Anticoagulation in Intracerebral Hemorrhage (ICH) Survivors for Stroke PrevenTIon and REcovery

STUDY COORDINATOR TRAINING

NINDS U01 NS106513

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Topics to be Covered

- Biobank Procedures
- Study Medication
  - Procedures
  - Adherence Support
  - Interruptions
  - Unblinding
- Participant Retention
- Risk Factor Management
- Toolbox Resources
- Site Readiness

ASPIRE Biobank – Blood Samples

- Blood sample collection kit will be provided and should be stored at room temperature.
- Blood samples may be obtained any time after consent.
- 2 tubes will be collected; no processing is needed.
- Samples should be shipped as soon as possible after collection.
  - If not possible, store samples upright in a refrigerator (2-8 Celsius, DO NOT FREEZE) until shipped.
- Only ship samples Sun-Thurs for arrival at Biobank Mon-Fri.
- In WebDCU, complete:
  - Biosample Collection form
  - Study Material Tracking>Specimen Shipping

See Biobank Procedures document in WebDCU>ASPIRE>Toolbox for full description of procedures for blood samples and neuroimages.

ASPIRE Biobank – Brain Imaging Studies

Baseline Imaging Studies

- Submit the following as one batch within 14 days of randomization
- First brain CT scan for the index ICH.
- If obtained,
  - One follow-up brain CT scan obtained after initial imaging for index ICH.
  - One vascular study (e.g., CTA or MRA) obtained for index ICH.
  - First brain MRI following index ICH.

Post-randomization Imaging Studies

- Submit as one batch asap after a new neurological event (stroke, ICH, head trauma, etc.) during participation
- All head CT scans and CT angiograms of head/neck
- All brain MRIs

Submit neuroimages via secure electronic upload to your site Neuroimaging Secure Box folder (preferred) or mailed CD.

Study Drug Shipments to Sites

- The StrokeNet Central Pharmacy will be notified by the ASPIRE Program Manager when a site to ready to receive their first drug shipment.

- When kits are received at your site, they must be accepted in the WebDCU system. This notifies the system that the kits are available and can be assigned to a subject.

- The Central Pharmacy will automatically be alerted by WebDCU when subjects are randomized, refills are needed, or study medication is damaged/expired.

See Clinical Performing Site Study Drug Procedures in WebDCU>ASPIRE>Toolbox for full description of procedures for study drug shipments.

Study Drug Labels

- Kits will be labeled and tamper evident sealed. The tamper evident seal should not be opened until a subject is assigned that kit number.
  - Please make sure your pharmacy staff is informed of this.
- Each bottle in the kit will also be labeled and sealed and the Subject ID should be written on each bottle as soon as they are assigned.
- If your site pharmacist/designee also creates an individualized subject specific label make sure the labels are affixed to the individual study bottles, not on the study kit box, and they do not cover the pre-existing study drug bottle labels.
- The study drug kit has a 3-digit verification code that should not be covered.

Study Drug Labels, cont.

To provide additional safeguards:

Bottle Label numbers:

- Aspirin and aspirin placebo bottles will have a #1 on the label – to help remind the subject to only take this medication once a day.
- Apixaban and apixaban placebo bottles will have a #2 on the label – to help remind the subject to take this medication twice a day.

Bottle Label colors:

- Apixaban 5mg and apixaban 5mg placebo label will have a light yellow label.
- Apixaban 2.5mg and apixaban 2.5mg placebo will have a light pink label.
- Aspirin and aspirin placebo will have a white label.

Study Drug Assignment and Dispensing

- When **Randomization form (F102)** is completed, a randomized treatment will be assigned by WebDCU for the subject.
- **Study Drug Kit Assignment form (F512)** must then be completed to receive kit and bottle numbers.
  - Data collected include body weight and serum creatinine;
  - Determines if full or reduced dose apixaban/matching placebo tablets are assigned.
  - Site pharmacist/designee should pull study kit from inventory that matches the assigned kit number.
- Before dispensing kit, the **Study Drug Kit Dispensing Form (F513)** must be started.
  - Record 3-digit verification code from the kit box on form as an additional safeguard to ensure correct medication is dispensed.
  - Record date drug is started by subject and save/submit the form.

Study Drug Accountability

- Log all dispensed/expired/damaged/replaced study drug in WebDCU.

- Once study drug is accounted for in WebDCU, returned, damaged, or expired bottles
  - May be destroyed at your site per local procedures, or
  - Returned to the Central Pharmacy.
    - Complete Study Drug Return Form and return with shipment. This form is available in ASPIRE Toolbox in WebDCU.

- Each site must maintain drug accountability records via the WebDCU system; additional internal recordkeeping for receipt and distribution of study medication may be required by local institutional policy.

- Sample templates of study drug dispensing and accountability logs are provided in **Clinical Performing Site Study Drug Procedures** in the Toolbox.

Adherence Support

Health Care Providers

- If possible, speak directly with primary care provider, cardiologist, and neurologist to ensure willingness to have subject's antithrombotic therapy managed by trial.
  - Emphasize that they are not to give subject any anticoagulant or antiplatelet therapy while subject is taking study medications.

- Send ***HCP Baseline Letter*** (available in ASPIRE Toolbox) to providers or provide letter to subject for them to give to primary care and other health care providers.

- Remind participant to carry the ***ASPIRE Alert Card.***

Adherence Support

At Baseline

Participants may be offered a pill organizer provided by the study.

Provide and review *Participant Information Sh*eet in detail with subject. Reinforce the following:

- Importance of taking the study medications at same time each day.
  - Assist with setting up convenient times to take -- e.g., 8 AM (1 tablet from Bottle 1 and 1 tablet from Bottle 2) and 8 PM (1 tablet from Bottle 2).
  - Have subject explain back what they are to do.
- Risk of thromboembolic complications if study medications are not taken.
- Importance of contacting the study team if they:
  - have any questions or problems
  - are thinking of stopping the study medication
  - are prescribed a new medication
  - are hospitalized for any reason

Adherence Support

During Follow-up

- At each follow-up visit (every 90 days), count remaining pills in returned bottles and assess interval adherence.

- Discuss with subject any barriers to adherence, e.g.,
  - Visible bruising
  - Fear of bleeding
  - Polypharmacy

- Engage caregivers and family members to help improve adherence.

- If possible, simplify concurrent medications subject is taking.

- Thank subject for participating.

Study Medication Interruption

Subjects may temporarily stop taking study medication during follow-up for:

- Bleeding complication
- Elective invasive procedure that requires cessation of study medication
- Potential outcome event
- Open-label antiplatelet or anticoagulant use or other prohibited medication use
- Development or recognition of excluded condition

Bleeding Complications

Major bleeding -- Defined as any intracranial hemorrhage, or non-intracranial hemorrhage that meets criteria for major bleeding (see MOP).

- In the event of a major bleeding event, study medications should be held until the bleeding is controlled and the site investigator judges the benefits of resuming outweigh the risk of recurrent bleeding.
    - If event is confirmed to be recurrent ICH after adjudication, study medications will be permanently discontinued.

- If it is considered likely that bleeding cannot be managed without measures specific to reversal of aspirin or apixaban, treating physicians and/or the site investigator can request unblinding by calling the study hotline (1-800-618-0643).

Bleeding Complications

Non-Major bleeding

- In the event of a bleeding event that does not meet criteria as ‘major’, appropriate measures to control bleeding should be undertaken.

- If the event requires hospitalization, surgical or procedural intervention, or transfusion, study medications should be held until bleeding has stopped and the site investigator judges the benefits of resuming outweigh the risk of recurrent bleeding.
    - A non-major bleeding event that requires study medication interruption and is not due to trauma is a reportable Adverse Event.

Elective Invasive Procedures

- Unblinding will not be performed for elective invasive procedures.

- Apixaban FDA label states:
  - "ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding.
  - ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled."

- Follow *American Academy of Neurology guidelines on periprocedural management of antithrombotic medications in subjects with ischemic cerebrovascular disease* (posted in ASPIRE Toolbox).

Potential Outcome Events

Ischemic Stroke or Myocardial Infarction

- Participants who have a suspected ischemic stroke or MI can continue taking the study drug as long as there is no clear clinical indication for open-label antiplatelet or anticoagulant treatment in the opinion of the treating physician or they may have the study drug temporarily discontinued.

- If the study medication is temporarily discontinued, the site investigator will be responsible for choosing and initiating appropriate antithrombotic therapy.

- Resumption of study medication will be determined by the site investigator in collaboration with the treating physician.

Other Reasons for Interruptions

Prohibited Medication Use

Study medication must be temporarily stopped if any of the following medications are started:

- Aspirin
- Non-aspirin antiplatelet (e.g., clopidogrel after implantation of a coronary artery stent)
- Anticoagulant at therapeutic dose (e.g., for treatment of DVT or PE)
- Paxlovid or other prohibited medication

Development or Recognition of Excluded Condition

Study medication will be held if contraindication to study drug develops/is newly recognized (e.g., creatinine ≥2.5 mg/dL, pregnancy, active hepatitis).

While off study medication, site investigator will be responsible for advising subject on appropriate antithrombotic therapy.

Unblinding

- Unblinding can occur if there is an emergency clinical need to know if subject is taking apixaban vs. aspirin. These clinical emergencies include, but are not limited to:
  - managing life-threatening bleeding
  - need for emergency surgery

- Unblinding may not be necessary for these emergencies if all of the following conditions are met:
  - no study medication has been taken for at least 48 hours,
  - subject's renal function is normal (GFR ≥60), and
  - subject's INR and PTT values are normal.

- Once subject is unblinded, they may not resume study medication.

Participant Retention

- Ideally, each randomized subject should be retained in study through completion of all follow-up visits.
- Losses can occur through subject's withdrawal of consent or becoming unable to locate.
- Losses can reduce both statistical power and team morale.

To Avoid Losses:

- Complete Subject Contact Information form (in Toolbox) (address, phone, email) for subject, family and/or close friends, HCPs) and keep up-to-date.
- Ask about preferred communication method (call, card, email, or text, if allowed).
- Ask subject for permission to notify PCP/neurologist/cardiologist of participation and provide information about the study.
- Send reminder 1-2 weeks before each scheduled follow-up visit.

Options for Completing Follow-up Visits

Clinic Visits

- Try to arrange trial visit to coincide with subject's regular clinic visit to minimize travel and inconvenience.
- Arrange taxi service or reimburse travel expenses.

Home Visits

- Are permitted by study, if allowed at your site.

Telephone Visits

- All CRFs may be collected via telephone or telemedicine contact.

Stroke Risk Factor Management

- Investigators are expected to follow guidelines for care apart from those related to antithrombotic therapy.

- At each visit, blood pressure will be assessed, and, at annual visits, subjects will be queried about (and advised against) cigarette smoking and excessive alcohol use.

- Consented patients may be offered a home blood pressure monitor provided by the study.

Site Readiness

- Readiness call will take the place of an initiation visit.
- ASPIRE Project Managers will arrange the readiness calls.
- Purpose of call is to ensure everything is in place at your site, all team members are listed and trained, and to address any questions before your site is released to enroll.
- A study coordinator and site PI must be on the call.

Readiness Checklist

- Readiness Checklist is posted in ASPIRE Toolbox in WebDCU and will be emailed to sites in advance of the call.
- Key items:
  - ✓ Site and Team documents have been uploaded to WebDCU
  - ✓ All personnel have appropriate training and WebDCU access
  - ✓ Plan for screening and recruitment at your site
  - ✓ Plan for drug storage and temperature monitoring
  - ✓ Blood draw kit is on site
  - ✓ Study drug kits are on site

ASPIRE Toolbox Resources

Assessing Eligibility

- Inclusion/exclusion criteria card (*will be supplied to sites*)
- Prohibited and Discouraged Medications list

Recruitment

- Study Brochure (*will be supplied to sites – available in English and Spanish*)
- Information video for patients/families (*posted on NIHStrokeNet.org>ASPIRE web*site)
- Recruitment Letter to Subject *(alerts patient you will be calling to discuss study)*
- Recruitment Phone Script *(use after recruitment letter sent or PCP gets OK from patient)*
- Checklists for Enrollment and Randomization
- Guidance for Partnering with Rehabilitation and Skilled Nursing Facilities
- How to talk to Cardiologist/PCPs about ASPIRE

Follow-up

- Visit Scheduler
- Follow-up Visit Checklist
- Visit Reminder Letter to Subject

Other

- Data Collection Guidelines

Thank You!

Please complete **Study Coordinator Training Attestation Form** and upload to WebDCU*.

**Study Coordinators also need to review the Protocol Training slides and complete the Protocol Training Attestation Form; both attestation forms should be uploaded as a single, combined PDF to placeholder for Protocol Training in WebDCU*.

Email ASPIRE@YALE.EDU if you have any questions about this material.