Cardiothoracic Surgical Trials Network

Protocol

RATE CONTROL VERSUS RHYTHM CONTROL FOR POSTOPERATIVE ATRIAL FIBRILLATION

Sponsored By NHLBI, NINDS, & CIHR

CT Surgical Trials Network Research Group

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TABLE OF CONTENTS

TABLE OF CHANGES

Revision	Section	Change	Reason	Page
1.0	Rhythm Control Strategy	Provided more detail on timing of cardioversion	Protocol clarification	15-16
1.0	Rate Control to Rhythm Control	Reworded criteria for a change in management plan for clarity	Protocol clarification	17
2.0	Cover Page, Footers	Updated Rev to 2.0 and date to September 2014	Protocol Update	All
2.0	Definitions, Acronyms & Abbreviations	Added TAVR to list	For consistency within protocol	5
2.0	Abstract: Enrollment Exclusion Criteria	Removed "Trans-apical" from description of TAVR; added Amiodarone within 6 weeks of index surgery as an exclusion criterion	Protocol correction and update	7
2.0	Data Collection Schedule	Added Rankin, NIHSS; removed Treatment Documentation; corrected and clarified other items	For internal consistency within protocol	9
2.0	Adverse Events	Added clarification of "other than AF or AFL" to arrhythmia description	Protocol clarification	12
2.0	Enrollment Exclusion Criteria	Removed "Trans-apical" from description of TAVR; added Amiodarone within 6 weeks of index surgery as an exclusion criterion	Protocol correction and update	14
2.0	Cerebrovascular thromboembolism	Removed duplicative language from description of assessment	Protocol update	20
2.0	Fatal bleeding	Clarified definition of fatal bleeding classification	Protocol clarification	21
2.0	Cardiac Arrhythmias	Added clarification of "other than AF or AFL" to supraventricular arrhythmia description	Protocol clarification	21
2.0	Physical Examination, Medications	Changed window to "Prior to initial surgical intervention"	For internal consistency within protocol	25
2.0	ECG or Telemetry Recording	Removed "handheld" from description of device	Protocol clarification	26
2.0	Neurological Dysfunction Assessment	Added description of Rankin and NIHSS assessments	Protocol clarification	27
3.0	Abstract: Number of Participants	Updated sample size to 520 patients based on SD of 6.3 and 30% overall crossover rate from sample size re-estimation done instead of formal interim analysis	Protocol update	7
3.0	Definitions and Measurement of Endpoints	Clarified that for ED visits > 24 hours, the number of calendar days in hospital will be counted towards the primary endpoint (not truncated to 2 days in the event visits exceed 48 hours)	Protocol clarification	19-20
3.0	Analytical Plan: Sample Size	Updated sample size to 520 patients based on SD of 6.3 and 30% overall crossover rate from blinded sample size re-estimation done instead of formal interim analysis	Protocol update	30-31
3.0	Analytical Plan: Interim Monitoring Guidelines	Replaced planned formal interim analysis with sample size re-estimation based on blinded assessment of observed variability; updated alpha of final analysis to 0.05 since no alpha was spent on a formal interim analysis	Protocol update	33

DEFINITIONS, ACRONYMS & ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AV	Atrioventricular
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CFR	Code of Federal Regulations
Clcr	Creatinine clearance
CNS	Central nervous system
Cr	Creatinine
CRF	Case report form
CT	Computed tomography
CTA	Clinical trial agreement
CTSN	Cardiothoracic Surgical Trials Network
CV	Curriculum vitae
DC	Direct current
DCC	Data coordinating center
DSMB	Data and safety monitoring board
EAC	Event adjudication committee
ECG	Electrocardiogram
ED	Emergency department
EDC	Electronic data capture
EP	Electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
InCHOIR	International Center for Health Outcomes and Innovation Research
INR	International normalized ratio
IRB	Internal review board
LBBB	Left bundle branch block
LOS	Length of stay
LV	Left ventricular
LVAD	Left ventricular assist device
MI	Myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIHSS	NIH Stroke Scale
NP	Nurse practitioner
OHRP	Office for Human Research Protections
PCI	Percutaneous coronary intervention
PDC	Protocol Development Committee
PFO	Patent foramen ovale
PI	Principal investigator
PT	Prothrombin time

PTT	Partial thromboplastin time
RBC	Red blood cell
SAE	Serious adverse event
SSL	Secure socket layer
STS	Society of Thoracic Surgeons
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
URL	Upper reference limit
VPN	Virtual private network

ABSTRACT

Background	Postoperative atrial fibrillation is the most common complication following cardiac surgery. Its occurrence is associated with adverse clinical outcomes and increased length of hospital stay and resource utilization. Numerous studies have evaluated strategies for prevention of postoperative atrial fibrillation, though even with the most successful of these approaches, 20% to 25% of adult cardiac surgery patients develop postoperative atrial fibrillation. Data to guide management of surgical patients who develop atrial fibrillation are lacking.
Study Design	Randomized (1:1) controlled open-label trial. Patients will be consented prior to surgery and randomized upon occurrence of AF (defined as atrial fibrillation and/or atrial flutter (AFL) after surgery but during hospitalization to a strategy of either rate or rhythm control.
Number of Participants	A total of 520 patients will be randomized to either rate or rhythm control. This will provide 90% power to detect a reduction of 2.0 days in hospital in the rhythm control arm from an assumed 10.4 average number of days in hospital in the rate control arm. The sample size assumes a standard deviation of 6.3 in both arms and an overall crossover rate of 30%.
Study Objectives	To compare the therapeutic strategies of rate versus rhythm control in cardiac surgery patient who develop in-hospital postoperative AF.
Trial Interventions	Patients will be randomized to rate or rhythm control. For each therapy, caregivers will be able to choose from a list of strategies aimed at either rate or rhythm control, depending upon the assigned therapy. Direct current (DC) cardioversion is included in the strategies for rhythm control. *Anti-thrombotic medications*: • Warfarin for patients meeting pre-specified criteria without contraindications. • Aspirin at the discretion of the treating surgeon
Enrollment Inclusion Criteria	• Age $\geq$ 18 years • Undergoing heart surgery for coronary artery bypass (on-pump or off-pump CABG) and/or valve repair or replacement (excluding mechanical valves), including re-operations • Hemodynamically stable

Enrollment Exclusion Criteria	• LVAD insertion or heart transplantation • Maze procedure • TAVR • History of or planned mechanical valve replacement • Correction of complex congenital cardiac defect (excluding bicuspid aortic valve, atrial septal defect or PFO) • History of AF or AFL • History of AF or AFL ablation • Contraindications to warfarin or amiodarone • Received amiodarone within 6 weeks of index surgery • Need for long-term anticoagulation • Concurrent participation in an interventional (drug or device) trial
Randomization Inclusion Criterion	AF that persists for > 60 minutes or recurrent (more than one) episodes of AF up to 7 days after surgery during the index hospitalization.
1^{o} Endpoint	Total number of days in hospital for hospital admissions that occur within 60 days of randomization.
2^{o} Endpoints	AF- or treatment-related events • Duration of hospital stay from randomization to eligibility for discharge based on AF-related criteria (regardless of whether patient is actually discharged) • Heart rhythm at hospital discharge • Heart rhythm (i.e., whether in a stable non-AF rhythm) at 30 and 60 days • Time to stable sustained non-AF rhythm < 7 days of randomization (or hospital discharge, whichever comes first) • Need for permanent pacemaker within 60 days of surgery Economic burden • Length of stay (LOS) (index hospitalization) • LOS (re-hospitalizations, including emergency department (ED) visits) • Outpatient interventions • Costs (hospital) as of surgery date Adverse events • Mortality • Cerebrovascular thromboembolism (stroke, TIA) • Non-cerebrovascular thromboembolism • Bleeding • Selected serious AEs

Ancillary Study Objective	To define factors that increase patients' susceptibility to developing postoperative AF.

DATA COLLECTION SCHEDULE

Assessment	Baseline	Onset of AF[+]	48 hours post onset of AF	Day of Discharge	30 Days *±5 days*	60 Days *±5 days*	Event Driven
General							
Informed Consent	X[1]						
Demographics	X						
Eligibility and Enrollment	X						
ECG or Telemetry Strip*		X		X	X	X	
Preoperative Parameters	X						
Randomization and Treatment Assignment[2]		X					
Surgical Procedure	X						
Medications	X	X	X[3]	X	X	X	X
Index Hospitalization				X			
Additional Procedures							X
Event Driven and Follow Up Assessments							
Follow-Up Assessment					X	X	
Adverse Events							X
Modified Rankin Scale							X
NIH Stroke Scale							X
Mortality							X
Re-Hospitalizations (includes ED and Short Stay Visits)							X
Study Completion						X	X
End of Study/Investigator Statement							X
Cost							
UHC Database						X	
UB-92 Forms & Hospital Bills						X	

[+] Onset of AF is within 7 days of surgical procedure

[1] All eligible patients will be consented prior to surgery

[2] AF that persists post-operatively for > 60 minutes or recurrent *(more than one)* episodes of AF during the index hospitalization

[3] Anticoagulation to commence if the patient has remained in AF continuously since the time of randomization *or* the AF was terminated but recurred one or more times during the first 48 hours after randomization *(i.e. the patient has had more than a single episode of AF)*

* 12 lead ECG, portable ECG, or telemetry monitor strip

OBJECTIVES

Purpose of the Study

The primary aim of this clinical trial is to determine if a strategy of rhythm control for atrial fibrillation and/or atrial flutter (AF) after cardiac surgery reduces days in hospital when compared to a strategy of rate control. The primary endpoint is total number of days in hospital that occur within 60 days of randomization. Utilizing the approach employed by the AFFIRM investigators (Olshansky, Rosenfeld et al. 2004), this trial will compare the general strategies of rate and rhythm control. Recognizing that different pharmacologic agents or procedures may be used to achieve these therapeutic goals, the trial design allows clinicians to choose from a variety of interventions within each arm. Ascertainment of the primary endpoint (total days in hospital within 60 days of randomization) will require active follow-up but not necessarily a return visit to the institution where the surgery was performed.

Primary Hypothesis

In patients who develop AF during hospitalization after cardiac surgery, a strategy of rhythm control will reduce days in hospital within 60 days of the occurrence of AF compared to a strategy of rate control.

Secondary Aims

- Determine time to conversion to sustained, stable non-AF rhythm <7 days of randomization (or hospital discharge) with each strategy
- Compare heart rhythm at hospital discharge and at 30 and 60 days after surgery
- Compare the economic burden associated with each strategy
- Compare the incidence of postoperative clinical events with each strategy

Ancillary Study

To define factors that increase patients' susceptibility to the development of postoperative AF, all enrolled patients will have baseline and operative data collected (including demographics, co-morbidities and cardiovascular medications); these variables will be analyzed as potential risk factors for postoperative AF.

BACKGROUND AND SIGNIFICANCE

The Problem

Postoperative atrial fibrillation is the most common complication after cardiac surgery (Echahidi, Pibarot et al. 2008; Imazio, Belli et al. 2013). Its incidence has been reported to be in the 20-50% range (Mathew, Parks et al. 1996; Lee, Klein et al. 2000; Maisel, Rawn et al. 2001; Lee, Klein et al. 2003; Mathew, Fontes et al. 2004; Echahidi, Pibarot et al. 2008; Ozaydin, Peker et al. 2008; Jongnarangsin and Oral 2009; Nair 2010; Chelazzi, Villa et al. 2011; Imazio, Belli et al. 2013), depending on the definition of postoperative atrial fibrillation and on the method used for screening.

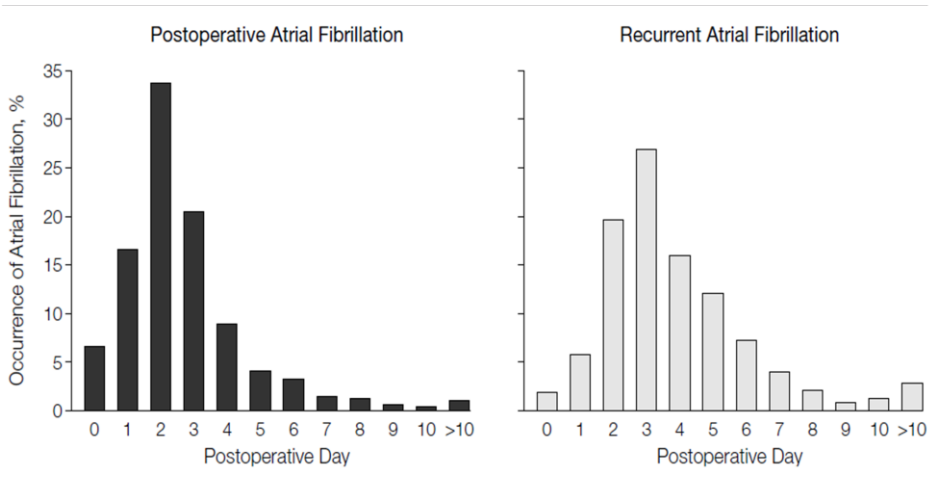

Figure 1: Incidence and Recurrence of Postoperative Atrial Fibrillation after CABG (*reproduced from* Mathew JP, Fontes, ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004; 291:1720)

It is associated with increased morbidity, mortality, hospital length of stay and cost. The annual cost of treatment of postoperative AF in the United States approaches $1 billion (2000). The vast majority of events (~90%) are first detected or recur in the first 7 days post-operatively with the peak first occurrence on days 2-4 (2000; Maisel, Rawn et al. 2001; Mathew, Fontes et al. 2004; Echahidi, Pibarot et al. 2008; Jongnarangsin and Oral 2009) (Figure 1).

AF in Other Clinical Settings

The AFFIRM trial enrolled 4060 patients to evaluate rate control versus rhythm control in non-surgical patients with AF. In that trial, treating physicians were given some latitude in clinical decision-making and asked to choose from a variety of agents to pursue the assigned strategy. The trial's key findings were: 1) that management of AF with rhythm control offered no survival advantage over the rate control strategy, and 2) that patients in the rhythm control arm were more likely to be hospitalized and more likely to experience adverse drug effects.

AF Prevention in Cardiac Surgery

Research of post-operative AF in cardiac surgery has predominantly focused on prevention as opposed to treatment (Lee, Klein et al. 2003). While a variety of strategies have been used to try to prevent the development of postoperative AF, none of them *eliminates* the problem entirely. Various medicines (preoperative beta blockers, antiarrhythmic drugs and even fish oil) and strategies (pacing, posterior pericardiotomy and others) can reduce the incidence of postoperative AF by up to 50% (Mayson, Greenspon et al. 2007). However, these strategies are inconsistently applied and remain the subject of intense study and debate (Al-Khatib, Hafley et al. 2009; Nair 2010).

Rate Control vs. Rhythm Control in Cardiac Surgery

Several retrospective studies suggest similar outcomes with rate control and rhythm control when the primary outcome is heart rhythm at one to two months. In a pilot prospective randomized controlled clinical trial comparing these strategies in 50 patients, investigators found that rhythm control significantly reduced hospital length of stay and recurrent AF with no difference in heart rhythm outcome at two months (at that point, more than 90% of patients in both groups had achieved normal sinus rhythm) (Lee, Klein et al. 2000; Lee, Klein et al. 2003). However, as in the AFFIRM trial, patients treated with rhythm control were more likely to experience adverse events (e.g. hypotension, nausea, bradycardia). All patients experiencing AF received anticoagulation; however, in the rhythm control arm anticoagulation could be stopped at the physician's discretion if sinus rhythm was maintained for 4 weeks or longer.

Current Practice

There is no consensus concerning the best approach to the management of postoperative AF (Mitchell, Crystal et al. 2005; Fuster, Ryden et al. 2006; Echahidi, Pibarot et al. 2008; Nair 2010; Fuster, Ryden et al. 2011). As a result of the paucity of rigorous data to guide clinical decisions concerning strategies for AF management and anticoagulation, treatment strategies vary widely. We conducted a survey of CTSN clinical sites surgeons and cardiologists, and found considerable variation among and within institutions. By far the majority of clinicians responded that they would have equipoise for a randomized trial of rate versus rhythm control. This supports the literature, which has argued that there is an important need for such clinical trials (Al-Khatib, Hafley et al. 2009). Because it is a transient phenomenon (within 2 months 80% to 90% of patients return to normal sinus rhythm), it is unlikely that any management strategy for AF in the peri-operative period will have an important impact on the ultimate heart rhythm. However, it is possible that rhythm control reduces length of time in hospital, including the need for readmissions to manage AF. Alternatively, a rhythm control strategy may expose patients to an excess hazard of adverse events. Confirmation of such findings would have important implications for patient management in a time of limited resources and strong incentives to reduce the costs of care.

In summary, the rationale for conducting this trial is that it addresses the single most common complication following cardiac surgery, with important economic implications. The results will have a broad impact on cardiac surgery practice, and surgeons and cardiologists in the Network have equipoise to randomize their patients.

ENDPOINTS

Primary

The primary endpoint is total number of days in hospital for any hospitalization that occurs within 60 days of randomization to AF treatment strategy. Postoperative AF frequently increases hospital length of stay and is a common reason for readmission after hospital discharge. Observational studies suggest that most patients will return to sinus rhythm within 60 days of surgery.

Secondary

AF-and/or treatment-related events

- Duration of hospital stay from randomization to eligibility for discharge based on AF-related criteria (regardless of whether patient is actually discharged)
- Time to conversion to sustained, stable non-AF rhythm < 7 days of randomization or hospital discharge with each strategy
- Heart rhythm (i.e. whether in a stable non-AF rhythm) at hospital discharge, at 30 days from date of randomization, and at 60 days from date of randomization
- Need for permanent pacemaker within 60 days of randomization

Economic burden

- LOS (Index hospitalization)
- LOS (re-hospitalizations, including ED visits)
- Outpatient interventions
- Costs (hospital) as of surgery date

Adverse Events

- Mortality
- Stroke
- TIA
- Non-cerebrovascular thromboembolism
- Bleeding
- Cardiac arrhythmias (sustained atrial and ventricular arrhythmias other than AF or AFL as defined below) and cardiac conduction abnormalities that require a permanent pacemaker
- Major infection
- Heart Failure
- Myocardial Infarction
- Renal Insufficiency
- Hyper or hypo-thyroidism
- QTc prolongation > 500ms
- Pericardial fluid collection (requiring drainage)

STUDY DESIGN

This is a multi-center, open label, randomized clinical trial. The trial will be conducted in up to 25 clinical sites, and 520 patients will be randomized. Accrual is expected to take 18 months, and all patients will be followed until they are 60 days out from randomization (unless they are readmitted within 60 days and still hospitalized, at which point they will be followed until re-discharge). See Figure 2 for study design schematic.

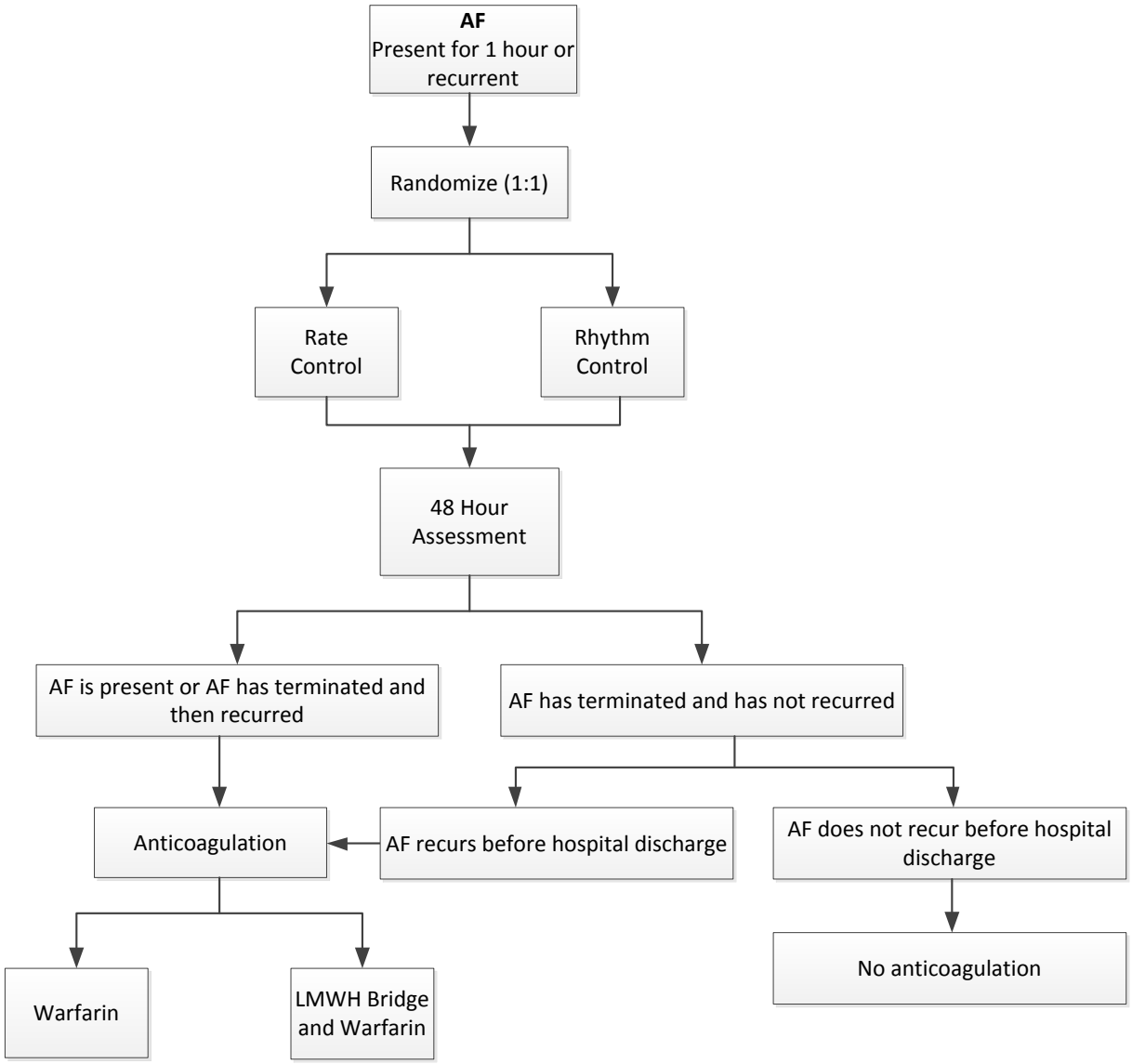

Figure 2: Study Design

RANDOMIZATION

Patients who develop postoperative AF will be randomized into one of two treatment groups:

Group 1: Rate control as the initial strategy

Group 2: Rhythm control as the initial strategy

Patients will be randomized in a 1:1 fashion. Randomization will be performed within 3 hours after the patient develops AF (first episode of AF) or upon occurrence of a second episode of AF in patients who have previously developed AF that did not last for 60 minutes. Treatment will begin immediately after randomization.

The "60 minute cut-off" for AF was used by the AFFIRM investigators. During the first 60 minutes after AF develops, patients may be treated with rate control agents as clinically indicated. If the patient is randomized to rhythm control, the treatment regimen will include a strategy from the list of options for rhythm control; rate control agents may be continued or added as necessary.

STUDY POPULATION

The study population for this trial consists of adult patients requiring cardiac surgery to treat coronary artery disease, valvular heart disease or a combination of both.

Enrollment Inclusion Criteria

- Age $\geq$ 18 years
- Undergoing heart surgery for coronary artery bypass (on-pump or off-pump CABG) and/or valve repair or replacement (excluding mechanical valves), including re-operations
- Hemodynamically stable

Enrollment Exclusion Criteria

- LVAD insertion or heart transplantation
- Maze procedure
- Transcatheter aortic valve replacement (TAVR)
- History of or planned mechanical valve replacement
- Correction of complex congenital cardiac defect (excluding bicuspid aortic valve, atrial septal defect or PFO)
- History of AF (including AFL)
- History of ablation for AF(including AFL)
- Contraindications to amiodarone
  - PR> 240 ms
  - 2nd or 3rd degree AV block
  - QTc> 480 ms
  - Untreated thyroid disorder
  - AST> 2x upper limit of normal
  - Hepatic cirrhosis
  - Interstitial lung disease
- Contraindications to warfarin
  - Active or recent bleeding
  - High risk of bleeding
  - Liver disease
  - Non-compliance
- Received amiodarone within 6 weeks of index surgery
- Need for long-term anticoagulation
- Concurrent participation in an interventional (drug or device) trial

Randomization Inclusion Criteria

All cardiac surgery patients who meet eligibility criteria will be consented and enrolled. Patients will subsequently be randomized if the following criteria are met:

- AF that persists for > 60 minutes or recurrent (more than one) episodes of AF occurring within 7 days of the surgical date (inclusive, with day of surgery labeled “day 0”) and
- Occurs during the index hospitalization.

Recruitment Strategies

Based on the CTSN prospective infection cohort study (which enrolled all cardiac surgery patients at the CTSN sites) and a survey of the clinical sites, it is estimated that approximately 1600-1800 patients could be enrolled annually and 320-360 randomized annually through active screening and recruitment by the participating Network centers. These strategies may include: mailings to referring physicians of the study

hospitals, symposia and health care events targeted towards this population; as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified goals, and additional interventions to increase enrollment will be implemented as needed. The Screening Log will identify numbers of patients screened and reasons for non-enrollment in the trial.

Inclusion of Women and Minorities

The inclusion of women and minorities in clinical trials is critical for scientific, ethical, and social reasons and for the generalizability of trial results. The Network is strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity. The CTSN intends to recruit at least 30% women and 25% minorities. The following measures will be employed to ensure adequate representation of these groups:

- Documentation of the number of women and minorities screened and enrolled via screening and exclusion logs;
- Monitoring of such logs from each clinical center on a monthly basis;
- If necessary, the development and implementation of outreach programs designed to recruit adequate numbers of women or minorities.

TREATMENT INTERVENTIONS

General Measures

The initial management should include correction of predisposing factors such as hypoxemia, electrolyte abnormalities (magnesium and potassium), fever and hemodynamic instability as well as pain management and withdrawal of stimulating factors such as inotropic agents and sympathomimetic bronchodilators as clinically indicated.

Rate Control Strategy

The target heart rate is < 100 beats per minute at rest. The treating clinician will choose agents from the list of rate control medications and employ these medications (singly or in combination) to achieve rate control. A patient who presents with AF and slow ventricular response rate (<60 beats per minute) may still be randomized to the rate control strategy; in such instances, rate control agents may be withheld or administered in low doses. Dose ranges, as defined in guidelines, for each of the rate control agents need to be adhered to. Simultaneous use of more than one of the categories of rate control agents should be done with caution due to risk of bradycardia.

Table 1: Rate Control Agents

Agent	Examples
Beta blockers	Metoprolol, atenolol, carvedilol, esmolol
Calcium channel blockers (nondihydropyridine)	Diltiazem, verapamil
Digoxin	

Rhythm Control Strategy

Patients assigned to an initial strategy of rhythm control will be treated with amiodarone alone or amiodarone plus direct current (DC) cardioversion if amiodarone alone does not eliminate AF within 48 hours. It may be necessary to change the dose or route of administration of amiodarone in order to achieve or maintain sinus rhythm. DC cardioversion is indicated at any point for hemodynamic instability. However, for patients who are hemodynamically stable but remain in AF, at least 24 hours of amiodarone should be administered before cardioversion is attempted. Cardioversion should be attempted, if possible, prior to the 48 hour duration to avoid the need for a TEE guided approach.

If AF has been present < 48 hours, DC-cardioversion *may* be attempted without preceding anticoagulation, though a final decision will be left to the discretion of the treating physician. If AF has been present for ≥ 48 hours and the patient has not been therapeutically anticoagulated, cardioversion should be TEE guided. The recommended loading and maintenance dosages of amiodarone are specified below in the Rhythm Control Intervention Table (Table 2).

Table 2: Rhythm Control Intervention

Agent	Notes
AMIODARONE **Initial Dose**[1] • Oral: 400 mg po TID for 3 days is recommended • For patients incapable of taking oral: 150 mg IV bolus over 10 min, then 1 mg/min over 6 hours followed by 0.5 mg/min over 18 hours[2] **Maintenance Dose** • Oral: at least 200 mg/day to be continued until 60 days after randomization • If drug cannot be given orally or via NG tube: 0.5 mg/min administered through central line (e.g., PICC) until oral dosing is started	Contraindicated in patients with untreated thyroid disorder, PR>240 ms, 2nd or 3rd degree AV block, QTc>480 ms, AST>2x upper limits, hepatic cirrhosis, interstitial lung disease
DC-CARDIOVERSION[3]	If within **48** hours of a loading dose of amiodarone, the patient remains in AF, DC-cardioversion is required. Cardioversion *may* be employed without anticoagulation if AF duration < 48 hours. If AF duration > 48 hours and the patient has not been therapeutically anticoagulated, TEE-guided cardioversion is recommended.

When deemed to be clinically appropriate, patients in the rhythm control arm may also be treated with a rate control medication (e.g. beta blocker). In particular, a rate control medication may be indicated at the onset of AF.

Patients in the rhythm control arm will be discharged on amiodarone with or without additional medications such as a beta-blocker. Patients may be eligible for discharge when they satisfy criteria for anticoagulation and they meet one of the following criteria regarding heart rhythm: (1) Absence of AF for 24 or more consecutive hours and no AF at time of discharge; (2) Presence of AF after treatment with amiodarone for at least 48 hours (which covers patients with paroxysmal AF) with adequate control of rate; (3) Presence of AF after treatment with amiodarone for at least 48 hours and one or more attempts at electrical cardioversion, with adequate control of rate (see also below).

[1] Loading dose could be reduced in case the patient develops bradycardia or GI or neuro side effects (i.e. 400 TID could be changed to BID or once a day in case of side effects)
[2] Repeat 150 mg IV amiodarone bolus could be used in case of uncontrolled or recurrent arrhythmia
[3] Repeat cardioversion in case AF recurs after an initial cardioversion is allowed and left to the treating physician's discretion

Cross-Overs
Patients will be assigned to an initial strategy of either rate control or rhythm control and the primary analysis will follow the intention-to-treat principle. All efforts should be made to minimize cross-overs, while maintaining patient safety.

Rate Control to Rhythm Control
If the treating clinician determines that 1) the patient has not returned to sinus rhythm after an initial strategy of rate control (see Table 1) and 2) rhythm control is indicated to improve the patient's hemodynamic status or to alleviate symptoms, the management goal may switch to rhythm control. Such a strategy should include DC-cardioversion in addition to amiodarone.

Rhythm Control to Rate Control
If the treating clinician determines that attempted rhythm control has failed to restore normal sinus rhythm and there is anticipated clinical difficulty with continuing amiodarone (see below), the management goal may switch to rate control. Rate control agents, without amiodarone, will be used to achieve a target heart rate of <100 beats per minute at rest.

The protocol accepted reasons to discontinue rhythm control with amiodarone are specified below (see Table 3).

Table 3: Reasons for Discontinuation of Amiodarone

Cardiac reasons	Symptomatic bradycardia
	Prolonged QTc (QTc >480 msec), PR > 240 msec
Side Effects	Thyroid dysfunction
	Central nervous system (tremulousness, dizziness, neuropathy)
	Hepatotoxicity
	Nausea
Other	Contraindicated because of interactions with other drugs

Postoperative Pacing
It is common practice to place temporary ventricular and/or atrial pacing wires on the surface of the heart at the time of heart surgery. If such leads are placed and a patient becomes bradycardic, these wires may be employed to pace the heart. Patients receiving pacing remain eligible to continue their participation in the study.

Postoperative Anticoagulation
The decision to anticoagulate a patient will be made 48 hours after randomization. A patient will be anticoagulated if:

1) The patient has remained in AF continuously since the time of randomization or
2) The AF was terminated but recurred one or more times during the first 48 hours after randomization (i.e. the patient has had more than a single episode of AF after randomization)

In addition, if the patient has no AF at 48 hours post-randomization but has a recurrence of AF before hospital discharge, that patient meets criteria for anticoagulation.

All patients in both arms *who meet a criterion for anticoagulation* will be treated with warfarin to achieve a target INR of 2-3. Preoperative presence of an absolute contraindication to warfarin is a reason for exclusion from the study. Continuous anticoagulation for 60 days is recommended in all patients.

However, anticoagulation may be stopped at the physician's discretion if normal sinus rhythm is maintained for at least 2 weeks or for complications. Newer oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban) have not been proven safe or effective in the immediate period after cardiac surgery and will not be utilized in this patient population. Concomitant aspirin may be given at the discretion of the treating physician, but is not an alternative to warfarin.

In patients who develop relative or absolute contraindications to postoperative anticoagulation, the treating physician will determine the appropriate management strategy and may withhold anticoagulant therapy if clinically appropriate.

If a patient does not meet criteria for anticoagulation at the time of discharge, but is found to have recurrent AF at a post-discharge follow-up visit, institution of anticoagulation with warfarin is recommended.

Discharge

Patients will be discharged at the discretion of the physician according to standard clinical criteria. At the time of discharge, patients who remain in atrial fibrillation or atrial flutter should have adequate rate control (resting heart rate < 100 beats per minute). Patients randomized to a rhythm control strategy will be discharged on amiodarone unless contraindicated. The recommended dose of amiodarone is the equivalent of 3 grams of oral amiodarone over a period of 3 days prior to discharge with a maintenance dose of 200 mg/day or a lesser quantity of amiodarone with successful DC -cardioversion to sinus rhythm.

Patients are eligible for discharge from a cardiovascular perspective (regardless of whether patient is actually sent home), if they meet the following AF-related criteria for discharge:

- If they qualify for anticoagulation with warfarin, they have achieved a target INR of 2.0-3.0 or if they are "bridged" with low molecular weight heparin, they can be discharged with an INR of less than 2.0.
- For patients receiving rate control, their ventricular rate at rest should be <100 bpm
- For patients receiving rhythm control, (a) absence of AF for 24 or more consecutive hours and no AF at time of discharge; (b) presence of AF after treatment with amiodarone for at least 48 hours (This covers patients with paroxysmal AF); or (c) presence of AF after treatment with amiodarone for at least 48 hours and one or more attempts at DC- cardioversion

Discontinuing Rhythm Control and Rate Control Agents

Regardless of treatment strategy, 90% of patients are expected to return to normal sinus rhythm by 60 days after operation. A minimum of 60 days of amiodarone is recommended for those in the rhythm control arm. Amiodarone may be discontinued prior to 60 days if the patient experiences amiodarone-related adverse events (symptomatic bradycardia, prolonged QTc interval (QTc >480 msec), PR interval > 240 msec, thyroid dysfunction). In addition, amiodarone may be discontinued for other unacceptable symptoms (i.e., nausea, mild neuropathy, tremulousness) and when contraindicated for use with other interacting drugs. There may be indications to continue beta blocker therapy indefinitely in many patients, particularly in those with coronary artery disease.

DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoint

The primary endpoint is total number of days in-hospital for any AND ALL hospitalizations that occur during the time frame extending from the day of randomization to 60 days after the day of randomization. A visit to the emergency department without hospital admission shall count as one day in the hospital if the emergency department stay is less than 24 hours; if the stay exceeds 24 hours, the number of calendar

days in the hospital shall be counted. Outpatient visits to physicians, whether scheduled or unscheduled, do not count toward the primary endpoint.

Secondary Endpoints

AF-related Endpoints

Duration of Hospital Stay (based on meeting discharge criteria)

Duration of hospital stay from randomization to eligibility for discharge based on AF-related criteria (regardless of whether patient is actually discharged).

Time to conversion to sustained, stable non-AF rhythm within 7 days of randomization or hospital discharge with each strategy

Patients will be monitored continuously by telemetry until hospital discharge. Time from randomization to sustained, stable non-AF rhythm will be determined from telemetry monitoring.

Heart rhythm at hospital discharge, at 30 days ~~(window 4 weeks to 6 weeks)~~ and at 60 days

The rhythm at hospital discharge will be determined either by 12-lead ECG or telemetry monitor. At 30 and 60 days, heart rhythm to be determined by 12-lead ECG, by app or stand-alone home device that will record an ECG, or by novel passive cardiac data collection device.

Need for permanent pacemaker within 60 days of randomization

Economic Endpoints

Length of stay (index hospitalization)

Overall length of stay for the index hospitalization will be measured (and broken down by days spent in the ICU versus days spent on telemetry and regular floors). In addition, we will capture discharge location.

Re-hospitalization

Readmission rates and duration will be calculated for the first 30 days following intervention and for the duration of follow-up (includes readmissions that occur within 60 days post randomization). Our definition of readmissions includes emergency room visits.

Outpatient visits

Outpatient visits, whether scheduled or unscheduled (excluding emergency room visits), for the duration of follow-up.

Cost

Inpatient costs will be measured through University Hospital Consortium (UHC) costing data and if sites, are not members, we will collect UB-92 forms or hospital billing sheets. In addition to index hospitalization costs, costs associated with subsequent readmissions will also be included in the study. Patients will also be asked at each follow-up if they have been hospitalized at another hospital and if yes for how long. Costs related to hospitalization at non-Network institutions will be imputed based on the average per day cost of hospitalization of study patients at Network hospitals. Outpatient costs incurred at non-Network hospitals will not be captured.

Adverse Events

Please refer to the *CTSN Clinical & Adverse Event Reporting and Adjudication Procedures* document for details about the reporting of adverse events.

Cerebrovascular thromboembolism

A new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (*TIA*), which is fully reversible within 24 hours (and without imaging evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is imaging evidence of infarction). The Modified Rankin Scale and the NIH Stroke Scale (NIHSS) must be administered within 72 hours following the event and at termination of follow up to document the presence and severity of neurological deficits. The Modified Rankin Scale and NIHSS can be found in Appendix I.

Ischemic or Hemorrhagic Stroke

Defined as a neurological deficit that persists beyond 24 hours or less than 24 hours associated with infarction or hemorrhage on an imaging study. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.

TIA

Defined as an acute neurological deficit that resolves completely within 24 hours with no imaging evidence of infarction or hemorrhage.

Non-cerebral thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes central nervous system neurological events.

Bleeding (Mehran, Rao et al. 2011)

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional.

Type 2: Any clinically overt sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) Bleeding Academic Research Consortium (BARC) bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug.

Type 3: Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

- Type 3a bleeding

- Any transfusion with overt bleeding
- Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.

- Type 3b bleeding
  - Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive drugs
- Type 3c bleeding
  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
  - Intraocular bleed compromising vision

Type 4: Coronary Artery Bypass Graft–related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output ≥2 L within a 24-hour period

Type 5: Fatal bleeding

Definite or probable bleeding that directly causes death with no other explainable cause. A fatal bleeding event is defined as

- Death due to hemorrhage

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event. Relationship to anticoagulation will be established for all bleeding events.

Cardiac Arrhythmias

Any documented arrhythmia that *results in clinical compromise* (e.g., hemodynamic compromise, oliguria, pre-syncope or syncope) or modification of medical management that requires hospitalization or requires a physician visit, an additional procedure or occurs during a hospital stay. Cardiac arrhythmias are classified as:

1. Sustained ventricular arrhythmia requiring defibrillation, cardioversion or ablation
2. Sustained supraventricular arrhythmia other than AF or AFL requiring drug treatment, cardioversion or ablation
3. Cardiac conduction abnormalities requiring permanent pacemaker
4. QTc prolongation > 500ms

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Pleural Effusion

Accumulation of fluid or clot in the pleural space documented by chest radiogram or chest CT that requires evacuation with surgical intervention or chest tube placement.

Major Infection

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Endocarditis

Signs, symptoms and laboratory findings consistent with endocarditis, including but not limited to fever $\geq 38.0^{o}$ C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of a new intra-cardiac vegetation with or without other signs and symptoms should be considered adequate evidence to support the diagnosis of endocarditis. TEE should be the modality of choice for diagnosis of prosthetic valve endocarditis.

Mediastinitis/Deep Sternal Wound Infection

Signs and symptoms consistent with mediastinitis, include but are not limited to fever, chills, leukocytosis and chest or back pain, *and* mediastinal inflammation documented by diagnostic testing (e.g., chest CT). Information regarding deep sternal wound infections will be collected.

Infectious Pericarditis

Signs and symptoms, including but not limited to fever, leukocytosis and pericardial inflammation, necessitating surgical exploration, drainage and treatment with intravenous antibiotics.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension. In addition, we will record systemic antibiotic use for presumptive sepsis.

Localized Infection

Infection localized to any organ system or region other than the mediastinum, pericardium, or endocardium without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Heart Failure

New onset of signs or symptoms of congestive heart failure *or* worsening of pre-existing heart failure by ≥ 1 NYHA class.

Myocardial Infarction

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction[1]:

Myocardial Infarction

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Peri-CABG Myocardial Infarction

For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft of native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

Renal Events

Three categories of renal events will be identified according to the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group(Bellomo, Ronco et al. 2004):

Risk of Renal Dysfunction

GFR Criteria: Increased SCreat x1.5 *or* GFR decrease > 25%
Urine Output (UO) Criteria: UO < 0.5ml/kg/h x 6 hr

Injury to the Kidney

GFR Criteria: Increased SCreat x2 *or* GFR decrease > 50%
UO Criteria: UO < 0.5 ml/kg/h x 12 hr

Failure of Kidney Function

GFR Criteria: Increase SCreat x3, GFR decrease 75%, *or* SCreat ≥ 4 mg/dl (acute rise ≥ 0.5

[1] Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*.2007;116:0-0.

mg/dl)
UO Criteria: UO < 0.3 ml/kg/h x 24 hr *or* Anuria x 12 hrs

Thyroid Dysfunction

Hypothyroidism
Abnormal thyroid function defined by thyroid stimulating hormone (TSH) levels ≥ 3.04 μIU/L, with or without free T3 levels ≤ 2.3 pg/mL or free T4 levels ≤ 0.8 ng/dL.

Hyperthyroidism
Abnormal thyroid function defined by thyroid stimulating hormone (TSH) levels ≤ 0.3 μIU/mL, with or without free T3 levels ≥ 4.2 pg/mL or free T4 levels ≥ 1.8 ng/dL.

Other
An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

CLINICAL CENTERS

The study will be conducted in up to 25 clinical centers participating in the NIH supported Cardiothoracic Surgical Trials Network. Each clinical center will be required to obtain IRB approval for the protocol in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the Data Coordinating Center with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile
The surgeon, cardiologist and coordinator(s) must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates prior to beginning enrollment to the DCC.

Conflict of Interest and Financial Disclosure Agreement
This statement verifies that all investigators have no conflict of interest with any institution that may influence their participation in this study. All investigators need to complete this statement. Investigators will also submit a financial disclosure agreement.

Site Approval
The following documents must be collected prior to site approval:

- Clinical Study Agreement
- Clinical site IRB roster
- Clinical site IRB approval, version and date for protocol and consent

A signed agreement between the clinical site and the DCC (Icahn School of Medicine at Mount Sinai) is required prior to site initiation. Prior to enrolling a patient, representatives from the DCC will conduct a site initiation for all investigators, coordinators, and any other health care professionals who may be involved in the study.

Patient Confidentiality
All patients' records will be kept confidential according to HIPAA guidelines. Study Investigators, site Institutional Review Boards (IRBs), the DCC and NHLBI personnel may review source documentation as necessary, but all unique patient and hospital identifiers will be removed. The aggregate data from this study may be published as per publication policy documented in the trial agreements; however, no data with patient identifiers will be published.

DATA COLLECTION

ENROLLMENT

Consent

Prior to protocol-defined data collection
Prior to protocol-defined data collection, a thorough explanation of the risks and benefits of the study will be outlined by the investigator or designee to the potential study subject. Study personnel should begin the informed consent process as soon as possible during the preoperative evaluation phase for each patient. Timing for the informed consent process must be consistent with the center's institutional IRB and privacy policies. This is to ensure that all subjects will be given adequate time to review the informed consent document, and consider participation in the trial. All questions will be answered to the satisfaction of the subject prior to signing the informed consent document. Site source records will include documentation of the informed consent process for each subject. For this trial, a patient will be considered enrolled once consent has been obtained.

Demographics

Prior to initial surgical intervention
The date of birth, ethnic origin, and sex will be captured on the demographics form. The EDC will generate a unique 5-digit identification code that will identify the patient throughout the course of the study.

Enrollment Eligibility Criteria

Prior to initial surgical intervention
The inclusion and exclusion criteria will be documented by the clinical site study coordinator and verified with the site Principal Investigator.

Physical Exam/Medical History

Prior to initial surgical intervention
This form captures the information pertaining to the medical history, including but not limited to previous myocardial infarction, myocardial revascularization, arrhythmias, stroke, heart failure, rheumatic heart disease, and other comorbidities such as diabetes, valve disease, cardiomyopathy, COPD, pulmonary hypertension and peripheral vascular disease. Information regarding the current medical condition is also captured, including but not limited to, height and weight, LVEF, sleep apnea, obstructive lung disease, anemia, neurological disorders.

Medications

Prior to initial surgical intervention
This form captures the information pertaining to the patient's medication, including but not limited to cardiovascular medications, statins, anticoagulation and antiplatelet medications.

PROCEDURE

Prior to randomization
This form captures information regarding procedure (CABG only, valve only, CABG + valve) and operative data that may affect the risk of developing post-operative AF such as on or off pump, cross-

clamp time, additional procedures performed at the time of the operation, intra-operative pharmacological agents, and intra-operative blood transfusions.

RANDOMIZATION DATA COLLECTION

Randomization Eligibility Criteria

Post-operatively, prior to randomization

Atrial fibrillation/atrial flutter will be detected in patients who are continuously monitored by telemetry post-operatively for the up to 7 days post-op during the index hospitalization. A consented patient is eligible for randomization after 60 minutes of continuous atrial fibrillation *or* after repeated (more than one) episodes of AF within 7 days of the surgical date (inclusive, with day of surgery labeled "day 0") during the index hospitalization.

Randomization

Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system once the checklist of inclusion and exclusion criteria has been completed and verified. Only a research staff member trained on the protocol and delegated by the PI to do so will be allowed to perform the randomization procedure in the EDC.

POST-RANDOMIZATION DATA COLLECTION

Treatment Documentation

At onset of AF

Medications, ECGs and cardioversion attempts as they pertain to the protocol treatment assignment will be recorded.

Index Hospitalization

Day of discharge

Length of stay and cardiac discharge eligibility criteria will be collected. INR will be collected for patients on an anticoagulation regimen.

ECG or Telemetry Recording

Day of discharge, 30 ± 5 days, 60 ± 5 days, event driven

Heart rate and ECG results and interpretation will be collected. The patient will be provided with a device which will be used to capture the ECG data at 60 days.

Follow-Up Assessment

At 30 ± 5 days and 60 ± 5 days

Patient status will be recorded. Patients will be asked if they have been hospitalized, or undergone any procedures, in particular pacemaker insertion, since the last assessment. Medications will be documented. Reasons for medication changes (discontinuations and/or additions) will also be recorded. These follow-up assessments may be completed in person (30 days) or by telephone (60 days).

EVENT DRIVEN DATA COLLECTION

Additional Procedures

Event driven

All procedures following the initial study defined surgical intervention must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the operation is to address a complication, the coordinator must also complete an adverse event report.

Adverse Events
Event driven
Detailed information regarding adverse events will be recorded at the time an adverse event occurs. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention as well as the relationship to the treatment assignment. All adverse events will be recorded until completion of the trial.

Neurologic Dysfunction Assessment
Event Driven
The Modified Rankin Scale and NIHSS (Appendix I) should be administered by a certified evaluator at the time of a cerebrovascular thromboembolic event (within 72 hours following the event) and at the termination of trial follow-up to document the presence and severity of neurological deficits.

Re-Hospitalizations
Event driven
All ED visits (of any duration) and re-hospitalizations (>24 hours for any reason) must be reported on the Re-Hospitalization Form. This form collects limited information about hospital procedures, length of stay, days in intensive care, and discharge if applicable, as well as patient condition and disposition for each hospitalization.

Outpatient Intervention
Event driven
All outpatient procedures following the index hospitalization must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the intervention is to address a complication, the coordinator must also complete an adverse event report.

Mortality
Event driven within 24 hours of knowledge of event
The investigator will record the date of death, immediate cause of death, primary underlying cause of death, notation of autopsy being performed, and clinical narrative of the event.

Study Completion/Early Termination
Event driven
This form records the date and reason for study completion or early termination. The reason(s) for a patient's early termination will be documented on this form.

Investigator's Statement
End of study
The Principal Investigator will review all of the electronic case report forms (eCRFs) and patient summaries. Their electronic signatures attest to the accuracy and completeness of the data collected.

DATA MANAGEMENT

All study data will be entered in the web-based electronic data capture (EDC) system (specified in detail in the operations manual). Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on individuals' roles and responsibilities. The application employs fine-grained role-based access control for data entry, viewing, and reporting options. All study data will be transmitted over an encrypted SSL (Secure Sockets Layer) connection that requires user authentication. This application is designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's Code of Federal Regulations (CFR) Number 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized

Systems Used in Clinical Trials, and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Quality Assurance

The data quality assurance tool has been designed as an automatic feature of the EDC system. When a form is submitted the system conducts instantaneous validation and cross-form validation checks. A query is generated and sent to the site coordinator electronically so that data may be verified and corrected. All changes made to a form are stored in an audit log.

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data and/or values that are outside the range of what is typically considered to be physiologically possible). Monitors will enter these queries through the EDC system for site coordinators to either correct or verify.

The case report forms (CRFs) for this study are designed to capture baseline demographics, surgical procedure information, and hospitalization data in the same format as the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database. Periodic STS data transfers from a subset of sites will be used to verify the data entered into the EDC. Data from the University Healthcare Consortium (UHC) will also be used to confirm that all re-hospitalizations and procedures are captured for sites that participate in UHC. The amount of agreement among the three data sources will be analyzed to inform the utility of collecting data solely from STS or UHC in future trials.

Monitoring

The DCC monitoring team employs a risk-based approach to centralized and on-site monitoring. This approach focuses efforts on the most crucial data and process elements to allow for more efficient monitoring practices while maintaining the quality of the overall study conduct. Through the combination of centralized and on-site monitoring, instantaneous electronic validation via the EDC system, and visual cross-validation by the InCHOIR monitors to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The centralized, or remote, monitoring of clinical trial data via the EDC is performed with a focus on safety, study endpoints, data completion and data outliers. DCC monitors will remotely monitor source documentation, study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event/IND Safety Report Log periodically to ensure that the sites are adhering to the study protocol and procedures. In collaboration with the DCC data management team, the monitors 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. As necessary when determined by the risk based monitoring algorithm, the DCC will conduct on-site monitoring visits to clinical sites.

Clinical sites will maintain copies of all source documents in the patient source binders at each site. Source documentation will be uploaded on a regular basis for remote review by the monitors.
The monitors will review the source documents to determine whether the data reported in the EDC system are complete and accurate. They will also verify that all adverse events exist on the source documents, are consistent with the protocol, and are documented in the appropriate format. Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission reports, consult notes, radiology reports, lab reports, clinic records, and other study-related

notes. At an onsite visit, the study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

The monitors will also confirm that the regulatory binder is complete and that all associated documents are up to date. The regulatory binder should include all revisions of the protocol and informed consent, IRB roster, IRB approvals for all of the above documents, IRB correspondence, investigator's agreements, delegation of authority log, CVs of all study personnel, institutional HIPAA certificates, monitor site visit log, telephone contact log, and correspondence with the DCC.

The monitor will verify a minimum of the following variables for all patients: initials, date of birth, sex, signed informed consent, eligibility criteria, date of enrollment, primary and secondary endpoints, adverse events, and mortality. These data will be 100% source data verified. All other data collection will be monitored as indicated by the data completeness and accuracy at each clinical site.
If problems are identified during the monitoring visit, e.g., poor communication with the DCC, inadequate or insufficient staff to conduct the study, missing study documents, etc., the monitor will assist the site in resolving the issues. Some issues may require input from the Operations Committee or the PI as well as the sponsor.

Given the combination of rigorous remote monitoring, risk assessment as well as on-site monitoring and ongoing monitoring using the EDC system that includes instantaneous electronic validation and visual cross-validation to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

ANALYTICAL PLAN

The primary goal of this study is to compare the therapeutic strategies of rate control and rhythm control in cardiac surgery patients who develop in-hospital postoperative AF. The primary outcome is the total number of days in hospital for any hospitalization that occurs within 60 days of randomization. Secondary outcomes of this study will include AF-related events, economic burden, and adverse events.

Sample size

Sample size is based on estimates of length of stay and re-hospitalization from the CTSN prospective infection study in addition to a blinded sample size re-estimation, which wasconducted in lieu of a formal interim analysis. We used the hospitalization data from the infection study for patients undergoing CABG, valve or CABG and valve surgery. Based on these data, we assumed that the average total number of days in the hospital within 60 days from randomization for the rate control group is 10.4. For patients randomized to rhythm control, we anticipated a reduction in total number of days in the hospital by 2 days. The standard deviation for the total number of days in the hospital in both arms was 8.8 days based on the infection study. The observed standard deviation from the first 148 patients enrolled in this trial (those who had completed the study by December 1, 2014), pooled across treatment groups, was 4.2 days. Using a conservative estimate of 6.3 days, a total of 520 patients (260 in each group), randomized with equal probability to each arm, provides approximately 90% power to detect a difference of 2.0 days between the two arms. Power is based on a 0.05 level two-tailed Wilcoxon Rank-Sum test assuming a lognormal distribution of the data. The sample size takes into account an overall 30% cross-over rate based on the cross-over rate observed at the time of the sample size re-estimation. Randomization will be implemented as described in the Randomization section.

Randomization Design and Procedure

Patients will be randomized using a 1:1 allocation to AF rate control and rhythm control. The randomization will be stratified by clinical center (i.e., a separate randomization scheme will be employed in each center). A random permuted block design will be employed, with blocks of size 2, 4, or 6

randomly chosen. Randomization will be implemented as described in Randomization Section, as previously described.

Statistical Analysis Plan

Primary Outcome

The primary outcome of this trial is the total number of days in the hospital for any hospitalization that occurs within 60 days from randomization. The null hypothesis is that there is no difference in the total number of days in the hospital between patients randomized to rate control compared to patients randomized to rhythm control. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.048 level two-tailed Wilcoxon Rank-Sum test.

The choice of the Wilcoxon Rank-Sum test for the primary analysis is motivated by the non- normal distribution of the primary outcome variable and to account for mortality within 60 days from the surgery. The 60-day incidence of mortality is expected to be approximately 5% and equally distributed between randomization arms. For the analysis, patients who die will be assigned ranks lower than the lowest observed rank, in ascending order based on the time of death (earliest to latest). We do not anticipate other reasons for missing data for the primary outcome.

Assessment of Balance of the Randomization

The success of the randomization procedure in balancing important covariates between randomization groups will be assessed at the interim analysis and at the final analysis. Continuous measures will be compared using t-tests, while chi-squared tests will be used to compare categorical variables. As > 400 patients will be randomized, no substantial imbalances are expected. However, should any covariate differ significantly between treatment groups at the 0.01 level, and be substantively large, we will adjust for those covariates in secondary analyses.

Secondary Outcomes

AF-related Endpoints

Time to conversion to sustained, stable non-AF rhythm within 7 days of randomization or hospital discharge with each strategy

Telemetry will be used to determine if and when patients first convert to sustained, stable sinus rhythm within the first 7 days of randomization or hospital discharge, whichever occurs first. The null hypothesis is that there is no difference in the time to conversion between treatment groups. Time to conversion will be described by Kaplan-Meier curves and differences between randomization groups assessed via the log-rank test.

Heart rhythm at initial hospital discharge

Heart rhythm will be assessed by telemetry or 12 lead ECG at discharge to determine if patients are in atrial fibrillation/atrial flutter or not. The null hypothesis is that there is no difference in the proportion of treatment successes (patients *not* in atrial fibrillation/atrial flutter at discharge) between treatment groups. The null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level chi-squared test. For simplicity, the benefit of rhythm control compared to rate control will be quantified as a simple difference in the proportion of patients not in AF at discharge in the two randomization groups along with the associated 95% confidence interval. The relative reduction in the risk of measured AF for patients randomized to rhythm control compared to patients randomized to rate control will be reported as the simple relative risk and associated 95% confidence interval. Patients who die prior discharge will be considered as treatment failures.

Heart rhythm at 30 days (window 4 weeks to 6 weeks) and at 60 days

Heart rhythm will be assessed by 12 lead ECG at patients' 30 day follow-up visits to determine if they are in sinus rhythm. Heart rhythm at 60 days will be assessed by handheld portable ECG devices or passive data collection devices at home to determine if patients are in AF. Analyses will be conducted in the same manner as for heart rhythm at initial hospital discharge.

Need for permanent pacemaker within 60 days of randomization
The difference in proportions of patients who receive a permanent pacemaker within 60 days of randomization will be assessed using a 0.05 level chi-squared test. "Success" will be defined as not receiving a permanent pacemaker. The benefit of rhythm control compared to rate control will be quantified as a simple difference in the proportion of patients in who need a permanent pacemaker within 60 days of randomization in the two randomization groups along with the associated 95% confidence interval. The relative reduction in the risk of needing a permanent pacemaker for patients randomized to rhythm control compared to patients randomized to rate control will be reported as the simple relative risk and associated 95% confidence interval. Patients who die prior discharge will be considered treatment failures.

Economic Endpoints
Length of stay (index hospitalization)
Length of stay and length of stay for AF criteria (as defined in the Discharge subsection of the Treatment Interventions above) will be analyzed in the same manner as the primary endpoint.

Re-hospitalization
A Poisson regression model will be used to compare the frequency of readmissions between groups for any cause, and specifically for AF-related hospitalizations, within 60 days of randomization. For the purposes of this study, an ED visit is considered a re-hospitalization.

Outpatient visits
A Poisson regression model will be used to compare the frequency of outpatient visits between groups for any cause, and specifically for AF-related causes, within 60 days of randomization.

Cost
Cost will be calculated by converting charges to cost using institution specific Ratio-of-Cost-to-Charges (RCCs). Institution-specific cost reports will be used to calculate RCCs for each major resource category. Costing data will be compared by Student's t test after log transformation. Independent predictors of cost, including baseline factors, operative factors and postoperative events, will be determined by multivariate regression analysis.

Adverse Events
Differences in the incidence of individual adverse events will be compared between randomization arms using Poisson regression. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual adverse events by treatment assignment will be computed.

Mortality
The proportion of deaths between randomization groups at 60 days post randomization will be compared by a chi-squared test of the equality of two proportions. Time to death will be described by Kaplan-Meier curves and differences between randomization groups will be assessed via the log-rank test.

Interim monitoring guidelines
The objectives of interim monitoring are to 1) monitor for evidence of toxicity, 2) track participant accrual rates, 3) track study participant adherence to the prescribed medication, and to 4) monitor the primary and secondary outcomes for early evidence of efficacy, harm or futility. To accomplish this,

summaries of data quality, accrual, adherence, distribution of baseline factors, toxicity, study endpoints and other analyses as requested will be prepared for review by the Data Safety Monitoring Board (DSMB).

In lieu of the originally planned formal interim analysis, the DSMB approved conducting a blinded assessment of the observed variability of the primary outcome (the total number of days in the hospital for any hospitalization that occurs within 60 days from randomization) and of the rate of treatment non-adherence. The final analysis will be conducted at a 0.05 two-sided alpha level (corresponding to a critical value of 1.98).

Ancillary Study: Predictors of AF
Demographic, medical history and surgical data will be collected for all consented patients. Multiple logistic regression models will be used to assess which variables are predictors of post-operative atrial fibrillation.

ORGANIZATION OF THE STUDY

This section describes the overall study organization. The study is conducted in up to 25 clinical sites selected by NHLBI, in collaboration with NINDS and CIHR. The following committees and institutions will be involved in the administration of the study.

Data and Safety Monitoring Board (DSMB)
To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians, biostatisticians, ethicists and bioengineers, who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC or the clinical sites, and will be appointed by the NHLBI. The DSMB will act in a senior advisory capacity to the DCC and the NHLBI regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events and mortality. They will communicate their findings directly with the DCC and the NHLBI. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

Data Coordinating Center (DCC)
A university-based DCC (InCHOIR) bears responsibility for monitoring interim data and analyzing the study's results in conjunction with the investigators and the sponsor. The DCC will coordinate and monitor the trial and will administrate the DSMB.

Executive Steering Committee
The Network Steering Committee (with the assistance of the protocol development committee) will provide the overall scientific direction for the study. The responsibilities of the Steering Committee are to: (a) maintain contact with study investigators to ensure high quality data collection; (b) approve and implement major protocol changes in response to advice from the DSMB; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the study.

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Appendix I: Modified Rankin Scale (mRS) and NIH Stroke Scale (NIHSS)

Modified Rankin Scale (mRS)

Instructions: Assessment should be completed by a certified evaluator.

1. Check the most single representative score
2. Screen: Score should reflect patient status prior to symptom onset of the present stroke.
3. Follow-up: Score should reflect patient status at the time of the exam
4. "Assistance" is defined as needing help from another person for mobility or other usual activities.

☐ 0= No symptoms at all

☐ 1= No significant disability, despite symptoms; able to carry out all usual duties and activities

☐ 2= Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance

☐ 3= Moderate disability; requiring some help, but able to walk without assistance

☐ 4= Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

☐ 5= Severe disability; bedridden, incontinent and requiring constant nursing care and attention

NIH Stroke Scale Administration Guidelines

The NIH Stroke Scale (NIHSS) is a standardized neurological examination intended to describe the neurological deficits found in large groups of stroke patients participating in treatment trials. The instructions reflect primary concern for reproducibility. The purpose of this form is to collect data representing the baseline stroke status of each participant and the stroke status at different exam time frames of the trial.

Please Note: The NIH Stroke Scale must be administered by a certified evaluator, i.e., the evaluator must be trained and certified in the NIH Stroke Scale. This is also part of the neurological exam conducted for suspected stroke during follow-up.

Date and time of form completion: Record the date (dd/mmm/yyyy) and time (24-hr clock) the form was completed.

Directions: Indicate one box for each category. If any item is left untested, a detailed explanation must be clearly written on the form in the comment section.

Level of Consciousness
Three items are used to assess the patient's level of consciousness. It is vital that the items be asked in a standardized manner, as illustrated in the Stroke Scale training tape. Responses must be graded based on what the patient does first. Do not give credit if the patient corrects himself/herself and do not give any clues or coaching.

1a. Level **of Consciousness (LOC).**
Ask the patient two or three general questions about the circumstances of the admission. Also, prior to beginning the scale, it is assumed that the examiner will have queried the patient informally about the medical history. Based on the answers, score the patient using the 4-point scale on the Stroke Scale form. Remember not to coach. A score of 3 is reserved for the severely impaired patient who makes, at best, reflex posturing movements in response to repeated painful stimuli. If it is difficult to choose between a score of 1 or 2, continue to question the patient about historical items until you feel comfortable in assessing level of consciousness.

1b. LOC **Questions.**
Ask the patient "how old are you now" and wait for a response. Then ask "what month is it now" or "what month are we in now". Count the number of incorrect answers and do not give credit for being "close". Patients who cannot speak are allowed to write. Do not give a list of possible responses from which to choose the correct answer. This may coach the patient. Only the initial answer is graded. This item is never marked "untestable". (Note: On Certification Tape #1 an intubated patient was given a series of responses from which to choose, but the score for this patient would still be 1. Deeply comatose (1a=3) patients are given a 2.

1c. LOC Commands.
Say to the patient "open your eyes...now close your eyes" and then "Make a fist...now open your hand". Use the non-paretic limb. If amputation or other physical impediment prevents the response, use another suitable one step command. The priming phrase is not scored, and these are used only to set the eyes or hand in a testable position. That is, the patient may be asked first to open the eyes if they are closed when you begin the test. Scoring is done on the second phrase "close your eyes". Count the number of incorrect responses and give credit if an unequivocal attempt is made to perform the operative task, but is not completed due to weakness, pain or other obstruction. Only the first attempt is scored and the questions should be asked only once.

2. Gaze.
The purpose of this item is to observe and score horizontal eye movements. To this end, use voluntary or reflexive stimuli and record a score of 1 if there is an abnormal finding in one or both eyes. A score of 2 is reserved for forced eye deviation that cannot be overcome by the oculocephaIic maneuver. Do not do caloric testing. In aphasic or confused patients, it is helpful to establish eye contact and move about the bed. This item is an exception to the rules of using the first observable response and not coaching. In the patient who fails voluntary gaze, the oculocephalic maneuver, eye fixation, and tracking with the examiner's face, are used to provide stronger testing stimuli.

3. Visual Fields.
Visual fields are tested exactly as demonstrated in the training video. Use finger counting or movement to confrontation and evaluate upper and lower quadrants separately. A score of 3 is reserved for blindness from any cause, including cortical blindness. A score of 2 is reserved for a complete hemianopia, and any partial visual field defect, including quadrant anopia, scores a 1.

4. Facial Movement (Facial Paresis).
Ask the patient "Show me your teeth ...now raise your eyebrows ...now close your eyes tightly". Assess the response to noxious stimulation in the aphasic or confused patient. A useful approach to scoring may be as follows: score a 2 for any clear cut upper motor neuron facial palsy. Normal function must be clearly demonstrated to obtain the score of 0. Anything in between, including flattened nasolabial fold, is scored a 1. The severely obtunded or comatose patient; patients with bilateral paresis, patients with unilateral lower motor neuron facial weakness would receive a score of 3.

5. Motor Arm-Right.
Perform the test for weakness as illustrated in the video. When testing arms, palm must be down. Count out loud to the patient, until the limb actually hits the bed or other support. The score of 3 is reserved for the patient who exhibits no strength whatsoever, but does minimally move the limb on command when it is resting on the bed. The patient may understand what you are 'testing if you use the non-paretic limb first. Do not test both limbs simultaneously. Be watchful for an initial dip of the limb when released. Only score abnormal if there is a drift after the dip. Do not coach the patient verbally. Count out loud in a strong voice and indicate count using your fingers in full view of the patient. Begin counting the instant you release the limb. (Note that on some of the video illustrating patients, the examiners erroneously delay seconds before beginning to count).

6. Motor Arm-Left. See explanation of 5.

7. Motor Leg-Right.
Perform the test for weakness as illustrated in the video. When testing motor leg, the patient must be in the supine position to fully standardize the effect of gravity. Count out loud to the patient, until the limb actually hits the bed or other support. The score of 3 is reserved for the patient who exhibits no strength whatsoever, but does minimally move the limb on command when it is resting on the bed. The aphasic patient may understand what you are testing if you use the non paretic limb first. Do not test both limbs simultaneously. Be watchful for an initial dip of the limb when released. Only score abnormal if there is a drift after the dip. Do not coach the patient verbally. Count out loud in a strong voice and indicate count using your fingers in full view of the patient. Begin counting the instant you release the limb. (Note that on some of the video illustrating patients, the examiners erroneously delay seconds before beginning to count).

8. Motor Leg-Left. See explanation of 7.

9. Limb ataxia.
Ataxia must be clearly present out of proportion to any weakness. Using the finger-nose-finger and the heel-test, count the number of ataxic limbs, up to a maximum of two. The aphasic patient will often perform the test normally if first the limb is passively moved by the examiner. Otherwise, the item is scored 0 for absent ataxia. If the weak patient suffers mild ataxia, and you cannot be certain that it is out of proportion to the weakness, give a score of 0. Remember this is scored positive only when ataxia is present. If this item is scored '0' or '9', skip to Item 12. Please indicate presence of ataxia in arms and legs.

10. Sensory.
Do not test limb extremities, i.e., hands and feet when testing sensation because an unrelated neuropathy may be present. Do not test through clothing.

11. Best Language.
It is anticipated that most examiners will be ready to score this item based on information obtained during the history taken and the prior items. The attached picture and naming sheet therefore should be used to confirm your impression. It is common to find unexpected difficulties when the formal testing is done, and therefore every patient must be tested with the picture, naming sheet, and sentences. The score of 3 is reserved for the globally mute or comatose patient. NEW aphasia would score a 1. To choose between a score of 1 or 2, use all the provided materials; it is anticipated that a patient who missed more than two thirds of the naming objects and sentences or who followed only very few and simple one step commands would score a two. This item is an exception to the rule that the first response is used, since several different tools are used to assess language.

12. Dysarthria.
Use the attached word list in all patients and do not tell the patient that you are testing clarity of speech. It is common to find slurring of one or more words in patients one might otherwise score as normal. The score of 0 is reserved for patients who read all words without any slurring. Aphasic patients and patients who do not read may be scored based on listening to the speech that they do produce or by asking them to repeat the words after you read them out loud. The score of 2 is reserved for the patient who cannot be understood in any meaningful way, or who is mute. On this question, normal speech must be identified to score a 0, so the unresponsive patient receives the score of 2.

13. Extinction and Inattention (formerly Neglect).
Place the hand in position exactly as shown in the training video. Fingers may be spread or together. The score of 0 is given only if the fingers maintain full extension for five seconds. The score of 2 is reserved for the hand that has no strength at all. Any change from the fully extended posture within five seconds scores a 1. Note: This item is open to significant variation among examiners, and all neurologists have slightly different methods of assessing neglect. Therefore, to the extent possible, test only double simultaneous stimulation to visual and tactile stimuli, and score a 2 if one side extinguishes to both modalities and a 1 if only to one modality. If the patient does not extinguish, but does show other well developed evidence of neglect, score a 1.

Total Score: Please provide the total score for the subject as determined by the 13 categories of questions. Do not include scores of "9" in total.

Assessment should be completed by a neurologist or certified coordinator. Check one box for each item.

1a. **LEVEL OF CONSCIOUSNESS**
- ☐ 0 Alert
- ☐ 1 Drowsy
- ☐ 2 Stuporous
- ☐ 3 Coma

1b. **LOC – QUESTIONS**
- ☐ 0 Answers both correctly
- ☐ 1 Answers one correctly
- ☐ 2 Both incorrect
- ☐ 9 Untestable

1c. **LOC – COMMANDS**
- ☐ 0 Obeys both correctly
- ☐ 1 Obeys one correctly
- ☐ 2 Both incorrect
- ☐ 9 Untestable

2. **GAZE**
- ☐ 0 Normal
- ☐ 1 Partial gaze palsy
- ☐ 2 Forced deviation

3. **VISUAL FIELDS**
- ☐ 0 No visual loss
- ☐ 1 Partial hemianopia
- ☐ 2 Complete hemianopia
- ☐ 3 Bilateral hemianopia
- ☐ 9 Untestable

4. **FACIAL MOVEMENT (FACIAL PARESIS)**
- ☐ 0 Normal facial movement
- ☐ 1 Minor paresis
- ☐ 2 Partial paresis
- ☐ 3 Complete palsy

5. **MOTOR RIGHT ARM**
- ☐ 0 No drift
- ☐ 1 Drift
- ☐ 2 Some effort against gravity
- ☐ 3 No effort against gravity
- ☐ 4 No movement
- ☐ 9 Untestable

6. **MOTOR LEFT ARM**
- ☐ 0 No drift
- ☐ 1 Drift
- ☐ 2 Some effort against gravity
- ☐ 3 No effort against gravity
- ☐ 4 No movement
- ☐ 9 Untestable

8. **MOTOR LEFT LEG**
- ☐ 0 No drift
- ☐ 1 Drift
- ☐ 2 Some effort against gravity
- ☐ 3 No effort against gravity
- ☐ 4 No movement
- ☐ 9 Untestable

9. **LIMB ATAXIA**
- ☐ 0 Absent
- ☐ 1 Present unilaterally in either arm or leg
- ☐ 2 Present unilaterally in both arm & leg or bilaterally
- ☐ 9 Untestable

10. **SENSORY**
- ☐ 0 Normal
- ☐ 1 Partial loss
- ☐ 2 Dense loss
- ☐ 9 Untestable

11. **BEST LANGUAGE**
- ☐ 0 No aphasia
- ☐ 1 Mild to moderate aphasia
- ☐ 2 Severe aphasia
- ☐ 3 Mute
- ☐ 9 Untestable

12. **DYSARTHRIA**
- ☐ 0 Normal articulation
- ☐ 1 Mild to moderate dysarthria
- ☐ 2 Near unintelligible or worse
- ☐ 9 Untestable

13. **EXTINCTION AND INATTENTION (formerly NEGLECT)**
- ☐ 0 No neglect
- ☐ 1 Partial neglect
- ☐ 2 Complete neglect
- ☐ 9 Untestable

14. **TOTAL NIH STROKE SCORE** ☐☐

☐ 0 No drift (computer calculated score)
☐ 1 Drift
☐ 2 Some effort against gravity
☐ 3 No effort against gravity
☐ 4 No movement
☐ 9 Untestable

7. **MOTOR RIGHT LEG**

☐ 0 No drift
☐ 1 Drift
☐ 2 Some effort against gravity
☐ 3 No effort against gravity
☐ 4 No movement
☐ 9 Untestable

References for NIH Stroke Scale:

National Institutes of Neurological Disorders and Stroke (NINDS), National Institutes of Health