I. OVERVIEW

A. POINT Trial: Protocol Summary

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

The target population is 18 or older with either a high-risk TIA, defined as an $ABCD^2$ score ≥ 4, or a minor ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) ≤ 3, who can be treated within 12 hours of the time last known free of new ischemic symptoms.

Those meeting the eligibility criteria will be recruited as trial participants. Consent is obtained directly from the patient prior to randomization. Participants who consent to the POINT Trial will then be asked to consent to the ancillary study consisting of a one-time venous blood specimen of 10mL collected at the time of enrollment in the trial. Patients who decline the ancillary study are not prohibited from participating in the POINT Trial.

B. POINT Trial: *Optional* Ancillary Biomarkers Study Protocol Summary

As an ancillary study to the POINT Trial, eligible patients are asked to consent to an *optional* one-time draw of approximately 10mL of venous blood. The ancillary biomarkers study will include testing of inherited clopidogrel resistance, and will be the first systematic study of this resistance in the setting of stroke prevention following TIA and minor ischemic stroke. Of primary interest will be the relative risk of vascular outcome events for carriers of specific ABCB1 and CYP2C19 genotypes versus non-carriers amongst those receiving clopidogrel. Of secondary interest will be a subgroup analysis by the enrolling/index event type performed separately for the TIA and minor ischemic stroke cohorts.

Study specimens will be used for testing the specific hypothesis as to whether clopidogrel-resistant genotypes modify the stroke prevention response in high-risk TIA and minor ischemic stroke patients. DNA will be extracted from the specimens by LabCorp Clinical Services and shipped for analysis and storage at the repository at the Neurogenetics Laboratory Mayo Clinic[1] in Jacksonville, Florida (MCF). Specimens will be handled as required by Federal and state regulations, including CFR Title 45, part 46. Specimens will be assigned randomly-generated unique identifiers which will be placed on the labels to track the specimen in the encrypted repository database. No personal identifying information will be kept with the specimen. Individual results of any analysis will not be shared with subjects.

II. COLLECTION, STORAGE AND USE OF COLLECTED SPECIMENS

A. Collection

Written informed consent for the ancillary study will be obtained from those patients who have consented to the POINT Trial; surrogate consent will not be permitted. A one-time

10mL specimen of peripheral venous blood will be collected from ancillary study participants at the time of enrollment. Specimens will be processed at the individual sites and prepared for shipping. DNA and plasma will be extracted from the whole blood specimens by LabCorp and shipped to the Neurogenetics Laboratory at the Mayo Clinic Florida. Plasma aliquots will also be shipped to MCF. To protect participant confidentiality and privacy, specimen labels will not contain any personally identifiable subject information. The POINT Study ID and POINT randomization numbers generated by the central study database will be placed on the specimen before shipment to the Neurogenetics Laboratory at Mayo Clinic, Jacksonville, Florida.

Upon arrival at the laboratory, the specimens will be assigned a randomly-generated, unique identifying pin number, or UPN, by the laboratory's Biological Automated Research Database (BARD). This UPN will be used to manage the banking, tracking and distribution of specimens from the repository.

B. Storage

Specimens collected for the POINT ancillary study will be stored for research purposes only at the Neurogenetics Laboratory of Mayo Clinic Florida (4500 San Pablo Road, Birdsall Room 225, Jacksonville, FL, 32224, 905-953-6280). The Laboratory maintains repositories of specimens collected from individuals with various neurological diseases.

Each specimen will be assigned a unique ID, accessioned into the biobanking informatics system, and stored in appropriately monitored and secure ultra-low freezers. Specimens will be stored at the Laboratory in a -80C freezer bank, with each freezer alarmed and monitored for temperature control 24 hours a day, 7 days a week. Measures to provide appropriate protections for individual privacy and for the confidentiality of clinical and research data are in place. Security clearance and a personal identification swipe card are required to gain access to the storage floor and to enter the freezer room. Specimen management, including banking and distribution, will be coordinated through the Biological Automated Research Database (BARD) database.

If for any reason a POINT participant decides that s/he does do not want his/her specimen to remain at the Neurogenetics Laboratory, the site will notify the repository and the specimen will be removed.

C. Future Use

Specimens may be used for testing the specific hypothesis whether clopidogrel-resistant genotypes modify the stroke prevention response in high-risk TIA and minor ischemic stroke patients. Genotyping results (raw data and summary data) will be provided to the POINT Trial Principal Investigator and lead statistician for incorporation into the existing trial data set into WebDCU. Analyses exploring an interaction between genotypes and treatment response will be done jointly, including testing of inherited clopidogrel resistance.

III. SPECIMEN ACCESS AND DISTRIBUTION

Additionally, the specimens will be a resource for future studies. The Mayo Clinic Florida is designed according to the repository guardian model; appropriate policies and procedures are in place to maintain privacy and confidentiality. The Neurogenetics Laboratory adheres to the policies and procedures of the POINT Trial, POINT Ancillary Biomarkers Study and NIH Guidelines on Research Using Human Specimens, (http://grants.nih.gov/grants/policy/hs/index.htm).

Before releasing specimens from its collection, the Neurogenetics Laboratory will require that the investigator requesting the specimens provides documentation from the investigator's Internal Review Board (IRB) that the research will be conducted in compliance with applicable Federal regulations, including CFR Title 45, part 46. Specimens are supplied from storage according to Neurogenetics Laboratory biospecimen resource SOPs that safeguard quality and confidentiality.

Oversight for appropriate compliance for the Mayo Clinic Florida Neurogenetics Laboratory's role in the ancillary study will be a function of the POINT Ancillary Biomarkers Study Scientific Advisory Board[2], working closely with the POINT Executive Committee.

The Mayo Clinic is committed to ensuring patient privacy through compliance with the Health Insurance Portability and Accountability Act (HIPAA) and requires Institutional Review Board (IRB) approval before banking or receiving specimens for their research. Mayo Clinic Florida will not distribute specimens to any investigator or institution without prior approval of the POINT Ancillary Biomarkers Study Scientific Advisory Board. In addition, the requesting institution must provide documentation of IRB approval for requesting and accepting these specimens, and for policies in place covering confidentiality, use, disposition, and security of specimens. A scientifically sound and appropriate research plan, and material transfer agreement must be included in access requests; a repository sharing agreement may be required, if applicable.

Investigators or institutions requesting specimens from the POINT Ancillary Biomarkers Study must also receive approval from the POINT Ancillary Biomarkers Study Scientific Advisory Board. Investigators requesting specimens must agree to these policies and procedures in writing prior to specimen collection. To protect subject confidentiality and privacy, specimens released to investigators do not contain any identifiable subject information; only the randomly-generated unique identifying pin number (UPN) assigned to the specimen by the Bard system will be provided with each specimen. Only select repository personnel will have the ability to match the specimen to a subject's ID and randomization numbers using a secured key. Specimens from subjects consenting to future research that are not utilized in any ancillary studies will be stored in the specimen bank for up to 20 years upon completion of the POINT Ancillary Biomarkers Study.

IV. SPECIMEN DESTRUCTION

After 20 years, all specimens will removed from storage at the Neurogenetics Laboratory at Mayo Clinic Florida and destroyed per the Laboratory protocol.

V. COMMERCIALIZATION OF RESEARCH RESULTS

There will be no commercialization of the specimen research results.

VI. INTELLECTUAL PROPERTY

Please refer to the guidelines described in the DHHS/NIH "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources (http://www.ott.nih.gov/policy/rt_guide_final.html, http://grants.nih.gov/grants/intell-property.htm) and the NIH National Human Genome Research Institute, Intellectual Property and Genomics policies (http://www.genome.gov/19016590#al-6).

VII. PRESENTATION AND PUBLICATION OF RESULTS

Please refer to the POINT Publications Policy.

[1]**Specimen Repository Address:**

Neurogenetics Laboratory of Mayo Clinic Florida
4500 San Pablo Road, Birdsall Room 225
Jacksonville, FL, 32224
905-953-6280

[2]**Scientific Advisory Board**: Drs. James Meschia, Brett Cucchiara, Brad Worrall, Clay Johnston, Andrew Southerland, Owen Ross, Jordan Elm and Katrina Gwinn