Cardiothoracic Surgical Trials Network

RATE CONTROL VERSUS RHYTHM CONTROL FOR POSTOPERATIVE ATRIAL FIBRILLATION

MANUAL OF PROCEDURES

Sponsored By NHLBI, NINDS, CIHR

CT Surgical Trials Network Research Group

Data Coordinating Center
InCHOIR
Icahn School of Medicine at Mount Sinai
New York

CONFIDENTIAL

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DEFINITIONS, ACRONYMS & ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
CABG	Coronary artery bypass graft
CCU	Cardiac care unit
CFR	Code of Federal Regulations
CPB	Cardiopulmonary bypass
CRF	Case report form
COI	Conflict of interest
CTA	Clinical trial agreement
CTSN	Cardiothoracic Surgical Trials Network
CV	Curriculum vitae
DC	Direct current
DCC	Data coordinating center
DSMB	Data safety monitoring board
EAC	Event adjudication committee
ECG	Electrocardiogram
ED	Emergency department
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive care unit
InCHOIR	International Center for Health Outcomes and Innovation Research
INR	International normalized ratio
IRB	Institutional review board
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MD	Doctor of Medicine
mRS	Modified Rankin Scale
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institute of Health
NIHSS	NIH Stroke Scale
NP	Nurse practitioner
NSVT	Non-sustained ventricular tachycardia
OR	Operating room
PA	Physician assistant
PI	Principal investigator
PIPEDA	Personal Information Protection and Electronic Documents Act
REB	Research Ethics Board
SAE	Serious adverse event

TIA Transient ischemic attack
UP Unanticipated problem

1. MANUAL OF OPERATIONS REVISIONS

Revision	Section	Change	Reason	Implementation Timeline	Page
1.1	Header & Footer	Revised date from March 2014 to July 2014 and added Rev 1.1	Update for Clarification		All
1.1	Entire Document	Administrative changes	Update for Clarification		All
1.1	Entire Document	Added ERB/EC to all IRB related sections	Update for Clarification		All
1.1	Regulatory Documentation	Updated list of documents required by all sites	Update for Clarification		8,9
1.1	Study Compliance	Added information regarding DCC timeline response on protocol deviation/violation	Update for Clarification		12
1.1	Protocol Training	Modified specifics on how training was conducted	Update for Clarification		13,14
1.1	Investigator and Study Personnel Training	Added Modified Rankin Scale training	Update for Clarification		14
1.1	Electronic Data Capture (EDC) System Training	Added details on EDC training for randomizer and Principal Investigator	Update for Clarification		15
1.1	Recruitment	Added quarterly milestone chart for enrollment and randomization targets	Update for Clarification		17
1.1	Randomization Eligibility	Added information on randomization criteria and Amiodarone use	Update for Clarification		23,24
1.1	Preoperative Parameters	Clarification on LVEF and LA volume data index collection	Update for Clarification		29
1.1	Data Collection	Update on pre-operative parameters	Update for Clarification		29
1.1	Medications	Added details on medication log on EDC	Update for Clarification		30
1.1	Index Surgical Procedure	Added information for Robotic Procedures	Update for Clarification		31

1.1	Index Surgical Procedure	Added information to Intra Operative blood product recording	Update for Clarification		31-32
1.1	Discharge and Follow up Visits	Added name of home ECG device (Cardio PAL SAVI)	Update for Clarification		33
1.1	Discharge and Follow up Visits	Added information on Cardio PAL SAVI device distribution and transmission of rhythm	Update for Clarification		34
1.1	Laboratory Assessment	Update on INR collection	Update for Clarification		37
1.1	Modified Rankin Scale and NIHSS	Added details on collecting source documentation	Update for Clarification		38
1.1	Mortality	Added information on mortality occurrence outside of enrolling site	Update for Clarification		38
1.1	Monitoring	Updated information on source documentation requirement	Update for Clarification		43,44
1.1	Remote Monitoring	Updated requirements on source documentation upload to EDC for Randomized and Non- Randomized patients	Update for Clarification		44,45
1.1	Monitoring	Added information on follow up letter post monitoring visit	Update for Clarification		47
2.0	Header & Footer	Revised date from July 2014 to October 2014 and added Rev 1.2	Update for Clarification		All
2.0	Entire document	Administrative changes	Update for Clarification		All
2.0	Investigator and Study Personnel Training	Updated information on Principal Investigator training in the EDC	Update for Clarification		14
2.0	Screening and Eligibility Criteria	Updated information on acceptable source documentation for eligibility criteria	Update for Clarification	Applies to any patients active at the time of this MOP's release	19
2.0	Randomization Eligibility	Updated information on concomitant procedures	Update for Clarification	Applies to any patients active at the time of this MOP's release	23
2.0	Randomization Eligibility	Added 24 hour call in number for DCC randomization eligibility questions	Update for Clarification		24

2.0	Randomization & Treatment	Updated information on usage of amiodarone for this trial	Update for Clarification	Applies to any patients active at the time of this MOP's release	25-26
2.0	Randomization & Treatment	Updated information on requirement for cardioversion on day of discharge	Update for Clarification	Applies to any patients active at the time of this MOP's release	26
2.0	Data Collection	Updated information on collection of Baseline Medication	Update for Clarification	Applies at the time of IRB approval of 2.0	29
2.0	Data Collection	Updated information on Heart Rhythm Recording	Update for Clarification	Applies retroactively to ALL patients	32
2.0	Data Collection	Index Surgical Procedure and Event Driven Additional Procedures	Update for Clarification	Applies to any patients active at the time of this MOP's release	32
2.0	Data Collection	Added information on ED visit or Hospitalization for AF	Update for Clarification	Applies at the time of IRB approval	38
3.0	Cover page, footers	Update Rev 3.0 and date to March 2015	MOP update		ALL
3.0	DCC Team Roster	Updated DCC Contact Information	MOP Update		8-9
3.0	Study Compliance	Protocol Deviation	Update for clarification		15
3.0	Recruitment	Updated study population sample size to 520 patients	Update for clarification	Applies at the time of IRB approval of 3.0	18
3.0	Recruitment	Randomization targets	Update for clarification	Applies at the time of IRB approval of 3.0	18
3.0	Randomization & Treatment	Post-operative anticoagulation	Update for clarification	Applies retroactively to ALL patients	28
3.0	Data Collection	Discharge & Follow up	Update for clarification	Applies retroactively to ALL patients	35
3.0	Data Collection	Heart rhythm recording	Update for clarification	Applies at the time of IRB approval of 3.0	35
3.0	Data Collection	Study Completion- Informed	Update for	Applies	41

		consent form	clarification	retroactively to ALL patients	
3.0	Throughout Document	Added Health Canada requirements (PIPEDA guidelines, documentation required)	MOP Update	Applies retroactively to ALL patients	
3.0	Remote Monitoring	Added information on remote monitoring via remote EMR access	Update for clarification	Applies retroactively to ALL patients	49
3.0	Entire document	Administrative changes, including change from “ERB/EC” to “REB”	Update for Clarification		All

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II. CLINICAL CENTERS

The study will be conducted in up to 25 CTSN clinical centers located in the United States and Canada. The participating sites are all highly experienced cardiothoracic surgical centers with established expertise conducting clinical trials in this area.

III. REGULATORY DOCUMENTATION

All regulatory documents are to be emailed to Karen O'Sullivan and Angela Villanueva or faxed to 212-731-7346. Sites are required to submit the following regulatory documents to the Data Coordinating Center (DCC) at the International Center for Health Outcomes and Innovation Research (InCHOIR) located at the Icahn School of Medicine, New York, New York, prior ***to site initiation, with no exceptions***:

- Signature & Delegation of Authority (DOA) Log
- Conflict of Interest (COI) Statements
- Protocol Document Approval Form

- IRB/REB roster
- Federal Wide Assurance (FWA) number and expiration date
- Copy of IRB/REB approval for protocol, informed consent (all sites), HIPAA authorization (US sites only), and Release of Medical information forms
- Signed and dated Curriculum Vitae (CVs) for all staff on DOA Log
    - CV must be dated within 2 years of submission date to the DCC
- Study site personnel licenses for all RNs, MDs, NPs, and/or PAs listed on DOA Log
- Clinical Center Laboratory Certification (CLIA) or other appropriate certification and normal ranges for local laboratory
- Specialized training certifications for staff listed on the DOA Log:
    - HIPAA or PIPEDA training, GCP, and Human Subjects Protection Training as required by the institution for all study staff
    - EDC Training
    - NIH Stroke Scale (NIHSS) Training
    - Modified Rankin Scale (mRS) Training

Because this trial is being conducted under a Clinical Trials Application in Canada, Canadian sites must also provide the DCC with:

- Health Canada Clinical Trial Site Information Form
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
-

Additionally, a Clinical Trial Agreement (CTA) with the DCC must be fully executed ***prior to site initiation and enrollment, with no exceptions***.

A. Maintenance of Regulatory Documents

The site will maintain a regulatory binder for the protocol that must be updated as new revisions of study documents are made and approvals are renewed. The following documents are expected to be current and readily available for monitoring at site visits. A randomly chosen subset of these documents will be monitored at each site visit to ensure compliance with regulatory requirements.

- Copies of all revisions of the protocol
- Copies of all Protocol Document Approval Forms
- Conflict of Interest (COI) Statements
- Copies of all revisions of the informed consent form (ICF)
- Informed Consent Log

- Protocol Consent Version Tracking Log
- All IRB/REB correspondence, including emails
- IRB/REB approvals for the protocol and informed consent
- Clinical Trial Agreement
- Signed and dated CVs for all study staff (updated every 2 years)
- Site Visit Log
- Site DOA Log
- Correspondence with DCC
- Specialized training certifications for staff listed on the DOA Log:
    - HIPAA or PIPEDA training, GCP and Human Subjects Protection Training as required by the institution for all staff
    - EDC Training
    - NIHSS Training
    - mRS Training
- Patient Contact Log
- Serious Adverse Event (SAE) Reports submitted to IRB/REB
- SAE log
- Protocol Deviation/Violation Log
- Manual of Procedures (all versions)
- Source Document Worksheets/Case Report Forms (CRFs) (CRFs are available on the home page of the Electronic Data Capture (EDC) system)

For sites participating in more than one CTSN trial, a cross-study binder may be maintained that will contain documents applicable to more than one study. This may include CVs, licenses, training documentation, IRB/REB roster, and laboratory information. This will assist the site in maintaining up-to-date records and will assist the DCC monitors in reviewing the files efficiently. The study-specific regulatory binders should contain a Note to File in each section where the cross-study binder will hold those documents (e.g., CVs) explaining the location of the documents.

The clinical site should follow the procedures listed below in their regulatory documentation:

- Ensure that for each section regarding personnel (CVs, licenses, trainings, site initiation) each staff member listed on the DOA log is represented.
- Ensure that IRB/REB approvals (including those for recruitment materials) are all on file in date order.
- Ensure that trial documents are all up to date, e.g., laboratory certifications, IRB/REB roster, FWA information.

- Verify that the most current versions of trial documents, e.g., protocol, MOP, consent forms, are stored in the regulatory binder. Old versions may be stored separately as long as a note to file with the archived versions' location is present.

Signature and DOA Logs should be drafted as follows:

- Staff titles should be consistent with the IRB/REB submission. Be careful to avoid titles such as "Co-PI" and "Sub-PI". Each study site has only one Principal Investigator (PI). The DCC recognizes Investigators either as a PI or as a Sub-Investigator.
- Principal Investigator responsibilities on the DOA Log should include all of the study related tasks whether he/she completes them or not.
- Make sure that staff listed for each task on the DOA Log is qualified for that task as shown by the staff member's CV and/or license. Be sure that each task is delegated to more than one person so that back-up is available for each type of assessment.
- Make sure that the staff member delegated for each task on the DOA Log is conducting only those study assessments delegated.

B. IRB/REB Requirements

Sites are required to follow their institutional guidelines for obtaining initial approval by the IRB/REB and for submitting continuing reviews to the IRB/REB . The DCC will send clinical centers an email reminder 90 days prior to the IRB/REB approval expiration date to help sites plan the annual renewal of the study accordingly. A copy of the IRB/REB letter of re-approval must be forwarded to the DCC and filed in the site regulatory binder upon receipt by the clinical site study team.

The informed consent must be reapproved in accordance with the clinical center's IRB/REB policies or at least annually.

The DCC will provide the sites with Data and Safety Monitoring Board (DSMB) protocol approval letters and any applicable correspondence during the course of the study.

C. Changes in Study Personnel

The DCC, specifically Karen O'Sullivan and Angela Villanueva, should be informed of any personnel changes in Principal Investigator, Sub-investigator, and/or coordinators in writing within 15 business days of the change. An email correspondence is an acceptable form of written communication.

Complete documentation for the new study personnel should be emailed to Karen O'Sullivan and Angela Villanueva or faxed to 212-731-7346. Documentation should include:

- Role in the Study

- Complete contact information including telephone, fax, email address, and beeper number
- Curriculum vitae (signed and dated within 2 years)
- GCP and HIPAA or PIPEDA certification as locally required
- Clinical Study agreement, as applicable (e.g., to reflect a change in PI)
- Specialized Training Certification, as applicable (e.g., NIHSS, mRS)
- Conflict of Interest Statement
- Protocol Training Attestation Form
- Signature on Delegation of Authority Log

IV. STUDY COMPLIANCE

A. Good Clinical Practices (GCP) Certificate, HIPAA Certification & Patient Confidentiality

All investigators, coordinators and other study staff who are involved in the care of study patients, and/or research data collection must submit documentation that they have successfully completed their institutionally required HIPAA or PIPEDA training, and GCP or Human Subjects Protection training to the DCC prior to site initiation.

Confidentiality of all patient records will be maintained according to HIPAA and PIPEDA guidelines. All unique patient and hospital identifiers will be removed prior to review of source documentation. Study Investigators, site IRBs/REBs, the DCC (InCHOIR), the Event Adjudication Committee (EAC), the NHLBI, and the Data and Safety Monitoring Board (DSMB) may review source documentation for enrolled patients as necessary to ensure patient safety.

B. Conflict of Interest

Conflict of Interest Statements will be collected from all study investigators to ensure that no investigator may exert undue influence that may bias the trial. Any conflict of interest identified must be explained in writing and will be reviewed by the NIH and managed in compliance with 21 CFR 54 and 42 CFR 50(f). Conflict of Interest Statements will be updated as potential new conflicts arise and no less than annually.

C. Protocol Deviations

Efforts to maximize adherence to the study protocol will be made through careful and comprehensive training, early review of study data submitted via the EDC system, and routine communication with all site investigators. Despite the best efforts of the clinical investigators, protocol deviations and/or violations may occur. They may include but are not limited to

enrolling an ineligible study participant, failing to obtain informed consent properly, failing to maintain IRB/REB and related study documents, administering the wrong treatment, incomplete assessments or out of window assessments.

All violations will be reported to the DCC, who will notify appropriate parties, including the study site Principal Investigator, NHLBI, NINDS, CIHR, and/or DSMB. Each clinical center will maintain a log of protocol deviations and/or violations and report them routinely to the Regulatory Manager and/or Trial Monitor.

All protocol deviations and violations are to be submitted to the DCC through the EDC within 5 business days of the PI becoming aware of the occurrence. These forms will be reviewed and signed by the DCC on a monthly basis. Please be mindful that the principal investigator will only be able to sign protocol deviation and violation forms after the DCC has signed the forms.

The following information will be documented on the Protocol Deviation/Violation Reporting Case Report Form (CRF) in the EDC:

- Date of occurrence
- Date site became aware of occurrence
- Subject ID
- Detailed description of violation/deviation
- Steps taken to resolve the particular occurrence

Once completed and submitted by the site coordinator, the Protocol Deviation/Violation CRF is reviewed by a member of the regulatory team at the DCC. The DCC will contact the site coordinator, when necessary, to address the deviation/violation and discuss the steps taken to resolve the occurrence. The CRF is released back to the clinical site following DCC review for PI signature.

All protocol deviations and violations will be listed in the protocol-specific Deviation/Violation log. This log must be maintained at each site. For protocol deviations and violations submitted to the local IRB/REB, the log will indicate the date of submission of the deviation or violation to the local IRB/REB and the date of IRB/REB acknowledgment. Clinical sites are to follow their institutional policies for reporting protocol deviations and violations to the local IRB/REB.

D. Notes to File

In situations in which information to complete the study file is not able to be added to source documentation or the CRF, a note to file may be the appropriate form of documentation.

A note to file should:

- Be generated on a case-by-case basis
- Include the subject and protocol it refers to
- Be signed and dated by the individual who is writing it
- Be legible if handwritten
- Explain clearly and specifically the reason for the error/omission/discrepancy or process/policy it aims to address.
- Should include any corrective action or follow-up when applicable.
- Be filed with the document, subject file or behind the study binder tab to which it applies

V. INVESTIGATOR AND STUDY PERSONNEL TRAINING

A. Protocol Training

Clinical site investigators and coordinators will be trained in the specifics of the protocol through a site initiation conference call. Training will ensure that the investigators and all members of the study team are thoroughly familiar with study procedures, the clinical trial protocol, the management of study participants, and each study member's responsibility in the trial. A study team member may not participate in study activities unless training has been completed. Additional protocol training is being conducted via bi-weekly coordinator conference calls during the startup phase of this trial. These calls may include, but are not limited to, discussion on the following topics:

- Protocol guidelines
- Enrollment targets,
- Screening log completion,
- Anticoagulation medications,
- Source documentation requirements,
- Home ECG device utilization,
- Follow up assessments,
- Randomization/eligibility criteria,
- Adverse event reporting,
- Data collection,
- Cross overs,
- Protocol deviations,
- Cardioversion,
- 24 hours coverage feasibility,
- Adjudication procedures,
- CRF completion,
- Budgets and contracts.

These calls will emphasize the need for close collaboration among the study team, provide the coordinators with an overview of the overall study flow, and provide an opportunity to share best practices within and between sites.

B. NIH Stroke Scale (NIHSS) Training

All study personnel responsible for administering the NIHSS, as noted on the Delegation Log, must receive on-line training and certification. Training and certification will be completed using the following website: http://www.nihstrokescale.org/. NIHSS certification is to be printed and filed in the site regulatory binder at the completion of training. Copies of all NIHSS certificates for study staff are to be forwarded to Karen O'Sullivan and Angela Villanueva.

C. Modified Rankin Scale (mRS) Training

All study personnel responsible for administering the mRS, as noted on the DOA Log, must receive on-line training. Training will be completed using the following website: https://secure.trainingcampus.net/uas/modules/trees/windex.aspx?rx=rankin-asa.trainingcampus.net .
Modified Ranking Scale training certification is to be printed and filed in the site regulatory binder at the completion of training. Copies of all mRS certificates for study staff are to be forwarded to Karen O'Sullivan and Angela Villanueva.

D. Electronic Data Capture (EDC) System Training

All site coordinators who are responsible for entering data and those study team members that will be randomizing study participants will be trained on the protocol's web-based electronic data capture system. This training will consist of a web-based teleconference demonstration.

Following the completion of the web-based EDC demonstration, the DCC Project Manager will provide the user with access to the EDC training site. Coordinators and study staff who randomize patients are required to show proficiency in the training site before production site access is provided. Once the coordinator has completed the EDC training, the PI may be trained by the coordinator on the EDC training website. An EDC training attestation form must be completed by the PI before production site access is given. Study personnel who will only be accessing the EDC to randomize study participants must show proficiency in completing the randomization process. All training participants are required to sign an attestation form documenting their training participation. Attestation forms must be on file at the DCC for an individual user before production site access is granted.

Study personnel who will solely be randomizing patients will need to be trained on the Protocol and EDC. A randomizer role will have limited access to the EDC. The following regulatory documents will be collected for this role:

- COI Form
- License, if applicable
- CV (Signed and Dated)
- DOA Log
- Signed Study Initiation form
- Signed EDC attestation form

Once the site coordinator has completed the EDC training, the coordinator will be able to train the Principal Investigator on their EDC role. This role may include training on all electronic CRFs or it can be limited to just the Investigator Statement and Protocol Deviation/Violation forms. The PI role on EDC may be site specific.

Please note: EDC user names and passwords must be kept confidential and not shared among study personnel.

E. Site Initiation

In order to be **eligible** for site initiation, the following requirements must be satisfied **with no exceptions**:

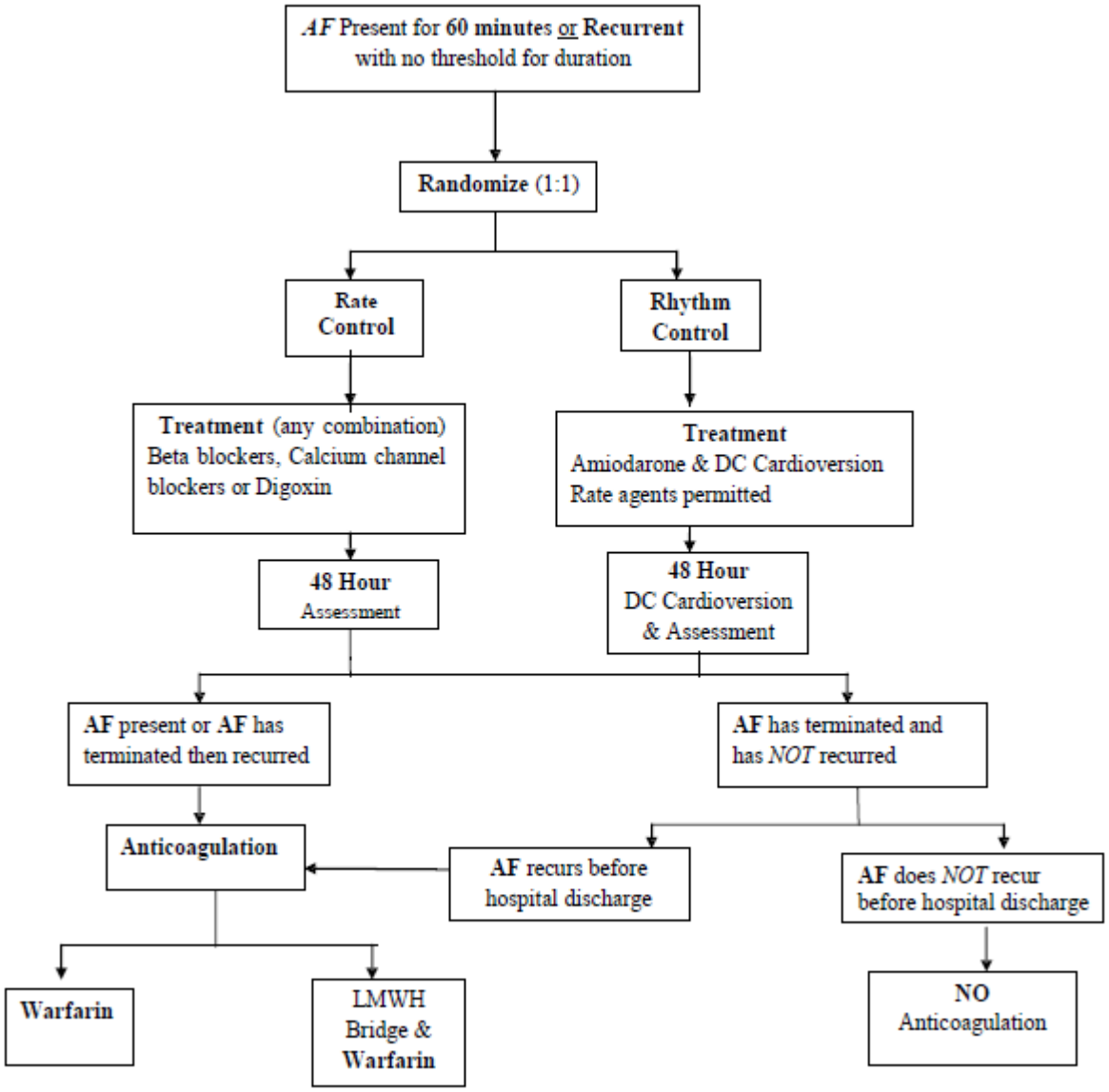
- IRB/REB Approval for Protocol
- Fully Executed Contract
- Regulatory Check List Completed
- Training Check List Completed

Representatives of the DCC will conduct the site initiation prior to enrollment of the first patient for each site. The Principal Investigator, sub-investigator(s), study coordinator, and regulatory coordinator are all required to attend the site initiation conference call.

If it is not possible to have all required parties convene on one call (extreme circumstances), the DCC will consider multiple site initiation calls, although it is preferable for all site participants to be present for the same discussion. Sites will not be opened to enrollment until all required parties have been initiated.

All site initiation participants must review the training slides and sign an attestation that they completed training. This document is to be filed in the site regulatory binder and a copy forwarded to the DCC.

VI. STUDY FLOW



VII. RECRUITMENT

A. Study Population

A total of 520 patients with postoperative AF (defined as atrial fibrillation and/or atrial flutter) that persists for greater than 60 minutes or recurrent episodes (more than one) of AF up to 7 days

after cardiac surgery during the index hospitalization will be randomized into either a rate control or rhythm control strategy.

B. Strategies

Based on data obtained from the clinical centers and previous clinical trials conducted by the CTSN, it is estimated that approximately 1600-1800 patients could be enrolled (consented) annually and accrual will be completed in 18 months. Strategies to enhance enrollment may include:

- Reaching out to referring physicians and providing an overview of the trial
- Implementing screening procedures as part of the initial workup for all patients being evaluated by cardiac surgery for coronary artery bypass (CABG) and/or valve repair or replacement
- Sending a letter to patients identified for CABG and/or valve repair or replacement prior to their initial clinic appointment to introduce them to the study. The letter would have to be IRB/REB approved and should include the Principal Investigator's signature.
- Presenting the trial during Cardiology Department Faculty meetings at local and neighboring institutions to educate colleagues on the trial and increase study awareness.

C. Randomization Targets

Original randomization milestone accrual plan:

Calendar Year	**1st** Quarter Jan - Mar	**2nd** Quarter Apr – June	**3rd** Quarter July - Sep	**4th** Quarter Oct - Dec	Total
2014	0	20	55	75	150
2015	80	80	80	80	320
Total					470

The revised milestone accrual plan, which includes actual accrual through December 2014 and anticipated accrual in 2015, is as follows:

Calendar Year	**1st** Quarter Jan - Mar	**2nd** Quarter Apr - June	**3rd** Quarter July - Sep	**4th** Quarter Oct - Dec	Total
2014	0	11	138	169	318
2015	134	68	0		202
Total	134	79	138	169	520

VIII. SCREENING AND ELIGIBILITY CRITERIA

A. Patient Screening

To determine initial study candidacy, the coordinator will conduct a chart review of all the available medical history against the eligibility criteria to assess whether the patient should be approached for participation. The site will need to follow their Institutional policies and procedures for accessing medical information in preparation for research, which typically includes obtaining a waiver for authorization from either the IRB/REB.

All adult patients requiring cardiac surgery to treat coronary artery disease, valvular heart disease or a combination of both are to be screened for this study. Patients who are deemed ineligible for participation and those patients eligible but who have not consented following chart review are pre-screening failures. These patients will be recorded using the Pre-Screening Failure Log. The data collected in the log is HIPAA and PIPEDA compliant and does not include patient identifiers, including sex and ethnicity. Sex and ethnicity will only be collected for consented participants.

The Pre-Screening Failure Log for this trial is an Excel document that is separate from the EDC and maintained by the site. For each pre-screen failure patient, the coordinator will document whether the patient refused to participate, patient did not meet eligibility criteria, patient died or other. Coordinators can select more than one reason in the log, if necessary. This screening log will be collected quarterly by the DCC and will provide the DCC and NHLBI an overview of why patients are not consented for trial enrollment.

The log must be submitted to Seth Goldfarb via email (Seth.Goldfarb@mountsinai.org) on a quarterly basis using the following schedule:

- First Quarter (January – March): End of business day on April 1st or the first business day in April.
- Second Quarter (April – June): End of the business day on July 1st or the first business day of July.
- Third Quarter (July – September): End of the business day on October 1st or the first business day of October.
- Fourth Quarter (October – December): End of the business day on January 1st or the first business day of January.

Pre-Screening Failure Logs will be monitored on a regular basis and compared against the enrollment volumes and surgery volumes reported by the clinical center.

B. Eligibility Criteria

Candidates who meet all inclusion criteria and no exclusion criterion as outlined in the protocol will be eligible for the trial regardless of gender, race, or ethnicity. When evaluating the exclusion criteria, it is important for the coordinator to work closely with the surgical investigator to review the surgical plan to determine whether it is appropriate for the patient to participate in the trial. Additionally, the referring cardiologist may need to be consulted to review prior history and the long-term patient management plan, which may exclude the patient from participation. Any lab value or ECG most proximal to the date of surgery should be used to determine eligibility.

IX. INFORMED CONSENT, HIPAA AUTHORIZATION, RELEASE OF MEDICAL INFORMATION

A. Informed Consent

<u>Consent Form Modifications</u>

Clinical centers are required to submit any consent form modifications to the DCC for review and approval prior to the initial IRB/REB submission at the clinical center. Consent form modifications are to be made using the track changes mode on the DCC approved consent template and emailed to Karen O'Sullivan and Angela Villanueva for review.

The DCC understands that revisions to the consent form may be required to satisfy institutional IRB/REB requirements and requests. For example, an IRB/REB may request that the consent form add additional language or remove DCC approved language. Clinical centers are allowed to remove or add additional consent language if required by their IRB/REB but recommends not volunteering any additional language when not specified by the IRB/REB. **Any consent form**

modifications requested by the IRB/REB are to be reviewed and approved by the DCC prior to re-submitting the consent form to the IRB/REB.

Patient Compensation

During the consent process a patient might ask about compensation for trial participation. Although the consent form template states participants will not receive compensation, the clinical center trial budget is provided as a "per patient" total amount allowing each clinical center to determine how funds are allocated for this trial. Please review your institutional policy on study participant compensation. Providing compensation, such as travel reimbursement or gift cards, might help with enrollment and patient retention and is supported by the DCC.

Consent Process

Obtaining informed consent and timing for the informed consent process must be consistent with the clinical center's institutional IRB/REB and privacy policies, and in accordance with CTSN guidelines. The investigator or a designated individual will provide a thorough explanation of the objective, patient responsibilities, risks and benefits of the study, and will fully address concerns raised by the patient and/or family. The consent process (and its documentation) must begin prior to all data collection and protocol procedures. This is to ensure that all potential study participates are given adequate time to review the informed consent document and consider participation in the trial.

A patient should be encouraged to have family or other support available during the informed consent process. They should be assured that declining to sign an informed consent document will in no way compromise their care, and that should they consent to participate in the study, they may revoke that consent at any time.

A signed copy of the consent form must be given to the study participant. All signed consent forms, including the initial consent and any re-consents, are to be uploaded into the EDC on the patient eligibility page.

The consent process must be documented in the study participant's record according to the institutional and CTSN requirements. The investigator or his/her designee must:

- Document any questions addressed with the patient and/or family during the informed consent process in the medical chart
- Confirm that all signatures on the informed consent are complete and dated
- File the original signed informed consent with study participant's research documents

Additional information on documenting the consent process can be found in Section XIV (Monitoring).

Non-English Speaking Patients

Clinical sites must abide by local institutional guidelines when approaching a patient who does not speak/read the language in which the consent is written for the informed consent process. Local IRBs/ERBs/ECs will have guidelines in place that must be followed. For all consented participants who do not speak/read the language of the written consent, the clinical site must document the information noted in the above paragraph but also specify such information as:

- A brief description of local policy on consenting a patient who does not speak/read the language in which the consent is written;
- A brief description of how this policy was followed in the consent process for this patient;
- The name of the translator and/or anyone else present at the time of consent;
- A statement that the patient was given the opportunity to ask questions and to receive answers about the study in his/her native language.

Visually Impaired or Low Literacy Level

Clinical sites must abide by local institutional guidelines in the informed consent process for visually impaired or patients with a low literacy level. As with consenting a speaker of a language other than the language in which the consent is written, the clinical sites must specify additional information on the consenting process including:

- A brief description of the local policy on consenting patients with visual impairments or literacy challenges;
- A brief description of how this policy was followed in the consent process for this patient;
- The name of the person reading the consent form to the patient and/or anyone else present at the time of the consent;
- A statement that the patient was given the opportunity to ask questions and to receive answers about the informed consent document as it was read to him or her.

B. HIPAA Authorization and Release of Medical Information Forms

Each site is required to follow their institutional policy for HIPAA Clinical Research Authorization (US sites only) and Release of Medical Information. Consent to authorize release of medical records to the trial investigators, monitors, sponsors (NHLBI, NINDS, CIHR) and the DCC must be obtained for trial participation.

C. Informed Consent Log

Each study participant will be listed on the informed consent log that collects information on the date of informed consent and version of the consent form used. This log will track reasons and dates of re-consent, if necessary.

X. RANDOMIZATION & TREATMENT

A. Randomization

All consented patients will be monitored by telemetry during their index hospitalization, as described in the protocol, to detect any occurrence of atrial fibrillation or atrial flutter within 7 days of the index surgery. The window for AF detection is calculated using date of index surgery labeled as "day 0." It is important to remember that not all consented patients will be eligible for randomization. Only those study participants meeting the AF threshold for randomization will be randomized into either rate control or rhythm control as outlined in the protocol and on the Randomization Eligibility CRF.

It is critical that each clinical center establishes, prior to its first randomization, the steps that are to be taken when a consented patient goes into AF and when the 3-hour randomization window begins. The plan should outline how postoperative AF care instructions will be distributed to the patient management team, the process for verifying randomization eligibility, establishing which study team members will be randomizing eligible study participants and how the treatment assignment will be communicated and initiated. The following questions are provided to facilitate logistical consideration for the site specific plan.

- How will trial participation be documented to ensure all individuals taking part in the patient's care know that this is a trial participant?
    - Will there be a note in the medical record that is visible for all treating clinicians to view easily?
    - Will consented participants be allowed to wear research identification bands on their wrists next to the medication band post-operatively?
- How will the patient management team alert the study team when an episode of AF begins for a hemodynamically stable study participant?
- What happens when the AF episode occurs outside normal business hours?
    - Is there a call schedule being implemented for the trial with the study team?
    - Where will the study team contact information be visible to those caring for the participant?
    - Is there remote access available to review medical records?
- Who will determine eligibility for randomization and how will it be documented?
    - What will be used, i.e. nursing note or telemetry report, at the site as the source document for AF episode length and/or occurrence?
- Who will randomize the patient and how will randomization assignment be conveyed to patient management team?
    - Does the study team member have remote access to the EDC for randomizations outside of normal business hours?
- How will orders for treatment be communicated?

A licensed clinician, e.g., MD, PA or NP, who reports the onset of AF in a study participant to a study team member, can perform the assessment of AF and provide treatment as it is within the clinician's scope of practice. Licensed clinicians that work with the study team to evaluate the additional eligibility questions and administer the treatment assignment do not need to be on the DOA Log as long as their role does not involve data entry or randomization in the EDC.

Randomization Eligibility

All study participants will have their randomization eligibility status documented in the EDC on the Randomization Eligibility CRF. The CRF is to be completed for all study participants either at the time that the study participant needs to be randomized or when it has been determined that the study participant is ineligible for randomization.

Only episodes of AF detected during the index hospitalization and occurring within 7 days of index surgery are to be assessed for randomization eligibility. Study participants must have a single AF episode of greater than 60 minutes **or** recurrent AF episodes, with no duration threshold, documented to meet the requirements for randomization. Any study participant discharged who subsequently develops AF still within 7 days of the index surgery is not eligible for randomization.

Eligible study participants are to be randomized within a 3-hour window. Please use the following guidelines for determining and calculating the 3-hour randomization window:

- Single episode of AF: randomization window starts at minute 61.
- Recurrent episodes of AF: randomization window begins upon the occurrence of the second AF episode regardless of episode duration.

Study participants may not be randomized once the 3-hour window has closed. Should the clinical site fail to randomize an eligible study participant within the 3-hour window, the study coordinator will mark that the participant was not randomized with the reason being "patient met AF eligibility criteria but randomization did not occur due to logistical reasons" on the Randomization Eligibility CRF. When necessary, interventions will be conducted to help overcome logistical reasons for enrolling willing and eligible participants at the site.

Study participants receiving rate control agents to treat an underlying cardiac condition, such as hypertension, prior to randomization may still be randomized to either rate control as initial strategy or rhythm control as initial strategy. Administration of rate control medications to treat the onset of AF is permissible. The patient should be treated with rate control medications based on the clinical guidelines the center site for AF.

Clinical sites are not to randomize study participants that receive amiodarone within 6 weeks prior to index surgery. The rev 2.0 of the protocol is revised to exclude patients that receive amiodarone within 6 weeks of index surgery from enrollment due to the medication's half-life. Additionally, study participants who leave the OR on an amiodarone drip are **not** eligible for randomization. However, study participants that receive a **one-time dose** of amiodarone intra operatively are eligible for randomization.

Study participants receiving heparin prior to randomization are **not** excluded from randomization.

Study participants may leave the operating room with pacing wires and still be eligible for randomization. For example, a study participant may leave the OR paced with epicardial wires for bradycardia or NSVT, and develop underlying or breakthrough AF within 7 days post-operatively. In this case, the study participant may be randomized into the rate control or rhythm control arm of the trial. Please remember that epicardial overdrive pacing wires could be used to cardiovert AF and plans should be made to prevent the treating clinicians from overdrive pacing AF without consulting the study team, except in the setting of hemodynamic instability or other clinically indicated caregiver decisions.

Study participants that undergo concomitant aortic surgery, e.g., aortic root, ascending aorta or arch work, **are** eligible for participation. For specific concomitant procedure questions, please contact the DCC project manager. Those study participants that receive a catheter based intervention are **not** eligible for randomization as the population being studied in this trial is those with an open sternum approach.

Randomization Procedure

Please be mindful that only study personnel with the randomization task listed on the Site DOA Log are authorized to randomize study participants. Residents, fellows, physician assistants and other clinicians who may treat study participants are allowed to randomize study participants but they must be trained on the protocol, submit the required regulatory material, and be listed on the DOA Log.

After randomization eligibility has been confirmed, the responsible study team member will randomize the study participant using the EDC. A representative from the DCC will be available 24 hours, 7 days per week to discuss any questions regarding randomization eligibility. To contact a DCC representative outside of business hours, please call the on-call service at 1-855-215-0461. The call service will take your name, contact information and question and will contact the DCC member on call who will return your call. DCC members are not able to randomize patients; therefore, the DCC IT should be contacted **for only** technical issues which prevent EDC access or randomization in the EDC. The EDC will prevent the user from

randomizing a study participant if the Eligibility and Enrollment CRF and the Randomization Eligibility CRF are not completed in the EDC.

Once the Randomization Eligibility form is completed and signed, the Randomization link will appear in the EDC. The study team member will randomize the study participant by clicking on the link. The Randomization CRF will appear indicating the randomization assignment.

B. Treatment

All study participants will continue to receive their prescribed standard of care medications, including rate control agents, to treat their underlying coronary artery disease, heart failure or any other type of related history.

Rate Control Strategy

For those study participants randomized to rate control as initial strategy, treating clinicians will choose agents from the list of rate control medications found in the protocol to achieve a target heart rate of < 100 beats per minute at rest. Those study participants with a slow ventricular response rate randomized to rate control may have their rate control agents withheld or administered in low doses. Treatment medications may be given singly or in combination to achieve rate control.

Please see Appendix II for the dose ranges for each of the rate control agents that should be followed using the guidelines defined on page 30 (Table 10) in the *2011 ACCF/AHA/HRS Focused Updates Incorporated into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: A Report on the American College of Cardiology Foundation/American Heart Association Take Force on Practice Guidelines.* (Internet address: http://circ.ahajournals.org/content/123/10/e269.full.pdf)

Please review the guidelines against your clinical site's institutional protocols for administering these rate control medications. It is expected that some variation may exist between the guidelines and institutional protocol(s). For this trial, deviations from the guidelines to adhere to the clinical site rate control institutional protocol(s) are not protocol deviations.

There may be cases where a rhythm control intervention is clinically indicated for a study participant that did not return to sinus rhythm after initial rate control intervention and when rhythm control is indicated to improve hemodynamic status or to alleviate symptoms. It is recommended that the treatment strategy for these study participants include direct current cardioversion in addition to amiodarone. Any rate control as initial strategy study participant that receives a rhythm control intervention will be considered a crossover to the rhythm control arm of the trial. The DCC will be tracking crossover rates across the Network and at the clinical centers closely and corrective actions may be required as crossover rates approach 15%.

Rhythm Control Strategy

For those study participants randomized to rhythm control as initial strategy, treating clinicians will treat the study participant with amiodarone alone or amiodarone plus direct current (DC) cardioversion as outlined in the study protocol. It is important to note that the loading and maintenance dosages of amiodarone outlined are recommended doses. Clinicians may deviate from the recommended doses without incurring a protocol deviation. However, clinicians may not discontinue amiodarone before day 60 or end of study unless there are clinical indications that are outlined in the study protocol. For those study participants who return back to continuous AF on day of discharge, the participant should remain in the hospital and DC cardioversion should be scheduled. If the study participant has *paroxysmal* AF on day of discharge no cardioversion is required and participant should be discharged on amiodarone. The footnotes to the Rhythm Control Intervention Table located in the protocol provide additional guidance for patient management.

Additionally, study participants randomized to rhythm control as initial strategy are allowed to be treated with rate control agents when clinically appropriate. Post randomization, rate control agents may be continued and new rate control agents may be added, as clinically indicated. When rate control agents are added, the study participant is still considered part of the rhythm control arm as long as amiodarone is continued.

While it is expected that all rhythm control study participants remain on amiodarone, as discussed in the protocol, there may be clinical circumstances where the treating clinician decides to hold the dose. Determining and documenting a held dose versus a discontinued dose is important for the purposes of identifying a crossover participant. Study participants are still part of the rhythm control treatment arm when amiodarone is being held for a clinical indication regardless of the duration of the hold. It is important that documentation be placed in the study participant's record to detail the reason for the amiodarone hold and length of hold. Please see the medications in the Data Collection section for instructions on documenting a held dose in the EDC.

It is expected that there will be cases when the management goal for the study participant needs to be switched to rate control treatment only. Reasons for switching a study participant to rate control include the failure to restore normal sinus rhythm and there is an inability to continue amiodarone. For those study participants switched to rate control, treatment will follow the guidelines set forth for the rate control arm. Amiodarone must be discontinued and rate control treatment active for the indication of AF for the study participant to be considered a crossover.

Postoperative Anticoagulation

All rate control and rhythm control study participants who meet the criterion for anticoagulation as outlined in the protocol will be treated with warfarin to achieve a target INR of 2-3. Anticoagulation is recommended for randomized study participants when their AF has remained continuous or when AF was terminated but recurred one or more times during the first 48 hours after randomization, as noted in the protocol.

While newer oral anticoagulation medications are available that do not require regular blood tests, these therapies are not to be prescribed to study participants. Aspirin is not an alternative for warfarin but may be given concomitantly to a study participant at the discretion of the treating clinician. Additionally, cardioversion may also be used when warfarin is not feasible for the study participant and should be documented as a procedure under event driven.

Continuous anticoagulation for 60 days is recommended in all study participants. Discretion may be used by the treating clinician to discontinue warfarin should normal sinus rhythm be maintained for 2 weeks or if complications develop. Warfarin may be held for those study participants that develop relative or absolute contraindications to postoperative anticoagulation.

Heparin can be administered post-randomization at the clinician's discretion and use prior to randomization will not prevent the study participant from being randomized.

If a randomized participant in this trial is administered an anticoagulation drug that is unrelated to the study indication of AF, continuation of this drug should be left to clinical judgment. These participants are NOT required to meet anticoagulation criteria as per this protocol. A protocol deviation form is not required to be completed. Coordinators will simply check "unable to complete" on POAF08 item #8 and enter these drugs in the medication log for documentation and monitoring purposes.

XI. DATA COLLECTION

Data collected for this study is outlined in the schedule of assessments and data collection section of the protocol. This section provides supplemental information to help coordinate and complete the assessments collected during the course of the trial.

In order to document investigator oversight in the study, the PI (or a delegated investigator) should sign and date laboratory reports, ECGs, and other source documentation with a note of significant findings, when applicable.

A. Study Participant Identification Numbers

All consented (enrolled) study participants will be issued a numeric patient identification number (Patient ID) that will be automatically generated by the EDC following the completion of the Eligibility and Enrollment CRF. The Patient ID will consist of the two digit site number followed by a three digit sequential site specific enrollment number, e.g. 01-001. Since all study participants will have baseline data collected, the letter "E" will appear before the Patient ID to distinguish non-randomized study participants in the EDC. Once a study participant has been randomized, the Patient ID will lose the "E." All source documentation will be de-identified using the numeric Patient ID, including but not limited to, index hospitalization source, adverse event source and follow-up visits.

B. Study Visits

For all study visits, **data collected is to be entered into the EDC within 5 business days post-visit**. Event driven data is to be reported via the EDC as outlined in the sections below.

Once a study participant has signed the consent form, the study coordinator should confirm the anticipated date of surgery. Baseline data collection windows are calculated from the date of surgical intervention. Please keep in mind that study participants scheduled for elective surgery are at risk for being rescheduled or postponed. It is important to verify that the date of collection for baseline data still falls within the acceptable window when a surgery is postponed or rescheduled. Any baseline data no longer within window must be revised in the EDC.

All baseline data will be collected for every study participant regardless of randomization status. Study participants that do not meet randomization eligibility criteria will have trial completion documented on the Randomization Eligibility CRF and no additional data will be collected. Those study participants that are randomized will have data collected pertaining to the index hospitalization, any subsequent hospitalizations, follow-up visits, additional procedures and adverse events.

The date of randomization will be used to calculate the follow-up visit windows. The EDC will auto-populate the follow-up windows with completion of the randomization CRF and display them on the visit folder via the visit windows button in the navigation panel of the EDC. Dates will appear on visit window folders, but they won't appear until closer to the visit.

Scheduling follow-up appointments with the study participant should be done with as much notice as possible to prevent scheduling conflicts and ensure visits are completed within the specified window. Following discharge, study participants will be required to complete study visits at 30 days post-randomization (± 5 days) and at 60 days post-randomization (± 5 days). It

is advised that 30-day and 60-day study visits be scheduled with the study participant at the time of their index hospitalization discharge.

Data to be reviewed and collected, when applicable, during the follow-up study visits at 30 days and 60 days post-randomization includes documentation of the patient status, occurrence of any hospitalizations, adverse events and/or cardiac procedures since last visit, amiodarone status, and assessment of heart rhythm. Cardiac medications of interest are to be reviewed as well for any medication regimen changes.

For the purposes of this trial, study visits are considered as having occurred when one or more data points for the visit are ascertained. Missed visits are only to be completed when no data is captured for the entire visit. This missed visit will be captured on a protocol deviation form in the EDC. Please remember that data may be gathered from a variety of sources and some data points, such as patient status, do not need to be collected from direct study participant contact.

Each clinical site is required to keep a Patient Contact Log (Appendix I) to document any and all mail, e-mail and telephone correspondences with randomized study participants. Any in-person visit should also be documented on the log. Please remember that all correspondence and visit details are to be documented in the study participant's record and will be reviewed against the Patient Contact Log during monitoring visits. The Patient Contact Log will also be reviewed as part of the remote monitoring procedures on a regular basis.

C. Preoperative Parameters (Medical History & Physical Exam)

Reviewing the entire medical history is important for determining eligibility against the inclusion and exclusion criteria and completing the CRFs once enrolled. Medical history for consented study participants is to be obtained within 3 months prior to index cardiac surgery with the physical exam (height and weight are the only values being collected from Physical Exam) data and entered on the preoperative parameter CRF.

The preoperative parameter data captured for this trial focuses on history of cardiovascular and vascular disease, cardiac procedures, neurological events, pulmonary disease, and common metabolic and endocrine co-morbidities found within the study population. While much of the study participant's medical history may already be established from the medical record, the study staff is required to review the medical history with the study participant to confirm that their entire history is documented accurately.

In addition to reviewing the medical history, the following information requires source documentation upload and entry into the EDC:

- Presence or absence of sleep apnea
- Height and weight at the time of baseline visit

- LVEF (This value can be obtained from any TTE that is used for surgical evaluation)
- Left atrial volume index (This value can be obtained from any TTE that is used for surgical evaluation. If obtaining this parameter is not considered standard of care at your institution, then you will not receive a protocol deviation if this parameter is missing from the EDC)

D. Medications

Medications will be recorded on the baseline medication CRF, the index surgical procedure CRF and the post-randomization medication log.

Baseline

The study coordinator will record in the EDC whether or not the cardiovascular therapies listed below were administered to the study participant prior to index cardiac surgery. No other medications will be collected, and dose, frequency and route are not recorded at baseline.

- Digoxin
- Nitrate
- Diuretic
- Beta Blocker
- Aldosterone Receptor Antagonist
- Angiotensin Converting Enzyme (ACE) Inhibitor Angiotensin II Receptor Antagonist (ARB)
- Calcium Channel Blocker
- Inotropic or Vasoactive Therapy

Intraoperative Pharmacologic Therapies

Medication collection is limited to focus on which, if any, cardiovascular therapy, anticoagulants and antiplatelet agents are administered during the index surgical procedure. Study coordinators will mark these therapies on the Index Surgical Procedure CRF. Dose, frequency, and route are not recorded for intraoperative medications.

Post-randomization

Once a study participant is randomized, study coordinators will use the Medication Log in the EDC to record **all study defined medications of interest the study participant receives from the time of ICU entry through the 60-day follow-up visit. Medications that are administered to participants prior to randomization should never be associated with an Adverse Event in the Medication Log (Only Adverse Events occurring after randomization are being captured in this trial).**

Medications of interest for this study are defined as follows:

- Antiarrhythmic Class I-IV Medications
- All Cardiovascular Therapies, including but not limited to:

  - Nitrates
  - Diuretics
  - Aldosterone Receptor Antagonists
  - ACE Inhibitors
  - ARBs
  - Calcium Channel Blockers
- Anticoagulants (Intravenous, Subcutaneous and Oral)
- Antiplatelet Agents

Every new medication of interest, change in medication of interest, and discontinuation of medication of interest must be recorded on the Medication Log. Study coordinators may update the Medication Log in real time as medication adjustments are reported, or they can wait until a study visit to provide the updates. The DCC recommends making revisions to the Medication Log when the study team becomes aware of medication changes.

The following guidelines should be used to document a "held" cardiac medication of interest in the EDC:

- Continuous intravenous cardiac medications of interest will have the stop date recorded only when the medication is held for > 24 hours.
- Non-continuous cardiac medications of interest will have the stop date recorded only when the medication is held for > 2 days.
- Resumption of the cardiac medication of interest will be recorded as a new medication (new row) in the Medication Log.

The status of amiodarone treatment at discharge and at the 30-day and 60-day post-randomization visit will also be recorded on the index hospitalization CRF and follow-up visit CRFs. Source documentation should clearly illustrate whether a cardiac medication of interest is being held due to a clinical indication or has been discontinued by the treating clinician. Reason for amiodarone hold or discontinuation will be collected regardless of treatment arm.

E. Index Surgical Procedure and Event Driven Additional Procedures

Index surgery data will be collected and recorded in the EDC for **all** study participants. Any procedure following the randomization must be reported for a randomized study participant. The OR report and/or procedure report will be uploaded directly to the corresponding CRF within 48 hours of becoming available to the study staff.

<u>Index Surgical Procedure</u>

For each study participant, information on the initial surgery is entered on the Index Surgical Procedure CRF. The primary procedure is captured in addition to operative parameters,

concomitant procedures and intraoperative medications and blood transfusions. For participants undergoing a **robotic procedure**, the skin to skin time will be recorded as the total operative time. It is expected that all index surgical data be entered into the EDC within 48 hours of the procedure.

Data collected for operative parameters include:

- OR entry time
- Whether study participant was on cardiopulmonary bypass (CPB) and the amount of time on CPB
- Whether the aorta was cross clamped and the amount of aortic cross clamp time
- Whether the chest was closed in the OR
- What the skin to skin time was

Any and all cardiac concomitant procedures, e.g., aortic septal defect repair, will be identified and recorded in the EDC.

All intraoperative medications will be recorded as described in the medication section. Additionally, intraoperative blood product administration will be captured with the number of units administered recorded. For the purposes of this trial, a unit of blood will equal 250 cc/ml and any portion thereafter will be converted to tenth decimal point.

Event Driven Additional Procedure

Additional procedures will be entered for all randomized study participants in the event driven folder in the EDC. Multiple procedures can be recorded on one event driven form and documented within 48 hours of the knowledge of event. Any surgical procedure not listed on the Additional Procedure CRF will be documented under "Other Procedure." The coordinator will select whether the procedure was related to an adverse event and document the adverse event identification number, when necessary.

F. Heart Rhythm Recording (ECG or Telemetry)

The trial does not require a baseline heart rhythm assessment; however, documentation of heart rhythm history is required for study participant eligibility. The absence of AF must be established in the medical history through prior heart rhythm recordings, progress notes, clinic notes or hospitalization records. It is recommended that the clinical center establish a consistent practice for reviewing and documenting heart rhythm history as source.

A licensed clinician will verify, sign and date heart rhythm ECGs performed at randomization.. An adjudication committee for this trial will adjudicate discharge, 30 and 60 day follow up ECGs uploaded to the EDC by the site or Medicomp. All heart rhythm source documents other

than the ECG performed by Medicomp will be uploaded into the EDC by ALL sites under the appropriate visit Electrocardiogram CRF for source documentation review by the DCC.

Please note, regarding randomization eligibility, if a patient has recurrent episodes of AF both ECGs must be uploaded to the EDC for source verification.

Continuous Telemetry Monitoring

In order to determine randomization eligibility, study participants will have to remain on continuous telemetry. Randomized study participants will remain on telemetry as per the institutional policies of the clinical site for patients with new onset AF. For many clinical centers, it is standard of care to remain on telemetry until the time of discharge following cardiac surgery. Each clinical center must provide a consistent heart rhythm source for their site to document the onset of AF and the conversion to normal sinus rhythm. Continuous rhythm strips are not necessary for source documentation.

Conversion to sustained, stable, non-AF rhythm is recorded on the Index Hospitalization CRF. Stable non-AF rhythm will be assessed and defined, as routinely would be the case, by the care protocols established by the clinical center for standard care of post-cardiac surgery patients. Further information on the conversion to sustained, stable non-AF rhythm can be found under the hospitalization in this document section.

Rhythm strips should be available during monitoring to confirm continuous monitoring of the study participant. Should review of the continuous monitoring not be available due to institutional policies, e.g., stored telemetry is lost following transfer from ICU to another unit, the DCC will collect the physician orders to initiate and discontinue telemetry.

48-hour Post-Randomization

Please note that the study participant's heart rhythm assessment at 48 hours post-randomization directly influences the anticoagulation treatment for the trial. It is important to have heart rhythm information for the 48 hours following randomization available as part of the source document to support anticoagulation management. However, there is not a separate heart rhythm recording CRF requirement to be completed for this time point.

Discharge and Follow-up Visits

All randomized study participants will have their heart rhythm assessed on the day of hospital discharge and 30 and 60 days post-randomization either by 12-lead ECG, portable ECG or telemetry monitoring. Any heart rhythm recording conducted within 24 hours of discharge may be used for the discharge data collection point.

The electrocardiogram CRF will be auto-generated in the EDC for the discharge visit once a discharge date has been entered into the index hospitalization CRF. Should the study

participant be discharged within the 30-day or 60-day post-randomization visit windows, the same heart rhythm recording may be used for both data collection time points.

For study participants discharged prior to the 30-day post-randomization visit window, it is anticipated that the 30-day post-randomization visit will coincide with a standard of care post-operative outpatient visit for many study participants in the trial. A clinician whose scope of practice covers the assessment can perform heart rhythm recording and interpretation. The study coordinator will be responsible for coordinating the heart rhythm recording collection with the clinician to ensure that the data is not missed. In rare circumstances when the study participant is unable to conduct an in-person visit during the 30-day post-randomization window, the clinical center may elect to conduct the heart rhythm recording using the Cardio PAL SAVI monitor.

Since the 60-day post-randomization visit does not overlap with a standard of care post-operative outpatient visit for many of the clinical centers participating in the trial, study participants may conduct the 60-day heart rhythm assessment remotely using the Cardio PAL SAVI monitor. Study participants unable to return for an outpatient visit at the clinical center or to their referring cardiologist office will be issued the Cardio PAL SAVI monitor by the study coordinator. Instructions for programming, completing and submitting the remote heart rhythm recording can be found in the Cardio PAL SAVI monitor brochures. Additional information and training can also be found on the YouTube links below.
Cardio PAL SAVI (for patients with a landline phone)
https://www.youtube.com/watch?v=ELxkFVw61fw&feature=youtu.be

SAVI Air (for patients without a landline phone)
https://www.youtube.com/watch?v=jewzELS9ofI&feature=youtu.be

For US sites only, the study coordinator is responsible for registering the study participant with Medicomp and providing training on the use of the Cardio PAL SAVI monitor. Once a study participant has been registered with Medicomp, a representative of the company will work directly with the study participant to schedule recordings and transmit the heart rhythms.
For Canadian sites, the coordinator will be responsible on providing training on the use of the Cardio PAL SAVI monitors and sending out the monitors directly to the participant. The coordinator will also be responsible for scheduling recordings and transmitting the heart rhythms. Medicomp representatives will be available for help via phone, if needed for the Canadian sites. All heart rhythm recordings received by Medicomp will be transmitted to the DCC for review by the adjudication committee. All heart rhythms done by Medicomp for this trial will be adjudicated by the adjudication Committee.

For participants that are hospitalized for the index hospitalization past the 30 and 60 day follow up window and have NOT been discharged during this period, coordinators should complete the 30 and 60 Day follow up forms in the EDC by checking off any adverse events or procedures that occurred during this period. The option for “Hospitalization/ED/short stay” should be left blank for the follow up visit being completed.

G. Hospitalization

To establish the primary endpoint for the trial, admission and discharge dates and times are required for all randomized study participants' hospitalizations. Furthermore, **hospitalizations extending past the 60-day post-randomization visit window are to be followed and the discharge date and time recorded in the EDC** once available to the study team.

For all hospitalizations, discharge summaries are to be uploaded directly in the EDC under the corresponding hospitalization CRF. It is important to note that the source documentation for admission and discharge dates and times should be consistent for each study participant at your clinical center. Prior to first randomization, the clinical center should identify where discharge dates and times are recorded for their institution and discuss how discharge dates and times will be collected and source documented for outside hospitalizations.

Index Hospitalization

The data captured on the Index Hospitalization CRF helps to establish the inpatient care costs, documents the status of amiodarone use at the time of discharge, includes the criteria used to establish cardiac discharge eligibility, documents INR at discharge for those on warfarin, and includes information on the disposition at hospital discharge of the study participant.

Length of Stay

While each study participant will have their hospital admission date recorded, index hospitalization length of stay is calculated from the date and time of ICU admission following the index surgical procedure. Any transfer between units or floors, e.g., ICU to cardiac step down unit, during the index hospitalization will also be collected with the date and time of admission and discharge recorded for each transfer. Admission, discharge and any transfer will be recorded in chronological order on the Index Hospitalization CRF. For this trial, there are specific guidelines to remember when documenting the length of stay during the index hospitalization include:

- ICU is defined as all critical care floors for all departments within the hospital, including Cardiac ICU, CCU, Neurological ICU, and Medical ICU.
- Telemetry/Step down is defined as continuous telemetry monitoring not on a critical care floor.
- Regular floor is defined as any floor within the hospital that is not critical care and/or when the study participant is not monitored by continuous telemetry.

Conversion to Sustained, Stable, Non-AF Rhythm

The Index Hospitalization CRF will also document whether the study participant converts to sustained, stable non-AF rhythm within 7 days of randomization or by the time of discharge. Each clinical center is required to provide consistent source documentation across their study

participants that clearly demonstrate the institutional care protocols being utilized for establishing stability of non-AF rhythm.

Any reoccurrence of AF following a return to a stable non-AF rhythm within 7 days of randomization while still hospitalized for the index surgery is not considered converted to a sustained, stable non-AF rhythm. Study participants need to remain in a stable non-AF rhythm till discharge for the study coordinator to answer 'yes' to question 3 on the index hospitalization CRF.

Amiodarone Status
The status of amiodarone treatment will be recorded for both treatment arms. Those randomized to and treated with rate control select No or Yes as applicable, randomized to rate control AND specify any reason for administration of Amiodarone.

For those that were randomized to rhythm control select No or Yes as applicable, randomized to rhythm control AND specify any reason for hold or discontinuation of amiodarone.

Cardiac Eligible and Hospital Discharges
For this trial, two discharge dates are recorded for the index hospitalization. Study participants will have their official date of hospital discharge recorded and the date of cardiac discharge eligibility. Cardiac discharge eligibility will be based on the criteria listed below and may not necessarily coincide with date of index hospital discharge.

For those study participants receiving warfarin, **one** of the following criteria must be met to be deemed eligible for cardiac discharge:

- Target INR of 2.0-3.0
- < 2.0 (*and* bridged with LMWH)

For those study participants being treated with rhythm control, **one** of the following criteria must be met to be deemed eligible for cardiac discharge:

- Absence of AF for 24 or more consecutive hours and no AF at time of discharge
- Presence of AF after treatment with amiodarone for at least 48 hours (which covers patients with paroxysmal AF) with adequate control of rate
- Presence of AF after treatment with amiodarone for at least 48 hours and one or more attempts of electrical cardioversion, with adequate control of rate

For those study participants treated with rate control, a ventricular rate at rest of less than 100 bpm meets the criteria for a cardiac eligible discharge.

Establishing the date of cardiac discharge eligibility might be easiest during a chart review of the inpatient medical record with the PI (or delegated MD investigator) at the time of or following

index hospital discharge. It is expected that the information for cardiac eligibility be obtained from the medical record through lab results, documented vital signs, and noted presence/absence of AF. Creating a worksheet that identifies the criteria and records where the source documentation is located is recommended. Please see Section XIV (Monitoring) under the sub-heading Source Documentation for information on acceptable trial source documentation.

The PI (or delegated MD investigator) is to review the source document(s) with the study coordinator to confirm that the criterion has been met and the date of cardiac discharge eligibility is accurate.

Event Driven Hospitalizations

Following index hospitalization discharge, all short stays (< 24 hours), emergency department (ED) visits (any duration) and re-hospitalizations (≥24 hours) will be captured using an event driven ED & Re-Hospitalization CRF. The CRF is an event driven form that captures the following information:

- Type of visit:
    - Short stay: Any hospital admission, typically same day surgical procedures, lasting less than 24 hours; examples include:
        - Cardioversion
        - Pacemaker/ICD implant or generator change
        - Arthroscopic surgery
        - Endoscopic procedures
        - Hernia Repairs
        - Biopsies
        - Cataract surgery
        - Oral surgery
    - Emergency Department (ED): Any ED admission with no threshold for duration of care. All ED admissions are recorded.
    - Re-hospitalization: Any hospital admission resulting in a greater than or equal to 24 hour length of stay.
- Admission date and time
- Reason for visit or stay:
    - All cardiovascular reasons will be recorded as either atrial fibrillation management/treatment or other with the specific cardiovascular reason documented
    - Specific non-cardiovascular reasons for visit/stay are not recorded
- Whether visit/stay is attributable to an adverse event
- Presence or absence of any cardiac procedure occurring during the visit/stay
- Discharge date and time
- Disposition at ED/hospital discharge

Any visit that is a short stay, ED visit or re-hospitalization will be recorded on an individual event driven ED & Re-Hospitalization CRF. For study participants admitted to the hospital through the ED, study coordinators will complete a single CRF selecting hospitalization and using the ED entry date and time in the admission fields. Additionally, please note that outpatient clinic visit and visits to urgent care facilities are **not** to be recorded under short stay visit.
Please note that with Rev 2.0 of the protocol, atrial fibrillation and atrial flutter (AF) have been removed from the protocol definition of the arrhythmia adverse event. Therefore, you will not need to report an adverse event for AF treated on an outpatient basis because it will be captured elsewhere in the data set as an endpoint. However, as with all re-admissions, should a patient require an ED visit or hospitalization for AF, you should create an adverse event to capture the reason for admission. The event classification would be listed under "Other" as AF.

H. Laboratory Assessment

INR on the day of discharge will be recorded on the Index Hospitalization CRF for all randomized study participants receiving warfarin. INR collected within the 24 hours prior to official discharge time will be accepted. Clinical centers will collect a blood sample according to the standard institutional procedures for blood collection and submit the sample to their local laboratory for analysis. Please review whether it is standard institutional practice for postoperative patients receiving warfarin to have their INR drawn on the day of discharge. It is anticipated that this measurement will be part of the standard of care labs collected on the day of discharge. Please include collection of INR value as part of your start up planning; to ensure INR is collected as per the protocol.
As a reminder, all INR results are to be reviewed, signed and dated by a study investigator.

I. Modified Rankin Scale and NIHSS

Following a cerebrovascular thromboembolic event, certified study personnel have 72 hours to administer the NIHSS and mRS to document the presence and severity of any neurologic deficit. The NIHSS and mRS will be administered a second time at the termination of trial follow-up.

The mRS and NIHSS are automatically generated on the EDC under event driven once a study coordinator has entered and saved a cerebrovascular thromboembolic event on an adverse event CRF. Information on administering these scales can be found in Appendix I of the protocol.

In the event that a cerebrovascular thromboembolic event occurs outside of the institution where the patient was treated and randomized, please make every effort to obtain as much source documentation as possible, including neurological exams, mRS, NIHSS, and imaging exams and reports. In the event that the mRS and NIHSS assessments are not administered, please note this on the CRF.

J. Mortality

The clinical site is required to notify the DCC of the death of a randomized study participant within 24 hours of knowledge of the event. Notification may occur electronically through the EDC using the Mortality CRF.

The clinical site will complete the Mortality CRF documenting the immediate cause of death, the primary underlying cause of death, the status of an autopsy, and the investigator's assessment of the relatedness to the index surgical procedure and to the randomization assignment. In addition, the investigator must provide the narrative of the events leading to the patient's death.
For mortalities occurring outside of the enrolling site and for which source documentation cannot be obtained promptly, sites should complete and submit to the DCC the *Principal Investigator Serious Adverse Events, Early Stopping Events, Unexpected Problems and Death Report* within 5 calendar days. This form will document the site's attempts to obtain source documentation. Sites should then continue to request the supporting source documentation, and provide the supporting source documentation to the DCC as soon as it is obtained.

The study coordinator may enter the data onto the Mortality CRF but source documentation must be available to support the investigator's assessments of relatedness and their narrative. More detail on timelines for submission of source documentation to the DCC is available in *the CTSN Clinical & Adverse Event Reporting and Adjudication Procedures* manual.

K. Study Completion

Randomization status determines the location for documenting study completion in the EDC.

<u>Non-randomized Study Participants</u>
Study completion will be documented using the Randomization Eligibility CRF. The study coordinator will select patient not randomized and enter the reason for why the participant was not randomized. Data collection for these participants will conclude with the completion of the Randomization Eligibility CRF. However, any existing CRFs that are incomplete are still required to be completed by the study coordinator.

<u>Randomized Study Participants</u>
Study completion and early termination for randomized study participants will be captured on the Study Completion/Early Termination CRF. Every effort should be made by the study team to have each randomized study participant complete all aspects of the study. Study coordinators are required to provide a narrative for all randomized study participants who are terminated early.

Extremely limited data collection will continue for any study participant hospitalized at the time of study completion or early termination. As a reminder, due to the primary endpoint analysis, any hospitalization, index or subsequent, extending past the 60-day post-randomization follow-up window still requires the collection of hospital discharge and time.

Please follow these instructions for entering the date of study completion for those study participants followed through the 60-day post-randomization visit:

- Not hospitalized: date is last data point collected for the 60-day post-randomization follow-up visit.
- Hospitalized: date study participant is discharged from hospital when hospitalization extends past the 60-day post-randomization visit window or last date of 60-day post-randomization window.

Please follow these instructions for entering the date of early termination:

- Mortality: date of death on the mortality CRF.
- Full consent withdrawn from the study: date of withdrawal obtained from the source document where official study withdrawal is recorded.
- Partial consent withdrawn from the study: Participants with partial consent withdrawn will have "consent withdrawn" checked with details about when consent was revoked and permission granted to allow their medical records to be searched until the end of 60 day follow up; but the date of study exit will be the last date information is collected from the medical record.
- Lost to follow-up: date of last known proof of life.

Contact documented in the medical record, including encounters with other services, correspondence with study team, or in-person visit are all known proofs of life; whichever chronological date is last will be identified as the known proof of life date. Clinical sites are required to record how the last known proof of life date was determined.

For all randomized study participants that did not complete the follow-up period, the reason for early study exit will be entered. Reason for early termination should be clearly recorded in the study participant's record. The clinical site is required to document the steps taken to locate the status of a study participant and show all efforts were made to track the participant when selecting lost to follow-up as the reason for early trial exit.

Demonstration of maximum effort to establish study participant status includes:

- Record of attempts, including those to relatives, to reach the study participant via telephone, e-mail and/or mail on the Patient Contact Log;
- Documentation of undeliverable certified letter;

- Verification that no evidence exists of a service visit or encounter in the medical record;
- Confirmation that a death notice is not available through research of media sources, e.g., internet or newspaper search

L. Investigator Statement

For all randomized study participants, the clinical site PI will electronically sign the Investigator Statement CRF to attest the accuracy and completeness of the data entered. Once the data for a randomized study participant has been monitored by the DCC and the data has been locked, access will be granted for the PI to electronically sign the Investigator Statement CRF.

XII. SELECTED ADVERSE EVENTS

Adverse events are collected for all study participants randomized in the trial. Therefore, from the time of randomization through the 60-day post-randomization visit is the reporting window for all adverse events defined in the protocol. Any ongoing adverse event that has not resolved at the time of study completion or early termination for a study participant will be marked on the adverse event CRF as 'Not resolved by end of study' under question 3.

Information describing the procedures for reporting adverse events (AEs) and unanticipated problems (UPs) and the process for reviewing and adjudicating events can be found in the CTSN *Clinical & Adverse Event Reporting and Adjudication Procedures* manual.

The main purpose of this section is to provide further clarification on determining how to report adverse events associated with neurologic and/or bleeding mechanisms. Understanding the distinction between the definitions of a neurologic event and bleeding event is important for successful reporting of the adverse events below.

A. Cerebrovascular Thromboembolism (TIA & Stroke)

As described in the protocol, cerebrovascular thromboembolism adverse events are to be identified through appropriate diagnostic testing and documented in the neurologist or other qualified treating clinician consultation note. These events are classified differently from a bleeding adverse event due to the initial presentation of a neurological deficit and thromboembolic mechanism. Based on the examining physician's documentation, the cerebrovascular thromboembolism will be classified as either a transient ischemic attack (TIA) or stroke.

Ischemic or Hemorrhagic Stroke

The main difference between this adverse event and the type 3c bleeding event is that the study participant will present with focal neurologic deficit(s) that persists beyond 24 hours or less than 24 hours with image confirmation of infarction or hemorrhage. The presentation of the focal neurologic deficient will trigger further evaluation and treatment by clinician(s).

TIA

Similar to the ischemic or hemorrhagic stroke event, the study participant will present with a neurologic deficit that will lead to further evaluation. In this case, imaging will not reveal any evidence of an infarction or hemorrhage and deficit will resolve within 24 hours of presentation.

B. Non- cerebral Thromboembolism

Similar to the cerebrovascular thromboembolism adverse event, non-cerebral thromboembolism events are not classified under the bleeding adverse event definition due to the thromboembolic nature of the event.

Thromboembolism must be confirmed by either diagnostic testing, directly observed as an operative finding and/or confirmed from the autopsy.

C. Bleeding

The bleeding adverse event definitions for this trial are based on the proposed universal bleeding definitions from the *Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report from the Bleeding Academic Research* Consortium (*Circulation*. 2011; 123:2736-2747). Please note that the bleeding definitions from the report have been adapted for the objective, patient population and endpoints of this trial.

Type of Bleed	Bleed Type Clarification
Type 1	• Evident minor bleeding, e.g., nose bleed, hematoma bruising, which does not require unscheduled medical attention, diagnostic testing or treatment. • Will typically be reported during inpatient hospitalizations as it will be documented in medical record as having occurred with no need for additional assessment or treatment.
Type 2	• Bleeding that requires intervention, defined as a healthcare professional-guided medical treatment or percutaneous intervention to stop or treat the bleeding. o Study participant on warfarin is unable to stop nose bleed or

Type of Bleed	Bleed Type Clarification
	treated with nasal packing. o Study participant has a laceration that requires local injection to reduce oozing. • Bleeding that leads to a hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. o Hospitalized study participant develops a GI bleed that lengthens their stay. o Study participant is hospitalized after car accident for internal bleeding without a surgical intervention. • Bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory & imaging), including, but not limited to, hematocrit testing, hemoccult testing, endoscopy, colonoscopy, computed tomography scanning or urinalysis. o Study participant reports black stool undergoes outpatient diagnostic testing. • A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.
Type 3a	• Any evident bleeding that requires a transfusion. • Any evident bleeding where a corresponding drop in hemoglobin, defined as ≥ 3 g/dL to < 5 g/dL, is directly attributed to the bleed.
Type 3b	• Any evident bleeding with a corresponding drop in hemoglobin ≥ 5 g/dL that is directly attributed to the bleed. • Cardiac tamponade that does not require re-operation. • Bleeding that requires surgical intervention for control that is not due to a hemorrhage or tamponade. • Bleeding requiring intravenous vasoactive drugs as treatment.
Type 3c	• Massive bleed due to destabilized vascular lesion or head trauma resulting in intracranial hemorrhage. Examples include: o Arteriovenous malformation (AVM) rupture o Spontaneous aneurysm rupture
Type 4	• Massive bleed due to destabilized vascular lesion or head trauma resulting in intracranial hemorrhage within 48 hours of the perioperative period. • Internal bleeding after the closure of sternotomy that requires re-

Type of Bleed	Bleed Type Clarification
	operation to control the bleed. • Chest tube output greater or equal to 2L within a 24-hour period. • Allogenic transfusions of ≥ 5 unit's whole blood or packed red blood cells within a 48-hour period.
Type 5	• Death linked to bleeding with no other explainable cause.A fatal bleeding event is defined as: o Death due to hemorrhage

XIII. MONITORING

A. Types of Monitoring and Trial Expectations

Remote Monitoring

The DCC monitoring team employs a risk-based approach to remote (or centralized) monitoring. The remote monitoring of clinical trial data via the EDC system is performed with a focus on safety, study endpoints, data completion, data outliers and data integrity.

Randomized Patients:

For randomized patients in this trial, a select group of CRFs require source documentation be uploaded directly in the EDC upon availability to the study team and within 10 days of study assessment completion. Submission of source documentation directly into the EDC will allow for 'real time monitoring' of these selected CRFs to ensure that data is being captured appropriately and in a timely manner. The selected CRFs and the requested source documents are as follows:

- Eligibility and Enrollment (include redacted consent form and consent progress note)
- Pre-Operative Parameters
- Index Surgical Procedure
- Randomization Eligibility
- Medication Log
- Follow-Up Procedures
- Hospitalizations
- Adverse Events

Timeline for source documentation upload to the EDC:

- Baseline Forms must be uploaded to the EDC within 10 days of surgery.
- Post Randomization forms must be uploaded to the EDC within 10 days of randomization date.
- Follow up assessment forms must be uploaded to the EDC within 10 days of the follow up visit.

Non- Randomized Patients:

The DCC will request source documents on a random subset of non-randomized patients. Data on non-randomized patients should be entered completely, and source documentation should be available for DCC review upon request.

Additionally, the DCC may request source documentation from the site for CRFs in the EDC not listed above. The site should provide requested source documentation within 10 business days of each request. The site may provide source documentation to the DCC for remote monitoring in any of several ways. Redacted source documentation may be uploaded to the EDC for the specific CRF to which it pertains. The site may also redact and e-mail source documentation to the DCC via a secure or encrypted messaging system approved by its own institution. Lastly, sites may provide DCC monitors with remote access to their Electronic Medical Record system.

Redacted source documentation sent to the DCC via EDC upload or via secure email must contain the patient ID on each page.

Patient informed consent documents and a consent progress note for each patient should be transmitted to the DCC monitors for review. The Site should upload a redacted copy of the informed consent documents to the EDC. The copy uploaded to the EDC should contain only the date the patient signed the form and the patient study ID on each page. This will allow the DCC monitors to review the consent process and to confirm that the correct version of the consent document was employed.

DCC Monitors will provide feedback as they source verify data points in the EDC via the EDC query system. Sites should review their EDC homepage for new queries often and respond to queries as soon as possible. The EDC will track the timeliness of query responses.

Remote Monitoring via access to the Site Electronic Medical Record (EMR)

Sites may provide DCC monitors with remote access to their institutional EMR systems for the purpose of remotely monitoring source documentation. If a site's institutional Informatics group allows for this remote access to be available, the site will assist DCC staff members to obtain credentialing for EMR access, provide DCC staff who are granted access with a brief tutorial of the EMR system and provide support as needed. While a majority of supporting source documentation will be included in the EMR and therefore will not require redacting and uploading to the EDC, certain types of source documentation will be required to be uploaded and **must be redacted and uploaded to the EDC per usual remote monitoring guidelines.** Those exceptions are as follows:

- All source documentation required for study monitoring but unavailable via the EMR system (i.e., consent forms, consent form progress notes, worksheets, patient follow-up progress notes, etc.). This may also include source documentation received from an outside hospital or from a cardiologist's office for follow-up purposes. This will vary by system; some institutions may include some or all of these documents in the EMR.
- All source documentation for any item requiring adjudication per protocol. All CTSN protocols require adjudication of adverse events and mortalities. The clinical center is responsible for choosing the appropriate source documentation to represent the entirety of the event. The source documentation for all adverse events and mortalities reported in the EDC must be redacted and uploaded to the appropriate CRF.
- In the POAF study, ECGs for discharge, Day 30 and Day 60 will be adjudicated, and therefore, the site must upload redacted source documentation to the appropriate CRF.

In collaboration with the DCC data management team, the monitor will create and utilize reports outlining data completeness and timeliness, missing and outlier values, as well as cross form consistency validations to generate queries and optimize reconciliation of data. This process significantly increases the efficiency of monitoring both remotely and while on site. These reports may provide insights that will lead to requests from the DCC for clarification, additional source documentation or other data verification at the site.

The monitor will centrally monitor study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event Log periodically to ensure that the site is adhering to the study protocol and procedures. The site must forward study documents to the DCC upon request for remote monitoring.

Regulatory documentation will also be monitored remotely to ensure that site essential document binders remain current in the interim between on-site monitoring visits. The site must forward updated study documents to the DCC upon request for remote monitoring.

<u>On-Site Monitoring</u>

InCHOIR also utilizes a risk-based approach to on-site monitoring, with a schedule that is informed by the investigational intervention, target population disease severity, phase of the trial, and site performance. Study coordinators are to have all source documents up to date and easily accessible to the monitors.

During an on-site monitoring visit, the DCC Clinical Monitor's responsibilities are to:

- Track the overall study process, including all data collected and entered, visit schedules, and patient screening and enrollment.

- Verify and ensure compliance with the protocol according to GCP and HIPAA or PIPEDA requirements.
- Ensure that appropriate data corrections are made, dated, explained and initialed by the investigator or a representative.
- Assess the impact of the site facility and personnel changes.
- Verify a minimum of the following data points for all patients: date of birth, sex, signed informed consent, eligibility criteria, medical history, date of enrollment, and protocol-defined SAEs and mortalities.
- Perform review of informed consent processes and review documentation of informed consent for completeness and correctness
- Perform on-site validation checks of recorded data by reviewing source documents to determine whether the data reported in the EDC system are complete and accurate. Source documents include medical charts, initial hospital admission reports, operative procedure records and other study related notes.
- Monitor patient safety by verifying that any AE, therapy modification or concomitant medications are reported in accordance with the protocol.
- Determine whether all AEs, protocol deviations and protocol violations are appropriately reported within the required time periods according to applicable regulatory requirements (such as GCP, protocol definitions and IRB/REB requirements).
- Verify that any missed study visits, tests and examinations that were not performed, as well as study withdrawals and/or dropouts are explained and clearly reported as such.
- Inform the site PI about any deviations from or violations of the study protocol, SOPs, GCP and/or regulatory requirements in order for appropriate actions to be taken to prevent recurrence of the deviations and/or violations.
- Inform the investigator of any major data entry error, delays in data entry, omissions or eligibility requirement errors.
- Verify that regulatory documentation is accurate, complete, current and properly maintained.

The study monitors reserve the right to copy coded records in support of all adverse events and outcomes. Copies of any coded source documents requested by the DCC must be sent via secure e-mail, secure fax, or FedEx on an as needed basis for the duration of the study.

The Monitor will inspect the site's facilities to verify that proper space and storage for study documents and equipment is available throughout the study. The Monitor will review source documentation for a subset of patients and compare this with the information entered in the EDC to verify data correctness (if necessary). Additionally, the Monitor will address any issues or concerns the site has encountered during the course of the study.

The DCC Monitor will submit a written monitoring visit report to the DCC and NHLBI and will send a follow-up letter with findings to the Principal Investigator (and Business Official) within 30 days of the visit. The report and letter will include a summary of the documentation reviewed by the Monitor, any significant findings, adverse events, protocol deviations and violations, missing regulatory documents and actions taken, to be taken or recommended to ensure compliance. The report and letter will include a list of Action Items. Sites are expected to complete the list of Action Items within 30 days of receipt.

B. Source documentation requirements

It is highly recommended that study coordinators use the CRFs and schedule of assessments in the protocol to develop a plan for identifying and standardizing where source documentation will be collected for all study participants at their clinical center. As part of study startup and prior to first enrollment, clinical sites are encouraged to conduct a gap analysis to identify any data points that are not routinely documented in the medical record. A source document template should be developed to document any data that is not routinely documented in the medical record.

The medical record is the gold standard for source documentation as it includes clinic notes, lab reports, pharmacy orders and dispensing records, admission/discharge notes, test results and so forth. However, the DCC understands that there may be data points required for this trial that are not collected as routine practice at a clinical site in the medical record for this patient population. Clinical sites may create source documents for the purposes of collecting source data that are not included in the medical record. **It is important to remember that "source" documentation is where the information is first recorded.**

Any source document that is not part of the medical record must be signed and dated by the study team member gathering the source data. Additionally, all hand-written source documentation must be initialed and dated on each page by the document's author with a full signature and date on the last page of a source document. Any corrections made on source documents need to be crossed out with a single line, signed and dated.

When using a CRF as source documentation please ensure that you are using the most up to date version of the CRF, as CRFs are updated periodically.

In order to document investigator oversight of the study, the PI (or a designated MD investigator) should sign and date laboratory reports, ECGs and other source documentation with a note of any clinically significant findings, if applicable.

For lab values with whole number values, any values of 0.5 or higher should be rounded to the next whole number. Values less than or equal to 0.4 should be rounded down to the lower whole number.

In preparation for upcoming study visits, study coordinators should review patient records for previously undocumented adverse events, procedures and hospitalizations.

The clinical site must ensure that all patient source documentation is complete, orderly and stored in a secure location. For electronic records, the site should abide by institutional policies for the storage of private health information (PHI). For paper records containing any PHI, sites must ensure that the files are double-locked, that is, in a locked filing cabinet within a locked office or suite.

C. Consent Form Documentation

Review each informed consent document prior to initiating the consent process to be sure the correct version is being employed. During the informed consent process, be sure that each space for initials, signature and date is complete. If deficiencies are identified after the informed consent process, document them in a progress note or note to file. Ensure that appropriate signatures, initials or dates are obtained at the next available opportunity.

Be sure that each patient needing to be re-consented (because of a newly approved version of the informed consent document) is approached at the next available opportunity.

Ensure that your documentation of the consent process in a progress note contains at least the following components:

- The patient was deemed to meet study eligibility requirements
- The patient was given the opportunity to ask questions and the questions were answered
- Documentation of any family members or witnesses who participated in the consent process
- The patient understands the study follow-up requirements and study procedures
- A copy of the consent form was provided to subject.
- All study procedures occurred after the ICF was signed.
- The study is optional and that the patient was informed of alternative procedures.

D. Queries

Coordinators should review monitor-generated queries in the EDC on a regular basis. Site coordinators are to respond to all queries within 10 business days of query generation. DCC monitors will respond to or close out queries within 15 business days of coordinator response.

E. Data Completion Reports

Although study enrollment is often viewed as the measure of a site's success, patient retention and data completeness are the deliverables required for each patient enrolled. Failure to capture study endpoints for each patient compromises the overall data set. The DCC will generate a monthly Data Completion Report to inform the clinical sites of outstanding data and to provide information on site performance. Site PIs should review each Data Completion Report to stay abreast of site performance and to be aware of any missing primary or secondary endpoint data. The DCC will track performance over time and will schedule a teleconference with the site PI if data completeness rates fall below 90% or do not improve after discussion with the study coordinator.

XIV. STUDY CLOSEOUT

Once the study has been completed and all data and finalized CRFs are submitted by the site, the DCC will send the PI and study coordinator(s) a copy of the policy for maintaining records and completing tasks identified as part of close-out. Some of the tasks that are part of close-out to be completed by the clinical site include:

- Completing any outstanding tasks outlined by the DCC
- Adding end dates and obtaining the PI signature on the DOA Log and submitting final DOA Log to the DCC
- Providing the DCC with the institutional policy on record retention for your clinical center
- Submission of IRB/REB acknowledgement of study closure to the DCC

Once a site has completed the tasks and all data has been monitored and locked, the PI will sign an attestation statement confirming the accuracy and completeness of the data collected for all pre-screening failures and study participants and verifying that the regulatory documents submitted are accurate and complete. The attestation statement will be sent to PI with the study coordinator copied via email. The statement is to be returned by email to Karen O'Sullivan and Angela Villanueva or faxed to 212-731-7346.

A final report will be generated by the monitor and sent to the site and NHLBI.

APPENDIX I: PATIENT CONTACT LOG

The Postoperative AF Patient Contact Log is to be used by each clinical site to document all patient contact that is not a protocol defined study visit. Any e-mail, telephone, mail or in-person visit that is not a study visit will be documented using the Log. Examples of contact to be documented include:

- E-mail reminder about upcoming study visit
- Telephone call asking study team to schedule upcoming visit
- Letter sent in the mail to confirm upcoming study visit
- In-person clinic visit for adverse event
- Telephone call to study participant reminding them about remote ECG

The Postoperative AF Patient Contact Log template is located on the next page and should be copied prior to first randomization at the clinical site. Clinical sites may elect to use one log to document all randomized study participant contact or to use separate logs for each randomized study participant. Logs that capture all randomized study participant contact are to be kept in the clinical site regulatory binder. Logs that are specific to an individual randomized study participant are to be kept with the source documentation in their research binder/file. All logs will be monitored on a regular basis.

Postoperative AF Trial Patient Contact Log

Patient ID	Person Initiating Contact	Date	Time	Method of Contact *(E.g. phone call, email, standard mail, priority mail, certified mail, etc.)*	Issue Discussed	Comments

APPENDIX II: RATE CONTROL MEDICATIONS

2011 ACCF/AHA/HRS Focused Updates Incorporated into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: A Report on the American College of Cardiology Foundation/American Heart Association Take Force on Practice Guidelines. (Internet address: http://circ.ahajournals.org/content/123/10/e269.full.pdf.)

Table 10. Intravenous and Orally Administered Pharmacological Agents for Heart Rate Control in Patients With Atrial Fibrillation

Drug	Class/LOE Recommendation	Loading Dose	Onset	Maintenance Dose	Major Side Effects
ACUTE SETTING					
Heart rate control in patients without accessory pathway					
Esmolol*†	Class I, LOE C	500 mcg/kg IV over 1 min	5 min	60 to 200 mcg/kg/min IV	↓ BP, HB, ↓ HR, asthma, HF
Metoprolol†	Class I, LOE C	2.5 to 5 mg IV bolus over 2 min; up to 3 doses	5 min	NA	↓ BP, HB, ↓ HR, asthma, HF
Propranolol†	Class I, LOE C	0.15 mg/kg IV	5 min	NA	↓ BP, HB, ↓ HR, asthma, HF
Diltiazem	Class I, LOE B	0.25 mg/kg IV over 2 min	2 to 7 min	5 to 15 mg/h IV	↓ BP, HB, HF
Verapamil	Class I, LOE B	0.075 to 0.15 mg/kg IV over 2 min	3 to 5 min	NA	↓ BP, HB, HF
Heart rate control in patients with accessory pathway§					
Amiodarone‡‖	Class IIa, LOE C	150 mg over 10 min	Days	0.5 to 1 mg/min IV	↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia
Heart rate control in patients with heart failure and without accessory pathway					
Digoxin	Class I, LOE B	0.25 mg IV each 2 h, up to 1.5 mg	60 min or more§	0.125 to 0.375 mg daily IV or orally	Digitalis toxicity, HB, ↓ HR
Amiodarone‡	Class IIa, LOE C	150 mg over 10 min	Days	0.5 to 1 mg/min IV	↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia
NON-ACUTE SETTING and CHRONIC MAINTENANCE THERAPY¶					
Heart rate control					
Metoprolol†	Class I, LOE C	Same as maintenance dose	4 to 6 h	25 to 100 mg twice a day, orally	↓ BP, HB, ↓ HR, asthma, HF
Propranolol†	Class I, LOE C	Same as maintenance dose	60 to 90 min	80 to 240 mg daily in divided doses, orally	↓ BP, HB, ↓ HR, asthma, HF
Diltiazem	Class I, LOE B	Same as maintenance dose	2 to 4 h	120 to 360 mg daily in divided doses; slow release available, orally	↓ BP, HB, HF
Verapamil	Class I, LOE B	Same as maintenance dose	1 to 2 h	120 to 360 mg daily in divided doses; slow release available, orally	↓ BP, HB, HF, digoxin interaction
Heart rate control in patients with heart failure and without accessory pathway					
Digoxin	Class I, LOE C	0.5 mg by mouth daily	2 days	0.125 to 0.375 mg daily, orally	Digitalis toxicity, HB, ↓ HR
Amiodarone‡	Class IIb, LOE C	800 mg daily for 1 wk, orally 600 mg daily for 1 wk, orally 400 mg daily for 4 to 6 wk, orally	1 to 3 wk	200 mg daily, orally	↓ BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia

*Onset is variable and some effect occurs earlier.

†Only representative members of the type of beta-adrenergic antagonist drugs are included in the table, but other, similar agents could be used for this indication in appropriate doses. Beta blockers are grouped in an order preceding the alphabetical listing of drugs.

‡Amiodarone can be useful to control the heart rate in patients with atrial fibrillation (AF) when other measures are unsuccessful or contraindicated.

§Conversion to sinus rhythm and catheter ablation of the accessory pathway are generally recommended; pharmacological therapy for rate control may be appropriate in certain patients.

‖If rhythm cannot be converted or ablated and rate control is needed, intravenous (IV) amiodarone is recommended.

¶Adequacy of heart rate control should be assessed during physical activity as well as at rest.

↓ BP indicates hypotension; ↓ HR, bradycardia; HB, heart block; HF, heart failure; LOE, level of evidence; and NA, not applicable.