POINT Trial

Manual of Procedures Version 4.0

TABLE OF CONTENTS

Contents

1.0 INTRODUCTION 5
1.1 Study Objectives 5
1.2 Background and Rationale 5
1.3 Study Sponsor 6
2.0 STUDY DESIGN 7
2.1 General Design 7
2.2 Primary Objective 7
2.3 Sample Size 7
3.0 STUDY ORGANIZATION 8
3.1 Principal Investigators 9
3.2 Administrative Structure 9
3.3 Participating Sites 13
3.4 Trial Committees 13
4.0 TRIAL COMMUNICATIONS 16
4.1 Individual Sites 16
4.2 Trial Websites 17
4.3 Partners 18
4.4 Communications with NINDS 18
4.5 Key Contact Information 18
5.0 TIMELINES 20
5.1 Overview 20
5.2 Study Milestones 20
6.0 STUDY POLICIES 21
6.1 Protection of Human Subjects 21
6.2 The HIPAA Privacy Rule 21
7.0 RESEARCH CONDUCT 23

7.1 Protocol Amendments 23
7.2 Protocol Violations 24
7.3 Unblinding 26
7.4 Ancillary Studies 26
7.5 Publications Policy 30
7.6 Manual of Procedures 30
7.7 Research Misconduct 31
7.8 Payment to NETT-CCC Hub Complexes and POINT CRC performance sites 32
8.0 ADVERSE EVENT HANDLING 35
8.1 Definitions 35
8.2 Classification of Adverse Events 36
8.3 SAE/Clinical Outcome Reporting 38
8.4 Site Monitoring and SAE reporting 41
8.5 Regulatory Documentation and Maintenance 41
9.0 TRAINING AND CERTIFICATION REQUIREMENTS 43
9.1 Human Subjects Protection/Good Clinical Practice 43
9.2 $ABCD^2$ Score 44
9.3 Modified Rankin Scale (mRS) 44
9.4 NIH Stroke Scale (NIHSS) 44
9.5 POINT Trial Protocol 44
9.6 Case Report Form (CRF) Completion 45
10.0 SITE INITIATION, MONITORING AND CLOSEOUT 47
10.1 Site Initiation and Activation 47
10.2 On-Site Monitoring 49
10.3 Source Documentation 49
10.4 Changes in Study Personnel 50
10.5 On-going Monitoring 50
11.0 STUDY PROCEDURES 51
11.1 Subject Identification 51
11.2 Screening Evaluation 51

11.3 Enrollment/Randomization 54
11.4 Study Procedures 56
11.5 7-day phone follow up 58
11.6 90-day Physician Follow-up/Final Visit 58
11.7 Event Visits 59
11.8 Subject Dropouts, Withdrawals, and Treatment Discontinuation 59
12.0 OUTCOMES 62
12.1 Definitions 62
12.2 Procedures If Clinical Outcome Occurs 67
12.3 Adjudication of Outcomes 68
13.0 PATIENT RECRUITMENT AND RETENTION 70
13.1 Recruitment 70
13.2 Retention Strategies 71
14.0 PATIENT ENCOUNTERS 72
14.1 Schedule of Assessments 72
15.0 CONTROL OF STUDY DRUG 73
15.1 Study Investigational Pharmacy 74
15.2 Study Medication Handling 74
15.3 Concurrent Treatments 75
15.4 Receipt of Study Drug 77
15.5 Packaging 77
15.6 Study Drugs 77
15.7 Pharmacy 78
16.0 CASE REPORT FORMS AND WORKSHEET COMPLETION 80
16.1 Overview of Forms and Requirements 80
17.0 DATA MANAGEMENT 81
17.1 Overview *81*
17.2 Data Acquisition and Central Study Database *81*
17.3 Modules *82*
18.0 CLOPIDOGREL PACKAGE INSERT 84

1.0 INTRODUCTION

1.1 Study Objectives

POINT is a randomized, double-blind, multicenter clinical trial to determine whether clopidogrel 75 mg/day given orally after a loading dose of 600 mg is effective in reducing the 90-day risk of stroke, myocardial infarction and vascular death (primary composite outcome) when initiated within 12 hours of transient ischemic attack (TIA) or minor ischemic stroke onset in patients also receiving aspirin 50-325 mg/day.

Several secondary analyses will be performed, including as treated analysis and evaluations of the impact of therapy on risk of the composite of major ischemic vascular events or major hemorrhage, and on risk of major systemic or intracranial hemorrhage separately.

Additional tertiary/exploratory analyses will include evaluation of the impact of therapy on: 1) ischemic stroke, 2) hemorrhagic stroke, 3) all-cause death, and 4) new handicap as measured by a change in the modified Rankin Scale score.

The impact of therapy on the composite outcome will also be evaluated in specific patient groups (e.g., African Americans, those previously taking aspirin, those with imaging evidence of new infarction).

1.2 Background and Rationale

TIAs occur in approximately 250,000-350,000 individuals 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, particularly in the first few days, even in patients treated with aspirin, the current standard of care.

Antithrombotic therapy may play a distinct role in this acute pathophysiology. Effective therapies in those with TIA could significantly reduce the overall burden of stroke if initiated immediately. However, no large-scale trial has evaluated an acute intervention in patients with TIA. Platelet aggregation is an important contributing factor in cerebral ischemia, as in other forms of ischemia. Antiplatelet agents reduce the risk of ischemic stroke in a variety of settings with distinct pathophysiologies (e.g., atrial fibrillation, small-vessel stroke, and large-vessel atherothrombosis).

Aspirin given to patients with a history of stroke or TIA reduces subsequent risk of stroke. Furthermore, aspirin initiated as an acute intervention after stroke reduces risk of death and recurrent stroke.

Trials of clopidogrel in combination with aspirin after stroke/TIA suggest that the combination reduces risk of stroke but increases risk of major hemorrhage. However, the risk of thrombosis is extremely high in the acute period after TIA and risk of hemorrhage is expected to be lower than after a completed stroke, so the combination may be particularly effective and relatively safe in this setting. Even more compelling, clopidogrel combined with aspirin reduced the 90-day risk of stroke by 36% compared to aspirin alone in a pilot trial of 392 patients treated acutely after minor stroke or TIA, and it was well tolerated.

Clopidogrel also has advantages in being oral, without major side effects other than hemorrhage, and it will be inexpensive by trial completion. Nonetheless, antiplatelet therapy has never been tested in a pivotal trial as an acute intervention after TIA or minor ischemic stroke, a setting with distinct pathophysiology that may favor the use of this class of agents; the POINT Trial will address this issue.

1.3 Study Sponsor

The POINT Trial is funded by the National Institute of Neurological Disorders and Stroke *(*NINDS*).* Sanofi is providing clopidogrel and its placebo for the study.

2.0 STUDY DESIGN

2.1 General Design

This is a prospective, randomized, double blind, multicenter trial in which 5,840 subjects from 350 centers with high-risk TIA ($ABCD^2 \geq 4$) or minor ischemic stroke (NIHSS≤3) will be randomized 1:1 to treatment within 12 hours of symptom onset with either clopidogrel 600mg loading dose, followed by 75mg/day or placebo.

All subjects will be treated with aspirin 50-325mg/day, with a recommended dosing schedule *of 150-200 mg daily for 5 days followed by 75-100 mg daily*.

Each subject will be followed for 90 days from enrollment. The primary endpoint is a composite of new ischemic vascular events: ischemic stroke, myocardial infarction or ischemic vascular death at 90 days.

2.2 Primary Objective

The primary objective of the study is to determine whether clopidogrel 75mg/day by mouth after a loading dose of 600mg is effective in improving survival free from major ischemic vascular events at 90 days when initiated within 12 hours of TIA or minor ischemic stroke onset in patients receiving aspirin 50-325mg/day.

2.3 Sample Size

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.

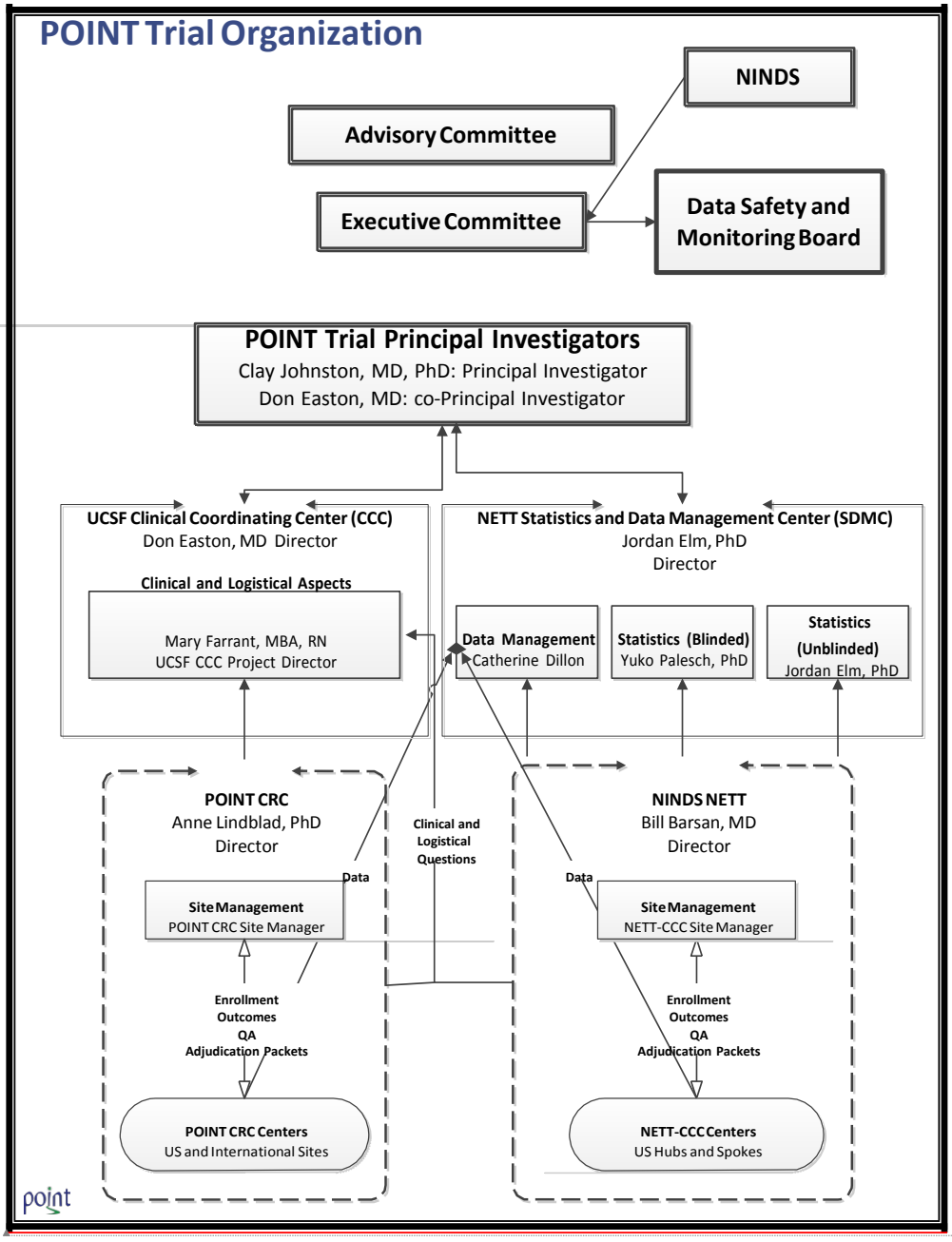
A detailed discussion of the sample size is provided in the study protocol.

3.0 STUDY ORGANIZATION

The POINT study is a collaboration of established research networks connected through the leadership of the Principal investigators. Day to day operational oversight is provided by an Operations Committee with assistance on clinical and implementation issues provided by an Advisory Committee. Each of the components and respective roles and responsibilities is detailed below.

Figure 1 provides a high level illustration of the organizational structure. See also **Appendix I** for more detailed organizational charts for POINT partners.

FIGURE 1: POINT TRIAL ORGANIZATIONAL STRUCTURE



3.1 Principal Investigators

S. Claiborne Johnston, MD, PhD is the Principal Investigator for the trial. He will oversee all administrative and clinical aspects of the trial and will coordinate efforts of all study personnel. He will chair the Operations Committee, which will meet weekly to orchestrate the overall functioning of the trial. He will also chair the Executive Committee, which will meet quarterly, and the Advisory Committee, which will meet annually. He will participate in site training, encourage enrollment and ensure quality.

J. Donald Easton, MD is Co-Principal Investigator. Dr. Easton will share supervision of the conduct of the trial and substitute for the Principal Investigator when he is not available. Dr. Easton will have a major responsibility for trial recruitment by regular monitoring, encouraging investigators through regular written and telephone communication, and, as necessary, making visits to sites to educate and stimulate interest and involvement (e.g., in Emergency and Neurology Department Grand Rounds and faculty and resident conferences).

Dr. Easton will respond to all clinical and policies questions, and sit on the Operations and Executive Committees. Dr. Easton will attend the meetings of the Operations and Executive Committees and be an ex-officio member of all the other committees. He will assist the PI as the liaison with NINDS as a member of the Executive Committee.

3.2 Administrative Structure

Three major entities are involved: the UCSF Clinical Coordinating Center (CCC), the NINDS Neurological Emergencies Treatment Trials (NETT) CCC, and the POINT Clinical Research Collaboration (CRC). Each of these has distinct and well defined functions.

3.2.1 UCSF Clinical Coordinating Center

Overall trial administration and management will occur through the UCSF CCC, directed by J. Don Easton, MD, the Co-Principal Investigator). The Institutional Principal Investigator, Anthony Kim,, MD, PhD will assist with trial oversight and will substitute for the Co-PI as necessary. The UCSF CCC will manage the overall performance and leadership functions of the trial, and will oversee the clinical aspects. It will provide clinical training to the sites, produce newsletters and other correspondence, arrange all leadership

meetings and oversee publications and applications for ancillary studies.

Mary Farrant, MBA (DBA), BSN, RN, the Project Director for the UCSF CCC, will be responsible for clinical oversight of the participating centers. Together with Drs. Johnston and Easton, she will respond to all clinical and policy questions, and will ensure eligibility criteria are met and that treatment protocols are followed. She will coordinate and oversee communications of the study with the assistance of existing web-based technologies.

A Project Manager, TBH, will function as technical liaison and support the study designing, coding, and testing technical solutions as well as contributing in general management aspects of the study. Under the supervision of the Project Director, the Project Manager will create and execute project work plans and revise as appropriate to meet those changing needs and requirements. The Project Manager will have responsibility as manager of the day-to-day operational aspects of the POINT Trial website and function as technical liaison in coordination with the MUSC for this aspect of the study. The Project Manager will work with Dr. Easton on all aspects of the training materials for the study from creation and editing, to housing, updating and maintaining those files. He or she will deliver online presentations that effectively communicate relevant project information.

A Project Coordinator, TBH, will support the study as a Research Associate. Under supervision of the Project Director, the Project Coordinator will coordinate all required IRB/IEC approval at UCSF. The Project Coordinator will have primary responsibility for the study's pharmacy services, serve as the first point of contact for patient inquiries, create collateral materials for study subjects, and maintain the on-call schedule for staff providing emergency support to sites and enrollees. The Project Coordinator will assist the investigators in manuscript preparations and assist with form entry, as needed.

3.2.2 NINDS Neurological Emergencies Treatment Trials (NETT) Network

The NETT network consists of 17 regional Hub Complexes, each with several affiliated Spokes, a Statistical & Data Management Center (NETT SDMC), and a Clinical Coordinating Center (CCC). Oversight of the network is provided by an NINDS appointed Advisory Group (NAG), the NINDS NETT Scientific Program Director and the NINDS NETT Administrative Program Director.

3.2.2.1 NETT Clinical Coordinating Center (CCC)

The NETT-CCC provides coordination of POINT performance sites at NETT Hub Complexes that have the needed clinical trial infrastructure already in place, standard operating procedures, an experienced site management team, and site monitoring expertise.

The NETT-CCC is housed in the Department of Emergency Medicine at the University of Michigan in Ann Arbor, MI. It is directed by Dr. William Barsan, the NETT-CCC Principal Investigator, with the assistance of NETT-CCC investigators and staff. The NETT-CCC Site Manager oversees the day-to-day activities of clinical sites in the NETT Network, and coordinates communication of trial activities (e.g., meetings, study updates).

The NETT-CCC Site Monitor works with the Site Manager and Hub Complex personnel to ensure the protection of human subjects, data quality and integrity, and assist with protocol related education endeavors at the clinical sites. NETT-CCC is in full compliance with the ICH-GCP Guidelines and FDA regulations for conducting clinical trials.

3.2.2.2 NETT Hubs

The NETT Network infrastructure consists of Hubs and Spokes, to promote and conduct clinical trials that will provide new and effective treatments for neurologic emergencies.

3.2.2.3 NETT Statistical and Data Management Center (NETT SDMC)

POINT is collaborating with the NETT SDMC which is housed in the Data Coordination Unit (DCU) in the Department of Public Health Sciences (DPHS) at the Medical University of South Carolina (MUSC) in Charleston, SC. The PI of the SDMC for the POINT Trial is Jordan Elm, PhD. The PI of the NETT SDMC is Yuko Palesch, Ph.D., who is a co-PI of the POINT SDMC. Aaron Perlmutter oversees the data management activities at the NETT SDMC for the POINT study. The responsibility of the NETT SDMC is to provide statistical design and analysis of the POINT study, liaise with the DSMB, and to provide efficient web-based data management. NETT SDMC is in full compliance with the ICH-GCP Guidelines and FDA regulations for conducting clinical trials.

Through its NETT SDMC, the NETT will provide reports to the DSMB and medical safety monitors, shielding the UCSF CCC and NETT-CCC 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.

3.2.3 POINT Clinical Research Collaboration (CRC)

The EMMES Corporation, Anne Lindblad, PhD, Director, has devoted its efforts exclusively to providing data management, biostatistical, epidemiological, computer systems development and support, as well as organizational and logistical support for clinical research, including multi-protocol and multisite domestic and international clinical research projects for the past 30 years.

EMMES' organization, staff, facilities, and work methods have been developed solely for the purpose of supporting clinical research programs.

The POINT CRC Site Manager oversees the day-to-day activities of POINT CRC clinical sites, and coordinates communication of trial activities (e.g. meetings, study updates).

The POINT CRC Site Monitor works with the POINT CRC Site Manager and POINT CRC site personnel to ensure the protection of human subjects, data quality and integrity, and assist with protocol-related education endeavors at the POINT CRC clinical sites.

3.2.3.1 POINT CRC Clinical Sites

Up to 150 US and 100 International Clinical sites from the POINT CRC will be activated to participate in POINT. POINT CRC and NETT-CCC sites are required to complete the same training and preparation activities to become certified to enroll subjects. POINT CRC sites will sign a letter of agreement with The EMMES Corporation to receive payment for participation. Both POINT CRC and NETT-CCC sites will enter study data using the NETT SDMC's data system.

3.2.3.2 POINT CRC Coordinating Center

The POINT CRC Coordinating Center is located at The EMMES Corporation in Rockville, Maryland and is responsible for identifying qualified sites to participate in POINT. A Central IRB/IEC is available through the POINT CRC for sites without a local IRB/IEC at no charge to the site. Each POINT CRC site is required to execute a letter of agreement with EMMES who acts as the payment Agent for the UCSF CCC. Study monitors at EMMES will be

responsible for site activation, monitoring POINT CRC site adherence to the study protocol, performing site visits and working with POINT CRC sites to insure adherence to regulatory obligations. The POINT CRC Coordinating Center is in full compliance with the ICH-GCP Guidelines and FDA regulations for conducting clinical trials.

3.2.4 Site Management

The NETT-CCC and POINT CRC each manage all aspects of the sites that they bring to the trial, including contract negotiation from fixed templates and with nonnegotiable reimbursement. They will be responsible for data inquiries not addressable directly on the online system, regulatory document collection and requirements, recruitment problems, and site monitoring. Issues identified will be discussed with the POINT Operations Committee through routine conference calls.

Sites will be visited at least once during the study and more often if needed.

3.3 Participating Sites

There are approximately 350 clinical centers involved in the POINT Trial including approximately 100 NETT-CCC sites and 250 POINT CRC sites. Participating sites are listed on the POINT website www.pointtrial.org following activation for enrollment.

3.4 Trial Committees

3.4.1 Operations Committee

The Operations Committee (OC), chaired by Dr. Johnston, will oversee the entire performance of the trial.

The OC will meet every week, with members outside San Francisco joining by teleconference. The Operations Committee will discuss all major decisions regarding the study. Members will receive reports from all other committees on a regular basis and will monitor the overall performance of the study and participating sites. The committee will supervise analysis and publication of primary results and subsequent analyses.

The Operations Committee will consist of members from the UCSF CCC, NETT-CCC and the POINT CRC, and will be led by Dr. Johnston. See **Appendix II** for a

listing of members.

3.4.2 Executive Committee

The committee will meet yearly in person and by telephone conference monthly and as necessary, and will assist the Operations Committee with all major decisions regarding the study. Members will receive reports from all other committees on a regular basis and will monitor the overall performance of the study and participating sites. The committee will supervise analysis and publication of primary results and subsequent analyses.

The Executive Committee will consist of members from the UCSF CCC, NETT-CCC and the POINT CRC, and will be led by Dr. Johnston. See **Appendix III** for a listing of members.

3.4.3 Advisory Committee

The larger Advisory Committee will include a number of experts in stroke care and research in addition to members of the Operations Committee from the UCSF CCC, NETT-CCC and the POINT CRC, and will be led by Dr. Johnston. This Committee will meet in-person annually to advise the Principal Investigator and the Operations Committee to assure excellence in the performance of the trial. Members will assist in the recruitment of active and dedicated centers. Between annual meetings, the committee may be convened by teleconference to advise on extraordinary issues. A majority vote of a quorum of the Advisory Committee will be required for protocol changes. The PI will change the membership of this committee as necessary as the trial progresses.

Members of the Executive Committee will attend Advisory Committee Meetings. See **Appendix IV** for a listing of the Advisory Committee members.

3.4.4 Adjudications Committee

The Adjudications Committee is charged with the responsibility of validation of all reported non-fatal outcomes and classification of death. See Section 12.3 for a review of the adjudications process.

The Adjudications Committee consists of three board-certified neurologists, and three board-certified internists/cardiologists. See **Appendix V** for a listing of all members.

3.4.5 Data and Safety Monitoring Board

The DSMB is organized, operated and appointed by NINDS to review and approve the initial POINT protocol, and to monitor safety, progress and data quality throughout the study. The DSMB assesses study data with particular consideration of participant safety. The Board will meet to review accumulated data on a regular basis and will convene ad hoc meetings to address any significant problems related to participant safety brought to its attention by any study participant or investigator. The DSMB will review the accumulated data and consider whether a protocol modification is necessary. If changes in the protocol are indicated, recommendations will be made to the Deputy Director of the NINDS who will consider and act on such recommendations in a timely manner.

During the trial, the DSMB generally reviews the following:

- Safety data for evidence of study-related adverse events (AEs)
- Adherence to the protocol
- Factors that might affect the study outcome or compromise the trial data (such as protocol deviations, lost to follow-up rates, etc.)
- Outcome data for assessment of efficacy or futility according to the interim monitoring procedures described in the statistical analysis plan

The members of the DSMB are appointed by the NIH/NINDS. See **Appendix VI** for a listing of all members.

4.0 TRIAL COMMUNICATIONS

The success of POINT will be dependent on the establishment and maintenance of a robust communications network.

4.1 Individual Sites

Sites will have on-going, frequent telephone contact with their assigned NETT-CCC or POINT CRC Site Manager to facilitate sufficient communication to meet the needs of the sites and the Operations Committee.

For calls related to randomization, call the WebDCU POINT Randomization Emergency Hotline (1-866-450-2016 A POINT team member will be available by cell phone 24 hours a day, 7 days a week, for emergency situation. For clinical help call the POINT Hotline (1-866-947-6468) or email Aaron Perlmutter (perlmutt@musc.edu). International sites will dial their country exit code, then 1-415-663-4444 or use the toll-free number provided to their country to connect to the study hotline.
For other matters, the POINT CRC sites should contact the POINT CRC Site Manager at 800-305-7811, or by e-mail at crc@emmes.com. The NETT-CCC sites should call the NETT-CCC at 734-232-2142, or e-mail them at trial@umich.edu. All communications relevant to the conduct of the trial will be documented and retained in both the clinical sites and the corresponding Coordinating/Statistical Center. These communications files will be made available to the clinical monitors when site visits are made. Use of email for these communications is highly recommended.

Information about POINT to be shared with participating sites includes, but is not necessarily limited to: study protocol, amendments to study protocol and regulatory documents, investigators' brochures, distributed reports and letters from/to oversight bodies, distributed reports and letters related to protocol unanticipated problems or performing community and academic sites.

Web-based meetings, with the site PI and key staff available to address questions, will occur intermittently. Clinical centers can forward any procedural questions about the study to the UCSF CCC through their appropriate NETT-CCC Site Manager or POINT CRC Site Manager. The UCSF CCC will formulate answers in consultation with the Operations Committee, and will periodically post a set of frequently asked questions (FAQs) and answers. These questions and answers can be searched by topic; the

answers to questions will be incorporated into Manual of Procedures revisions. Study email lists will be used for all communications with sites about the study.

4.2 Trial Websites

4.2.1 WebDCU™: Web-based Clinical Trial Data Management System

Located at https://webdcu.musc.edu/NETT/index.asp, the WebDCU™ is a web-based clinical trial data management system developed by the NETT SDMC, the Data Coordination Unit at MUSC. WebDCU™ contains features that allow for real time study monitoring and reporting, on-line randomization of subjects, data entry of CRFs, tracking of subject progress based upon the protocol scheme, and uploading of regulatory documents.

There are 2 components: the NETT-CCC Regulatory Document Database (where all regulatory documents are managed) and the POINT Clinical Database (where the POINT CRF data, drug accountability, and randomization are managed).

4.2.2 POINTtrial.org

The POINT Trial website, located at http://www.POINTTrial.org is the public website for the trial. It is the main portal for the study and has basic information about the trial hosted at the website with training materials for investigators and sites and with links to the secure MUSC Testing module and WebDCU™. The site will be updated on a regular basis with information regarding the trial and is maintained by staff at UCSF.

POINT maintains public and password protected areas. The password protected area is where study investigators can find links to training. Training requires a separate log in and password as does regulatory document upload. Successful completion of these training tests will grant users a certificate that must be uploaded into the regulatory document site on WebDCU™ (see 4.2.3). The POINT website will be updated on a regular basis with information regarding the trial and is maintained by staff at UCSF.

4.2.3 Training Tests for Certification

https://sitemaker.umich.edu/nett/point_resources_and_training

Training tests for all aspects of the POINT Trial will be hosted by NETT-CCC. A

secure log-in will be required to access this material.

Successful completion of these training tests will grant users a certificate.

4.3 Partners

Communication among partners in the POINT Trial will be maintained via several methods:

- Telephone conference calls of the Operations Committee will be held every week
    - Audio and transcribed minutes of these conferences will be available within one week of the meeting.
- Telephone conference calls of the Executive Committee will be held monthly and as needed
    - Audio and transcribed minutes of these conferences will be available within one week of the meeting.
- The Advisory Committee will meet in person annually and by teleconference on an as needed basis.
- In-person meetings held annually.
- Email lists will be used when sending emails with key study information, including the study newsletter and any scheduled and unscheduled reports and bulletins about the study.

4.4 Communications with NINDS

Communication with the NIH/NINDS will be maintained through the UCSF CCC, led by the POINT PI. This team will submit to the designated program officer quarterly and annual progress reports. These reports will include a brief description of work performed, problems and any anticipated change of plans for the next quarter or year, as appropriate. Progress will be reported specifically by number of subjects enrolled, data records transmitted and meetings attended during the period. These reports will be reviewed by the Executive Committee member prior to submission.

4.5 Key Contact Information

Contact information for key study staff is as follows:

POINT Trial Key Contacts

	Study Role	Contact Information
UCSF CCC	Emergency Contact	1.866.94.POINT (1.866.947.6468) & 415.663.4444 (OUS sites)
Clay Johnston	PI	clay.johnston@utexas.edu Office 512.495.5001 Cell 415.379.0787
J. Donald Easton	Co-PI/Event Clinician Monitor/Unblinding resource	EastonJD@neurology.ucsf.edu Cell 401.965.6446
Brian Scott	CEM	Brian.J.Scott@Lahey.org Office 781.744.8630
NETT-CCC	Support for NETT-CCC sites	POINT-trial@umich.edu 734.232.2142
POINT CRC	Support for POINT CRC sites	crc@emmes.com 800.305.7811
SDMC	WebDCU™ support	Aaron Perlmutter perlmutt@musc.edu Office 843.876.1261
	WebDCU™ passwords	Aaron Perlmutter perlmutt@musc.edu Office 843.876.1261

5.0 TIMELINES

5.1 Overview

The trial will be completed in 7 years, with 5,840 subjects recruited 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 0.42 subjects/site/month.

5.2 Study Milestones

First Patient In (FPI)	5/28/2010
FPI @ 90 days	8/1/2010
Last Patient In (LPI)	9/30/2017
LPI @ 90 days	12/31/2017

Study milestones subject to change.

See **Appendix VII** for detailed study milestones.

6.0 STUDY POLICIES

6.1 Protection of Human Subjects

Participating sites must maintain a human subjects protection program compliant with 45 CFR 46 and 21CFR 50 and 56 and with state, local or institutional requirements related to the protection of human subjects, an approved Assurance for human subjects research and an IRB/IEC registration number. Enrolling local institutions must also ensure the safe and appropriate performance of the research at its institution. This includes, but is not limited to, monitoring protocol compliance, managing any major protocol violations, managing any serious adverse events occurring at the institution, ensuring qualifications of research staff and providing a mechanism by which complaints about the research can be made by local study participants or others.

Prior to enrolling subjects in POINT, each site must submit documentation that the study has been approved by the local IRB/IEC, including locally approved informed consent forms.

Written informed consent must be obtained from each POINT participant as part of the subject enrollment process only after the investigator is satisfied that the participant understands the potential risks and benefits of participation in the study.

6.2 The HIPAA Privacy Rule

Under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule, POINT investigators are required by the Department of Health and Human Services (HHS) or the Food and Drug Administration (FDA) Protection of Human Subjects Regulations (45 CFR part 46 or 21 CFR parts 50 and 56, respectively) to take measures to protect personal health information (PHI) from inappropriate use or disclosure. PHI includes identifiable health information about subjects of clinical research gathered by a researcher who is a covered health care provider.

Compliance with HIPAA regulations is considered a local context issue and remains the purview of the local institution and local IRB/IEC. The HIPAA Privacy Rule is concerned with the risk to the subject's privacy associated with the use and disclosure of the subject's PHI, and permits researchers, as health care providers and therefore covered entities, to use or disclose PHI for research under certain circumstances and conditions, including if the subject of the PHI has granted specific written permission through an Authorization that satisfies section 164.508 and if the PHI has been de-identified in accordance with the standards set by the Privacy Rule at section 164.514(a)- (c) in which case, the health information is no longer PHI.

The individual POINT IRB/IEC will act as Privacy Boards (required by HIPAA) to review the use and disclosure of PHI and to determine whether subjects should sign a Subject Authorization for Release of PHI for Research in addition to the consent to participate in research, or if a Waiver of Authorization may be granted analogous to a Waiver of Consent under the Common Rule.

For a more detailed discussion of permitted uses or disclosures of PHI for clinical research under the Privacy Rule, refer to Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule; Research Repositories, Databases, and the HIPAA Privacy Rule; Institutional Review Boards and the HIPAA Privacy Rule; and Privacy Boards and the HIPAA Privacy Rule.

7.0 RESEARCH CONDUCT

7.1 Protocol Amendments

7.1.1 Modification Requirements

Full protocol amendments are prepared to incorporate significant changes, those involving more than minimal impact on participant safety and risk-to-benefit ratio of participation in POINT, and will result in the generation of a new protocol version with a new version number. Amendments also are required to incorporate a significant increase in the number of participants to be enrolled in the study. When amendments are prepared, any prior protocol modifications specified in a contract or agreement are also incorporated into the amendment.

In accordance with 45 Code of Federal Regulations (CFR) 46.103(b) (4) (iii) and 21 CFR 56.108(a) (4), changes to the POINT protocol or its related consent document must be approved by the IRB/IEC prior to implementation except where necessary to eliminate apparent immediate hazards to participants.

Examples of changes requiring a full protocol amendment include:

- change to inclusion or exclusion criteria
- new safety information on drugs in the protocol
- changes in subject population, recruitment plans
- revised consent requirements, research procedures, study instruments, study sites or investigators/key study personnel

Protocol amendments are developed by the UCSF CCC and must be reviewed by the UCSF Committee on Human Research CHR unless a waiver is granted. The POINT PI and co-PI will confirm whether additional review is required, such as by the DSMB or sponsor.

Once finalized, the UCSF CCC submits amendments to the NIH if applicable, and distributes amendments to all team members and participating study sites. Sites must then seek IRB/IEC approval of the protocol and other associated documents for the amended version of the protocol.

Revised procedures specified in the amendment may not be conducted until after protocol registration is obtained. Participants enrolled in a study after approval and registration of a protocol amendment must be consented to the study using the revised informed consent form associated with the amended version of the protocol.

For participants enrolled prior to approval and registration of an amendment, guidance on whether re-consenting is required (using the revised informed consent form associated with the amendment) will be provided by the CCC, typically in the summary of changes that accompanies the amended protocol. Regardless of protocol team's recommendations, site IRB/IECs may require re- consenting of previously enrolled participants; in such cases, IRB/IEC requirements must be followed.

Significant protocol amendments will be incorporated into the written protocol to ensure that there is only one complete protocol, with the revision dates noted on each revised page and the first page. A change to the protocol will be accompanied by a request for approval of a change on the POINT Trial Request for Amendment Form, **Appendix VIII**.

Required information includes: a signed amendment, a description of the proposed change, an explanation of why the change is needed (if the change is proposed by the study sponsor, the sponsor's formal notice of a change or revised protocol will be included), a description of the implications for the subjects and revised consent documents, if the change will affect the human subjects.

7.2 Protocol Violations

In accordance with Good Clinical Practices and 21 CFR 312 Sponsor Responsibilities, the POINT Trial requires that participating institutions develop written policies and procedures for handling reports of noncompliance with the regulations, requirements of the study protocol, IRB/IEC or sponsor, and to report protocol deviations.

7.2.1 Protocol Violations

Any change, divergence, or departure from the study design or procedures of

the POINT research protocol that affects the subject's rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data constitutes a protocol violation. If the event meets any of the following criteria, it is considered a protocol violation.

7.2.1.1 Risk to Subjects

Harmed or posed a significant or substantive risk of harm to the research subject.

7.2.1.2 Compromise to Scientific Integrity

Compromises the scientific integrity of the data collected for the study.

7.2.1.3 Breach of Human Subject Protection

Is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s).

7.2.1.4 Serious or Continuing Noncompliance

Involves a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

7.2.1.5 Inconsistent with NIH Program

Inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles.

Reported deviations may be reviewed by a member of the UCSF CCC who may request clarifications or further information from the site PI to properly evaluate the deviation. The deviation is evaluated to determine if it had a significant effect on subject's rights, safety, or welfare, and/or on the integrity of the resultant data. After review and evaluation of the deviation, the actions that may be taken include, but are not limited to: warning with instructions on how to avoid further infractions, an audit by the NETT or CRC.

7.3 Unblinding

Unblinding is likely to be rare in the study. There are no data suggesting that taking clopidogrel is a contraindication to thrombolytic therapy. A major hemorrhagic event may result in the discontinuation of study medications, but knowledge of treatment assignment is unlikely to change therapy for these patients, 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 will call the UCSF CCC toll free emergency phone number 1-866-94-POINT (1-866-947-6468) for US sites, and 415-663-4444 for OUS sites. The site PI or his/her designee will then provide the authorized on-call CCC personnel with a very detailed clinical explanation for unblinding. If unblinding is determined to be necessary, the UCSF CCC personnel will navigate to the unblinding option in the WebDCU™ database and enter the subject ID number and the number of the study drug bottle administered to the subject. The local site would be granted access to see the unblinded treatment assignment for that particular subject through the WebDCU™ system at the randomization page.

At the time of unblinding, an automatic email notification will be triggered to the POINT Executive Committee notifying them of the event.

7.4 Ancillary Studies

Proposals for ancillary studies will be reviewed by the Executive Committee; these studies will require funding outside this 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 patient enrollment.

Pharmaceutical industry representatives have not been involved with the trial design and will not participate routinely in the execution of the trial or presentation of the results. Data will be controlled by the Executive Committee,

which will review requests for access and specific analyses. Monitoring during the trial will be dictated by safety and scientific concerns rather than regulatory requirements. Publication of the results of these studies 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 **Appendix IX**.

7.5 Publications Policy

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.

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 **Appendix X**.

7.6 Manual of Procedures

The development and use of a Manual of Procedures has the potential to improve the capacity of researchers to address the complex, multifaceted issues associated with conducting research in today's healthcare environment. The POINT Trial manual facilitates communication, standardizes training and evaluation, and enhances the development and standard implementation of clear policies, processes, and protocols.

The entire POINT operations team participates in the development, review, and acceptance of the Manual of Procedures. The manual is updated quarterly and

reviewed by the Operations Committee and Executive Committee. The POINT Manual of Procedures is maintained as a separate document.

7.7 Research Misconduct

Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Research misconduct does not include honest error or differences of opinion. The POINT Executive Committee will respond fully and fairly to all allegations of research misconduct. This policy is based on the principle that quality research requires adherence to the highest standards of integrity in proposing, conducting, and reporting research, and compliance with the reporting requirements of applicable funding agencies found in 42 CFR Parts 50 and 93, Public Health Service Policies.

In accordance with UCSF's Integrity of Research policy, any institution receiving PHS funding must have an assurance on file with ORI stating that it will comply with an administrative process for responding to allegations of research misconduct in PHS-supported research in accordance with 42 CFR 93.

ORI assurance is obtained in two ways:

- an institution establishes assurance when an official signs the face-page (SF 424 (R&R) or PHS 398) of the grant application form
- an institution files a separate assurance form by requesting an Initial Assurance Form (PHS Form 6315)

Once an institution has established assurance, it is maintained by filing an Annual Report on Possible Research Misconduct (between January 1 and March 1 each year) and submitting their policy for responding to allegations of research misconduct for review when requested by ORI.

If any POINT staff member or member of the research team suspects that misconduct has occurred, the incident should immediately be reported to the POINT PI and Co-PI.

Examples of situations that may be suspicious of misconduct include:

- Subject or laboratory records that have multiple modifications or modifications to key data (e.g., dates of records that determine eligibility), appear to be backdated or modified without proper documentation and attribution, use of pencil in source documentation
- Subject or laboratory records that are without flaws or, over time, are all written in the same handwriting with the same pen without modifications
- Variables or measurements that would be expected to exhibit biological or measurement variance over repeated time points (e.g., temperature, WBC) that have little or no variation
- Modifications have been made to the records, but the original entry cannot be read (e.g., use of correction fluid, use of pencil, obliteration of the initial entry with magic marker or correction tape) or an audit trail cannot be reconstructed from the value recorded in the database to the source document
- Inability or reluctance on the part of clinical center staff to produce requested source records or answer questions about them

7.8 Payment to NETT-CCC Hub Complexes and POINT CRC performance sites

Each NETT-CCC Hub Complex and POINT CRC performance site is budgeted for startup costs. These funds will be disbursed according to the schedule specified below. Funds may be used at the discretion of the respective Principal Investigator to defray one or more of the following expenses: partial salary effort of the trial investigators and/or the site Clinical Coordinator to conduct the initial trial organization at that site, including recruitment costs, training costs, IRB/IEC approval, required project assurances, and completion of contracts.

Prior to any recruitment and/or receipt drug at the site, each NETT-CCC Hub Complex and CRC performance site must execute an agreement with the appropriate coordinating center and submit the required regulatory documents

to WebDCU™. Exceptions to execution of contracts such as operating under hardship or pending agreements will be evaluated on a case-by-case basis. Annual amendments and/or extensions of subcontract/agreements will need to be executed for subsequent years of the POINT trial.

An agreed-upon per-patient reimbursement will be made to NETT Hub Complex and CRC performance site as patients are recruited into the trial and data are entered and submitted in WebDCU™ with no outstanding queries pending. It should be emphasized that payments are based upon actual enrollment and not the projections made in the grant application.

7.8.1 Startup Payments [Amount defined in NETT Hub or EMMES CRC site agreement (inclusive of F&A costs)]:

Payment 1 - After the first IRB/IEC approval is obtained, uploaded and accepted into WebDCU™.

Payment 2 - After NETT Hub Complex or CRC performance site is certified to begin enrollment. *Certified to begin* is defined by the project staff and includes submission of all required regulatory documents submitted and completion of study specific trainings.

7.8.2 Per-subject Payments [$3,900 total (inclusive of F&A costs)]:

Payment 1 - $1,950 after completion of enrollment and initial visit. Completion is defined as proper informed consent on file for an eligible subject and all CRFs for the visit are entered into WebDCU™ with no queries pending. *Subjects considered to be ineligible (i.e. did not meet inclusion criteria, etc.) will not be considered for payment.*

Payment 2 - $1,950 after completion of the 90-day visit. *Completion* is defined as all CRFs for the subject for the entire study period are entered into WebDCU™ with no queries pending.

Each NETT Hub Complex will submit invoice(s) to the appropriate clinical coordinating center for payment on a frequency no less than bimonthly. The anticipated months for submitting invoices for eligible payments are February, April, June, August, October and December. NETT spoke institutions within a NETT Hub Complex will be reimbursed per the policies and subcontract terms developed within each individual Hub Complex. All invoices must specify Site/Institution Name, PI Name, Purchase Order Number (assigned upon

execution of contract), Patient Number, Remit-To Address, and visit or milestone being billed.

Remit NETT invoices to:	Payments are automated for CRC sites.
Email: NETT-invoice@umich.edu US mail: University of Michigan 24 Frank Lloyd Wright, P.O. Box 381 Ann Arbor, MI 48106	All other correspondence can be sent via e-mail or US mail, attn: POINT CRC Email: crc@emmes.com US Mail: The EMMES Corporation 401 N Washington St, Suite 700 Rockville, MD 20850

The coordinating centers will process all payments within a reasonable period of time upon receipt of each invoice (NETT Hubs) with confirmation that all indicated information or documentation has been submitted and/or received into the WebDCU™ system.

8.0 ADVERSE EVENT HANDLING

In accordance with the U.S. Code of Federal Regulations governing IND safety reports (Code of Federal Regulations 21, 312.32), adverse events (AEs) are reported from research sites to the local IRB/IEC and the Clinical Coordinating Center and from the Coordinating Center to local IRB/IECs and outside agencies according to different procedures depending on the nature, severity, and attribution of the event.

8.1 Definitions

8.1.1 Adverse Events

NOTE: Only SERIOUS Adverse Events (SAEs) and Clinical Outcomes will be collected in the trial.

8.1.1.1 Serious Adverse Event

Any adverse event that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, requires intervention to prevent permanent impairment or damage, or any event that the treating clinician or Clinician Event Monitor judges to be a significant hazard, contraindication, side effect, or precaution.

8.1.1.2 Life Threatening Adverse Event

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

8.1.1.3 Unexpected (Unanticipated) Adverse Event

An event that was “not anticipated” as a risk in the IRB/IEC-approved protocol, consent form, or clopidogrel package insert, or an event that occurs at a greater frequency or intensity than anticipated.

8.1.1.4 Anticipated Adverse Event

Events previously described in the package insert for clopidogrel and those

anticipated based on the natural history of TIA and minor ischemic stroke.

8.2 Classification of Adverse Events

8.2.1 Definition of Severity: Severity versus Seriousness

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 4.0 (CTCAE). 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 4.0) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Severity is not the same as seriousness. Seriousness is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Severity is used to describe the intensity (severity) of a specific event (as in mild, moderate, severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. Most AEs include clinical criteria that describe patient/event outcomes or indicated interventions to more clearly substantiate seriousness.

A serious adverse event (SAE) would be any event in Grade 4 or 5, and any event in Grade 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 i.e., Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

8.2.2 Classification System

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe

- Grade 4: Life-threatening or Disabling
- Grade 5: Fatal/death

8.2.3 Relationship to study treatment

One of the most important components of SAE reporting is determining the cause of the SAE. It is imperative that the investigator assess SAE causality in terms of overall study participation and make an independent determination as to whether the SAE was thought to be related to any study related activity (i.e., study intervention, test article administration, study-related tests or procedures). Determination may be particularly challenging in POINT since typical criteria for assessing causality such as evaluation of the effects of de-challenge and re-challenge are not possible within the scope of this protocol in which study interventions are isolated single exposures of short acting medications.

For each SAE, the relationship to the study treatment must be recorded as one of the choices on the scale described in Section 8.2.4.

8.2.4 Classification of Relationship

Not Related

1. The temporal relationship between treatment exposure and the serious adverse event is unreasonable or incompatible, and/or
2. adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2)

May have reasonable or only tenuous temporal relationship to intervention.

1. Could readily have been produced by the subject's clinical state, or environmental or other interventions.
2. Does not follow known pattern of response to intervention.

Possibly (must have 2)

1. Has a reasonable temporal relationship to intervention.

2. Could not readily have been produced by the subject's clinical state or environmental or other interventions.
3. Follows a known pattern of response to intervention.

Probably (must have all 3)

1. Has a reasonable temporal relationship to intervention.
2. Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
3. Follows a known pattern of response to intervention.

Definitely (must have all 3)

a. Has a reasonable temporal relationship to intervention.
b. Could not possibly have been produced by the subject's clinical state or have been due to environmental or other interventions.
c. Follows a known pattern of response to intervention.

Modified for POINT [in which dose reductions and re-introduction of intervention do not occur].

8.3 SAE/Clinical Outcome Reporting

8.3.1 Recording into the Study Database

All SAE/Clinical Outcomes occurring until participation in study has ended are recorded on the online SAE/Clinical Outcome case report form (CRF) through the WebDCU™. The Site PI or Study Coordinator is responsible for entering any and all SAE/Clinical Outcomes 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, non-serious AEs that are not clinical outcomes will not be recorded.

For SAE/Clinical Outcomes, the data entry must take place within 24 hours of discovery of the event.

The Hub PI for NETT-CCC sites and site PI for others are responsible for the monitoring and follow-up of all SAE/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 SAE/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 SAE/Clinical Outcome must be completed, if not done so earlier.

8.3.1.1 Reporting Recurrent Adverse Events

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 SAE/Clinical Outcome CRF must be completed. Resolution is the normalization or return to baseline of laboratory values, clinical signs or symptoms related to the event.

8.3.1.2 Procedure for Expedited Reporting of SAE/Clinical Outcomes

The process for reporting SAE/Clinical Outcomes is as follows:

1. Within 24 hours of the site's awareness of the SAE/Clinical Outcome, the Clinical Site staff data and submits the SAE/Clinical Outcome CRF, which includes date and time of onset; relatedness to study medications; action taken as a result of the SAE/Clinical Outcome; the outcome and date of resolution, if applicable; and, a narrative of the event.

If other pertinent CRFs for the subject have not been entered into the database by this time, they must be entered immediately.

2. When the SAE/Clinical Outcome Form (CRF 19) is submitted, the WebDCU™ system triggers an automatic e-mail notification of the SAE/Clinical Outcome to the NETT-CCC/POINT CRC Site Manager, depending on the organization responsible for the site. The appropriate Site Manager reviews the SAE/Clinical Outcome information for completeness.

If the SAE/Clinical Outcome information is insufficient, an email

notification is sent to the site requesting additional information.

3. If the SAE/Clinical Outcome information is sufficient, an automatic email notification is triggered to the Clinician Event Monitor who reviews the event materials to ensure completeness.

Again, if the SAE/Clinical Outcome information is insufficient, the Site Manager and site PI will be asked for additional information.

4. The Clinician Event Monitor, who will remain blinded throughout the trial, accesses the SAE/Clinical Outcome data via the WebDCU™. The Clinician Event Monitor blindly reviews the data independently, but may contact the Clinical Site investigators for clarifications and additional information.

The Clinician Event Monitor designates online within 72 hours of being notified of the SAE occurrence whether the SAE/Clinical Outcome is serious, unexpected and related to the study drug.

5. The review process closes at the end of the 72 hours.

6. 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 within 48 hours of receipt of the notification email (CEC assessment) for 7-day reportable events and within 7 days of receipt of the notification email (CEC assessment) for 15-day reportable events. The CRC Medical Monitor sends the completed CIOMS form to the country-level Regulatory Manager for sites outside the US. The country level manager submits the form to the country level regulatory agency.

7. All unexpected, drug-related SAEs are posted to WebDCU™ Participating sites and DSMB members will immediately be sent an email with a link to the website informing them that a new unexpected, study drug related SAE has been reported.

8. The POINT Study Site staff must submit unexpected, drug-related SAEs to their IRB/IEC in accordance with the local guidelines and procedures.

8.3.1.3 Reporting Hemorrhagic Transformations

If a subject experiences an ischemic stroke with no hemorrhagic transformation on initial imaging, the site will submit a Form 19 with the “Ischemic stroke” box

checked. NOTE: Index events will not be reported.

If a subject experiences an ischemic stroke with hemorrhagic transformation on initial imaging, the site will submit a Form 19 with one box checked, either "Symptomatic hemorrhagic transformation of an ischemic stroke" or "Asymptomatic hemorrhagic transformation of an ischemic stroke" (the WebDCU™ form will not allow the site to check two boxes). The subsequent page will ask the question, "If 'Symptomatic hemorrhagic transformation of an ischemic stroke' or 'Asymptomatic hemorrhagic transformation of an ischemic stroke', specify 'Of Index stroke' or 'Of outcome stroke'." NOTE: Count as both hemorrhagic transformation and ischemic stroke in analysis, if not of the index stroke.

If the patient has hemorrhagic transformation on initial presentation, the CRF 19 will be filled out with symptomatic/asymptomatic hemorrhagic transformation, and with a subcategory "of outcome stroke" will be checked in question #15. If the patient arrives without hemorrhagic transformation, the initial CRF 19 will have ischemic stroke checked as the outcome. If the patient later develops hemorrhagic transformation, the site will modify the initial CRF 19 to reflect that the outcome is in fact a hemorrhagic transformation of an ischemic stroke, with a subcategory of outcome stroke. This way, the site will not fill out two CRFs for the same event, but instead will make a modification to the initial CRF. NOTE: It is not necessary to record time of onset of transformation.

8.4 Site Monitoring and SAE reporting

During a site monitoring visit, the NETT-CCC or POINT CRC Site Monitor will verify appropriate documentation and reporting of SAEs at each site. In addition, if the site monitor identifies an unreported SAE/Clinical Outcome appropriate documentation and reporting will be initiated.

8.5 Regulatory Documentation and Maintenance

It is imperative that accurate records be maintained for all subjects participating in the study. It is recommended that each subject enrolled in the study have a research folder or binder that contains a copy of the signed consent form, source documents, all data collection sheets, a copy of the outpatient study visit encounter form, a copy of the treatment/evaluation schedule, medical records notes and all study-related drug prescriptions as well as demographic and contact information. For each study, the PI is ultimately responsible for the conduct of the

research trial. The PI will delegate various responsibilities to members of the research team.

9.0 TRAINING AND CERTIFICATION REQUIREMENTS

The training of the clinical site investigators and coordinators will be done through mandatory website training modules prior to the enrollment phase of the study. All modules can be accessed through the POINT Website. The study protocol, the Manual of Procedures, handling of study medications and case report forms will be reviewed with the study site prior to receipt of investigational product and subject recruitment. The NETT-CCC Site Manager/POINT CRC Site Manager will conduct these calls respectively.

Training will be an ongoing process, with recertification required at specified intervals. At each annual International Stroke Conference, an investigator meeting for the coordinators and study investigators attending the conference, will be held to review study progress and study procedures, particularly those that may be problematic. This meeting will provide an opportunity for the coordinators and investigators to discuss mutual concerns and find solutions. If a site has a change in coordinators, the Site Manager will develop a plan to train the new coordinator.

9.1 Human Subjects Protection/Good Clinical Practice

Adequate training is required by the principles of the ICH, Guideline for Good Clinical Practice (GCP).

See ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance and ICH Guidelines for Good Clinical Practice.

Acceptable documentation of GCP training will be maintained for all study personnel (including Contract Research Associates) throughout their participation in the POINT Trial, and will be provided by each site for each participating research staff member.

Training for GCP and HSP is available at the POINT Resources and Training page, hosted at the NETT University of Michigan site:
(https://sitemaker.umich.edu/nett/point_resources_and_training)

(Good Clinical Practice training: https://connect.umms.med.umich.edu/gcp/)

(Human Subjects Protection: http://my.research.umich.edu/peerrs/ or https://www.citiprogram.org/)

The tables in **Appendix XI** will serve as tools to help sites establish the necessary structure to maintain proper GCP and QA with the study.

9.2 ABCD^2 Score

Dr. J. Donald Easton, Co-PI of the POINT trial, has developed a training module for the ABCD^2 Score. The training consists of an informational slide deck with narration and a testing component that will be hosted at the NETT University of Michigan site:
(https://sitemaker.umich.edu/nett/point_resources_and_training)

Upon completion, candidates should be able to consistently apply appropriate ABCD^2 scores for patients with TIA. Copies of the documentation will be uploaded and maintained in WebDCU™.

9.3 Modified Rankin Scale (mRS)

The Modified Rankin Scale (mRS) is commonly employed in the world as a measure of global outcome after stroke. Modified Rankin Scale training and testing will be made available at the NETT website:
(https://sitemaker.umich.edu/nett/point_resources_and_training) Copies of the documentation will be uploaded and maintained in WebDCU™.

9.4 NIH Stroke Scale (NIHSS)

NIHSS training and certification will be made available at the NETT website (https://sitemaker.umich.edu/nett/point_resources_and_training). This certification is required by those study team members who are on the 1572 and who will be interacting with patients. Re-certification must occur before the expiration date stated on the certificate.

Copies of the certification/re-certification documentation will be uploaded and maintained in WebDCU™.

9.5 POINT Trial Protocol

Protocol specific and protocol related training is required of all study staff participating in the conduct of the POINT trial. Documentation of protocol-specific training will be documented in the following ways:

1. Attendees of protocol specific training meetings will be verified and included within the meeting summary or minutes. The summary or

meeting will serve as the documentation of training.

2. Study staff who do not attend protocol specific training meetings will undergo training either online or at the site as appropriate.

3. Study staff training at the site will be documented by the person(s) providing the training in a visit report or a summary document as appropriate. Verification of trainings for study personnel will be entered into WebDCU™.

9.6 Case Report Form (CRF) Completion

Study Coordinators will be trained (train-the-trainer) in study procedures, drug accountability, subject enrollment, and data entry procedures at the POINT Initiation call. The goal of the training is to standardize the methods of data collection to help ensure comparability of data across sites. Once the Study Coordinator has been trained, it is the responsibility of that person to train other personnel at the site, as needed.

WebDCU™ training videos are available on the NETT website and the NETT SDMC will conduct data training via webcasts on an as needed basis for anyone wishing to receive additional training. Additionally, the WebDCU™ User Manual, which contains step-by-step data entry instructions, is also available online, and SDMC personnel are available during working hours to answer questions regarding data collection and entry.

9.6.1 Data Acquisition and Central Study Database

9.6.1.1 Modules

The WebDCU™ offers a full collection of web-enabled modules for randomization, protocol and site management (e.g., drug accounting and shipping, automated SAE/Clinical Outcome reporting, regulatory document tracking), study monitoring, data entry and validation, and report generation. The system provides a web-based collaborative environment for study team members across all participating clinical sites and provides all the required tools for site coordination and data management in one efficient and easy to use system.

9.6.1.2 Schedule of Activities and Assessments

See **Appendix XII**.

9.6.1.3 Case Report Forms (CRFs)

See **Appendix XIII**.

9.6.1.4 CRF Completion Guidelines (POINT Data Collection Completion Guidelines)

See **Appendix XIV**.

10.0 SITE INITIATION, MONITORING AND CLOSEOUT

10.1 Site Initiation and Activation

The rationale for monitoring visits is to ensure that the conduct of the trial is in compliance with the current version of the IRB/IEC approved protocol, GCP/ICH Guidelines, and all applicable regulatory requirements. It is paramount that the rights and well-being of human subjects are protected and that the trial is performed in accordance with all regulatory requirements and protocol criteria. The site will demonstrate that the investigator and staff are fully aware of their obligations and responsibilities with regard to the conduct of POINT including compliance with the study protocol and specified procedures, timelines, number of subjects required, GCP guidelines, applicable governing agency regulations, informed consent requirements, and adverse event reporting 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.

The site initiation visit will take place by telephone after the site is deemed "Regulatory Ready". Sites will not be allowed to enter patients into the trial until all regulatory documents are complete. All regulatory documents must remain current throughout the course of the trial. For NETT-CCC sites, it is the

Hub's responsibility to ensure regulatory compliance is maintained. The POINT CRC will routinely monitor POINT CRC sites. Both the NETT-CCC and POINT CRC will routinely monitor the WebDCU™ for sites out of regulatory compliance.

Regulatory documents specific to the POINT trial include:

- 1572 or CRC Investigator form
- Package Insert for clopidogrel
- Documentation of Full Study IRB/IEC Application Submittal
- IRB/IEC approval of POINT Protocol/Full Study IRB/IEC approval
- IRB/IEC Approved Informed Consent Form
- IRB/IEC FWA
- Delegation of Authority Log
- Laboratory Certifications (CLIA is sufficient; both CAP and CLIA are preferred)
- Current Medical/Professional license
- IRB/IEC Membership List
- Current CV
- NIHSS Certification
- mRS Certification
- POINT ABCD^2 Certification
- Human Subjects Training Certification or Waiver
- GCP Training Certification or Waiver
- HIPAA Training Certification or Waiver
- POINT Protocol Training Certification
- POINT Data Training Certification
- Protocol Signature Page

The investigator and staff will demonstrate that they have received instruction and training on electronic data entry, and certification in the use of the NIH Stroke Scale, the Modified Rankin Scale, the ABCD^2 Score, POINT eligibility,

Human Subjects Protection and Good Clinical Practices. Case Report Forms (CRFs) and the CRF completion requirements will be reviewed, as well as the security and proper storage of subject specific documents and the test article, and dispensing and accounting procedures and records. Source document requirements will also be reviewed. The Monitor and Site Manager will hold specific discussions with the PI and lead Coordinator regarding plans for recruitment and retention of subjects.

A description of each requirement and what needs to be uploaded into WebDCU™ can be found on the WebDCU™ Regulatory database under Project Management/Project Documents. Once these documents are uploaded into the WebDCU™ Regulatory database, the site initiation will follow.

Following the site initiation visit, a Site Initiation Visit Report will be entered in WebDCU™ and the findings issued to the site PI and the POINT Operations Committee within 28 days of the visit.

10.2 On-Site Monitoring

The NETT-CCC/POINT CRC Site Monitor will coordinate/perform the on-site monitoring for the POINT study sites. Please refer to the Site Monitoring Plan in the NETT POINT Toolbox https://sitemaker.umich.edu/nett/point_toolbox

10.3 Source Documentation

Source documents are any documents on which study data are recorded for the first time. Source documents include but are not limited to electronic or paper medical records (inpatient or outpatient); worksheets developed for study use (if used); and laboratory reports as necessary (if relevant to an AE).

The source documents necessary to validate the information that has been entered into WebDCU™ must be made readily available during site monitoring visits. These documents should be in good order, and may be placed in a study titled binder or clearly marked file.

Monitoring visits will be logged electronically in WebDCU™ by the NETT-CCC/POINT CRC Site Monitor and a member of the Clinical Site staff at each visit. A Monitoring Report will be uploaded into WebDCU™ by the NETT-CCC/POINT CRC Site Monitor within 28 days after the visit.

10.4 Changes in Study Personnel

When there are any changes to site personnel during the study, it is the Hub's responsibility to update WebDCU™. The site must then upload the following information into WebDCU™ for all additions/changes/deletions:

- Amended 1572 (required only for personnel listed on the 1572)
- All required regulatory documents
- Updated Delegation of Authority Log
- IRB/IEC approval for change in study team as POINT IRB/IEC Study Modification Notifications

10.5 On-going Monitoring

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.

In addition, the Site Monitor will verify 100% of the subjects randomized for each site on a weekly basis by reviewing the Randomization CRF in WebDCU™.

11.0 STUDY PROCEDURES

11.1 Subject Identification

Each site will be responsible for identifying and recruiting participants into the study. Once potential participants are identified, the site will collect information about them to make a determination of their eligibility for the study. The determination of eligibility will be made using the data collected from tests and examinations performed as part of the potential participant's routine care, as well as additional screening tests specific to the study described below.

Potential participants who are eligible for and are interested in the study will be asked to sign an informed consent with subsequent enrollment into the study. The site will track potential participants from the time they are identified until they are enrolled, or not enrolled. Each site will document and report a summary of recruitment and enrollment progress.

11.2 Screening Evaluation

11.2.1 Overview

Screening is defined as any procedure done solely for the purpose of determining a potential subject's eligibility or to enter a subject into a research study. Federal regulations and institutional policy must be followed when screening subjects to determine potential eligibility.

Potential subjects will be identified by neurologists, local emergency department, 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 enrolled as quickly as possible after presentation to the Emergency Department.

11.2.2 Screening Evaluation Procedures

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.

A licensed physician will be required to confirm the diagnosis of TIA (traditional definition) or minor ischemic stroke. The physician investigator must confirm eligibility and review the calculation of the NIHSS and $ABCD^2$ scores, either in person or on the phone with a properly trained and certified non-physician investigator prior to randomization into the study. Any investigator with an MD may do the confirmation and review. Participants may be enrolled by any certified study personnel as long as a site physician investigator has reviewed and approved eligibility prior to randomization.

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. Local physicians will be responsible for interpretation. Since ECG and head imaging are recommended for all patients presenting with TIA and stroke, the study will not cover these costs.

1. 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 normal), symptoms, duration of symptoms (if resolved), and pertinent review of symptoms should be obtained.

2. If the patient is felt to have a TIA or stroke by a certified, trained licensed physician investigator and is within the 12 hour window after symptom onset, screening should continue.

3. If the patient has had a TIA, $ABCD^2$ score should be calculated by the certified trained study personnel and reviewed by a certified site physician investigator.

4. If the patient has had a stroke, NIHSS should be performed by the certified trained study personnel and reviewed by a certified site physician investigator.

5. Take a focused medication history.

6. Take a focused past medical history.

7. Send screening laboratories: CBC and creatinine. For woman premenopausal or postmenopausal 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) a pregnancy test should be done.

8. Ability to swallow should be assessed.
9. If the patient has had a TIA, symptoms may be adequate.
10. If the patient has had a stroke, swallow evaluation should be considered.
11. Take blood pressure.
12. Obtain ECG.
13. Obtain brain imaging with CT or MRI, and record results on CRF 11. 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
14. Urgent carotid artery imaging is encouraged but not required. If these studies are done, results should be recorded on CRF 13.
15. The final inclusion/exclusion criteria checklist should be reviewed after collecting all of the information.

11.2.3 Informed Consent Process

Human research subjects are protected by informed consent procedures. The signing of an informed consent form is a criterion for eligibility to participate in the study. Each study site will determine the eligibility of the potential participants and will obtain their consent before enrolling them in the study. 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. The consent document explains the risks and potential benefits of the therapy, the procedures for the trial, and alternatives to participation. The informed consent form addresses four major protections:

- Each participant must be fully informed of all study procedures and requirements in order to be considered a "knowing" participant.
- The study design must minimize risks to the participants and maximize the benefits.
- The study participants must be selected in a non-discriminatory way so that

no class of individuals will benefit more than any other based on the selection procedures.

- Participation is voluntary and all information provided by participants will be kept confidential.

Research personnel at each site will be formally responsible for ensuring that written informed consent to take part in the study is obtained from each participant. In addition, the Institutional Review Board (IRB/IEC) at each site must approve the informed consent form and procedures. In the development of its own informed consent, each site will use the template as a guide. All information in the prototype informed consent must be included in the individual site forms.

Administration of the informed consent should occur after the participant has been provided with background information about the study and its requirements. The requirements of the study, the implications of randomization and the necessity for completing the required procedures should be emphasized with each potential participant.

When the informed consent is provided to the potential participant, s/he must be offered sufficient time to carefully read the document and must be given sufficient opportunity to have all questions regarding the study answered before s/he is asked to make a decision on enrollment.

11.2.3.1 Obtaining Informed Consent

If a patient *meets all criteria*, he or she should be approached for informed consent by a trained researcher. The patient should be told why they were selected for screening, the purpose of the screening, and how results of the screening are used to determine eligibility.

11.3 Enrollment/Randomization

11.3.1 Overview

A subject will be considered to have enrolled into the study once randomization to study drug has occurred. Randomization will take place centrally via the WebDCU™. The data to be collected prior to randomization include: Eligibility form, $ABCD^2$ Score, NIH Stroke Scale, Medical History Form, Prior Medications, Index TIA/Stroke Symptoms, Vital Signs, CT/MRI Scan, Electrocardiogram, and Carotid Artery Imaging (if applicable).

11.3.2 Randomization Procedure

The randomization system allows clinical sites to perform subject randomization around the clock. Upon presentation of a potential subject, the procedure for randomization is as follows:

A study patient's eligibility is determined by site personnel. Before accessing the web-based randomization system, the site investigator and/or coordinator should complete and review the Eligibility Form (Form 00) to assess that the subject meets enrollment criteria. Any uncertainty regarding the subject's eligibility should be referred to the UCSF CCC prior to proceeding to the web-based randomization.

The Eligibility Form must be data entered and submitted into WebDCU™ with all eligibility criteria met or randomization will be blocked.

For more information, refer to the WebDCU™ User Manual.

11.3.2.1 Random Number Generation

Once eligibility has been established, the randomization form must be data entered and submitted. If the computer deems the patient to be eligible based on the information provided, it evaluates the treatment arm distribution and generates a randomization number based on the randomization scheme. (Note: The randomization number corresponds to one of the medication bottles at the clinical site.)

A randomization number appears on the screen and an automatic confirmatory e-mail is sent to the POINT Executive Committee.

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 (RVF).

11.3.2.2 Obtaining Study Drug

Site personnel obtain the medication bottle with the corresponding randomization number.

11.3.2.3 Dispensing Study Drug

The study medication bottle (both study drug and placebo) contains 97 tablets: 8 tablets for the initial loading dose, and for the subsequent 89 days at 1

tablet/day. The clinical site will oversee dispensation and return of study medication.

The subject should be given the medication plus details regarding dosage, administration, expected side effects and potential adverse events. Subjects should be encouraged to keep a medication log to record their doses of study drug and aspirin for the length of the study. Subjects will be given a wallet-sized Alert Card with contact numbers for the subject's site and the UCSF CCC toll free number.

In addition, the subject should be informed about the requirements for drug compliance, including the Morisky Questionnaire and pill count at 90 days. Patients should be reminded that all bottles must be returned at the 90 day visit.

11.4 Study Procedures

11.4.1 Procedures

a. The subject should take the first eight pills of the study drug (loading dose) while the study investigator is present.

b. The subject should be given their first dose of aspirin while the study investigator is present. The dose of aspirin (50-325mg) should be determined by the treating physician (with a dose of 150-200 mg daily for 5 days followed by 75-100 mg daily strongly recommended).

c. The schedule for continuing to take the study drug and aspirin throughout the study period. Each patient should take one pill of study drug or placebo, as well as one prescribed dose of 50-325mg aspirin daily. The importance of compliance with the study medications should be explained to each subject, and they should be asked to contact the study investigator if they stop the medications for any reason. Subjects should be instructed to contact their treating physicians before taking any new medications.

d. The study investigator or site coordinator should discuss a schedule for an appropriate time and day to call the subject for their 7 day follow up telephone call. The subject's phone number should be confirmed.

e. Risk factor evaluation and management: treating clinicians are encouraged to follow standard recommendations on evaluation and management of risk factors. See the POINT study protocol for a full

listing of recommendations.

i. If carotid imaging was not done prior to randomization, then it should be done as soon as possible. An ultrasound, CT angiography, or MR angiography suggesting a stenosis greater than 50% should be followed by additional carotid imaging to confirm the degree of stenosis.

ii. Further lab testing should be considered as appropriate, including fasting cholesterol panel, HbA1c, erythrocyte sedimentation rate, syphilis serology and hypercoagulable screening should be considered when appropriate.

iii. 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.

iv. Counseling and treatment to assist with smoking cessation should be offered.

v. Cardiac disease should be managed appropriately in consultation with a cardiologist.

vi. Alcoholism should be treated through formal cessation programs.

vii. High-dose, high-potency statin (e.g., atorvastatin 80 mg daily) is recommended in all patients unless LDL is < 70 mg/dL or there is a contraindication.

viii. Tight control of diabetes is recommended to maintain HbA1c < 7%.

ix. Physical exercise should be encouraged (>30 min for ≥3 days/week).

x. Patients with atrial fibrillation or an obvious cardiac source of embolus should be discontinued from study medications and treated with anticoagulation unless there is a contraindication.

xi. Patients with an internal carotid artery stenosis of 70-99% that may have been responsible for the index event should be considered for urgent endarterectomy.

xii. Patients with an internal carotid artery stenosis 50-69% that may have been responsible for the index event should be considered for endarterectomy if risks of surgery are considered minimal.

11.5 7-day phone follow up

11.5.1 Overview

Each participant will have a telephone evaluation with their site coordinator on day 7 (+/- 2 days) after randomization. The site coordinator should have discussed an appropriate time to call with the patient at the time of baseline evaluation, and the subject's telephone number should have been confirmed.

11.5.2 Procedures

The Questionnaire for Verifying Stroke-Free Status (QVSFS), Morisky Questionnaire, Seven Day Follow up CRF form, Concomitant Medications and the SAE/Clinical Outcome Reporting Form (if applicable) should be filled out during this visit.

In addition, if the subject had carotid imaging since the last assessment, this should be recorded on the Carotid Artery Imaging Form.

11.5.3 Scheduling 90-Day Follow-up Appointment

An appointment for the 90-day follow up face-to-face visit should be scheduled during this telephone call. This can be scheduled for 90 days +/- 14 days from randomization.

11.5.4 Scheduling Event Visit

If an outcome event or adverse event has occurred, the patient should be scheduled for a face-to-face event visit.

11.6 90-day Physician Follow-up/Final Visit

11.6.1 Overview

Each participant will have a final visit with the study physician 90 +/- 14 days after randomization.

11.6.2 Procedures

During this visit, the modified Rankin Scale, the NIH Stroke Scale (if applicable),

the QVSFS, the Morisky Questionnaire, the Concomitant Medications form, SAE/Clinical Outcome Reporting form (if applicable), Study Drug Compliance, and End of Study forms should be completed.

In addition, if the subject had carotid imaging since the last assessment, this should be recorded on the Carotid Artery Imaging Form.

11.7 Event Visits

11.7.1 Overview

Any time subject contact suggests that a clinical outcome may have occurred, an Event Visit will be scheduled with a study physician. These clinical outcomes may be discovered during the 7-day follow up telephone call, the 30-day follow up phone call or in person visit or may be reported to the site coordinator or study investigator at another time during the subject's enrollment.

During these visits, the following CRFs should be completed: modified Rankin Scale, NIH Stroke Scale, CT/MRI Scan (if applicable), Electrocardiogram (if applicable), QVSFS, Morisky Questionnaire, Concomitant Medications, and SAE/Clinical Outcome Reporting Form.

11.7.2 Stroke Outcome Event

If the subject's outcome event is a stroke, a modified Rankin Scale Score and NIHSS should be obtained. Head imaging with CT or MRI is strongly encouraged.

11.7.3 Stroke and TIA events can be evaluated via telemedicine when necessary. Cardiac Outcome Events

If the subject's outcome event is an MI, documentation of the ECG and cardiac enzymes is required as part of the event narrative. Event visits for MI may be conducted over the telephone.

11.7.4 Appropriate Laboratory Testing

Appropriate laboratory testing is required for documentation of systemic hemorrhage or other systemic complications.

11.8 Subject Dropouts, Withdrawals, and Treatment Discontinuation

11.8.1 Definitions

a. Drop-out: A subject that is lost to follow-up after study enrollment due to not appearing at scheduled follow-up visits or the inability to reach the subject. Multiple attempts should be made to reach the subject if they have missed a scheduled follow up for rescheduling.

b. Withdrawal of Consent: A subject who withdrawals consent after subject randomization. All data up until the time of withdrawal of consent should be entered into the study database.

c. Temporary Treatment Discontinuation: discontinuation of either the study medication or aspirin for a period of <10 days. This may be necessary if a subject has an intercurrent medical condition that requires discontinuation of the treatment, such as a surgical procedure. In these cases, treatment should be discontinued for the shortest time period felt safe by the treating physician, and study treatment should be reinitiated as soon as possible. The subject should continue to be followed until 90 days. The primary analysis will be done as intention-to-treat, and therefore we would like any subjects who can restart medication to do so.

d. Permanent Treatment Discontinuation: discontinuation of the study medication or aspirin for a period of >10 days. The study drug should be restarted when it is felt to be medically safe, even if the discontinuation is for >10 days, but it will be classified as a permanent treatment discontinuation. The reason for this classification is for the purpose of a per-protocol analysis. The subject should continue to be followed until 90 days. The primary analysis will be done as intention-to-treat, and therefore any subjects who can restart medication should do so.

Examples of situations in which treatment may need to be permanently discontinued:

- 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.
- Pregnancy will lead to definitive treatment discontinuation in all cases.

11.8.2 Tracking Procedures

Information regarding premature study termination (withdrawal of informed consent/lost to follow up) will be captured on the End of Study form.

11.8.3 Follow Up

All subjects should remain in the study and be followed per the protocol (i.e., to 90 days, a primary outcome event, or death) regardless of treatment discontinuation.

12.0 Outcomes

12.1 Definitions

12.1.1 Neurologic Outcome Events

a. 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 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, and/or no evidence of a non-ischemic etiology.

b. 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).

c. Symptomatic hemorrhagic transformation of an ischemic stroke

Any extravascular blood within an area of known acute/subacute ischemic 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):

a. Imaging evidence (by CT or MR) of extravascular blood within the area of infarction.

b. 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.

d. Asymptomatic hemorrhagic transformation of an ischemic stroke

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

Criteria (must meet both of the following)

a. Imaging evidence (by CT or MRI) of extravascular blood within the area of infarct.

b. No symptoms related to the hemorrhagic transformation, or clinical deterioration with less than a 4-point increase in score on the NIHSS judged to be related to the hemorrhagic transformation.

e. 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 (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 patient 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.

f. 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 patient 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.

g. 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 patient 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.

h. 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 patient 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.

12.1.2 Cardiac Outcome Events

a. Myocardial infarction with coronary revascularization

Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, 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.

i. Angioplasty/stent

ii. Coronary Artery Bypass Graft

b. Myocardial infarction without 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 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.

c. 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.

12.1.3 Systemic Outcome Events

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. 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. This may

include bleeding events related to surgical procedures but not those related to accidental trauma.

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.

12.1.4 Deaths

If a death occurs, it will be adjudicated according to the cause of death. For each outcome (such as ischemic stroke, intracerebral hemorrhage, MI, etc.), there will be a checkbox to indicate that the event was fatal. Deaths related to an event may occur at the time of the event, or days or weeks later if in the best clinical judgment it is directly linked to the event. One way to help define what may be related to an outcome event is by asking the question, "would the death have occurred without the preceding outcome event?" For example, this may include hospital acquired infections or new congestive heart failure following MI. Deaths that are not related to any of the cerebrovascular, cardiovascular or systemic hemorrhagic events will be adjudicated as "Other Serious Adverse Event" with fatality. For all deaths, please indicate whether the death was ischemic, hemorrhagic or nonvascular in etiology.

a. 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.

b. Hemorrhagic Vascular Death

   Death due to intracranial or systemic hemorrhage.

c. Nonvascular Death

   Any death felt not to be related either to an ischemic event or a hemorrhagic event. Examples: death related to neoplasm, infection, trauma, or toxin.

12.2 Procedures If Clinical Outcome Occurs

12.2.1 Event Visit

See Section 11.7.

12.2.2 Outcome Event Reporting

Outcomes will be detected by the participating centers during follow-up evaluations or may be reported to the site coordinator or study investigator at another time during the subject's enrollment. The participating centers will data enter and submit the SAE/Clinical Outcome CRF within 24 hours of first knowledge of the event, will compile an event packet, comprised of the hospital discharge summary and other relevant documents, and will send the packet to the appropriate coordinating center to be distributed for adjudication. 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.

12.3 Adjudication of Outcomes

12.3.1 Adjudications Committee Review

Since members of the Adjudications Committee have been appointed, in part, because of their clinical expertise, reported cardiac events will be reviewed independently by two cardiologists/internists. Similarly, reported ischemic and hemorrhagic strokes will be reviewed independently by two neurologists and classified by the TOAST criteria. All deaths and hemorrhages (other than intracerebral hemorrhages) will be reviewed independently by a cardiologist/internist and a neurologist and classified as hemorrhage, ischemic stroke, myocardial infarction, other vascular and non-vascular.

See also **Appendix XV**.

12.3.2 Process

12.3.2.1 Both Adjudicators Agree

If both adjudicators agree with reported outcome or classification, the Adjudication System will close the record and remove it from the Adjudicator's worklist, and the UCSF CCC will enter the final adjudicated classification in WebDCU™.

12.3.2.2 Both Adjudicators Disagree

If the Adjudicators disagree with each other on the event classification, a third Adjudicator will be assigned the Event Packet by the POINT Adjudication System, and will adjudicate the outcome event and complete the Adjudication CRF. 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. The UCSF CCC will enter the final adjudicated classification in the WebDCU™.

12.3.2.3 Third Adjudicator disagrees with both of the two Adjudicators on the event classification

If the third Adjudicator disagrees with both of the original Adjudicators, then the POINT Adjudication System will trigger an email to set up a conference call to review the discrepant event classification with the Adjudication Committee Chair. The Chair will adjudicate the outcome event and complete the Adjudication CRF. The Chair will attempt to gain consensus; however, decision of the Chair will be the final classification of the event. The UCSF CCC will enter the final adjudicated classification in the WebDCU™.

If all three adjudicators disagree on the event classification, a conference will be held by the three adjudicators and the Adjudication Committee Chair to discuss the possible diagnoses. Based on this discussion, the chair will assign a final adjudication to the event. The UCSF CCC will enter the final adjudicated classification in WebDCU™.

13.0 Patient Recruitment and Retention

13.1 Recruitment

13.1.1 Recruitment Sources

Potential subjects will be identified by neurologists, local emergency department, and clinic staff in conjunction with study personnel. A licensed physician will be required to confirm the diagnosis of TIA (traditional definition) or minor ischemic stroke. 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 non-physician investigator prior to randomization into the study.

The UCSF CCC will monitor recruitment. This monitoring activity will enable the CCC to identify any problems with recruitment and to redirect recruitment resources, if necessary. A Cumulative Recruitment Summary Report will be produced based on the information transmitted to the CCC by the NETT-CCC and POINT CRC, and will detail the numbers of patients screened, enrolled and randomized.

13.1.2 Recruitment Materials

To aid in the recruitment process of participants by the clinical centers, the UCSF CCC will develop a wall poster and a laminated pocket card as recruitment materials that can be provided to potential participants.

The wall poster will include general study information such as the trial purpose, study contact information, and inclusion/exclusion criteria, and should hang in areas that are influential to recruitment progress. Staff will become more familiar with the study existence, eligibility, and purpose of the study through this visual reminder.

The pocket card will include eligibility criteria and study contact information. This will be a useful resource for study team members to use for determining eligibility.

13.1.3 Study Press Release

The UCSF CCC will work with the UCSF News Office to prepare and distribute news releases about the trial. The UCSF News Office is responsible for communicating news about UCSF's teaching, research, patient care, and

community service programs. The main phone number for the office is (415) 476-2557. This number is covered 24 hours a day, weekends and holidays. After regular business hours (8 a.m. to 5 p.m. Pacific Time), a News Office staff person is on-call and available to help. The fax number for the office is (415) 476-3541.

13.1.4 Study Website

The website for the trial can be found at http://POINTtrial.org. See Section 4.2 for additional information.

13.1.5 NETT-CCC and POINT CRC Role in Recruitment

The NETT-CCC and POINT CRC will assist in the recruitment process by developing a close working relationship with participating sites. This relationship will consist of correspondence, conference calls, and site visits that will help encourage recruitment progress. Through these methods, recruitment will be tracked and noted. Screen failure logs will be reviewed weekly to identify recruitment problems.

13.1.5.1 Recruitment Reports

The UCSF CCC will monitor recruitment. This monitoring activity will enable the CCC to identify any problems with recruitment and to redirect recruitment resources, if necessary. A Cumulative Recruitment Summary Report retrievable from WebDCU™ will detail the numbers of patients screened, enrolled and randomized.

13.1.4.2 Contractual Agreements/Investigator Payment Schedule

The POINT CRC Operations Center and NETT-CCC will pay sites based on data completion via reports provided by the Data Coordinating Center. The SDMC does not send invoices for payments due; the database will indicate when a site is due for payment.

13.2 Retention Strategies

Low rates of recruitment and retention have a number of negative implications, such as longer duration of the clinical trial, which may lower staff and participant morale; a costlier clinical trial, since extra resources may need to be dedicated to the recruitment effort; and less statistical power for both the study and the validity of the results.

14.0 PATIENT ENCOUNTERS

14.1 Schedule of Assessments

See Data Management Section 17 for Schedule of Assessments, and **Appendix XII.**

15.0 CONTROL OF STUDY DRUG

In compliance with 21 CFR §312.60, investigators in the POINT Trial are responsible for:

- ensuring that the investigation is conducted according to the signed statement, the investigational plan, and applicable regulations
- protecting the rights, safety, and welfare of study participants
- controlling drugs under investigation

Adequate control and handling of investigational drug includes all of the following:

- The investigator should ensure that the investigational drug is used only in accordance with the IRB/IEC/CHR-approved protocol.
- An investigator must administer the investigational drug only to participants under the investigator's direct personal supervision or under the supervision of a sub-investigator directly.
- The investigator must not supply the investigational drug to any person not authorized to receive it.
- An investigator is required to maintain adequate records of the disposition of the investigational drug, including dates of dispensing, quantity currently maintained for dispensing, and amount of the investigational product dispensed to participants.
- If the investigation is terminated, suspended, discontinued or completed, the investigator must return any unused supplies of the investigational drug to the study pharmacy, or otherwise provide for disposition of the unused supplies as directed by the UCSF CCC, study pharmacy and/or sponsor.

POINT investigators are required to adhere to the following regulations for documentation of the investigational drug:

- Prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. [21 CFR §312.62]
- Maintain case histories, including the case report forms and supporting data (e.g., signed and dated consent forms and medical records including progress notes of the physician, the individual's hospital chart(s), and the nurses'

notes). The case history for each individual will document that informed consent was obtained prior to participation in the study.

15. 1 Study Investigational Pharmacy

The UCSF Drug Product Services Laboratory (DPSL) will function as the Central Pharmacy for the study for U.S. and international sites, in partnership with Sharp Clinical Services. The DPSL is the retail compounding pharmacy of the School of Pharmacy, Department of Clinical Pharmacy at the University of California, San Francisco.

Sharp Clinical Services will produce labels, with computer generated randomization codes, that are to be used for the bottle. Labels will be supplied to the DPSL by Sharp, and applied to the bottles of study drug.

15.2 Study Medication Handling

15.2.1 Study Medications

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. The tablets are pink, round, slightly biconvex, not engraved, and film-coated.

Sanofi will manufacture and supply the study drug and the placebo in amounts adequate to accommodate a minimum of 5,840 study subjects, in a 1:1 ratio between clopidogrel and placebo.

15.2.2 Clopidogrel

The clopidogrel used in the study will be supplied by Sanofi and distributed by the UCSF Drug Products Services Laboratory (DPSL) or in partnership with Sharp Clinical Services. It will be supplied in 75mg tablets.

The group assigned to clopidogrel will receive:

- Day 1: 8 tablets of clopidogrel 75mg (loading dose of 600mg) in addition to open label aspirin 50-325mg at the discretion of the treating physician
- Day 2-Day 90: one tablet of clopidogrel 75mg and 50-325mg of aspirin daily. Minor side effects are unusual with the medication, 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.

15.2.3 Placebo

The placebo used in the study will be supplied by Sanofi and distributed by the UCSF Drug Products Services Laboratory (DPSL) or in partnership with Sharp Clinical Services. The placebo is indistinguishable from clopidogrel tablets: identical in size, shape, color, appearance and taste.

The group assigned to placebo will receive:

- Day 1: 8 tablets of placebo (loading dose of 600mg) in addition to open label aspirin 50-325mg at the discretion of the treating physician.
- Day 2-90: one tablet of placebo and 50-325mg of aspirin daily. An aspirin dosing schedule *of 150-200 mg daily for 5 days followed by 75-100 mg daily* is recommended.

15.2.4 Aspirin

Aspirin tablets will be open label with the dose in a range of 50-325mg daily determined by the treating physician.

An aspirin dosing schedule *of 150-200 mg daily for 5 days followed by 75-100 mg daily* is recommended.

15.3 Concurrent Treatments

15.3.1 Prohibited concurrent 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
- Open-label thienopyridines (ticlopidine, clopidogrel)
- Dipyridamole

- All heparins
- Oral anticoagulants (e.g., warfarin)
- 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 patient 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.

15.3.2 Proton Pump Inhibitors

Clopidogrel is a prodrug (a substance administered in an inactive form that is then metabolized in the body *in* vivo into the active compound) that must be converted to its active form by liver cytochrome P-450 enzymes, particularly CYP2C19. 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].

- NOTE—PPIs are discouraged in patients enrolled in POINT
    - If a patient is felt to need a medication for gastroesophageal reflux disease, the preferred medications would be H2 blockers, such as famotidine 20mg twice daily, or ranitidine 150mg twice daily.

- If a patient is felt to require treatment with a PPI during enrollment, and is not felt to be a candidate for another medication such as an H2 blocker, the first choice of PPI agent would be pantoprazole 40mg daily.

Proton-pump inhibitors (PPIs) also are metabolized by CYP2C19 and when taken concomitantly with clopidogrel can decrease the antiplatelet effectiveness of clopidogrel. One of the PPIs, pantoprazole, can be metabolized by enzymes other than CYP2C19. 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.

See **Appendix XVI** for a listing of prohibited medications.

15.3.2 Permitted concurrent medications

Any drugs other than those listed above are permitted at the discretion of the Investigator.

Any medication which is taken within the course of the study will be documented on the Concomitant Medication CRF.

15.4 Receipt of Study Drug

The DPSL and/or Sharp Clinical Services will receive, inspect and store the bottles of study drug provided by Sanofi. The bottles will be stored until they are packaged and shipped, expire or are no longer needed.

An inventory record of study drug on hand will be maintained by the DPSL and/or Sharp Clinical Services.

15.5 Packaging

Each patient will be assigned 97 tablets of study drug (8 for loading dose, and 89 for subsequent daily use) according to the randomization assignment, to be used as directed.

15.6 Study Drugs

15.6.1 Baseline Visit

The subject should take the first eight pills of the study drug (loading dose) and

the first dose of aspirin while the POINT study investigator or study coordinator is present. The dose of aspirin (50-325mg) should be determined by the treating physician, but a dose of 150-200 mg daily for 5 days followed by 75-100 mg daily is strongly recommended.

The subject should continue to take the study drug and aspirin throughout the study period. Each subject should take one pill of study drug or placebo, as well as one prescribed dose of 50-325mg aspirin daily.

15.6.2 Follow up Visits

Each participant will have a telephone evaluation with their site coordinator on day 7 (+/- 2 days) and on day 30 after randomization. The Morisky Questionnaire for assessing compliance with the study medication regimen will be administered during this telephone call. The final study visit at 90 days will also include administration of the Morisky Questionnaire and a pill count to determine medication regimen compliance.

15.6.3 Dispensing Schedule

Subjects in the study will be given a single bottle containing 97 tablets of either active drug or placebo. Subjects will be encouraged to complete a log documenting their compliance with the study medication regiment.

15.7 Pharmacy

15.7.1 Control: Shipping, Packing, Storing

Sanofi will ship active drug and placebo direct to the UCSF DPSL and/or Sharp Clinical Services. The drug will be supplied in sealed bottles containing 97 tablets; no repackaging will be necessary. The drug can be stored at room temperature, with permitted excursions. The DPSL and/or Sharp Clinical Services will receive an automatic email notification when a site has been initiated and is ready to receive study drug.

15.7.2 Dispensing

Drug will be shipped to and distributed to each participating site following its own approved local procedures. The study allows drug to be shipped to and distributed from a pharmacy or from the clinical offices of the participating site. Sites will track receipt, usage, and disposal of study medications in WebDCU™. Participating sites should use their own approved local procedures for disposal

of any unused study medication.

15.7.3 Drug Accountability

See the WebDCU™ Manual for more information.

16.0 CASE REPORT FORMS AND WORKSHEET COMPLETION

16.1 Overview of Forms and Requirements

See **Appendix XIII** for POINT Trial CRFs. See also Data Collection Guidelines Manual.

17.0 DATA MANAGEMENT

17.1 Overview

Data management will be handled by the NETT-SDMC which is housed in the Division of Biostatistics and Epidemiology in the Department of Medicine at the Medical University of South Carolina (MUSC). All activities will be conducted in coordination with the UCSF CCC, the NINDS NETT Network, and the NINDS CRC.

The data is managed the WebDCU™ system. This web-based database system is developed and validated by the NETT-SDMC. It enables web-based real-time subject randomization, data entry and validation, project progress monitoring, subject tracking, drug shipment tracking, user customizable report generation and secure data transfer.

17.2 Data Acquisition and Central Study Database

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be entered by the Spoke/Site personnel via a web-based Clinical Trial Management System. In order to provide user-friendly and easy-to-navigate interfaces, the WebDCU™ data capture screens are designed based on individual CRFs.

The latest version of each CRF is available as a PDF file on the study website for use as worksheets and source documents by study personnel. The most current version of the case report forms can be found on the study website.

The data validation procedure is implemented in two stages. The study database has extensive consistency checks programmed into the forms during the development of the database. These checks are in place to flag potential data entry errors and protocol violations, including missing required data, data out of a pre-specified range, data conflicts and disparities within each CRF and across different CRFs.

When data that violates the consistency check is entered, a rule violation message appears on the data entry screen alerting the data entry person to address it. The choices are to:

(1) correct the entry immediately;

(2) correct the entry at a later time; or

(3) dismiss the rule with an explanation if the entered data is confirmed to be correct.

Secondly, for some checks that are more complicated, additional consistency checks are periodically run after data entry occurs at the site. All data items that fail these secondary consistency checks are queried via the data database by NETT-SDMC data managers. Site monitors are also able to generate Data Clarification Requests (DCRs) when discrepancies are found during source to database verification. The DCRs will be generated, communicated to the Spokes/Sites, and resolved on the secure study website. Any changes made in the system have a full audit trail.

17.3 Modules

17.3.1 Randomization

The NETT-SDMC developed a web-based randomization module that will be used by all authorized Spoke/Site personnel for the purpose of randomizing eligible patients. The WebDCU™ subject randomization module automatically generates unique subject IDs without storing any personal identifying information. The Spoke/Site personnel log onto the WebDCU™ POINT web-based system using a unique username and confidential password. Then, the user enters the required information into the Randomization CRF including eligibility criteria. The computer program checks for accuracy and completion of this information prior to assigning a unique randomization number. In addition, an automatic e-mail notification of enrollment is sent to the appropriate parties (*e.g.*, the POINT Executive Committee, UCSF CCC, the NINDS NETT Network, and the NINDS CRC). If, under rare circumstances the web system is not available, the Study Coordinator can call the emergency hotline to obtain the randomization number.

For more information, see the WebDCU™ User Manual.

17.3.2 Drug Accounting

The Drug Accounting module of the WebDCU™ is designed to facilitate communication between the Spokes/Sites and the UCSF Investigative Drug Center. WebDCU ™contains a web-based study drug shipping and management component which allows for automated maintenance of the appropriate amount

of study drug at the Spokes/Sites, web-based confirmation of drug receipt, and reporting of damaged study drug kits.

Prior to study start up at each Spoke/Site, the Central Pharmacy will send an initial shipment of approximately 4 bottles of investigational product. The shipping is entered into WebDCU ™ by the Central Pharmacy. The Spokes/Sites will receive notification on WebDCU ™once the study drug kits have been shipped. When the shipment is received, the Spoke/Site staff will confirm receipt of each study drug bottle in the website. The Spokes/Sites will also document Study Drug Preparation and Study Drug Retirement in the Drug Accounting Module. After the initial distribution of study drug, additional study drug will be sent on an 'as needed' basis. The WebDCU™'s automated drug distribution system informs the Central Pharmacy when additional kits are needed at a Spoke/Site.

For more information, please see the WebDCU™ User Manual.

17.3.3 Reporting Module

The WebDCU™ system also has a real-time reporting component which allows authorized users the ability to view protocol specific reports as data listings and in a summary format, overall and by Spoke/Site, at any time during the study via the password protected system. The Report Module includes reports on enrollment, SAEs, CRF processing, and subject progress. The reports are presented in a manner that protects the integrity of the study (*e.g.*, blinded).

For more information, see the WebDCU™ User Manual.

18.0 CLOPIDOGREL PACKAGE INSERT

For clopidogrel Package Insert, please visit: http://products.sanofi.us/plavix/plavix.html