Standard Operating Procedures for POINT Trial European Union Clinical Sites: Study Drug Handling

SOP-DH-EU.01 v1.0

This version supersedes all previous versions.

Approved By: _____ Approval Date: 12/4/13
POINT CRC Representative

Mary Farrant

1 December 2013

Approved By: _____ Approval Date: _____
UCSF CCC Representative

TABLE OF CONTENTS

1. INTRODUCTION

The Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial is a randomized, double-blind, international, multicenter trial designed to compare a clopidogrel/aspirin combination versus an aspirin alone regimen. Since many Clinical Sites around the world are participating in the trial, a standard is needed to ensure that study products are handled consistently. This document outlines the general standards for the trial which all Clinical Sites should follow.

2. PURPOSE

This Standard Operating Procedure (SOP) describes the process for investigator, study personnel, and research/investigational pharmacists involved in handling active drug and placebo for the European Union Clinical Sites participating in the Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial.

This SOP covers receipt, restocking, storage, dispensing, and accounting for the study drugs dispensed in the study. This SOP does not cover the preparation of the study drugs by the manufacturer, sponsor, or Clinical Site research pharmacy; drugs are supplied in seal, prepackaged bottles, and no additional preparation is required.

3. SCOPE

This SOP is intended as a template and reference to provide the requirements of the POINT Trial related to the appropriate handling of study products (active drug and placebo) in compliance with applicable federal, state, and European Union regulations and institutional policies and procedures. This document only provides general standards and requirements pertaining to study product handling. Additional instructions may be found in the study protocol, the Manual of Procedures (MOP) and any study-specific standard operating procedures (SOPs) maintained by the individual participating European Union Clinical Sites.

4. RESPONSIBLE PERSONNEL AND CONTACT INFORMATION

Clinical Site

- Principal Investigator (PI)
- Co-Investigator(s)
- Primary Study Coordinator
- Secondary Study Coordinator(s)
- Primary Study Drug Recipient
- Secondary Study Drug Recipient(s)
- Research/Investigational Pharmacy Contact

NOTE: Responsible personnel may vary by site depending on staffing and study requirements.

University of California San Francisco (UCSF) Clinical Coordinating Center (CCC)

- POINT Operations Director: Mary Farrant, MBA BSN RN
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POINT Central Pharmacy: University of California San Francisco (UCSF) Drug Product Services Laboratory (DPSL)

- Director, Pharmacy Services & Laboratory: Marcus Ferrone, Pharm.D.
  FerroneM@pharmacy.ucsf.edu Ph: 415-502-8151
- DPSL Pharmacist: Marcos Contreras, Pharm.D
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- Program Manager: Catherine Dillon, CCRP
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  perlmutt@musc.edu Ph: 843-876-1261

POINT Clinical Research Collaboration (CRC) Coordinating Center

- Central Mailbox and Call Line for all POINT inquiries:

  crc@emmes.com Ph: 800-305-7811

POINT Trial Toll-Free Number for Emergency Unblinding

- 1-866-94POINT (1-866-947-6468)

  NOTE: International callers please dial your country exit code + 1-415-663-4444 or use the toll free number provided to you to connect to the hotline.

5. DEFINITIONS/ABBREVIATIONS AND RESOURCES

- **Central Dispensing.** Study drugs provided to the research pharmacist at the Clinical Site.
- **Clinical Site.** Discrete locations including hospitals and outpatient clinics where qualified professionals conduct the POINT Trial in accordance with Good Clinical Practices (GCP).
- **Dispensing.** Study drugs provided to the study participant by the research pharmacist or other appropriate designee. In some cases, this will be a secondary process in which the drug is dispensed to the study nurse or coordinator for delivery to the participant.
- **OUS.** Outside the United States
- **Research Pharmacist.** An appropriate, qualified individual (i.e., licensed and/or registered and trained, if appropriate) designated by the Clinical Site PI to perform the day-to-day pharmacy activities and study drug management including storage, dispensing, and final disposition.
- **Research Pharmacy.** Any facility, building, room, or secure area used to perform one or more of the following functions: storage, dispensing, and management of study drugs for POINT. The research pharmacy uses local written SOPs to cover study drug-related procedures in clinical trials.
- **Storage.** Location where study drugs are kept following receipt of the drugs from the Central Pharmacy or Sharp Clinical Services Phoenixville or United Kingdom.
- **Study Drugs.** The substances being evaluated in the study, i.e., clopidogrel, the active drug; and placebo, an inert substance manufactured to match clopidogrel.
- **Unblinding.** Providing access to study participant's treatment assignment.
- **WebDCU™.** The web-based clinical trial data management system developed by the Data Coordination Unit (DCU) at MUSC that contains features that allow for drug accountability and randomization in POINT.

POINT Trial Protocol, available at
https://sitemaker.umich.edu/nett/point_resources_and_training#Protocol

POINT Manual of Procedures, available at https://sitemaker.umich.edu/nett/point_mop

POINT Randomization and Enrollment FAQs, available at https://sitemaker.umich.edu/nett/point_faqs#RandomizationEnrollment

WebDCU™ Manual, available under Project Management +, Project Documents within WebDCU™

ICH GCP Section 5.13: Manufacturing, Packaging, Labeling, and Coding of Investigational Products

ICH GCP Section 5.14: Supplying and Handling Investigational Products

Food and Drug Regulations, Division 5: Drugs for Clinical Trials Involving Human Subjects section C.05.012, 3(e).

California Pharmacy Law Business and Professions Code Section 4070-4078

6. PROCESS DETAIL DESCRIPTION

6.1 Shipment from UCSF DPSL to Sharp Clinical Services, Phoenixville, PA

UCSF CCC will send an email requesting shipment of a predetermined inventory quantity of active and placebo unlabeled bottles of study drug from UCSF DPSL to Sharp Clinical Services Phoenixville to:

- UCSF DPSL
- Sharp Clinical Services, Phoenixville, PA
- WebDCU™

The DPSL will ship unlabeled active and placebo to the Phoenixville, PA, address maintained in WebDCU™. An automatic email will be sent from the courier to Sharp Clinical Services Phoenixville with tracking information for the shipment.

6.2 Shipment from Sharp Clinical Services, Phoenixville, PA to Sharp Clinical Services, United Kingdom Servicing European Union Clinical Sites

Once authorized by the POINT CRC Director, Sharp Clinical Services, Phoenixville will ship initial study drug supplies to Sharp Clinical Services in the United Kingdom:

Sharp Clinical Services
Elvicta Business Park, Crickhowell, Powys
Wales NP8 1DF, United Kingdom
T +44 (0)1873 813591 **F** +44 (0)1873 813599

Sharp Phoenixville, PA will provide the WebDCU Data Manager with a spreadsheet of drug ID's shipped to Sharp Clinical Services United Kingdom and staff supporting WebDCU will accept the shipment in WebDCU once confirmation of receipt of all bottles is received from Sharp Clinical Services United Kingdom.

6.3 Shipment from Sharp Clinical Services, United Kingdom to European Union Clinical Sites

6.3.1 Initial Shipment

Once a European Union Clinical Site has completed all requirements for the POINT Trial and is ready to enroll subjects, the POINT CRC will convert the site's status to "Actively Enrolling" in WebDCU™ and will send an email notification to:

- UCSF CCC
- Sharp Clinical Services, Phoenixville, PA
- Sharp Clinical Services, United Kingdom
- WebDCU™ DCU

The email distributed by the CRC must include the following:

- Name of the site
- Name of the site principal investigator
- Name of the primary drug recipient
- Primary drug recipient phone number
- Pack List Invoice number

Once the DCU receives confirmation from the POINT CRC that a site is released to enroll, the DCU Data Manager will manually select the study drug IDs to be sent to the site. This selection will generate the pick/packing slip in WebDCU™. The DCU Data Manager will email the POINT CRC, Sharp Clinical Services Phoenixville, and Sharp Clinical Services, United Kingdom when this step is completed.

Once Sharp Clinical Services, United Kingdom receives the email from the DCU Data Manager, Sharp Clinical Services, United Kingdom will login to WebDCU™, retrieve the pick/packing slip and will use the pick/packing slip to prepare the selected bottles for an initial shipment of **6 bottles** of study drug to the European Union Clinical Site. From receipt of the request to delivery of the bottles will take three to four days. Delivery is via courier using next business day afternoon delivery. Sharp Clinical Services, United Kingdom will only send shipments Monday through Thursday; there is no weekend delivery.

The Sharp Clinical Services, United Kingdom will ship drug to the address of the European Union Clinical Site listed on the pack list invoice. The Sharp Clinical Services, United Kingdom will login to WebDCU™ and confirm the study bottles were shipped to the Clinical Site and key in the tracking # in the Comments section. There must be at least one and preferably several people at Sharp Clinical Services, United Kingdom with WebDCU™ accounts so that the study drug bottles can be acknowledged as shipped in the database. Contact the Data Coordination Unit (contact information above) to request the account. The person's name and email address must be provided to establish the WebDCU™ account.

The Clinical Site will login to WebDCU™ and confirm receipt of study drug on its arrival by entering the date of receipt of each individual study drug bottle. If the Clinical Site has not acknowledged receipt of study drug in WebDCU™ within 5 days of shipment, the DCU Data Manager will follow-up with the Clinical Site.

6.3.2 Subsequent Shipments

The initial shipment of 6* bottles is intended to last one year, including expiration, and excepting subsequent restocking shipments.

After the initial shipment of study drug, WebDCU's™ drug distribution system automatically informs Sharp Clinical Services Phoenixville when additional bottles are needed according to the procedures outlined below.

Once the initial study drug supply reaches 2* bottles, Sharp Clinical Services Phoenixville, Sharp Clinical Services, United Kingdom, and UCSF CCC are alerted via WebDCU™ automated email notification to ship 8* more study drug bottles to supply the clinical site for the remainder of the year, or 3 months before expiration.

Sharp Clinical Services, United Kingdom personnel follow the same procedure as described for initial shipment for European Union Clinical sites to retrieve a pick/packing slip and log drug shipment.

Clinical Site personnel follow the same procedure as described for receipt of initial shipment in WebDCU™ when the restocking shipment is received.

*Current parameters for initial and restocking of study drug; subject to change.

6.4 Inventory Management

Active and placebo bottle inventory tracking and replenishment forecasting for Sharp Clinical Services Phoenixville and the Sharp Clinical Services, United Kingdom are maintained by UCSF CCC.

6.5 Storage

Adequate space, equipment, and supplies for storage, preparation, packaging, and dispensing of study drugs must be assessed prior to study drug delivery. Proper storage conditions for study drugs, including segregation and controlled environmental conditions, will be verified by the appropriate POINT study monitor. Proper storage conditions for drugs stored outside the pharmacy should address issues such as temperature, light, moisture, and ventilation, as applicable per the protocol.

Upon receipt from the Sharp Clinical Services, United Kingdom, all study drugs supplied for POINT should be stored in the research pharmacy at the Clinical Site. Study drugs not stored in the pharmacy (e.g., stored in a clinic or research space) are subject to additional guidelines provided locally for storage in such cases, including requiring a separate locked area, access limited to essential and authorized research personnel, systems in place for identifying and alerting staff when proper security conditions have been compromised, and segregation of study drugs from nonstudy drugs.

Study drugs for POINT should be stored at a controlled room temperature of 25° C (77° F) with excursions permitted to 15°-30° C (59°-86° F). Temperature excursions outside this range render study drug damaged. Temperature of storage area (including drug not stored in the pharmacy) should be recorded daily and/or an alarm system maintained so study personnel will be notified if temperature exceeds or falls below the parameters specified.

In the event of study drug damage, the site should complete documentation in WebDCU™ and notify the POINT CRC, Sharp Clinical Services Phoenixville, and the UCSF DPSL and CCC. See detailed guidance in the WebDCU™ Manual. Clinical Site inventory will be updated automatically when appropriate WebDCU™ documentation is completed to automatically trigger a new shipment of study drug for replacement of damaged drugs.

6.6 Expired Study Drug

Expiration of study drug must be documented in WebDCU™. See the WebDCU™ Manual for instructions on expiring drug. An expiration date will be listed on the study drug bottle label.

6.7 Dispensing

Dispensing of POINT study drugs should be coordinated through the Clinical Site research pharmacy. Supplies of study drug should be shipped directly to the research pharmacist or designee at the Clinical Site. Final verification of all study drugs will be completed by the research pharmacist or designee to ensure that correct inventorying is accomplished. This will be done prior to dispensing and/or delivery to the study site and/or subject.

POINT study drugs (active and placebo) are prepackaged in sealed, labeled bottles of 97 tablets and do not require any type of manipulation such as mixing, formulating, or compounding. See Appendix A for an example bottle label.

Study drugs (active and placebo) are pink, round, slightly biconvex, not engraved, and film-coated.

All study drugs should be dispensed in accordance with the study protocol and randomization scheme, and it is the Clinical Site PI's responsibility to ensure that an accurate record of study drug issued and returned is maintained.

Research personnel designated by the Clinical Site PI to distribute the study drugs must ensure that the participant understands when and how to take the medications.

Compliance by the subject with the medication regimen/procedures described in the protocol should be verified. Discrepancies between amounts of the drug used by subjects and amounts returned, and the reasons underlying any discrepancies, should be documented.

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.

6.7.1 Subject Enrollment and Randomization

A patient will be considered enrolled in the study once randomization to study drug has occurred. Randomization will take place centrally via the WebDCU™. The computer will generate the randomization assignment and will display the bottle number to be used for that subject on the screen. A screen shot of this form can be printed using the print function in the browser toolbar if a hard copy of the bottle number is needed.

To minimize crossover during randomization, **Form 10: Randomization** includes a link to the **Randomization Verification Form**, which should be printed and taken to the research/investigational pharmacy (or other study drug storage location) and completed by Clinical Site personnel when study drug is dispensed. Clinical Site personnel are required to compare the **4-digit Study Drug ID pre-printed on the form** as assigned automatically by WebDCU™ to the **4-digit Study Drug ID on the bottle** of study drug that is dispensed. Verification that the two Study Drug numbers match **must** take place before the loading dose is given to the subject. The completed, signed Randomization Verification Form should be filed with the other source documents for the subject.

6.7.2 Loading Dose – Day 1

The Clinical Site PI or designee should explain correct use and storage of study drugs to each participant.

6.7.2.1 Study Drug (Active and Placebo)

The study medication bottle (both active drug and placebo) contains 97 tablets: **8 tablets** for the initial loading dose (LD) and **89 tablets for the subsequent 89 days at 1 tablet/day**. The subject should take the loading dose of 8 pills of the study drug while the Clinical Site PI or designee is present. The investigator must facilitate dispensing the medication and ensure it is taken within the 12-hour treatment window, recording the date and time of the dose.

The time between randomization and treatment should be minimized: drug treatment should be considered STAT, administered in the **two hours following randomization.** If the loading dose is administered outside this two-hour window, this will be noted as a **protocol violation**. (See **Form 21** for additional information.)

If a patient has already taken clopidogrel within the 12 hours prior to presentation, the following guidelines are suggested:

- The subject should be given the **full loading dose (8 pills) of study drug i**n the ED regardless of whether or not he/she took a home dose of clopidogrel.
- If the subject was first seen at an outside ED, given a loading dose of clopidogrel while there, and then transferred to another facility, s/he can still be evaluated for eligibility and given the **full loading dose (8 pills) of study drug** when enrolled.

See POINT Trial FAQs for additional guidelines regarding crushing study medication: https://sitemaker.umich.edu/nett/point_faqs

6.7.2.2 Aspirin

The subject should be given the first dose of aspirin while the Clinical Site PI or designee is present. The investigator must facilitate dispensing the aspirin and ensure it is taken within the 12-hour treatment window, recording the date, dosage and time of the dose.

The time between randomization and aspirin dose should be minimized: aspirin dose should be considered STAT, administered in the **two hours following randomization**. While the dose of aspirin during enrollment is 50-325mg daily, at the discretion of the treating physician, the ***strongly recommended dose*** is **150-200 mg daily x 5 days followed by 75-100 mg for 85 days.** Sites are encouraged to follow the recommendation to use the lower dosage of aspirin daily based on the results of the SPS3 and other trials. See detailed justification in FAQ #2 at http://sitemaker.umich.edu/nett/point_faqs

If a patient has already taken some aspirin within the 12 hours prior to presentation, supplementing the prior dose to meet the above guidelines is suggested:

- If a patient has taken a dose of 75-100mg within 12 hours of presentation, they can be given another 75-100mg.
- If a patient has already taken ≥ 200mg within 12 hours, s/he does not need to get another dose until the following day.
- If it has been more than 12 hours since a patient's prior dose of aspirin, then the patient should be given a full dose (suggested dose is 150-200mg).

6.7.3 Subsequent Doses – Day 2 through Day 90

Each participant should take one pill of study drug as well as one prescribed dose of 50-325mg aspirin daily. A dose of 150-200mg for each of days 2, 3, 4 and 5 and a dose of 75 -100mg each day for the following 85 days is recommended. A *POINT Study Calendar* will be made available to each participant to facilitate tracking of daily doses of study drugs, and scheduled telephone and in-person follow-up appointments. The importance of compliance with the study medications should be explained to each subject, and they should be asked to contact the Clinical Site if they stop the medications for any reason.

Each Clinical Site should establish caring connections with subjects at and immediately after enrollment, either in person or by telephone, to inquire about how they are doing, whether they have any concern or questions, and re-emphasize the importance of taking their study medication for the 90 day study period when they are at highest risk for a stroke. Waiting for the one-week follow-up for this contact is too late.

Each Clinical Site should call the subject's primary physician, explain that their patient experienced a TIA/minor stroke and has enrolled in the POINT the trial, and be certain that the physician receives an information letter about the trial by email or fax, and has a contact and opportunity to ask questions.

Subjects should be given a copy of the *POINT Trial Alert Wallet Card* and *Medication Information Sheet* when they receive their study drug.

6.8 Unblinding

The randomization procedures as specified in the POINT protocol, Manual of Procedures and WebDCU™ Manual should be followed at all times. If Clinical Site personnel feel unblinding is necessary, the Clinical Site PI or designee must first call the POINT toll free number, 1-866-94POINT (1-866-947-6468) and speak to the UCSF CCC On-call Physician. International callers dial your country exit code + 1-415-663-4444.

If the UCSF CCC on-call physician agrees that unblinding is necessary, that individual can initiate the request in WebDCU™. Once the request for unblinding has been completed in WebDCU™ by the UCSF CCC on-call physician, the physician should instruct the Clinical Site PI or designee to open the Randomization CRF for the subject. The subject's treatment assignment will be listed at the bottom of the Randomization CRF screen and available for viewing for 30 minutes only.

6.9 Destruction

Study drugs should be destroyed at the Clinical Site following local medical waste standards, site guidelines, and any local SOPs in place for disposition of unusable study drug.

For verification purposes, all study drug and study drug bottles returned by subjects should be retained at the Clinical Site until after the first monitoring visit has been completed. Thereafter, study drug should be destroyed per local pharmacy guidelines. Destruction of the study drugs must be documented; Sharp Clinical Services Phoenixville, the POINT CRC, and/or the UCSF DPSL may request a copy of this documentation.

At the conclusion of the study, the study drug should be inventoried and then destroyed in accordance with the requirements of the local Clinical Site after the closeout visit.

All documentation regarding receipt, storage, dispensing, and destruction must be complete and accurate. A copy of all accountability documents will be maintained in the Regulatory files.

Appendix A

Sample European Union study drug bottle label.

Revision History and Tracking

Date	Version	Description	Author	Reason for Change	Planned Review
09/25/2013	1.0	Initial Document	Lindblad	N/A	October 2014