatal or require use of intravenous inotropic medication to maintain blood pressure, interventional treatment (including surgical, endoscopic or endovascular interventions), 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 other than intracranial hemorrhage: All hemorrhagic events leading to interruption or discontinuation of the study drug but not classifiable as major hemorrhagic events [24]. This may include bleeding events related to surgical procedures but not those related to accidental trauma.

Ischemic vascular death: Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause.

Hemorrhagic Vascular death: Death due to intracranial or systemic hemorrhage.

Other Serious Adverse Event: Any adverse event, not belonging to the other outcome event categories, that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, or requires intervention to prevent permanent impairment or damage.

5 PARTICIPANT SELECTION

During the course of the trial, approximately 350 sites will enroll approximately 5,840 subjects with TIA or minor ischemic stroke. Before enrolling subjects into the study, all collaborating sites will obtain approval from local IRBs or ethics committees, which will have access to all study documentation and educational materials.

5.1 Study Population

The study will include both TIA and minor ischemic stroke, with the latter accounting for no more than 50% of enrollment; if 2920 subjects with minor ischemic stroke are enrolled, only TIAs will be permitted in the trial subsequently. Most enrolled subjects will be elderly (mean age 72 years with 78% older than 60 years in the Northern California study), with about an equal number of males and females (53% were female in the Northern California 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 safety of clopidogrel is not established in this population, and this drug may increase risk of harm to the fetus. Women at risk for pregnancy (see Exclusion Criteria) will also be excluded. No other vulnerable population will be excluded from the study.

5.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Neurologic deficit (based on history or exam) attributed to focal brain ischemia and EITHER:
    - High risk TIA: Complete resolution of the deficit at the time of randomization AND ABCD^2 score ≥4

    OR

    - Minor ischemic stroke: residual deficit with NIHSS ≤3 at the time of randomization.
- Ability to randomize within 12 hours of time last known free of new ischemic symptoms.
- Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess, that could explain symptoms or contraindicate therapy.
- Ability to tolerate aspirin at a dose of 50-325 mg/day.

Exclusion Criteria

- Age <18 years.
- TIA symptoms limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo.
- In the judgment of the treating physician, a candidate for thrombolysis, endarterectomy or endovascular intervention, unless the subject declines both endarterectomy and endovascular intervention at the time of the evaluation for eligibility.
- Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to index event.
- Gastrointestinal bleed or major surgery within 3 months prior to index event.
- History of non-traumatic intracranial hemorrhage.
- Clear indication for anticoagulation (e.g., warfarin, heparin) anticipated during the study period (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, antiphospholipid antibody syndrome, hypercoagulable state).
- Qualifying ischemic event induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy <3 months.
- Contraindication to clopidogrel or aspirin:
    - Known allergy

  - Severe renal (serum creatinine >2 mg/dL or 176.8umol/L) or hepatic insufficiency (prior or concurrent diagnosis, with INR>1.5, or any resultant complication, such as variceal bleeding, encephalopathy, or icterus)
  - Hemostatic disorder or systemic bleeding in the past 3 months
  - Current thrombocytopenia (platelet count <100 $x10^9$/l) or neutropenia/granulocytopenia (<1 $x10^9$/l)
  - History of drug-induced hematologic or hepatic abnormalities
- Anticipated requirement for long-term (>7 days) nonstudy antiplatelet drugs (eg, dipyridamole, clopidogrel, ticlopidine), or NSAIDs affecting platelet function (such as prior vascular stent or arthritis).
- Not willing or able to discontinue prohibited concomitant medications.
- Inability to swallow medications.
- At risk for pregnancy: premenopausal or postmenopausal woman within 12 months of last menses without a negative pregnancy test or not committing to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence).
- Unavailability for follow-up.
- Signed and dated informed consent not obtained from patient.
- Other neurological conditions that would complicate assessment of outcomes during follow-up.
- Ongoing treatment in another study of an investigational therapy that may potentially interact with study drug, or treatment in such a study within the last 7 days.
- Previously enrolled in the POINT study.

6 TREATMENTS

6.1 Study Drugs

This randomized double-blind study is primarily designed to compare a clopidogrel/aspirin combination versus an aspirin alone regimen. The two types of study tablets (75 mg active clopidogrel and placebo) are indistinguishable, identical in size, shape, color, appearance, and taste.

Minor side effects are unusual with the medication [102], so it is not anticipated that either subjects or clinicians will be able to differentiate the placebo from the active drug. Standard laboratory tests cannot detect the effects of clopidogrel.

Investigators will not have access to the randomization (treatment) code, except in exceptional circumstances, such as occurrence of a serious adverse event for which knowledge of the study medication would be considered essential for treating the subject.

Sanofi supplied the blinded study drugs, clopidogrel 75mg and matching placebo, distributed by the UCSF Drug Product Service Laboratory (DPSL) for US sites and Pharmacy Services partners for OUS sites

in quantities sufficient to last through May 2016. From June 2016 forward, additional supplies of blinded study drug (clopidogrel and matched placebo) after that date will be provided by Sharp Clinical Services, Inc. in quantities sufficient to last through the end of enrollment.

Aspirin tablets will be open label with the dose in a range 50-325 mg daily determined by the treating physician. A dose of 150-200 mg daily x 5 days, followed by 75-100 mg daily will be strongly recommended.

The clopidogrel/aspirin group will receive the following treatment:

- Day 1*: 8 tablets of clopidogrel 75 mg (loading dose of 600 mg)
- From D2 to D90: one tablet of clopidogrel 75 mg and 50-325 mg of aspirin per day

The placebo/aspirin group will receive the following treatment:

- Day 1*: 8 tablets of placebo 75 mg (loading dose of 600 mg)
- From D2 to D90: one tablet of placebo 75 mg and 50-325 mg of aspirin per day

*Subjects will receive open label aspirin (50 mg – 325 mg), with dose at the discretion of the treating physician.

6.2 Assignment to a Treatment Group

The randomization will take place centrally via the WebDCU™. Subjects will be randomized 1:1 (clopidogrel: placebo), stratified by clinical center. The computer program developed at the NETT-SDMC makes the treatment assignment based on the current status of treatment group distribution within each clinical center as well as overall balance of treatment assignment.

7 STUDY DRUG HANDLING

7.1 Supply and Storage

The manufacturer Sanofi supplied the blinded study drugs (clopidogrel 75mg tablets, and placebo to match clopidogrel tablets) used in POINT and distributed by the UCSF Drug Product Services Laboratory (DPSL) to sites in the United States, and by Pharmacy Services partners to sites outside the US in quantities sufficient through May 2016. Additional supplies of study drug after that date will be provided by Sharp Clinical Services, Inc. in quantities sufficient to last through the end of enrollment.

There will be at least four drug shipments for the study: Sanofi will initially ship clopidogrel and placebo to the UCSF DPSL in April 2010 with a second shipment in 2012 and a third shipment will be sent in the second quarter of 2014. The fourth shipment will be handled by Sharp Clinical Services in May 2016. A fifth shipment may be necessary, and will depend on the expiration dates and the rate of enrollment into the study. After May 2016, supplies of study drug will be shipped directly from Sharp Clinical Services or the Pharmacy Services partner or depot to the research pharmacist/drug recipient at the POINT Clinical Site. Final verification of all study drugs will be completed by the research pharmacist or designee to ensure that the site maintains correct inventory.

Aspirin tablets will be open label with the dose in a range of 50-325 mg daily determined by the treating physician. A dose of 150-200 mg daily x5 days, followed by 75-100 mg daily will be strongly recommended.

All investigational drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individual, and under the conditions described on the labeling.

Study drug will be stored at a controlled room temperature of 25° C (77° F); excursions permitted to 15°- 30° C (59° - 86° F) Note: This temperature guideline should be followed; it differs from the USP guideline for controlled room temperature.

Storage temperature should be monitored and recorded daily, preferably by a continuous automated measuring and recording device. A daily manual temperature log must be maintained if automated temperature surveillance is not possible.

Systems must be in place for identifying and alerting staff when proper temperature storage conditions have been compromised (e.g., thermometer with alarm functions).

If storage conditions have been compromised (e.g., temperature exceeds allowable range) or if there is any suspicion that study product(s) have not been stored properly, the following actions must be taken:

- Quarantine study products suspected of improper storage
- Maintain products under correct storage conditions until further notice
- Contact the UCSF-CCC and, if necessary, Sanofi (through May 2016) and Sharp Clinical Services thereafter
- Document the occurrence, including amount of storage/temperature violation and amount of storage violation time
- Determine whether drug will need to be replaced and take steps to dispose of study drug and secure replacement drug

Procedures outlining roles and responsibilities should be in place at the local Pharmacy to ensure that storage issues have been addressed and rectified in an efficient manner. Sites will receive a template Local Site Pharmacy Standard Operating Procedures (SOP). This template SOP provides a customizable written format for documenting such procedures and responsibilities.

7.2 Packaging

Each subject will be assigned 97 tablets of study drug (eight (8) tablets for loading dose, and an 89-day supply for one tablet daily) according to the randomization assignment, to be used as directed.

The labels for shipments one to three, with computer-generated randomization codes that are to be used for the study drug bottles, will be produced centrally via the NETT SDMC, since the information on the labels is linked to the trial's randomization scheme. The labels have been designed in compliance with CA Code 4076 requirements for prescription container labeling and international guidelines. The labels for shipments four and five will be produced by Sharp Clinical Services and affixed to the bottles of study drug by Sharp.

7.3 Responsibilities

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense study drug will be responsible for ensuring that the study drug used in the clinical trial is securely maintained and in accordance with the applicable regulatory requirements.

All study drug shall be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of study drug issued and returned is maintained. Any remaining drug will be destroyed by the site after a subject has completed participation.

Any quality issue noticed with the receipt or use of a study drug (deficient in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly reported. Drug Accountability logs will be maintained within the WebDCU™ study database.

7.4 Concurrent Treatment

7.4.1 Prohibited Concomitant Treatments

Use of the following medications after randomization and during the study period represents a protocol violation. However, if there is a clinical need that justifies the added risk of these interventions in the setting of study drug use, they should be employed at the discretion of the treating physician.

- NSAIDs, Cox1 inhibitors. If absolutely necessary, NSAIDs may be given for as short a time as possible but not sooner than 8 days after randomization
- Anticoagulants (both oral and parenteral, see listing on CRF 18)
- Open-label thienopyridines (e.g., ticlopidine, clopidogrel)
- Dipyridamole
- Other antiplatelets
- Thrombolytics (e.g., tPA)
- Vascular intervention (surgery and / or angioplasty of any vessel).

If intervention is absolutely necessary within the three months after randomization, study drug will be stopped 5 days prior to the intervention. Study treatment will then be restarted unless the subject needs to take open label clopidogrel or aspirin. In this case, study drug will be restarted only when treatment with open label antiplatelet therapy other than aspirin has been stopped.

7.4.2 Permitted Concurrent Treatments

Any drugs other than those listed above are permitted at the discretion of the Investigator. Given uncertainty about an interaction between omeprazole and other proton-pump inhibitors (PPIs) and clopidogrel, those previously taking a PPI will be evaluated for the appropriateness of other agents, such as H2 blockers. New prescriptions for PPIs will be avoided whenever an H2 blocker or other agent is an acceptable option. Similarly, other drugs that theoretically may affect clopidogrel metabolism

will be avoided, with others substituted. This list includes: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), and fluvoxamine (Luvox).

7.5 Treatment Discontinuation

The study drug should be continued whenever possible. 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. 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.

If the study drug is stopped, it should be determined if the discontinuation can be made temporarily; permanent study drug discontinuation should be a last resort. Pregnancy will lead to definitive treatment discontinuation in all cases. In any case, all randomized subjects should remain in the study and followed per the protocol to 90 days from randomization, or to death, whichever comes first, even if the subject discontinues the POINT study drug regimen, unless the subject withdraws consent to participate in the trial.

7.5.1 Permanent Treatment Discontinuation

A subject should discontinue the study drug for any of the following reasons:

- Intercurrent condition that requires discontinuation of the study (e.g. lab abnormalities, surgical procedure, serious bleeding)
- Positive serum pregnancy test or desire to become pregnant
- Clear indication for anticoagulation (e.g., atrial fibrillation)
- Contraception cessation

Subjects will be followed according to the study procedures as specified in this protocol up to the scheduled date of study completion. All subjects who have discontinued the study drug will be followed per the protocol up to 150 days from randomization, or to death, whichever comes first, unless the subject withdraws consent to participate in the trial.

For subjects considered lost to follow-up, CRFs must be completed up to the last visit performed. For subjects who do not complete any assessments for the 90 Day visit, the Investigator should make every effort to contact the subject and to identify the reason why he/she failed to attend the visit and to determine his/her health status at 90 days by telephone contact with the subject or the subject's alternative contacts. Complete guidelines can be found in the CRF Data Collection Guidelines.

Subjects who have withdrawn consent from the study cannot be included again in the study. Their subject number and treatment must not be reused. The investigator will indicate treatment discontinuation and/or the subject's withdrawal in WebDCU™. Randomized subjects will not be replaced.

7.6 Blinding System and Emergency Unblinding Procedure

Medication bottles 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 accessible to unblinded personnel when preparing unblinded (closed) reports for the DSMB.

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 subjects [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 call the POINT emergency call number (1-866-94POINT or 415-663-4444), activate the pager system, and enter a call-back number. Within 20 minutes, the UCSF CCC On-call Physician will return the call. If it is determined that unblinding is necessary, the UCSF CCC On-call Physician will log onto the WebDCU™ study database and initiate the unblinding request with the subject's ID number or randomization number. Once this is completed, the site PI or designee can log onto WebDCU and review the Randomization Form for the subject, which will have the treatment assignment displayed. The treatment assignment is revealed for 30 minutes only. After 30 minutes, the treatment assignment is concealed.

After the unblinding, the Randomization CRF will have a message stating that the subject's treatment assignment has been unblinded due to site request.

Prior to the unblinding, the randomization form will have a message that states: "Subject has NOT been unblinded". This process will generate an automatic email notification of the unblinding to the POINT Executive Committee.

8 SAFETY

8.1 Protection/Minimization of Risk

The greatest risk to subject health is the study medication, clopidogrel, when combined with aspirin. These agents have not been tested specifically after TIA and minor ischemic stroke, so rates of hemorrhage must be estimated from studies of stroke and acute coronary syndromes. All subjects 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]. The absolute increase in risk of life-threatening hemorrhage in the MATCH trial, which is most similar to POINT, was 1.3% (2.6% for the combination vs. 1.3% for clopidogrel alone), and this risk was spread out over 18 months follow-up. Subjects are followed for 90 days and only TIAs and minor ischemic strokes are included, so a 1% excess absolute risk is realistic, and is consistent with other trials. The combination may increase the risk of complications with interventions, such as endarterectomy, or may delay the performance of these procedures due to

concerns about bleeding risk. 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 the subject's care is another potential risk. There is also a small risk of loss of confidentiality.

8.2 Serious Adverse Events

The greatest risk to subject 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, use of this drug will be prohibited.

Unexpected SAEs will be reported to the DSMB in a timely fashion and on a schedule that is determined by the DSMB.

8.2.1 Management of SAEs/Clinical Outcomes

WebDCU™ has an integrated web-based SAE/Clinical Outcome Reporting module that provides the mechanism by which serious adverse events or clinical outcomes are reported and reviewed. SAEs/ clinical outcomes will then be made available to the appropriate Project Management staff and the designated blinded Clinician Event Coordinator (CEC) for review. Reviews are performed on-line. If additional documentation is required, this will be requested of the site by its overseeing organization (NETT or CRC) or the CEC. Integration of the Clinician Event Coordinator functionality into the data entry system facilitates rapid review and reporting of events to the DSMB and regulatory bodies. The CRC Medical Monitor is notified when an event is determined to be a serious, unexpected, adverse reaction by the CEC. The CRC Medical Monitor completes the Council for International Organizations of Medical Sciences (CIOMS) form and sends it to the country-level Regulatory Manager for sites outside the US. The country level manager submits the form to the country level regulatory agency.

8.3 Definitions

Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental treatment regardless of whether it is considered related to the treatment (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

Non-serious AEs are not being collected in the POINT trial, unless they qualify as a Clinical Outcome as defined in section 4.6.1.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly or requires intervention to prevent permanent impairment or damage.

Unexpected (Unanticipated) Adverse Event

An unexpected AE is defined as an event that was "not anticipated" as a risk in the IRB or EC-approved protocol, consent form, or package insert, or an event that occurs at a greater frequency or intensity than anticipated.

Anticipated Adverse Event

Anticipated adverse events in this trial will be those previously described in the package insert for clopidogrel and those anticipated based on the natural history of TIA and minor ischemic stroke.

8.4 Classification of Adverse Events

Severity is used to describe the intensity of a specific event. Severity of SAEs/clinical outcomes will be documented using the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE) (see Manual of Procedures). The CTCAE provides descriptive terminology that will be used for recording and reporting SAEs/ clinical outcomes that occur in POINT. The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v 4.03) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Grade 1:	Mild AE
Grade 2:	Moderate AE
Grade 3:	Severe AE
Grade 4:	Life-Threatening or Disabling AE
Grade 5:	Death related to AE

Note: Severity is not equivalent to seriousness. A serious adverse event (SAE) would be any event in category 4 or 5, and any event in category 3 that required or prolonged hospitalization. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade Selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

See also http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

8.5 SAEs/Clinical Outcomes

8.5.1 SAEs/Clinical Outcomes into the Study Database

All SAEs/Clinical Outcomes occurring until participation in study has ended are recorded on the online SAE/Clinical Outcome Reporting Form (CRF 19) through the WebDCU™. The Site PI or Study Coordinator is responsible for entering any and all SAEs into the database and updating the information (e.g., date of resolution, action taken), as needed, in a timely manner. Given the vast amount of data on AEs associated with clopidogrel, only SAEs/Clinical Outcomes will be recorded; data entry must take place within **5 days (within 24 hours for sites in the UK)** of discovery of the event.

The Hub PI for NETT sites and site PI for others are responsible for the monitoring and follow-up of all SAEs/Clinical Outcomes until resolution (or end of study for that subject) and appropriate documentation in the subject research record. In addition to performing protocol-specified follow-up,

the participating PI must review all previously reported ongoing SAEs/Clinical Outcomes to evaluate the current status.

Upon completion of the study by the subject, premature withdrawal from the study by the subject, or subject's death, all information regarding each SAEs/Clinical Outcome must be completed, if not done so earlier.

8.5.2 Reporting Recurrent SAEs/Clinical Outcomes

If a SAE/Clinical Outcome that was previously reported on the SAE/Clinical Outcome CRF fully resolves and then recurs at a later date, the second occurrence is considered a new SAE/Clinical Outcome and a new CRF must be completed. Resolution is the normalization or return to baseline of laboratory values, clinical signs or symptoms related to the event.

8.5.3 Procedure for Expedited Reporting of SAEs/Clinical Outcomes

Clinical outcomes may be discovered during the 7-day telephone follow-up, the 30-day phone contact, the 90-day follow-up appointment, or at any point during the study period. For subjects considered lost to follow-up, efforts should be made for up to 150 days from randomization to determine if an outcome event occurred during the subject's 90 days in the study. When a clinical outcome is discovered, the Site PI is responsible for submitting it **within 5 days (within 24 hours for sites in the UK) of the discovery of the event** on the online SAE/Clinical Outcome case report form.

The Hub PI (for NINDS NETT-CCC Network sites) or Site PI (for POINT Clinical Research Collaboration (CRC) sites) are responsible for the monitoring, follow-up and appropriate documentation of all clinical outcomes until resolution or the end of study for the subject. The Site/Hub PI will work with the appropriate Site Manager to prepare an Event Packet for outcome events, including copies of discharge summaries, neurology, cardiology or other consultation notes, head imaging reports, appropriate laboratory values, and a narrative summary, plus any supplemental documentation based upon adjudication category assigned to the event, with all unique identifiers removed.

When the SAE/Clinical Outcome CRF is submitted for a fatal SAE or a clinical outcome, the appropriate Site Manager is then responsible for reviewing the information for completeness. If the information is deemed insufficient, the Site Manager will request additional information from the site.

The Site Manager will work with the Site/Hub PI to prepare an Event Packet, as described above. When the SAE/Clinical Outcome information is deemed sufficient by the Site Manager, the Clinician Event Coordinator (CEC) is charged with performing the Clinical Outcome Review (COR). The COR includes review of both Clinical Outcomes and SAEs.

The CEC, who is blinded, will then review the SAE/Clinical Outcome CRF and the Event Packet independently. If clarifications or additional information are required, the CEC will request them from the Site Manager (from either the NETT-CCC or POINT CRC), who obtains the information. The CEC can also request the information directly from the site. When all information necessary for adjudicating a clinical outcome is available and the event requires adjudication (as defined in section 8.5.5) the event will be assigned to the appropriate Adjudicators, as described in section 8.5.5.

A detailed description of the process for adjudication of clinical outcomes is found in the Manual of Procedures.

As part of the COR, the CEC will review SAEs, verifying that the accompanying narrative is complete.

The CEC, who will remain blinded throughout the trial, accesses the SAE/Clinical Outcome data. The CEC blindly reviews the data independently, but may contact the Clinical Site investigators for clarifications and additional information. The CEC designates within 72 hours of notification of the SAE/Clinical Outcome occurrence whether the SAE/Clinical Outcome is unexpected and related to the study drug.

The review process closes at the end of the 72 hours. The Clinical Site staff submits SAEs to their IRB/EC in accordance with the local guidelines and procedures.

Timelines for completion of CIOMS Form by the CRC Medical Monitor:

- 7-day reportable events- within 48 hours of receipt of the notification email (CEC assessment).
- 15-day reportable events- within 7 days of receipt of the notification email (CEC assessment).

Unexpected SAEs will be reported to the DSMB in a timely fashion and on a schedule that is determined by the DSMB.

8.5.4 Site Monitoring and SAE/Clinical Outcome Reporting

During a site monitoring visit, the NETT or CRC Site Monitor will verify appropriate documentation and reporting of SAE/Clinical Outcomes. In addition, if the site monitor identifies an unreported SAE/Clinical Outcome, appropriate documentation and reporting will be initiated as guided by the site monitor.

8.5.5 Clinical Outcome Event Reporting

All efficacy and safety clinical outcome events listed in **section 4.6.1** will be reported using the identical mechanism as described in section 8.5.3 above. In addition, Event Packets will be prepared by the site in conjunction with the NETT CCC or CRC Site Managers. These will include copies of discharge summaries, neurology consultation notes, head imaging reports, and a narrative summary prepared by the site, all with unique identifiers removed. Documents requiring translation will be checked for deletion of PHI by the country level manager, and a request for translation will be made to the CRC. The CRC will provide the translated documents back to the country level manager for upload. In addition to CRF 19 and the other core documents, additional required documents are available on the *POINT Clinical Outcome-Specific Checklists for Preparing Event Packets*, and must be included as part of the Event Packet. The Event Packet will be accessible to the Clinician Event Coordinator (CEC), who will review them for completeness.

Based on the CEC's judgment, all events will be assigned to two independent Adjudicators:

The following events will be assigned to <u>two neurologist Adjudicators</u>: ischemic stroke, intracerebral hemorrhage (symptomatic or asymptomatic), and other intracranial hemorrhage (symptomatic or asymptomatic).

The following events will be assigned to <u>two cardiologist/internist Adjudicators</u>: myocardial infarction (with or without coronary revascularization) and coronary revascularization without myocardial infarction.

The following events will be assigned to one neurologist and one cardiologist/internist Adjudicator: major hemorrhage other than intracranial hemorrhage and other serious adverse events resulting in death.

The assigned Adjudicators will review the reported event and the related Event Packet, and come to independent classifications of the event. If clarifications or additional information is/are required, the Adjudicators may contact the CEC, who will review requests and ask for additional information or clarification when necessary.

If the Adjudicators disagree with each other on the event classification, a third Adjudicator will be assigned to adjudicate the outcome event. If the third Adjudicator's classification of the event matches that of one of the two initial reviewers, this will be the final classification of the event.

If the third Adjudicator disagrees with both of the original Adjudicators, then there will be a conference call to review the discrepant event classification with the Adjudication Committee Chair. The Chair will attempt to gain consensus; however, the decision of the Chair will be the final classification of the event.

8.6 Protocol Violations

Protocol violations are any unapproved changes, deviations, or departures from the study design or procedures of a research project that are under the investigator's control, have not been reviewed and approved by the local or central IRB/Ethics Committee/Committee on Human Research (CHR), and have already occurred without prospective review by the IRB/EC/CHR prior to initiation or implementation.

Protocol violations are divided into **two categories**: major (reportable) or minor (non-reportable; also known as *deviations*) violations.

Major (reportable) Protocol Violations
Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB, EC, or CHR-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. **All major violations must be reported to the IRB/EC/CHR following local guidelines.**

Criteria for defining major violations include any of the following:

- The violation has harmed, or posed a significant or substantive risk of harm, to the research participant.
- The violation resulted in a change to the participant's clinical or emotional condition or status.
- The violation has damaged the scientific completeness or soundness of the data collected for the study.
- The violation is evidence of willful or knowing misconduct on the part of the investigator(s).
- The violation involves serious or continuing noncompliance with federal, state or local regulations.

Examples of major protocol violations include, but are not limited to:

1) Enrollment of participants who did not meet all inclusion/exclusion criteria

2) Randomization errors
3) Failure to obtain informed consent prior to initiation of any study-specific tests/procedures
4) Failure to follow protocol procedures that specifically relate to primary safety or efficacy endpoints of the study
5) Study medication dispensing or dosing error
6) Receipt of a prohibited concomitant medication
7) Incorrectly stored study medications

Minor (non-reportable) Protocol Violations (also known as Protocol Deviations)
Minor protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB/EC/CHR-approved protocol that **do not have a major impact** on either the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Minor protocol violations are **not** reportable to the CHR/HRPP, but should be documented in the study files.

Criteria for minor violations include all of the following:

- The violation did not harm or pose a significant risk of substantive harm to the research participant, and
- The violation did not result in a change to the participant's clinical or emotional condition or status, and
- The violation did not damage the completeness, accuracy and reliability of the data collected for the study, and
- The violation did not result from willful or knowing misconduct on the part of the investigator(s).

Examples of minor protocol violations (deviations) include, but are not limited to:

1) Data collection that occurs outside the planned time window or location
2) Failure to follow approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity
3) Investigators miss giving a study-required self-administered questionnaire to a participant

9 STUDY PROCEDURES

Any patient with a TIA or minor ischemic stroke meeting the inclusion criteria and not having an exclusion is a potential candidate for the study. The patient will receive complete information about the study, orally and in writing.

9.1 Screening Evaluation

Potential subjects will be identified by neurologists, local emergency departments, and clinic staff in conjunction with study personnel. When a potential candidate is identified, the site PI and/or the

Study Coordinator should be contacted to begin the screening process. Patients should be screened and randomized as quickly as possible after presentation to the Emergency Department.

The Eligibility CRF (Form 00) will be completed at this time to determine whether a potential participant is eligible; the form captures all the Inclusion and Exclusion criteria for the study, many of which are based on tests performed for clinical reasons.

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, abscess, or other TIA mimic. A CT or MRI scan done at a spoke/outside hospital is acceptable as baseline imaging, following review by site investigator; an official report is still required. The results are recorded on CRF 11. 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.

The patient's presentation history should be taken, evaluating for the possibility that the event was a **TIA or minor ischemic stroke.** Specifics about the event, including time of onset (or time last known free from new ischemic symptoms), symptoms, duration of symptoms (if resolved), and pertinent review of symptoms should be obtained.

If the patient has had a **TIA**, **ABCD^2** score should be calculated. If the patient has had a **stroke**, **NIHSS** should be performed. (In the case of a patient with blindness that precedes the onset of a TIA or minor stroke, the Manual of Procedures should be consulted for details on scoring the patient using the appropriate assessment scale.)

Certified, trained study personnel will be required to calculate the ABCD^2 score and NIH Stroke Scale score. The physician (MD or DO), PA or NP investigator must confirm eligibility and review the calculation of the NIHSS and the ABCD^2 scores, either in person or by phone with a properly trained and certified physician, or properly trained and certified study personnel prior to randomization into the study. Participants may be randomized by any certified study personnel as long as a site certified physician investigator has reviewed and approved eligibility prior to randomization.

A focused medication history will be taken, as will a focused past medical history.

Screening laboratories of CBC and creatinine will be reviewed. For a woman premenopausal or postmenopausal within 12 months of last menses without a negative pregnancy test or not committing to adequate birth without a negative pregnancy test or not committing to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence) a pregnancy test will be done.

Ability to swallow should be assessed. If the patient has had a stroke, swallow evaluation should be considered. Swallow evaluation is not a standard component in the evaluation of TIA; TIA patients should require no swallow evaluation, unless having a preceding neurological disorder with dysphagia.

Blood pressure should be taken, and ECG obtained. Brain imaging should be performed with CT or MRI, and the results recorded on CRF 11.

Urgent carotid artery imaging is encouraged but not required. If these studies are done, results should be recorded on CRF 13.

The final inclusion/exclusion criteria checklist should be reviewed after collecting all of the information.

For sites having trouble meeting their enrollment goals, a screen failure log will be completed for all patients who are screened but not randomized into the study. This log will not include any personal

identifiers and thus will not require consent. These screen failure logs will be useful in determining whether there are modifiable approaches available to increase enrollment.

Those meeting the eligibility criteria (Section 5.2) will be recruited as trial participants. Subjects already taking aspirin or another antiplatelet agent may be randomized at the discretion of the treating physician, as is consistent with current American Stroke Association guidelines [99]. Consent will be obtained directly from the patient prior to randomization. Participants who consent to the POINT Trial will be asked to consent to an optional ancillary study consisting of a one-time venous blood sample of approximately 10mL collected at the time of enrollment in the trial. Those patients who decline the ancillary study will not be prohibited from participating in the POINT Trial.

Since neurological deficits will have resolved or be minimal at the time of randomization, consent from a responsible family member or legal surrogate is not allowed in the study.

9.2 Baseline Evaluation

Inclusion and exclusion criteria will be assessed, including recording the $ABCD^2$ score for patients presenting with TIA, and the NIH Stroke Scale Score for subjects presenting with minor ischemic stroke. The baseline evaluation will include subject demographic information, symptoms of the index event, prior medications, past medical history, smoking history, blood pressure, and laboratory evaluation. Results of head imaging, laboratories (CBC, INR, glucose), and ECG will be recorded using standardized instruments. Urgent carotid artery imaging will be encouraged but not required. If further diagnostic studies are performed, such as cervicocerebral MRA or CTA, results will be recorded. Signed written informed consent will be obtained prior to randomization. Antiplatelet and anticoagulant agents other than aspirin will be discontinued prior to randomization.

9.3 Randomization

Upon presentation of a potential subject, the procedure for randomization is as follows:

1. A study subject's eligibility is determined by site personnel.
2. Qualified site personnel then access (with username and password) WebDCU™.
3. Qualified site personnel complete the Eligibility and Randomization forms in WebDCU™, which include protocol-specific eligibility.
4. If the WebDCU™ system deems the subject to be eligible based on the information provided, it evaluates the treatment arm distribution and generates a randomization number based on the randomization scheme. (The randomization number corresponds to one of the medication bottles in inventory at the clinical site).
5. An automatic confirmation e-mail is sent to notify the study team of the randomization.
6. The randomization number generates an ID number that corresponds with a particular study drug bottle and with the Study ID pre-printed on the Randomization Verification Form (RVF) that matches the study Drug ID.
7. Qualified site personnel obtain the study medication bottle with the corresponding randomization number after verifying that the Study Drug ID number on bottle. For complete details of the process, see the Manual of Procedures.

8. Qualified site personnel administer and witness the loading dose.
9. At discharge, the study medication bottle is given to the subject with appropriate instructions for daily administration.

9.3.1 Treatment Protocols

Time to treatment is the crucial element in POINT. Therefore, it will be considered a protocol violation if a subject is given the initial 600mg loading dose outside of 2 hours following randomization

After randomization, subjects will be given a medication bottle containing their study drug for the duration of the trial. Qualified site personnel must ensure that the number on the medication bottle given to the subject is the same as the randomization number issued by the WebDCU™ study database. Subjects will be provided with a POINT Trial Alert Card (wallet card) that briefly describes the study protocol, identifies an Emergency Contact, the Primary Physician and POINT Trial contact (with contact numbers), and lists the UCSF CCC emergency contact number.

Subjects randomized to clopidogrel will receive clopidogrel 600 mg (eight 75 mg tablets), and will be given a bottle containing a supply of clopidogrel 75 mg, with instructions to take one tablet on day 2, and 1 additional tablet each day through the 90 day follow up. Those not randomized to clopidogrel will receive eight tablets of an identical-appearing placebo on day 1, and will be given a bottle with placebo and instructions to take one tablet each day on days 2 through 90. All subjects will also take 50-325 mg of open-label aspirin daily; the dose will be determined by the treating physician but a dose of 150-200 mg daily x 5 days, followed by 75-100 mg daily will be strongly recommended. 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 as soon as it is considered safe by the subject's neurologist or primary care physician. Study medications will be restarted after carotid endarterectomy (Section 7.5). 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; under the intent-to-treat principle subsequent events will be included in the primary analysis. If patients are already on clopidogrel, they can be enrolled in POINT and given the full loading dose. Patients who initially presented at an outside Emergency Department and were loaded with clopidogrel can also be evaluated for participation in the study.

There is uncertainty about whether proton-pump inhibitors (PPIs) interfere with the effectiveness of clopidogrel and this has caused regulatory authorities (the European Medicines Agency -EMEA, UK Medicines and Healthcare Products Regulatory Agency -MHRA and US FDA) to recommend that concomitant use of clopidogrel and PPIs be discouraged unless necessary.

Clopidogrel is a *prodrug* that requires conversion to its active metabolite by liver cytochrome P450 2C19 (CYP2C19). PPIs also are metabolized by CYP2C19 and when taken concomitantly with clopidogrel can decrease the antiplatelet effectiveness of clopidogrel. Enzymes other than CYP2C19 can metabolize one of the PPIs, pantoprazole.

Some studies have shown that patients on clopidogrel and a PPI have more thrombotic outcomes than those on clopidogrel alone. Three explanations for why that might be the case, have been proposed:

- PPIs may interfere with the conversion of clopidogrel to its active metabolite
- PPIs may directly cause harm, and
- The effect may be due to confounding in the reported studies. Patients taking clopidogrel plus a PPI were much older and sicker than those taking clopidogrel alone.

The studies on which these concerns rest are all observational. Data from clinical trials (CREDO and TRITON) have shown no interaction.

Another point of uncertainty is whether there may be differences between individual PPIs, with some pharmacodynamic studies suggesting an interaction with omeprazole but not with pantoprazole. It is known that omeprazole is metabolized by the CYP2C19 enzyme, which converts clopidogrel into its active metabolite. While pantoprazole can also be metabolized by this enzyme, it also uses other routes.

For these reasons, POINT recommends that H2 antagonists be used when possible in subjects requiring gastroesophageal protection and for those not controlled with H2 antagonists and deemed to require a PPI, pantoprazole may be the best choice.

9.3.2 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]. Key recommendations are outlined below.

Evaluation

- An ECG, a complete blood count, electrolytes, creatinine, glucose, and head CT or MRI are all part of routine practice for patients with TIA and minor stroke. Results of these tests are required to assess eligibility for the trial.
- Best practices typically include that if an ultrasound, CT angiography, or MR angiography suggest a stenosis greater than 50% , additional carotid imaging to confirm the degree of stenosis is warranted. For sites where standard of care includes carotid imaging, it should be performed as soon as possible, preferably prior to study entry, and those with >50% internal carotid artery stenosis should not be randomized unless the patient declines both carotid endarterectomy and endovascular intervention at the time of evaluation for eligibility.
- Fasting cholesterol panel, HbA1c, 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 a hypercoagulable state should be considered in those with no apparent risk factors for stroke.

Management

- 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 (e.g., atorvastatin 80 mg daily) is recommended in all subjects unless LDL is < 70 mg/dL or there is a contraindication.
- Tight control of diabetes is recommended to maintain HbA1c < 7%.
- Physical exercise should be encouraged (>30 min for ≥3 days/week).
- Subjects 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.
- Subjects with an internal carotid artery stenosis of 70-99% that may have been responsible for the index event should be considered for urgent endarterectomy. If the stenosis is identified prior to randomization, the patient is excluded from the trial, unless:
    - the investigator does not consider the subject to be a candidate for either carotid endarterectomy or endovascular intervention, OR
    - the patient declines both carotid endarterectomy and endovascular intervention.
- Subjects 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. If the stenosis is identified prior to randomization, the patient is excluded from the trial, unless:
    - the investigator does not consider the subject to be a candidate for either carotid endarterectomy or endovascular intervention, OR
    - the patient declines both carotid endarterectomy and endovascular intervention.

9.4 Follow-up

9.4.1 Follow-up 7 Day Phone Call

The Site Coordinator will contact subjects by telephone (or in person) at 7 days. A review of SAEs/Clinical Outcomes, concomitant medications and compliance with study medication will be assessed. The QVSFS, a screen for stroke-free status questionnaire [155] will also be administered. If subject contact suggests that a possible stroke, TIA or myocardial infarction may have occurred, an Outcome Event Visit will be scheduled.

9.4.1.1 30 Day Phone Contact

The Site Coordinator will contact subjects by telephone at 30 days to uncover any issues or concerns that might impact study drug compliance and retention in the study.

While no study data will be collected for the 30-day phone contact, if subject contact suggests that a possible stroke, TIA or myocardial infarction may have occurred, an Outcome Event Visit will be scheduled.

9.4.2 90 Day In-Person or Phone Follow- up

A review of SAEs/Clinical Outcomes, concomitant medications and compliance with study medication (via the Morisky questionnaire) will be assessed. The QVSFS, mRS and NIHSS will also be administered.

At the 90 Day 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 subjects who can afford clopidogrel or have medical coverage for it. For others, aspirin 75-100 mg will be prescribed, consistent with American Stroke Association guidelines. 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.

The 90 Day follow-up should be completed during an in-person visit whenever possible; under limited circumstances, for example, if the subject is unable to come in for follow-up, the visit may be completed by telephone. CRF completion for the visit will be guided by whether the visit was conducted by phone or in person. For visits completed over the phone, the omission of the NIHSS assessment will not result in a protocol deviation. The 90-day assessment does not have to be completed by the PI. It can be completed by anyone on the study team that has completed the appropriate POINT study training and whose certifications are current.

9.4.2.1 Subjects Considered Lost To Follow-up

A subject is considered to be lost to follow-up (LTFU) when continued contact with the subject cannot be maintained and, despite an active follow-up effort, the site is unable to collect reliable information about the outcome event status of the subject up to 150 days following randomization (the 90 day enrollment period, and up to 60 days after the projected end of the subject's enrollment).

Information about outcome events that occurred during the subject's 90 day enrollment will be considered *reliable* when Form 14: Questionnaire for Verifying Stroke Free Status and/or Form 19: SAE/Clinical Outcome Reporting are completed based on contact with the subject, or the subject's caregiver or alternate contact. Events reported in this way will be adjudicated and included in the primary analysis.

A subject can be considered lost to follow-up when the clinical site can show documented attempts to reach the subject, and the period beyond the final scheduled study visit has reached 60 days (i.e., 150 days after randomization). For any subject who may be lost to follow-up, the POINT Clinical Site must discuss the subject with the appropriate NETT or CRC Study Manager and the UCSF Clinical Coordinating Center team before assigning that subject lost.

POINT Clinical Sites will need to demonstrate and document in WebDCU (Form 17 - End of Study: General Comments field) at least three (3) attempted telephone contacts by research personnel. A progress note, including the time and date of each attempt, should be added to the participant's study file for each contact. After attempts at phone contact are considered unsuccessful, or a subject has been reached but fails to appear for the 90 day visit, research personnel at sites must also generate and send at least one (1) letter using institutional letterhead and envelope. The letter should be sent

using Certified Mail™ with Return Receipt Service (or equivalent in other countries) for evidence of delivery to the participant's address, allowing a week for the subject to respond to the site. The receipt should be added to the participant's file, and a progress note, along with a copy of the letter(s), should also be placed in the subject's study file. When subjects cannot be contacted despite the site team implementing these approaches, investigators should attempt to determine the subject's vital status at 90 days (i.e., living or deceased) using locally-approved resources.

9.4.2.2 End of Study

A subject is considered to have completed the study when the 90 Day Visit is completed. For those subjects who fail to complete a 90 Day Visit, subjects are considered to have exited the study at the time of withdrawal of consent or death occurring prior to the 90-day visit window, or, for those considered lost to follow-up, at 150 days from randomization, when the 90-day visit plus 60 days window closes.

Form 17: End of Study should be completed in the WebDCU™ system for every subject once the subject has exited the study.

9.4.3 Event Visit

An Outcome Event Visit should be conducted if a subject experiences an ischemic stroke, TIA, or myocardial infarction. Outcome Event Visits should be conducted in person unless the subject experiences a myocardial infarction or refuses to come for an in-person visit. CRF completion for the visit will be guided by whether the visit was conducted by phone or in person. Event visits are conducted as needed, and can be done more than once for the same subject.

A listing of data collected during event visits is included in Section 1.2. SAEs/Clinical Outcomes, concomitant medications, mRS, NIHSS, QVSFS, and Morisky Questionnaire will be recorded. Head imaging with CT or MRI will be strongly encouraged 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. If study medications are discontinued due to an outcome or SAE, they should be restarted as soon as felt to be safe by the treating physician. Event visits may occur on the same day as the 90-day visit since it is expected that clinical outcome events may often be identified at the 90 day visit. Each subject will continue to be followed through 90 days post randomization.

9.4.4 Adherence to Treatment

Subject adherence with the study drug (clopidogrel and placebo) and aspirin will be assessed by administering the Morisky medication adherence questionnaire at the 7 day telephone call, the 90 day visit, and at the event visit. The 4-question Morisky scale is a simple, commonly used, validated adherence measure (*Morisky, DE; Green, LW; Levine, DM. 1986, Medical Care, 24, 1. p.67-74*). This will serve as the primary measure of adherence. A participant is considered compliant with study medication if he/she reported at least medium compliance on the study adherence questionnaire. The investigator will be responsible for monitoring subject adherence. A subject will be counseled on the importance of complying with the study medication.

In addition, for clopidogrel, compliance with the study drug will be documented at the 90-day visit. Those subjects taking more than 80% of tablets on days 2-90 (71 or more tablets) will be considered adherent as assessed by pill count and subject/care-giver report. NOTE: Since the loading dose is observed by the study investigator or other member of the study team (see Manual of Procedures section 11.4, Study Procedures) and recorded on CRF 7, subjects will be considered to be in compliance with the loading dose. Therefore, a subject is adherent if he/she has taken at least 79 tablets (8 at loading dose + 71 on days 2-90).

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 recorded at follow-up visits.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis Plans

This section is an overview of the statistical considerations. Complete details can be found in the Statistical Analysis Plan (SAP). It provides the general specifications for the analysis of the data to be collected and presented in the Clinical Study Report. A final SAP will be issued by the SDMC prior to database lock and before code breaking. The SAP will define all "pre-specified, planned analyses."

10.1.1 Randomization Scheme

Randomization will be implemented centrally via the WebDCU™ system. The randomization scheme will ensure treatment is balanced within site and overall. The study will include both TIA and minor ischemic stroke, with the latter accounting for no more than 50% of enrollment.

10.1.2 Sample Size Estimates

Primary Null Hypothesis

In patients with high-risk TIA or minor ischemic stroke 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 subjects are randomized within 12 hours of time last known free from new ischemic symptoms. The primary outcome is a composite consisting of ischemic stroke, myocardial infarction, or ischemic vascular death; the primary safety outcome is major hemorrhage.

The original maximum sample size to detect a relative risk reduction (RRR) of 23% is 4,150 subjects. As stipulated in the Statistical Analysis Plan, following the first interim analysis, the maximum sample size has been re-estimated to be 5,840 subjects. The original sample size estimation is based on 90% power and a two-sided alpha of 0.05, 12% crossovers, and 2% losses to follow-up. The RRR of 23% translates to a hazard ratio of 0.75 assuming the proportion of subjects with events in the placebo group to be 15%, and inflation to account for two interim analyses for efficacy at equal intervals using O'Brien and Fleming stopping boundaries.

10.1.3 Secondary Outcomes

A number of other secondary outcomes will be evaluated separately, including risk of ischemic stroke, intracranial hemorrhage, and major hemorrhage, and the composite of the primary outcome and major hemorrhage. The influence of index event type (TIA vs. minor stroke), sex, and race/ethnicity will be evaluated in subgroup analyses.

10.2 Statistical Analyses

10.2.1 Primary Outcomes

The primary analysis will be intention to treat, with inclusion and treatment group defined per the randomization assignment. Missing values will remain missing and subjects will be censored at their last follow-up assessment (end of study or last visit prior to loss to follow-up). Kaplan-Meier estimates of the cumulative risk of an event will be reported for the maximum 90-day follow-up, and the log-rank test will be used to evaluate the statistical significance of the treatment effect. The Type I error for the primary analysis will consider two-sided alpha=0.05 significant.

10.2.2 Secondary Outcome Events

The analysis strategy outlined for the primary outcome will be used for most of the secondary analyses. Each secondary outcome event at the two-sided alpha of 0.05 will be tested, recognizing the dangers of inflating the Type I error probabilities. These tests will be viewed as exploratory hypotheses that may or may not support the results of the primary analysis.

10.3 Data and Safety Monitoring Procedure and Plan

An external **Data Safety and Monitoring Board (DSMB)** is appointed by and reports to the NINDS. Open and closed reports will be prepared by the NETT-SDMC statisticians. The DSMB will meet approximately every 6 months with additional meetings scheduled as they require. At intervals defined by the DSMB, reports of safety events will be submitted to the DSMB by NETT-SDMC statisticians.

A blinded **Clinician Event Coordinator** will review safety data on SAEs as they become available to the UCSF CCC, including adjudicating whether events are serious, related to the study drug, or unexpected (in addition to the review of the site investigator). The safety data will be made available to the Clinician Event Coordinator on the WebDCU™ system to allow real-time access, review and reporting.

10.3.1 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, as outlined in NINDS guidelines, to assure subject safety; additional interim analyses may be requested by the DSMB. 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.

Superiority or Inferiority Established Prematurely. The number of interim evaluations of the primary outcome data will be determined by the DSMB and will be described in the Statistical Analysis Plan.

11 ETHICAL AND REGULATORY STANDARDS

11.1 Ethical Considerations

The study will be conducted in accordance with the U.S. Food and Drug Administration's (FDA) Code of Federal Regulations (CFR Title 21), ICH Good Clinical Practice (GCP) guidelines, and the relevant regulations for clinical trials for each investigational site.

11.2 Regulatory Requirements

Prior to initiating the study, each site will obtain IRB or Ethics Committee approval for the protocol, Informed Consent Forms and materials used to recruit subjects. In addition, each investigator will sign an Investigator Agreement with the study sponsor. IRB/IEC-approved informational videos and quizzes designed to inform physicians and supplement the informed consent process may be presented on tablet devices and online to study physicians and potential subjects. Signatures of study subjects documenting their consent will be collected on paper and/or digitally. Prior to their participation, subjects will be provided printed paper copies of the signed consent form, as required by ICH GCP 4.8.11 and 21 CFR 50.27. Protocol amendments are not allowed by any investigator without prior approval from the Executive Committee. All changes to the protocol approved by the Executive Committee must be submitted to the site's IRB/IEC for review and approval as appropriate. The trial has received a waiver from IND requirements from the FDA. However, each investigator at sites outside the U.S. must assure that any necessary approvals, or applicable waiver(s), have been obtained from the appropriate regulatory authority and/or national competent health authority, with authorization to proceed.

11.3 Institutional Review Board (IRB) or Ethics Committee (EC)

Prior to initiating the study, each Investigator must submit the following to an IRB/IEC: the Informed Consent Form, this protocol and materials used to recruit subjects for this clinical trial. No study subjects may be recruited until documented IRB/IEC approval (or favorable opinion) is obtained for that site. Any addendums or revisions to the above documents must be resubmitted for review and approval. Each investigator will follow the requirements of his or her IRB/IEC on periodic reporting of the progress of the study, reporting of serious or unexpected adverse events, safety monitoring reports, and termination of the study.

11.4 Informed Consent

Each eligible patient who wishes to participate in this study will be required to give written informed consent. Written informed consent will include signatures collected on paper and/or digitally and subjects will be provided printed paper copies of the consent form. Before the consent form is signed, a trained researcher will explain why the patient was selected for screening and the purpose of the

screening and how results of screening are used to determine eligibility. IRB/IEC-approved informational videos and quizzes designed to inform physicians and supplement the informed consent process may be presented online, and on tablet or similar electronic devices to study physicians and patients. The patient will be informed that, if he or she meets all of the inclusion criteria and none of the exclusion criteria, and agrees to participate, he or she will be enrolled in a clinical trial of clopidogrel and placebo. The consent document explains the risks and potential benefits of the therapy, the procedures for the trial, and alternatives to participation. There will be no surrogate consent in the study. Subjects must personally consent to participation and sign the approved consent form(s) which will be retained by the investigator and may be reviewed by the sponsor's authorized monitors or auditors, and authorized representatives from regulatory authorities.

12 STUDY MONITORING

12.1 Site Monitoring, Quality Assurance and Remedial Actions

Quality Assurance activities will be a collaborative effort between the POINT CRC and the NETT CCC.

12.1.1 Site Visits

The POINT CRC monitoring staff or contractors will perform all site visits to CRC investigators, on a jointly acceptable schedule. Similarly, the NETT-CCC will perform all visits for its sites. The site Readiness Call will take place via telephone contact prior to any participants being enrolled. Required regulatory documents will be stored in the regulatory module of WebDCU™. Subsequent site visits are scheduled on an as-needed basis based on recruitment, data quality, or continued noncompliance (for cause). Every site will receive at least one visit during the course of the study. The visit will include review of regulatory documents maintained at the site, verification of the appropriate version and completion of Informed Consent Forms, supplemental videos and quizzes, protocol compliance, study drug accountability, discussions with the site PI and staff regarding study conduct, and a data audit against source documents, as available. The site visits will follow the CRC and NETT Standard Operating Procedures/Monitoring Plan for conducting visits. A site visit report summarizing the findings will be issued to the Study PI and the Operations Committee within 28 days of the visit.

12.1.2 Remedial Action

Sites that demonstrate difficulty complying with study procedures, recruitment, or maintaining data quality will be discussed with the Executive Committee. Action may include direct phone contact with the site PI by the POINT CRC or NETT Site Monitor to discuss the issues and create a corrective action plan, subsequent site visit by the Site Monitor, and/or a probationary period until effective corrective action has been taken. If the situation remains unresolved, the Executive Committee may suspend the site from the study. Specifically, with regard to recruitment, sites that are certified to enroll study participants but do not enroll a participant in 90 days, will be contacted by the CRC or NETT Site Monitor via telephone to determine the site's continued interest in study participation, and to create a plan to increase enrollment of participants.

12.2 Data Management

12.2.1 Data Quality Monitoring

The POINT CRC monitoring staff will have access to real-time data that describe the quality of the data submitted by CRC physicians, and the NETT CCC will do the same for its sites. These data include recruitment, missing values and other data anomalies, missing forms, missed visits, late visits, subject ineligibility post enrollment, and other protocol deviations and violations.

13 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. The trial results will be published as soon as possible after database lockdown.

This trial will produce detailed data on treatment effects, medical care, and outcomes in a cohort of 5,840 subjects with TIA or minor ischemic stroke. Three years after the primary publication associated with this work is submitted, a HIPAA-compliant, de-identified version of the database will be made available publicly. POINT biostatisticians will be consulted to assure that it is impossible to uniquely identify any participant. This may mean removing or categorizing certain variables. A data use agreement will not be required for access to this dataset. Data in comma-delimited text format will be sent to parties that express interest, including a data dictionary in a text file.

The goal of the POINT Trial Publications Policy is to provide guidelines for preparing, reviewing, submitting and maximizing productivity of high-quality peer-reviewed publications. In addition to overseeing the performance of the trial, the Executive Committee is responsible for encouraging paper production, ensuring timely publication of data, maintaining a high standard for the quality of papers produced for POINT, and determining appropriate authorship. When the Committee is discussing manuscripts associated with ancillary studies, the PI of the ancillary study and his/her designee will also join the Executive Committee for that discussion (see Section 14, Ancillary Studies).

Manuscript proposals will be submitted to the Executive Committee. These proposals will include the type (primary, secondary, tertiary and quaternary), list of authors and their qualifications for authorship, a statement that no others deserving authorship have been omitted, the scientific rationale for the paper, the data needed and a description of the proposed analyses and any deadlines for submission of abstracts or presentation dates if applicable. The Publications Policy can be found in the Manual of Procedures.

14 ANCILLARY STUDIES

Proposals for ancillary studies will be reviewed by the Executive Committee; these studies will require funding outside the original study grant. The committee will assure that all such studies are hypothesis driven, methodologically robust and contain complete and accurate data. Approval will follow the ancillary study approval process which defines the standard procedures for proposing, reviewing, and approving ancillary studies and/or substudies conducted within the trial. It will meet each month by teleconference the first 6 months of enrollment, and every other month for the duration of subject 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. Publication of the results will be governed by the policies and procedures developed by the Executive Committee. Sites will not be required to participate in any ancillary study that requires additional data collection, but they will be encouraged to participate in accepted studies. The Ancillary Studies Policy can be found in the Manual of Procedures.

14.1 Optional POINT Biomarkers Ancillary Study

Participants who consent to the POINT trial will be asked to consent to an optional ancillary study consisting of a one-time venous blood sample of approximately 10 mL, collected at the time of enrollment in the trial. Subjects indicating consent to the Biomarkers Study by checking the appropriate box will be asked for a one-time sample of approximately 10 mL of peripheral venous blood. Consent will be collected for both the blood sample and the optional ancillary study. Those patients who decline the ancillary study will not be prohibited from participating in the POINT Trial.

Plasma and DNA will be prepared for genotyping analysis and stored at the Neurogenetics Laboratory at the Mayo Clinic in Jacksonville, Florida (MCF) as required by Federal and state regulations. The study samples will be used for testing the specific hypothesis as to whether clopidogrel resistant genotypes modify the stroke prevention response in high-risk TIA patients. Subjects will be assigned numbers which will be placed on the sample labels and allow researchers to link the sample to the encrypted ancillary study database. No personal identifying information will be kept with the samples. Results of the genotyping analysis will not be shared with subjects.

Of primary interest is the relative risk of vascular outcome events for carriers (of specific ABCB1 and CYP2C19 genotypes) versus non-carriers amongst those receiving clopidogrel. Of secondary interest is a subgroup analysis by the enrolling/index event type (either TIA or minor ischemic stroke cohort) performed separately for the TIA cohort and the minor ischemic stroke cohort.

Genotyping results (raw data and summary data) will be provided to the POINT Trial Principal Investigator and lead statistician for incorporation into the existing trial data set into WebDCU. Analyses exploring an interaction between genotypes and treatment response will be done jointly, including testing of inherited clopidogrel resistance. This would be the first systematic study of clopidogrel resistance in the setting of stroke prevention following TIA. The stored samples will also be a resource for future studies in this patient population.

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