PLATELET-ORIENTED INHIBITION IN NEW TIA AND MINOR ISCHEMIC STROKE (POINT)

MONITORING PLAN

Version 2.0
Updated 11 May 2017

Monitoring Plan

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1.0 Introduction

This monitoring plan for the Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial and Biomarker Ancillary Study will be implemented in conjunction with the Standard Operating Procedures (SOPs) that are established by the University of California, San Francisco's POINT Trial Clinical Coordinating Center (UCSF POINT Trial CCC). The UCSF POINT Trial CCC site management and site monitoring activities are provided in partnership with the National Institute of Neurological Disorders and Stroke (NINDS), the Neurological Emergencies Treatment Trials Clinical Coordinating Center (NETT-CCC) network for US Hubs and Spokes and the POINT Clinical Research Collaboration (POINT-CRC) for US and international sites. Monitoring will be performed by qualified Site Monitors in accordance with this monitoring plan and with the operating procedures of each partner organization.

2.0 Purpose

This monitoring plan defines the responsibilities of and facilitates compliance with ICH Good Clinical Practice (GCP) and other US and international guidelines which require Monitors to verify that:

1. The rights and well-being of human subjects are protected
2. Reported trial data are accurate, complete, and verifiable from source documents
3. The conduct of the trial is in compliance with the currently approved protocol, with GCP standards, and with applicable regulatory requirements

This monitoring plan identifies key monitoring activities and specifies the data to be reviewed over the course of the clinical trial. The Site Monitors will conduct monitoring visits at the participating sites to evaluate their compliance with the protocol and applicable training requirements according to this plan.

3.0 Review and Evaluation

3.1 Schedule

This monitoring plan will be reviewed and approved annually, with updates incorporated as needed per partner discussions. The review schedule will be based upon the anniversary of the initial date of approval, July 2011.

3.2 Review and Approval

The plan is reviewed and updated by staff representing the UCSF POINT Trial CCC, the NETT-CCC, and the POINT-CRC. At minimum, all operating versions of the monitoring plan shall be approved by the following individuals:

S. Claiborne Johnston MD, PhD: POINT Principal Investigator (PI)

J. Donald Easton MD: POINT co-Principal Investigator (co-PI)

Anthony S. Kim MD, MAS: POINT co-Principal Investigator (co-PI)

Requirements for obtaining additional approvals from representatives of other collaborating centers will be at the discretion of the PI and Co-PIs.

4.0 Summary of Study Design

The POINT Trial is a prospective, randomized, double-blind, international, multicenter trial with the primary null hypothesis that, in patients with TIA or minor ischemic stroke treated with aspirin 50-325 mg/day, there is no difference in the event-free survival at 90 days in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared to placebo when randomization occurs within 12 hours of time last known free of new ischemic symptoms.

4.1 Study Objectives

The primary objective in POINT is to determine whether clopidogrel 75 mg/day by mouth after a loading dose of 600 mg of clopidogrel is effective in preventing major ischemic events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days when randomization occurs within 12 hours of time last known free of new ischemic symptoms in patients receiving aspirin 50-325 mg/day.

4.2 Study Population and Sample Size

A total of 5,840 subjects diagnosed with a TIA or minor ischemic stroke who meet eligibility criteria will be enrolled at up to 350 study sites. Subjects must be at least 18 years of age to participate in the trial. Subjects will be randomized 1:1 to clopidogrel or placebo; randomization will be stratified across all sites.

4.3 Subject Visit Schedule

Subjects complete a total of 4 scheduled study contacts involving data collection and CRF completion: a Baseline/Randomization Visit, a 7-day telephone follow-up, a 30-day telephone follow-up and a 90-day in-person, telephone or telemedicine visit. A telephone contact at 30 days is required but is not documented on a CRF. Pill counts for visits performed over the phone or by telemedicine must be obtained by subject report, caregiver report, or by the coordinator after receipt of the bottle returned to the site in person or by overnight FedEx or other delivery method. The documentation requirements for attempts at contacting the subject are described in the protocol and Manual of Procedures (MoP). Event visits also occur as indicated when subjects are considered to have experienced an outcome event as defined in the protocol.

A subject can only be considered lost to follow-up (LTFU) when the clinical site can show documented attempts to reach the subject, and the period beyond the final scheduled study visit has reached 60 days (i.e., 150 days after randomization). For any subject who may be lost to follow-up, the POINT Clinical Site must discuss the subject with the appropriate NETT or CRC Study Manager and the UCSF Clinical Coordinating Center team before considering that subject lost. See protocol *Section 9.4.2.1 Subjects Considered Lost to Follow-Up* for details on documenting attempts to contact subjects prior to considering them LTFU.

5.0 Internal Monitoring Review Activities

5.1 Readiness Calls

5.1.1 Purpose

A Readiness Call will be held to initiate a POINT Trial Hub (for NETT-CCC sites), and/or a POINT Trial Spoke (for NETT-CCC and POINT-CRC sites). In some cases, a NETT-CCC Hub will conduct a Readiness Call with one or more of its own Spokes. The Readiness Call will ensure that POINT sites have all regulatory and other trial documents uploaded to WebDCU™, and that logistical aspects of the POINT Trial (Study Drug Handling SOP, Subject Enrollment and Maintenance of Research Records, etc.) are in place.

5.1.2 Preparation and Coordination

POINT-CRC and NETT-CCC staff confirm that all site regulatory, staffing, and training requirements are complete within the appropriate study databases. The consolidated *POINT Readiness Call Questions and Checklist* is compiled for each site and distributed prior to the call. For international sites, a PowerPoint version of the information from the checklist may be prepared and distributed. Once confirmed, the site staff is contacted to schedule the readiness call. At minimum, the site PI, Primary Study Coordinator and Pharmacist should be available for the call. An email confirmation, including the conference line information, is distributed to the site study team and to POINT PI, co-PIs, and Project Director. The email also includes the site's POINT Readiness Call Questions and Checklist and an agenda as attachments.

5.1.3 Facilitating the Call

The Site Manager facilitates the call using the POINT Readiness Call Questions and Checklist as a general guide for discussion. During the call, the Site Manager evaluates the site team's responses to ensure understanding of the protocol requirements and associated regulatory obligations. Clarification of protocol procedures may be provided as needed. Should the Site Manager lack confidence in a site team's readiness to conduct the trial as a result of the discussion, a NETT-CCC or POINT-CRC supervisor and the POINT Project Director and Investigators should be consulted for further guidance.

Whenever feasible, the Site Monitor will be present during the call to address any questions relevant to monitoring.

5.1.4 Reports

The completed POINT Readiness Call Questions and Checklist will be reviewed during the Readiness Call, and will serve as a report of topics discussed and items addressed. Completed electronic versions of the checklist are stored locally.

5.1.5 Site Activation

Upon completion of the Readiness Call and resolution of any associated action items, the Site Manager will change the status in WebDCU™ to "Actively Enrolling." This change will trigger an automatic email message so that the initial drug shipment will be sent according to the study drug handling SOP specific

to either the US or to the enrolling country. A site is considered ready to enroll once the study drug has been received in WebDCU™.

Appropriate personnel are required to verify the number of bottles, lot numbers, and expiration dates, and to complete the WebDCU™ accountability record for shipping and receiving upon study drug receipt.

Neurological Emergencies Treatment Trials Clinical Coordinating Center (NETT-CCC) and POINT-Clinical Research Consortium (CRC) staff may distribute correspondence to the site as documentation of the site activation date.

5.2 Database Review

NETT-CCC and POINT-CRC staff conduct scheduled reviews of study subject data to allow for timely follow-up with participating study sites regarding incomplete data, outstanding visits, subject safety, and assessment of recruitment activities. Scheduled review of study data may also contribute to improved efficiency in general site monitoring activities. The review schedule is described below in **Table 1**.

Table 1: Review Schedule

Activity	Schedule
Verification of randomization (includes verification associated case report forms (CRFs) are complete)	Weekly
Verification of subject recruitment	Weekly
Verification of serious adverse events (SAEs)	Weekly
Data Clarification Requests	Weekly
POINT Screen Failure Log (if applicable)	Monthly

5.3 Monitoring Review Calls – POINT-CRC Sites

5.3.1 Purpose

POINT-CRC staff are responsible for promoting and maintaining effective communication with study site teams. Monitoring review calls enable study site teams and POINT-CRC staff to discuss study conduct issues in between monitoring visits. Discussions may include review of procedural updates, protocol

and regulatory compliance, data management, recruitment, and site successes and challenges in conducting the study.

Though review by teleconference is preferred, in rare instances, limitations in site staff schedules and resources may require the review to be conducted via email correspondence.

5.3.2 Preparation and Coordination

5.3.2.1 Scheduling

All CRC sites are required to participate in monitoring review calls. Review calls are scheduled based upon site recruitment, performance, the site monitoring visit schedule, and close out requests. POINT-CRC staff distributes an agenda to the site via email prior to the call.

5.3.2.2 Data and Compliance Review

Prior to the call, the Site Manager reviews a site's regulatory files, IRB submissions, data entry reports, action items, and other study materials to identify expiring documents, pending training requirements, or unresolved data clarification requests to review during the call.

5.3.2.3 Facilitating the Call

The Site Manager facilitates the call with available study staff. In many instances, the site's Study Coordinator may be the only personnel available to participate. Items reviewed may include:

- Additions/Modifications in Study Team Staffing
- Recruitment, Screening, Enrollment
- Protocol Adherence
- Subject Compliance
- Regulatory Document Review
- Data Management
- Review of Action Items from Previous Visits/Contact
- Site Successes and Challenges
- Informed Consent Process
- Adverse events (AEs)/serious adverse events (SAEs)

- Preparation for Upcoming Monitoring Visits
- Biomarker Substudy, if applicable
- iPad Consent Supplemental Use, if applicable

5.3.3 Review Call Summaries

A report summarizing the discussion is compiled and distributed to the site via email. The POINT-CRC Site Manager and/or Monitor is/are responsible for ensuring resolution of pending action items.

6.0 Site Monitoring Visits

6.1 Initiation Visits

In general, a *Readiness Call* (see Section 5.1) is conducted for each site in lieu of a site initiation visit. Initiation visits may be conducted at sites that are new to the NETT-CCC or POINT-CRC, or under other circumstances as determined based on the guidance of the POINT PI, Co-PIs and Project Director. Monitors asked to conduct initiation visits will be responsible for ensuring the site facilities are sufficient and the study team is appropriately qualified to participate in the study. This includes the components identified on the Readiness Call Questions and Checklist as they pertain to staff training, PI obligations, SAE reporting, and protocol and regulatory compliance.

Procedures for preparing for the visit and distribution of an associated report are consistent with those described under Section 6.2 – Interim Monitoring Visits.

6.2 Interim Monitoring Visits

Routine interim monitoring visits are conducted to ensure Hub Spokes and CRC sites are compliant with applicable regulations, subject safety is being adequately followed, data is captured in a timely and reliable manner, the Investigational Product is stored/reconciled according to protocol guidelines and there are no significant deviations from the study protocol, and to verify that source documentation is properly stored.

6.2.1 Frequency

At least one on-site Monitoring Visit will occur at each study site after the first 2 subjects enrolled at the site have completed the 90 day follow-up visit. Additional monitoring activities will be scheduled at the

discretion of the NETT or CRC based on enrollment, staffing changes, safety/outcome events, study performance, or for cause as described in Section 6.3, Investigator-Initiated Visits.

At minimum, a second monitoring visit or teleconference will be conducted at all sites. The second visit/contact may occur within the last year of study enrollment, prior to site closure, or be combined with site closeout activities. If no additional enrollments have occurred since the first visit, close out activities can be conducted remotely.

6.2.2 Scheduling and Coordination

NETT-CCC and POINT-CRC staff are responsible for coordinating and scheduling site monitoring visits together with each study site team based on each group's respective internal procedures. At minimum, the Study Coordinator should be available for the duration of the visit, and the site PI should be available for at least one hour during the visit to discuss study procedures and review monitoring observations. Depending on a site's organizational structure, a study pharmacist or other site staff may also need to be available.

Monitoring staff distribute a confirmation letter or email to the site team to confirm the date(s) and time(s) and other logistical information regarding the visit following NETT-CCC or POINT-CRC internal SOPs.

6.2.3 Preparing for a Visit or Call

Prior to a visit, the site monitoring team should review the following materials to ensure that significant pending issues are prioritized and addressed efficiently.

- Essential documents that are not on file or require updates
- Collect and review any documents that need to be distributed to the site
- Changes in site study staff and associated training requirements
- Recruitment initiatives and enrollment
- Data quality (e.g. CRF Data Entry report, data clarification report (DCR) report, Rule Violation report in WebDCU™)
- Concomitant Medications CRFs

- Other CRFs due for review, including CRF 22 if the site is participating in the Biomarker Ancillary Study
- Site Clinical Outcomes and Serious Adverse Events (e.g. AE FU Required report; and site's SAE/Clinical Outcome Reporting Form list in WebDCU™)
- Site performance metrics provided by the Data Coordination Unit (DCU) at the Medical University of South Carolina (e.g. overall SAE rates and funnel plot demonstrating possible outliers)
- Premature study drug discontinuation data provided by the DCU Action Items from previous monitoring reports/contacts

The monitor should also review the "Monitor Visit Planner" table within WebDCU™ that includes the following status updates:

- Regulatory documents and certifications scheduled to expire
- Screen failure log summary (if applicable)
- Site enrollment and retention summary
- Active study team members

The "Monitor Site Action Review" table in WebDCU™ will also provide a list of action items and/or corrective and preventive action (CAPA) responses that may require follow up from the site.

6.2.4 Expectations

Site Monitors should review regulatory and subject materials present when on-site at a study Hub/Spoke. The Monitor should also review the WebDCU™ regulatory database **prior** to the visit/call to address any issues with the site. As study enrollment progresses, this may not be feasible for all subjects at each site.

Table 2 below describes the *minimum* requirements for site monitoring activities. The Monitor will review subjects in addition to the minimum requirement (as deemed appropriate) within the time allotted for each scheduled visit/call.

In general, Monitors should use their discretion based upon the results of minimum review requirements, associated outcome and safety evaluation, and site interactions in determining whether additional review is required. When overall compliance, data completion and/or accuracy are deficient, or when a pattern of non-compliance is observed in relation to a specific study activity, further review should be instituted.

Table 2: Minimum Requirements for Site Monitoring

Item	First Visit Requirements (On-site)	On-site Interim/Closeout Visit Requirements	Remote Interim/Closeout Monitoring
Site Facilities	Full review	As needed (e.g., facility changes)	Discussion as needed/possible (e.g., facility changes)
Staffing and Training NOTE: Remote monitoring may limit access to those documents available in WebDCU.	Full review of CVs, license, certifications, IRB approval for trial participation, WebDCU™ Project Spoke Team Member table, and verification that study team member listed on delegation of authority (DoA) log.	Full review of certifications, license, CVs, IRB approval for addition/deletion, WebDCU™ Project Spoke Team Member table, verification that team member listed on log.	Full remote review of certifications, licenses, CVs, IRB approval for addition/deletion, WebDCU™ Project Spoke Team Member table, verification that study team member listed on log.
Informed consent process and approved document NOTE: Restrictions may apply to remote review, including access to electronic medical record (EMR) (especially for international sites).	100% review for all subjects enrolled	Goal is 100% review for all subjects enrolled since previous visit and/or those requiring re-consent.	Goal 100% remote review of consent documents and process documentation within EMR for all subjects enrolled since previous visit and/or those requiring re-consent (as permitted by facility policy/access)
Eligibility Forms: Eligibility, Randomization	100% review for all subjects enrolled	Goal is 100% review of these 2 forms for at least 10% of subjects enrolled since previous visit.	Goal is 100% remote review of these two forms for eligibility documentation within EMR for at least 10% of subjects enrolled since previous visit (as permitted by facility policy/access)

Item	First Visit Requirements (On-site)	On-site Interim/Closeout Visit Requirements	Remote Interim/Closeout Monitoring
Regulatory File NOTE: Remote monitoring may limit access to only those documents available in WebDCU.	100% in WebDCU™ prior to visit; updates addressed as needed.	100% in WebDCU™ prior to visit; updates addressed as needed.	100% in WebDCU™; updates addressed as needed.
CRFs	Minimum of 100% review for first 2 subjects enrolled	Goal is 100% review for at least 10% of subjects enrolled at site since previous visit. Sampling plan at discretion of NETT or CRC.	Goal is 100% review for at least 10% of subjects enrolled at site since previous visit, as possible via remote review. Sampling at discretion of NETT/CRC.
Source Documents (Deviations/Violations, unreported Clinical Outcomes/SAEs) NOTE: Remote monitoring may limit access to only those documents available in WebDCU.	100% review of source documents for first 2 subjects enrolled	Goal is 100% of at least 10% of subjects enrolled at site since previous visit. Sampling plan at discretion of NETT/CRC. **Note:** If unreported SAEs identified, scope of review to be expanded to include review for additional participants; number of additional reviews at discretion of NETT/CRC (100% for new/updated/previously incomplete SAE/COs)	Goal is remote review of 100% of at least 10% of subjects enrolled at site since previous visit. Sampling plan at discretion of NETT or CRC. **Note:** If unreported SAEs identified, scope of review to be expanded to include review for additional participants; number of additional reviews at discretion of NETT/CRC
Reported SAE / Clinical Outcomes submitted via CRFs: SAE/Clinical Outcomes Reporting Form	100% for all subjects	100% for all subjects	100% remote review for at least 10% of subjects enrolled at site since previous visit to extent possible
Drug Accountability	100% Review	100% Review	100% (or as possible) remote review (e.g., temp logs, de-identified accountability logs) NOTE – drug accountability also monitored on-site

6.2.4.1 Site Facilities

The Site Monitor will ensure that the monitoring visit include, but not be limited to, confirmation of the following:

- The facilities used by the study team continue to be acceptable for purposes of the trial
- Offices/examination rooms are adequate and remain unchanged
- Appropriate laboratory facilities are available
- Study drug storage appropriately labeled, secure, and within temperature requirements as indicated within the drug package insert and relevant SOPs
- Adequate storage space for study materials is available
- Maintenance of research records as required for the trial (e.g., locked cabinet)
- Source documents are readily available for review
- Adequate equipment is available for study, and equipment maintenance is verified (e.g., internet access to a computer for randomizing subjects in WebDCU™)

6.2.4.2 Staffing and Training

The Site Monitor will insure that the Monitoring Visit include, but not be limited to, confirmation of the following:

- Activities being carried out by qualified staff appropriately listed on DOA log
- Study staffing remains unchanged and/or study personnel/new personnel are adequate; documentation of staff qualifications is available (i.e., updated Delegation of Authority log, listed on the project spoke team member table in WebDCU™, and an IRB approval letter for adding new team members)
- Investigator and/or Sub-Investigator is/are actively participating in the study

6.2.4.3 Informed Consent (IC) Process

The Site Monitor will have the goal to conduct a 100% review of signed and dated informed consent (IC) forms, and report any deviations (e.g., verify correct version of IC signed and dated for all participants). Subject files will also be monitored to ensure the site is appropriately documenting the consent process. The informed consent process should be documented within the research records, using the outline provided in the NETT Toolbox and noting the following:

- Date and time consent obtained
- Consent signed by subject (no surrogate consent allowed in the study)
- Statement to confirm the subject received a copy of the signed consent
- Assessment of the subject's ability to understand the information provided
- Statement to confirm review of consent with subject (e.g., risks/benefits, voluntary participation, confidentiality, compensation, questions answered)
- Statement to confirm subject meets eligibility criteria

6.2.4.4 Verification of Eligibility

The Site Monitor will verify that Inclusion/Exclusion criteria are met for enrolled participants.

6.2.4.5 Protocol Review and Compliance

The Site Monitor will ensure that:

- The POINT Trial protocol and procedures are being followed
- Procedures for collecting, processing, storing and shipping specimens collected for the optional biomarker ancillary study are being followed
- Protocol changes have been reviewed and approved by/reported to the IRB
- Accurate, complete, and timely reports being made to UCSF POINT Trial CCC and to the IRB
- Visit dates are appropriate and accurately recorded
- Clinical and laboratory evaluations are complete and results filed
- Latest versions of SOPs, protocols, essential documents, consents are on file
- A review is conducted of any follow-up items from previous Monitoring Visit(s)
- An audit is conducted of CRFs and Source Documentation following schedule in **Table 2**
- A review is conducted of data collection/data entry operations following schedule in **Table 2**

6.2.4.6 Regulatory Review and Compliance

The Site Monitor will conduct a review of the Investigator regulatory file, and/or any other regulatory documents and/or obligations. The regulatory requirements for the POINT trial are defined in the Manual of Procedures (MoP).

In addition, the Site Monitor will ensure that the investigator and staff are fully aware of their obligations and responsibilities with regard to the conduct of the trial including compliance with the study protocol and specified procedures, timelines, recruitment goals, good clinical practice (GCP) guidelines, applicable governing agency regulations, informed consent requirements, and safety event reporting requirements.

6.2.4.7 CRF and Source Document Review

The Site Monitor will ensure that reported study data are complete, accurate, and verifiable from source documents. Priority for review will be placed on subject data and associated source documentation associated with study outcomes and safety.

6.2.4.8 Study Drug Storage and Accountability

The Site Monitor will ensure that the facilities used by the study team for drug storage and dispensing continue to be acceptable for the purposes of the POINT Trial. At minimum, monitors will evaluate the following:

- The study drug is stored in a secure, temperature-controlled environment, and has not expired
- Temperature logs are current and maintained daily
- Dispensing of the study drug is limited to study personnel who are appropriately trained
- Instructions present for storage, handling, and preparation for use, including how to identify, report and handle temperature excursions outside the acceptable range
- The study drug is properly labeled for investigational use
- The site maintains documentation of shipment dates, receipt, and content
- The site maintains documentation of study drug destruction
- The site maintains appropriate records for dispensing study drug
- Verify that drug dispensed to subjects is consistent with Randomization Verification Form

6.2.4.9 Clinical Outcomes/SAEs

The Site Monitor will conduct a review of SAEs and Clinical Outcomes to ensure that all are thoroughly documented and reported within WebDCU™ and reported to ethical and safety officials as appropriate per local guidelines.

6.2.4.10 Optional Ancillary Biomarker Study

The Site Monitor will conduct a review of the site facilities, equipment, specimen collection and shipment supplies, informed consents and source documentation to ensure that procedures are conducted in accordance with the study protocol, the ancillary biomarker specimen procedure manual and study specific guidelines, applicable regulations and GCP.

The Site Monitor will verify that:

- Study staff participating in the collection, storage and shipping of biological specimens have been properly trained and documentation of the training is filed on-site.
- Site facilities and equipment are sufficient for the conduct of study procedures and capable of adhering to secure storage requirements.
- Study supplies (including specimen collection and shipment materials) and reorder forms are sufficient for the conduct of the study procedures.
- Subjects have been properly informed of the risks and benefits of the Biomarkers Study, and have indicated consent to the optional biomarker study by entering their initials in the appropriate boxes on the consent form.
- Source documentation is present to verify that biological specimens have been collected and securely stored in accordance with the study protocol, the ancillary biomarker specimen procedure manual and study-specific guidelines.
- The site has written procedures and appropriate documentation for collecting samples for the ancillary study, which includes procedures for labeling, storing and shipping, ensuring the chain of custody of samples (refer to the Ancillary Biomarker Study Laboratory Manual).
- Documentation of quality assurance of critical laboratory processes (e.g., documentation of instrument calibration, monitoring of temperature of refrigerators/freezers).
- Subject confidentiality is maintained for records and stored samples.

6.2.4.11 Action Items

The Site Monitor will conduct a review of any follow-up items from previous Monitoring Visit(s) including the Monitor Site Action Review table within WebDCU™ as applicable.

6.2.4.12 Site Team Meeting

The Site Monitor will conduct a debriefing with the site Principal Investigator, Study Coordinator, and other study staff as appropriate to review findings of the Monitoring Visit. In the event that the Principal Investigator and/or Study Coordinator are not available for a meeting, the Site Monitor will schedule a follow-up teleconference to ensure that observations are summarized with the study team.

6.2.4.13 Follow-up Activities

Site Monitors and site management from the NETT-CCC and POINT-CRC coordinate follow-up activities with the site to ensure timely completion of action items resulting from monitoring visits as indicated in the final site monitoring report.

6.3 Investigator-Initiated Visits

6.3.1 Purpose

Investigator-Initiated Visits (IIV), also known as “For Cause Visits” are conducted when suspected or actual significant performance deficiencies in study conduct and/or site staffing are identified, and when results of internal monitoring activities or site monitoring visits indicate a need for further in-person evaluation.

If a site requires an Investigator-Initiated Visit, the Monitor should submit a request to the UCSF POINT Trial CCC team and NETT-CCC/POINT-CRC Administrator for approval.

The criteria below may be considered as a general guidance for scheduling this type of visit:

- At the request of the UCSF POINT Trial Executive Committee
- Outcome from a previous monitoring visit
- Accrual rate (high and low recruiting sites)
- Number of data corrections required
- History of protocol deviations or non-compliance with GCPs
- Staffing issues
- DSMB or IRB request

6.3.2 Scheduling and Coordination

See Section 6.2.2 above.

7.0 Major and Minor Violations

The Site Monitor will review and evaluate all major and minor violations as defined in the POINT MoP and Section 8.6 of the protocol.

A *major* violation affects the subjects' rights, safety, or welfare, and/or on the integrity of the resultant data. Specifically, the following will be considered *major* violations:

- Participant entered the study but did not meet entry criteria
- Failure to obtain documented informed consent prior to performing protocol specific procedures
- The subject received the wrong treatment or incorrect dose
- The subject was given or otherwise took an excluded or prohibited medication
- Failure to report serious adverse events
- Unblinding outside of the protocol procedures
- Changing the protocol without sponsor and/or IRB approval
- Inadvertent loss of samples or data
- Falsifying research or medical records
- Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing)
- Working under an expired professional license or certification
- Failure to follow federal and/or local regulations and intramural research policies
- Repeated minor deviations
- A breach of confidentiality

A *minor* protocol violation is any deviation from the study design or procedures of POINT protocol that has not been approved by the IRB and which *does not* have a major impact on the subject's rights, safety, or well-being, or the completeness, accuracy, and reliability of the study data. The following are

examples of *minor* violations:

- Visits conducted outside of the protocol window period
- Randomization occurs outside the 12 hour enrollment criterion

All major and minor violations should be documented and reviewed with the site PI and Coordinator. Immediate correction of individual violations should be undertaken and documented. The Site Monitor should ensure that all violations, and where applicable, major and/or minor are reported to site's IRB.

8.0 Corrective Action and Preventive Action (CAPA) Plans

Observed patterns of deviations/violations should be addressed in a written CAPA plan designed to reduce the frequency of such deviations in the future. The plan should include clear documentation of the observation and associated compromise in regulatory obligations, protocol compliance, subject protection, or safety. Reasonable timelines for actions and staff responsibilities, and a method to track completed actions, should also be included in the plan.

9.0 Monitoring Reports

9.1 Preparation and Distribution

A site monitoring report summarizing visit observations will be compiled using the POINT site monitoring report template or electronic template in WebDCU™ according to the respective procedures of the NETT-CCC and POINT-CRC. The POINT CCC Project Director will also be copied on all monitoring reports or monitoring report email notifications. **Table 3** below defines the report timelines for each type of visit.

Table 3: Report Distribution Timelines

Visit/Contact Type	Report Distribution Timeline
Initiation (when applicable)	Within 14 days of visit
Interim (On-site and remote)	Within 28 business days of visit
Closeout	Within 14 business days of visit

Investigator-Initiated Visit (IIV)	Within 14 business days of visit

9.2 Follow-Up Activities

Site Monitors and site management from the NETT-CCC and POINT-CRC coordinate follow-up activities with the site to ensure timely completion of action items resulting from monitoring visits.

10.0 Suspected Significant Study Misconduct

Site Monitors may encounter site activities or documentation suggestive of serious study-related misconduct during a monitoring visit. These may include but are not limited to:

- Apparent falsification of data
- Apparent omission of data
- Repeated under-reporting of significant safety concerns
- Repeated violations of approved informed consent procedures
- Serious breaches of subject confidentiality (e.g., missing laptop containing unencrypted data)

In such instances, the Monitor should take the following action in a professional and confidential manner:

- Immediately document the observed conditions and facts
- Preserve, when possible, any relevant records at risk of destruction or alteration
- Immediately notify a NETT-CCC or POINT-CRC supervisor; supervisory staff will consult with UCSF POINT Trial CCC Project Director and Principal Investigators
- Schedule meeting with the site investigator and primary study coordinator to discuss occurrence and follow up action

11.0 Close-Out

Close out activities are conducted at the completion of the trial and/or site's participation and may be completed during an on-site visit or remotely. Close out monitoring activities are conducted to:

- Ensure all CRFs and reports are completed and submitted in WebDCU™

- Ensure completeness, accuracy, legibility, and validity of the trial data
- Ensure GCP and protocol compliance
- Ensure proper procedures are in place for human subjects protection
- Verify final study drug accountability and disposition follow institutional and protocol guidelines
- Ensure documentation is submitted to the IRB for study close-out notification
- Verify the site's record retention plan
- Review the publication policy with the Investigator and Co-Investigators

12.0 Source Review Process

The Site Monitors will ensure that the reported study data are complete, accurate, and verifiable from source documents. Specific data points are validated by available source documentation, defined as but not limited to the following: laboratory results, progress notes, EMS and flight run sheets, physician notes, nursing notes, discharge summaries, medical history sheets, and some electronic case report forms (must be well defined and verifiable for the data collected). The instructions for completing CRFs can be found in the POINT Data Collection Guidelines.

POINT TRIAL MONITORING PLAN
APPROVAL SIGNATURE PAGE

Approved By: S. Claiborne Johnston, MD, PhD: POINT Principal Investigator (PI)

Signature: _____

Date: 15 September 2017

Approved By: J. Donald Easton, MD: POINT co- Principal Investigator (coPI)

Signature: _____

Date: 15 September 2017

Approved By: Anthony S. Kim MD, MAS: POINT co-Principal Investigator (co-PI)

Signature: _____

Date: 15 September 2017