**STANDARD OPERATING PROCEDURE**

**Subject: POINT Trial Clinical Site: Study Drug Handling**

**PURPOSE**

This Standard Operating Procedure (SOP) describes the processes for Investigators, study personnel and research/investigational pharmacists involved in handling active drug and placebo for the 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 sealed, prepackaged bottles and no additional preparation is required.

**SCOPE**

The scope of this SOP is 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 and state 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 Clinical Site.

**BACKGROUND**

The Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial is a randomized, double-blind, multicenter clinical trial designed to compare a clopidogrel/aspirin combination versus an aspirin alone regimen.

**RESPONSIBLE PERSONNEL**

* **Clinical Site**
* Principal Investigator (PI); Co-Investigator(s)
* Primary Study Coordinator(s); Secondary Study Coordinator(s)
* Primary Study Drug Recipient
* Pharmacy Contact

**Note** – Responsible personnel may vary by site depending on staffing and study requirements.

* **POINT Central Pharmacy – Sharp Clinical Services, Inc.**

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* **WebDCU™**
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* **UCSF Clinical Coordinating Center (CCC)**
* POINT CCC Director: Mary Farrant, MBA BSN RN

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* **POINT Trial Toll-free Number (Emergency Unblinding)**
* **1-866-94POINT** (1-866-947-6468)

**DEFINITIONS**

* **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 Practice (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.
* **Research Pharmacist –** An appropriate, qualified individual (i.e., licensed and/or registered and trained, if appropriate), designated by the POINT 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.
* **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.

**PROCEDURES**

**Notification to SHARP CLINICAL SERVICES**

* Once a site has completed all requirements for the POINT Trial and is ready to enroll subjects, the following steps occur:
  + The site will be switched to *Ready to Receive Investigational Product\** in WebDCU™ by NETT/CRC personnel, if this status was not selected previously.
  + After the site status has been changed, the drug request(s) will post in WebDCU™ and an email notification will be sent to Sharp and NETT/CRC.
  + Once study drug arrives at the site and has been entered into WebDCU™, the site status can be changed to *Actively Enrolling*.
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* Once Sharp receives the email confirmation from either the NETT-CCC or the POINT-CRC that the Clinical Site is ready to receive investigational product and the automated email from WebDCU™ that a shipment request has been created, an initial shipment of **4 bottles** of study drug, *2 active drug* and *2 placebo (US)/ 6 bottles of study drug, 3 active drug and 3 placebo (OUS)*, will be sent to the site overnight. Study drug will only be shipped Monday through Thursday; there is **no** Saturday delivery.
* Sharp will ship drug to the address maintained in WebDCU™; an automatic email will be sent from the courier to UCSF and the appropriate partner with tracking information for the shipment.

**Receipt of Study Drug**

* All study drug supplied for POINT must be accounted for in the electronic accountability log on WebDCU™.
  + Accountability of study drug must be documented from the time of initial study drug receipt, through dispensation, and final disposition.
* Sharp receives notification that site is ready to enroll subjects; prepares initial shipment of 4 bottles (US)/6 (OUS) of study drug; enters shipment details into WebDCU™; generates packing slip; packs bottles; and ships using an overnight courier service to Clinical Site.
* UCSF and the appropriate partner receive automatic email notification from courier with tracking information for shipmentonce study drug shipment scheduled by Sharp.
* When initial shipment of 4 bottles (US)/6 bottles (OUS) is received, designated Clinical Site personnel check the shipment to ensure what has been received corresponds with what was sent from Sharp including quantity shipped, randomization numbers and address.
  + Site personnel enter date of receipt of each individual study drug bottle on WebDCU™.
* Study drug must be entered as received in WebDCU™ before it will be available for randomization.
* If any discrepancies are discovered at the Clinical Site upon receipt of the study drugs, Sharp should be promptly notified.
* If any evidence of study drug breakage, compromised storage conditions or product tampering, WebDCU™, Sharp, the UCSF CCC, and the appropriate partner should be notified promptly and this notification must be dated and documented.
* The affected study drug must be quarantined from other study drug until further instructions from the UCSF CCC, or NETT/CRC personnel are received by the site team.
* Any supply requiring destruction will be destroyed following local guidelines. For sites outside the US, this may require maintaining the quarantined supply until the drug can be returned to a regional depot for destruction.
* Drug requiring destruction should be updated to a status of “damaged” in WebDCU™ by a member of the site team.

**Restocking of Study Drug**

* After initial distribution of study drug, WebDCU™’s drug distribution system informs Sharp when additional bottles are needed; requests for re-supply of study drugs will be automated.
* When available study drug is reduced to a minimum inventory of two (2) bottles at the site, a recruitment-based resupply algorithm will be used to calculate number needed for the next 12 months, based on previous rate of recruitment.
* Sharp is instructed via WebDCU™notification to ship more study drug bottles based on output from resupply algorithm.
* Site personnel follow same procedure as described for receipt of initial shipment to enter date of receipt of each individual study drug bottle on WebDCU™ when restocking order is received.

**Storage of Study Drug**

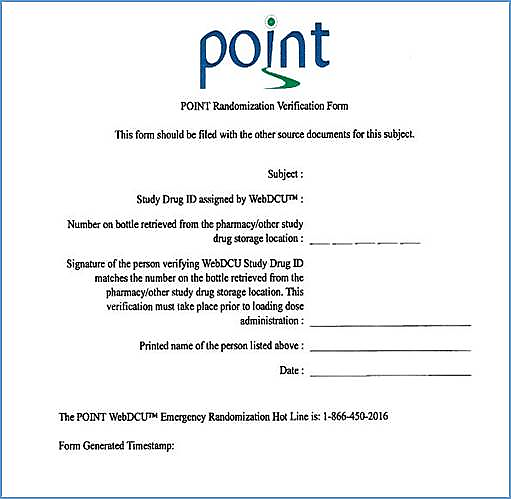
* Adequate space, equipment, and supplies for storage, preparation, packaging, and dispensing of study drugs must be assessed prior to study drug delivery.
* Proper storage conditions for study drugs, including segregation and controlled environmental conditions, will be verified by the appropriate POINT 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 Sharp, all study drugs supplied for POINT should be stored in 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 25⁰ C (77⁰ F) with excursions permitted to 15⁰- 30⁰ C (59⁰-86⁰ F).
  + Temperature excursions outside this range may render study drug damaged. In the event of study drug damage, the site needs to complete documentation in WebDCU™, notify the NETT or CRC (as applicable), who will inform the UCSF POINT CCC and Sharp Clinical Services.
  + See detailed guidance in the WebDCU™ Manual.
  + Pharmacy inventory will be updated automatically when appropriate WebDCU™ documentation is completed, to automatically trigger new shipment of study drug for replacement of damaged drugs.
* 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.

**Expired Study drug**

Expired study drug must be documented in WebDCU™; see User Manual for instructions on handling expiring drug.

**Dispensing**

* Dispensing of POINT study drugs should be coordinated through the research pharmacy or other personnel with primary responsibilities for drug storage and/or dispensing. A primary designee for dispensing drug must be identified among sites that will not utilize a research pharmacy.
* Supplies of study drug should be shipped directly to research pharmacist or other designated personnel at the Clinical Site.
  + Final verification of all study drugs will be completed by research pharmacist to ensure that correct inventorying is accomplished. This will be done prior to dispensing and/or delivery to the study site and/or subject.
* The study drugs (active and placebo) supplied for POINT are prepackaged in sealed, labeled bottles of 97 tablets, and do not require any type of manipulation, such as mixing, formulating, or compounding.
  + - The study drugs (active and placebo) are pink, round, slightly biconvex, and film-coated.
* **NOTE - PPIs are discouraged in patients enrolled in POINT.** 
  + - If a patient is considered by a clinician to need a medication for gastroesophageal reflux disease (GERD), the preferred medications would be H2 blockers, such as famotidine 20mg twice daily, or ranitidine 150mg twice daily.
    - If a patient is considered to require treatment with a PPI during enrollment, and is not considered to be a candidate for another medication such as an H2 blocker, the first choice of PPI agent would be pantoprazole 40mg daily.
* A patient will be considered enrolled in the study once randomization to study drug has occurred.
* Randomization will take place centrally via WebDCU™.
* The computer will generate the randomization assignment and will display the bottle number to be used for that subject on the screen.
* The POINT PI or designee notifies the research/dispensing pharmacist that a patient has been randomized for the study.
* The POINT PI or designee obtains the study drug with the bottle number for that participant from the research pharmacy.
  + To minimize crossover during randomization, **Form 10: Randomization** includes a link to the ***Randomization Verification Form (RVF)***, which must be printed and taken to the investigational pharmacy (or other study drug storage location) and completed by site personnel when study drug is dispensed.
    - Site personnel are required to compare the **Study Drug ID** assigned automatically by WebDCU™ and pre-printed on the form, to the  **Study Drug ID** on the bottle of study drug that is dispensed by the pharmacy.
    - 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.



* All study drugs should be dispensed in accordance with the study protocol and randomization scheme, and it is the Investigator's responsibility to ensure that an accurate record of study drug issued and returned is maintained.
* Research personnel designated by the PI to distribute the study drugs must ensure that the participant understands when and how to take the medications and is advised to contact the study physician before taking other medications or stopping study drug.
* Research personnel designated by the PI to distribute the study drugs must ensure that the hospital personnel are aware of prohibited and discouraged medications in the study for the participant if admitted to the hospital.
* Participant understands when and how to take the medications and is advised to contact the study physician before taking other medications or stopping study drug.
* 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.

**Loading Dose – Day 1**

* The POINT Investigator or designee should explain correct use and storage of study drugs to each participant.
* The study medication bottle (both active drug and placebo) contains 97 tablets: **8 tablets** for the initial loading dose, and for the **subsequent 89 days at 1 tablet/day**.
* The subject should take the first eight (8) pills of the **study drug** (loading dose) while the study investigator or other study team member is present. Non-study team witnesses of loading dose dispensing in lieu of study team member presence is not sufficient. 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 in WebDCU™.
  + Furthermore, 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: Protocol Deviations/Violations** in WebDCU™ for additional information.)
    - See POINT Trial FAQs for additional guidelines on crushing study medication.
  + If a subject has already taken clopidogrel within the 12 hours prior to presentation, the following guidelines are suggested:
    - The subject should be given the **full 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.
  + Starting with Day 2, each participant should take **one pill** of the study drug (active/placebo).
* The subject should be given the first dose of **aspirin** while the study investigator or other study team member is present. The investigator must facilitate dispensing the aspirin and ensure it is taken within the 12-hour treatment window, recording the date and time of the dose in WebDCU™.
  + Furthermore, 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 (162mg for US sites) daily x 5 days followed by 75-100 mg (81mg for US sites) daily.** 
    - It is recommended that all sites be encouraged to use the lower dosage of aspirin daily, based on the results of SPS3 and other trials.
    - See detailed justification in FAQ #2.
  + 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. For example:
    - 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 ≥150-200mg 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 150-200mg/161 mg for US sites).
* Blood samples for patients participating in the Biomarkers sub-study can be collected before or after the loading dose is taken by the patient.

**Subsequent Doses - Day 2 through Day 90**

* The second dose should be scheduled so that it is administered ≤ 24 hours after the loading dose.
* Each participant should take one pill of study drug, as well as one prescribed dose of 50-325mg aspirin daily.
* 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 study investigator if they stop the medications for any reason.
* Subjects should be given a copy of the *POINT Trial Alert Wallet Card* and *Medication Information Sheet* when they receive their study drug.

**Destruction of Study Drug**

* Study drugs should be destroyed on site following local medical waste standards, site guidelines and any local SOPs in place for disposition of unusable study drug.
* For verification purposes, all returned study drug should be retained until after the first monitoring visit has been completed and authorization to destroy returned supply has been granted.  Thereafter, study drug should be destroyed per local pharmacy guidelines. Sites outside the US may need to retain study drug until it can be shipped to a depot for destruction.
* Destruction of the study drugs or distribution to a depot for destruction must be documented; Sharp and/or the CCC 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.
    - * 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.

**Randomization and Unblinding**

* The randomization procedures 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 site investigator 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.

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| **Country** | **Number** |  | **Country** | **Number** |
| United States | 1-866-94POINT |  | Germany | 08001809055 |
| Australia | 1800199291 |  | Mexico | 0018553250300 |
| Canada | 1-415-663-4444 |  | New Zealand | 0800001085 |
| Finland | 0753251127 |  | Spain | 90 086 85 17 |
| France | 0805083553 |  | United Kingdom | 08000488302 |

* + - 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 on WebDCU™, the on-call physician should instruct the site investigator or designee to open the Randomization CRF for this 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.

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**RESOURCES**

* POINT Trial Protocol:

<https://nett.umich.edu/sites/default/files/docs/point_protocol_v6_0_19mar2016.pdf>\*

* POINT Manual of Procedures:

<https://nett.umich.edu/clinical-trials/point/mop>\*

* POINT Randomization and Enrollment:

<https://nett.umich.edu/clinical-trials/point/faqs#RandomizationEnrollment>\*

* WebDCU™ User Manual (<https://nett.umich.edu/sites/default/files/docs/nett_webdcutm_user_manual_v19_0.pdf>) \*
* ICHGCP 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**

\*Require a user ID and password for access

**Revision History**

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| --- | --- | --- | --- | --- |
| **Revision** | **Date** | **Author** | **Change Reference** | **Reason for Change** |
| 1.0 | 25MAY2010 | Farrant | N/A | Initial release |
| 2.0 | 08JUN2010 | Farrant | Unblinding steps | Clarification |
| 3.0 | 07JUL2010 | Farrant | Procedures | Personnel Changes |
| 4.0 | 30AUG10 | Farrant | Dispensing/Loading Dose | Clarify Study Procedures |
| 4.1 | 07SEP10 | Kressy | Purpose | Typographical |
| 5.0 | 14SEP10 | Farrant | Procedures | Procedure Change |
| 6.0 | 10NOV10 | Farrant | Procedures | Procedure Change |
| 7.0 | 10MAR2011 | Farrant | Procedures | Clarify Study Procedures |
| 8.0 | 28JUL2011 | Farrant | Procedures | Clarify Study Procedures |
| 9.0 | 23JUL2012 | Farrant/Lam | Procedures; Resources | Clarify Study Procedures |
| 10.0 | 27AUG2012 | Farrant/Lam | Initial shipment quantity, trigger quantity for restocking | Quantity Change |
| 11.0 | 19AUG2013 | Farrant | Responsible Personnel | Update DPSL Personnel |
| 12.0 | 10APR2014 | Farrant/Sankaran | Procedures | Personnel Changes  Revise Dosages |
| 13.0 | 23JAN2015 | Farrant/Sankaran | Procedures | Personnel Changes  Clarify Study Procedures |
| 14.0 | 11MAY2017 | Farrant/Zurita | Procedures | Personnel Changes  Clarify Study Procedures |
| 14.1 | 09JUN2017 | Zurita | Responsible Personnel  Header | Personnel Changes  Clarify SOP Number |