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 kits 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
  - Lab Kit Tracking Module

Email aspire@yale.edu if you have any questions about the Biobank.

ASPIRE Biobank – Brain Imaging Studies

Baseline Imaging Studies

- All head CT scans and CT angiograms of head/neck obtained in 1st week after index ICH admission
- All brain MRIs obtained after index ICH and before randomization
  - Submit as one batch within 14 days of randomization

Post-randomization Imaging Studies:

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

Submit neuroimages via secure electronic upload to the ASPIRE Neuroimaging folder (preferred) or mail using courier express service.

Study Drug Shipments to Sites

- The 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.
- After the initial supply, the number of study drug kits sent to your site will depend upon the enrollment rate and expected refills (up to a maximum number of kits permitted on site at one time).

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 bottles 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 completed.
  - This form records date drug is dispensed to subject, and
  - Kit ID and 3-digit verification code from the kit label – as an additional safeguard to ensure correct medication is dispensed.

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 Toolkit 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 the *ASPIRE Pharmacy Procedures MOP* in the Toolkit.

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 Toolkit) 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

Review instructions for taking the study medications in detail with the subject and reinforce the following:

- Importance of taking the study medications at the same time each day
  --Assist subject with setting up convenient times to take study medications, e.g.,
    - 8 AM (one tablet from Bottle 1 and one tablet from Bottle 2) and
    - 8 PM (one 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
- 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 (1-800-638-0643).

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

- Participants who have a suspected ischemic stroke may have the study medication temporarily discontinued by the site investigator who will be responsible for appropriate post-stroke antithrombotic therapy.
- Resumption of study medication will be determined by the site investigator in collaboration with the treating physician.

Myocardial Infarction

- Participants who have an MI can continue taking the study medication as long as there is no clear clinical indication for open-label antithrombotic therapy in the opinion of the treating physician.

Other Reasons for Interruptions

Open-label Antiplatelet or Anticoagulant 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 any dose (e.g., for prophylaxis or treatment of venous thromboembolism).

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 antiplatelet 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:

- Obtain complete contact information (address, phone, email) for subject, family and/or close friends.
- 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

- If subject is unwilling or unable to complete in-person visit, the necessary information can be collected over the phone.

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 measured, and, at annual visits, subjects will be queried about (and advised against) cigarette smoking and excessive alcohol use.

- See *AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage 2015* and *AHA/ASA Secondary Stroke Prevention Guidelines 2014*, (both posted in ASPIRE Toolkit).

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.
- Study drug will not be shipped until site completes a readiness 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 kits are at site

ASPIRE Toolbox Resources

Assessing Eligibility

- Inclusion/exclusion criteria card
- Prohibited and Discouraged Medications list

Recruitment

- Study Brochure
- 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)*
- Enrollment and Randomization Checklists

Follow-up

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

Other

- Data Collection Guidelines
- Follow-up Visit Checklist
- FAQ

Thank You!

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

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