

Network for CT Surgical Investigations Protocol

SURGICAL ABLATION VERSUS NO SURGICAL ABLATION FOR PATIENTS WITH PERSISTENT OR LONGSTANDING PERSISTENT ATRIAL FIBRILLATION UNDERGOING MITRAL VALVE SURGERY



Sponsored By NHLBI, NINDS & CIHR

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Table of Changes

Revision	Section	Change	Reason	Page
2.0	Abstract	Deleted the inclusion criterion on women of childbearing age who do not agree to be on adequate birth control... and added it to the exclusion criteria	Protocol update	10
2.0	Specific Aims	Primary Endpoints heading, modified section on primary analysis	Protocol refinement for clarity	16
2.0	Specific Aims	Under Secondary Endpoints section heading Freedom from Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences, modified second and third bullet points	Protocol update	16
2.0	Study Population	Moved the inclusion criterion on women of childbearing age who do not agree to be on adequate birth control to the exclusion criteria	Protocol update	18
2.0	Definition and Measurement of Endpoints	Under Primary Endpoints heading, modified section on primary analysis	Protocol update	24
2.0	Definition and Measurement of Endpoints	Under Secondary Endpoints section heading Freedom from Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences, modified second and third bullet points	Protocol update	26
2.0	Data Monitoring and Analysis	Under Randomization Design and Procedure heading, modified the block design to 4 or 8 chosen at random	Protocol update	47
2.0	Data Monitoring and Analysis	Under Methods of Analysis heading, updated the description of primary analysis	Protocol update	47
2.0	Data Monitoring and Analysis	Under Freedom from Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences Added the word ablation to third treatment failure description	Protocol refinement for clarity	51
2.0	Organization of the Study	Modified the description of the Echo Core Lab	Protocol refinement for clarity	54
2.1	Post Randomization Data Collection	Under Transtelephonic Monitoring section, added visit window definition and updated weekly transmission schedule	Protocol update	41
2.1	Post Randomization Data Collection	Under Telephone Follow-up section, modified the visit window definition for the 3 month phone call	Protocol update	41
3.0	Entire Document	Replaced the word non-paroxysmal with persistent AF	Protocol update	All
3.0	Title Page	Updated CTSN logo	Protocol update	Title
3.0	Title Page	Updated revision number to 3.0 and date to September 2009	Protocol update	Title
3.0	Clinical Centers	Added "Core" to Clinical Centers title	Protocol update	2

3.0	Abstract	Under Objectives, added 6 month time point for long-term monitor	Protocol refinement for clarity	10
3.0	Abstract	Changed total study duration from 24 to 33 months	Protocol update	10
3.0	Abstract	Deleted primary from MVS inclusion criterion and added organic MV disease, functional non-ischemic MV disease, and ischemic mitral regurgitation with evidence of concomitant structural MV disease	Consensus of PIs	10
3.0	Abstract	Under inclusion criteria, italicized section on concomitant procedures and added concomitant CABG and aortic arch or aortic valve procedure	Consensus of PIs	10
3.0	Abstract	Under inclusion criteria, added description of persistent AF for 6 months prior to randomization lasting at least 7 days or if less than 7 days, requiring cardioversion	Consensus of PIs	10
3.0	Abstract	Under exclusion criteria, deleted cardiac and added mitral valve surgery	Consensus of PIs	10
3.0	Abstract	Deleted functional MR as an exclusion criterion	Consensus of PIs	10
3.0	Abstract	Deleted previous heart surgery as an exclusion criterion	Consensus of PIs	10
3.0	Abstract	Deleted ascending aorta or aortic arch pathology, coronary artery disease, aortic valve disease as exclusion criteria	Consensus of PIs	10
3.0	Data Collection Schedule	Added Pre-Screening Failure Form	Protocol update	11
3.0	Data Collection Schedule	Changed Screening Log and Registration to Demographics Form	Protocol refinement for clarity	11
3.0	Data Collection Schedule	Changed Eligibility Criteria to Eligibility Criteria/Eligibility Evaluation Form	Protocol refinement for clarity	11
3.0	Data Collection Schedule	Deleted Screening Outcome Section	Protocol refinement for clarity	11
3.0	Data Collection Schedule	Added Follow-Up Surgical Procedures point under Event Driven Data	Internal consistency within protocol	11
3.0	Objectives	Under Primary Hypothesis Heading, updated the text on the duration of AF	Consensus of PIs	12
3.0	Study Design	Deleted 10 and added up to 20 clinical sites	Protocol update	17
3.0	Study Design	Deleted 12 and added 21 months for expected accrual time	Protocol update	17
3.0	Randomization	Deleted attempted cardioversion and added following anesthesia and TEE to randomization guidelines	Consensus of PIs	18
3.0	Masking	Added clarification of masking procedures	Protocol refinement for clarity	18
3.0	Characterization of Patient Population	Added definition of persistent AF from the Heart Rhythm Society Task Force	Consensus of PIs	18
3.0	Inclusion Criteria	Under inclusion criterion, #3, deleted primary from clinical indications for mitral valve surgery	Consensus of PIs	19

3.0	Inclusion Criteria	Under inclusion criterion #3, added functional non-ischemic MVS and ischemic mitral regurgitation with evidence of concomitant structural MV disease	Consensus of PIs	19
3.0	Inclusion Criteria	Under inclusion criterion #3, italicized section on concomitant procedures and added concomitant CABG and aortic arch or aortic valve procedure	Protocol update	19
3.0	Inclusion Criteria	Under inclusion criterion #4, added persistent AF within 6 months prior to randomization lasting at least 7 days or if less than 7 days, requiring cardioversion and updated requirements for documentation of AF	Consensus of PIs	19
3.0	Inclusion Criteria	Under inclusion criterion #4, deleted uncertain duration references	Consensus of PIs	19
3.0	Exclusion Criteria	Deleted other cardiac and added mitral valve to first exclusion criterion	Consensus of PIs	19
3.0	Exclusion Criteria	Added footnote to further define exclusion criterion #2	Consensus of PIs	19
3.0	Exclusion Criteria	Deleted functional MR as an exclusion criterion	Consensus of PIs	19
3.0	Exclusion Criteria	Deleted previous heart surgery as an exclusion criterion	Consensus of PIs	19
3.0	Exclusion Criteria	Deleted ascending aorta or aortic arch pathology, coronary artery disease, and aortic valve disease as exclusion criteria	Consensus of PIs	19
3.0	Recruitment Strategies	Added up to 20 clinical centers	Protocol update	20
3.0	Treatment Interventions	Deleted section on cardioversion	Consensus of PIs	20
3.0	Treatment Interventions	Revised description of TTE at baseline	Per Echo Core Lab request	20
3.0	Treatment Interventions	Under Pre-PVI Pacing Protocol heading, added clarification of cardioversion guidelines in OR	Protocol refinement for clarity	21
3.0	Treatment Interventions	Under PVI alone or with Biatrial Maze Lesion Set heading, added clarification of box lesion and confirmation of conduction block guidelines	Protocol refinement for clarity	22
3.0	Secondary Endpoints	Updated section on timeframe for rhythm strip transmission	Protocol update	25
3.0	Definitions and Measurement of Endpoints	Under Secondary Endpoints heading, added the phrase "non-mutually exclusive" to the rhythm documentation on TTM	Protocol refinement for clarity	26
3.0	Quality of Life	Added clarification that inability to participate in QoL due to language barriers does not preclude a patient from enrollment	Protocol refinement for clarity	27
3.0	Adverse Events	Under Causality heading, updated the relationship of the event to the surgical procedure and ablation	Protocol refinement for clarity	28
3.0	Secondary Endpoints	Under Probable Causality heading changed "repair" to "procedure", modified the	Protocol refinement for clarity	29

		second bullet and deleted the third bullet		
3.0	Reporting of Serious Adverse Events	Added explanation of unexpected serious adverse events	Protocol refinement for clarity	29
3.0	Reporting of Serious Adverse Events	Added the reporting of deaths via e-mail to NHLBI program officer	Protocol update	29
3.0	Specific Adverse Event Definitions	Added pleural effusion heading and description	Protocol update	31
3.0	Clinical Centers	Deleted 10 and added up to 20 clinical centers	Protocol update	35
3.0	Qualifications and Training	Changed to 10 surgical AF ablation <i>and</i> 10 MV procedures over 2 year period and added option for certified surgeon to participate in procedure with non-certified surgeon	Consensus of Network PIs	36
3.0	Screening & Baseline	Added Pre-Screening Failure Form Section	Protocol update	37
3.0	Screening & Baseline	Changed Screening Log and Registration to Demographics Form	Protocol refinement for clarity	37
3.0	Screening & Baseline	Changed Eligibility Criteria to Eligibility Criteria/Eligibility Evaluation Form	Protocol refinement for clarity	39
3.0	Screening & Baseline	Updated the Eligibility Criteria/Eligibility Evaluation Form to include process for documenting the non-randomization of screened patients	Protocol refinement for clarity	39
3.0	Screening & Baseline	Moved sentence explaining the DCC's availability to assist with eligibility questions to Eligibility Criteria section	Protocol refinement for clarity	39
3.0	Screening & Baseline	Under Cardiovascular Rhythm Assessment section, updated duration of AF and deleted section on unknown duration of AF	Consensus of PIs	39
3.0	Screening & Baseline	Deleted Screening Outcome Section	Protocol refinement for clarity	39
3.0	Post-Randomization Data Collection	Updated Blood, Urine, & Tissue Sample Collection Schedule	As per request of NHLBI biorepository team	40
3.0	Post-Randomization Data Collection	Revised description of TTE at 12 months post-discharge	Per Echo Core Lab request	42
3.0	Event Driven Data Collection	Added Follow-Up Surgical Procedures section	Protocol refinement for clarity	43
3.0	Data Management	Added clarification of the collection of source documents for deaths and AEs	Protocol refinement for clarity	44
3.0	Event Driven Data Collection	Replaced the word enrollment with randomization	Protocol refinement for clarity	44
3.0	Organization of the Study	Under the Echocardiography Core Lab heading, identified the Network Echo Core Lab and director	Protocol update	55
3.0	Organization of the Study	Under the Electrophysiology Core Lab heading, identified the Network EP Core Lab and director	Protocol update	54
3.1	Entire Document	Added "or longstanding persistent" to the	Per request of the FDA	All

		phrase “patients with persistent AF”		
3.2	Title Page	Updated revision number to 3.2 and date to November 2009	Protocol update	Title
3.2	Abbreviations	Added UADE	Per request of FDA	9
3.2	Abstract	Revised definition of persistent AF	Per request of FDA	10
3.2	Data Collection Table	Added 12-lead ECG procedure in OR	Per request of FDA	11
3.2	Study Design	Changed number of clinical sites to 10	Consensus of Network PIs	17
3.2	Study Population	Changed definition of persistent AF	Per request of FDA	18
3.2	Inclusion Criteria	Revised AF documentation	Per request of FDA	19
3.2	Recruitment Strategies	Changed number of clinical sites to 10	Consensus of Network PIs	20
3.2	Treatment Interventions	Added ECG	Consensus of Network PIs	21
3.2	Reporting SAEs	Add reporting of UADE	Per request of FDA	30
3.2	Clinical Centers	Revised number of clinical sites to 10	Consensus of Network PIs	35
3.2	Cardiovascular Rhythm Assessment	Revised AF documentation	Per request of FDA	39
3.2	Blood, Urine and Tissue Specimen Collection	Updated Blood, Urine, & Tissue Sample Collection Schedule	As per request of NHLBI biorepository team	40
3.2	Method of Analysis	Added analyses of poolability	Per request of FDA	48
3.2.1	Data Collection Schedule	Clarified when rhythm strips vs 12-lead ECGs will be recorded and added a collection point at baseline for the biological specimens	Administrative Update	11
3.2.1	Electrocardiogram	Clarified that a 12-lead ECG is not required upon arrival in the OR	Administrative Update	21
3.2.1	Post-Randomization Data Collection	Updated Blood, Urine, & Tissue Sample Collection Schedule	As per request of NHLBI biorepository team	40
4.0	Title Page	Updated revision number to 4.0 and date to November 2010	Protocol update	Title
4.0	Study Sponsors	Added Wendy Taddei-Peters, PhD; Neal Jeffries, PhD, Nancy Geller, PhD to NHBLI contacts	Protocol update	2
4.0	Abbreviations	Added SAE and UP; removed AE	Protocol update	10
4.0	Study Duration	Clarified expected duration of study	Protocol clarification	11
4.0	Inclusion Criteria	Revised definitions of persistent AF and long standing persistent AF	Consensus of PIs; to align with HRS consensus document	11
4.0	Study Design	Changed number of clinical sites from 10 to 13	Achievement of recruitment goals	18
4.0	Study Population	Revised definitions of persistent AF and long standing persistent AF	Consensus of PIs; to align with HRS consensus document	19
4.0	Inclusion Criteria	Revised definitions of persistent AF and long standing persistent AF	Consensus of PIs; to align with HRS	20

			consensus document	
4.0	Recruitment Strategies	Changed number of clinical sites from 10 to up to 13	Achievement of recruitment goals	21
4.0	Safety	Revised sections on adverse event reporting	To be in agreement with our recently updated reporting procedures	29-32
4.0	Clinical Centers	Changed number of clinical sites from 10 to up to 13	Achievement of recruitment goals	37
4.0	Laboratory Assessment	Changed number window for laboratory assessments from 7 days to 30 days	Consensus of PIs	40
4.0	Cardiovascular Rhythm Assessment	Added “will be” to text	Correction to protocol	41
4.0	Cardiovascular Rhythm Assessment	Revised definitions of persistent AF and long standing persistent AF	Consensus of PIs; to align with HRS consensus document	41
4.0	Cardiovascular Rhythm Assessment	Expanded window on echocardiogram at baseline from 30 days to 3 months	Consensus of PIs	41
4.0	Blood, Urine and Tissue Specimen Collection	Changed volume of blood collected from a total of 55mls to a total of 39mls	Consensus of PIs	42
4.0	Transtelephonic Monitoring	Removed Saturday, Sunday and Monday before noon as transmission window	Consensus of PIs; to allow more flexibility in reporting.	43
4.0	Functional Status	Changed text to indicate that blinded personnel must conduct the NYHA at 12 months.	Protocol clarification	45
4.0	On-site Monitoring	Added “study device log” to list of regulatory binder items	Protocol update	48
4.1	Inclusion Criteria	Removed “willing and” from inclusion criterion	Consensus of PIs to improve enrollment	11
4.1	Inclusion Criteria	Removed “willing and” from inclusion criterion #5	Consensus of PIs to improve enrollment	20
4.2	Study Design	Changed number of clinical sites from 13 to 23	Achievement of recruitment goals	18
4.2	Recruitment Strategies	Changed number of clinical sites from 13 to up to 23	Achievement of recruitment goals	21
4.2	Clinical Centers	Changed number of clinical sites from 13 to up to 23	Achievement of recruitment goals	37
4.2	Blood, Urine and Tissue Specimen Collection	Addition of language clarifying Biorepository	Protocol clarification	42
4.3	Clinical Centers	Added new Ancillary and Satellite Sites	Protocol update	2
4.3	Study Sponsors	Added Albert Lee, PhD to sponsor list	Protocol update	2
4.3	Protocol Development Committee	Formatted list	Formatting update	2
4.3	Abstract	Deleted “need for home oxygen therapy”	Consensus of PIs to improve enrollment	12
4.3	Study Design	Changed number of clinical sites from 23 to	Achievement of	19

		24	recruitment goals	
4.3	Recruitment Strategies	Changed number of clinical sites from 23 to up to 24	Achievement of recruitment goals	22
4.3	Exclusion Criteria	Deleted “need for home oxygen therapy”	Consensus of PIs to improve enrollment	22
4.3	Surgical Ablation and Pacing Procedures	Added updated devices to list of protocol approved ablation devices	To include commonly used ablation devices	23
4.3	Clinical Centers	Changed number of clinical sites from 23 to up to 24	Achievement of recruitment goals	38
4.3	Screening and Baseline Data Collection	Changed window for physical examination, NYHA classification, medications, medical history and Quality of Life questionnaires from 7 days to 30 days prior to baseline	Protocol update	41
4.3	On-Site Monitoring	Added information about centralized monitoring practices	To be consistent with FDA guidelines on Centralized Monitoring	48-49
4.4	Exclusion Criteria	Removal of exclusion criterion regarding evidence of left atrial thrombus	Consensus of PIs	12
4.4	Exclusion Criteria	Removal of exclusion criterion 3	Consensus of PIs	21
4.4	PVI Pacing Protocol	Added descriptions of cases in which the PVI Pacing Protocol is not appropriate	Due to safety concerns	23

1. ABBREVIATIONS

AAD	Anti-arrhythmic drugs
AF	Atrial Fibrillation
AFSS	Atrial Fibrillation Severity Scale
CABG	Coronary artery bypass grafting
CHF	Congestive heart failure
CK	Creatine Kinase
CPB	Cardiopulmonary bypass
CV	Curriculum Vitae
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ERO	Effective Regurgitant Orifice
ELWAF	Emory living with atrial fibrillation scale
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
InCHOIR	International Center for Health Outcomes & Innovation Research
LA	Left atrium
LAA	Left atrial appendage
LV	Left ventricle
MACE	Major adverse cardiac event
MI	Myocardial infarction
MR	Mitral regurgitation
MV	Mitral valve
MVOA	Mitral Valve Opening Area
MVS	Mitral Valve Surgery
NHLBI	National Heart Lung & Blood Institute
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OR	Operating Room
PAP	Pulmonary Artery Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PVI	Pulmonary Vein Isolation
PVR	Pulmonary Vascular Resistance
QoL	Quality of Life
SAE	Serious Adverse Event
SF-12	Short Form – 12
TEE	Trans-esophageal echocardiography
TTM	Trans-telephonic monitoring
UADE	Unanticipated adverse device effect
UP	Unanticipated Problem

2. ABSTRACT

Objectives	- o To compare the effect of mitral valve surgery (MVS) alone or in combination with atrial fibrillation (AF) ablation on postop heart rhythm in patients with MV disease and persistent or longstanding persistent AF - o Compare 2 different techniques for post-ablation heart rhythm monitoring (long-term monitor at 6 and 12 months vs. weekly rhythm strips) to guide follow-up strategies for future studies of rhythm control in AF patients - o Compare quality of life (QoL) in persistent or longstanding persistent AF patients who undergo surgery for mitral valve disease and receive surgical ablation for AF to those who receive MVS alone - o Obtain preliminary estimates of the relative benefit of pulmonary vein isolation (PVI) alone vs. a biatrial lesion set for ablation in MVS patients
Study Design	Randomized controlled trial; patients randomized with equal allocation to MVS alone or to MVS + ablation for AF; patients randomized to MVS + ablation further randomized (1:1) to PVI or ablation with biatrial lesion set.
Target Population	Adult patients with persistent or longstanding persistent AF who are undergoing MVS.
Rx arms	MVS alone versus MVS + AF ablation
Sample Size	260 patients; provides 90% power to detect a 20% difference (25% versus 45%) in freedom from AF (measured at 6 and 12 months)
Duration	24 months follow-up following randomization.
1° Endpoints	Efficacy: Freedom from AF in patients with mitral valve disease and persistent or longstanding persistent AF; this will be assessed with 3-day continuous monitoring at 6 and 12 months post-ablation. Safety: Composite of death, stroke, serious AEs (cardiac and non-cardiac), and cardiac re-hospitalizations < 30 days post-procedure or hospital discharge.
2° Endpoints	AF load; freedom from any electrocardiographically documented arrhythmic recurrence; anti-arrhythmic interventions;; survival (all-cause mortality); safety (i.e., MACE and incidence of protocol-defined and serious adverse events <i>within 12 months after randomization</i>); QoL
3° Endpoints	Functional status; hospitalizations; inpatient costs
Inclusion Criteria	Able to sign Informed Consent and Release of Medical Information forms; age ≥ 18; clinical indications for MVS for the following: organic MV disease, functional non-ischemic mitral regurgitation, or ischemic mitral regurgitation with evidence of concomitant structural MV disease; <i>(may include need for surgical management of functional tricuspid regurgitation or patent foramen ovale; may also include concomitant CABG, aortic arch or aortic valve procedure; may include sternotomy or minimally invasive procedure)</i> ; persistent AF (defined as non self-terminating AF lasting greater than 7 days or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion) within 6 months prior to randomization or longstanding persistent AF (a sub-category of persistent AF defined as continuous AF of greater than one year duration); able to use heart rhythm monitor
Exclusion Criteria	AF w/o indication for mitral valve surgery; AF is paroxysmal; active infection; patient does not understand nature, significance and scope of study; surgical management of hypertrophic obstructive cardiomyopathy; previous catheter ablation; life expectancy < 1 year; absolute contraindications for anticoagulation therapy; current enrollment in other drug or device trials; uncontrolled hypo- or hyperthyroidism; patients with FEV1 < 30% of predicted value; women who are pregnant as evidenced by positive pregnancy test; women of childbearing age who do not agree to be on adequate birth control throughout the period of the trial

3. DATA COLLECTION

Assessment	Baseline	Procedure	Pre-Discharge	Weekly	3 Mos	6 Mos	9 Mos	12 Mos ¹	18/24 Mos	Event driven
General										
Pre-Screening Failure Form	X									
Informed Consent	X									
Release of Medical Information	X									
Demographics Form	X									
Medical History	X									
Medications	X		X		X	X	X	X	X	X
Physical Exam	X		X							
Laboratory Assessment	X									
Eligibility Criteria/Eligibility Evaluation Form	X	X ²								
Hospitalization	X									X
Surgical procedures ³		X								
Telephone Follow-up					X	X	X	X	X	
Cardiac										
Echocardiogram	X	X ⁴						X		X
ECG	X*	X ^Δ	X*							
Weekly TTM ⁵ /event recorder			X ⁶	X ⁷						X
72-hr Holter Monitoring						X		X		
Patient diary			X	X						X
Anti-arrhythmic interventions ⁸					X	X	X	X	X	X
Anti-arrhythmic drug termination					X					X
Biological Specimen Collection ⁹	X	X								
Quality of Life & Functional Status										
SF-12	X							X		
AFSS	X							X		
ELWAF	X							X		
NYHA Class	X							X		
Event Driven Data										
Adverse events			X		X	X	X	X	X	X
Follow-Up Surgical Procedure										X
Missed Phone / Visit Assessment										X
Mortality					X	X	X	X	X	X
Modified Rankin/NIHSS										X
Study Completion/Early Termination									X	X
End of Study/Investigator's Statement										X
Cost										
UB-92 Forms & Hospital Bills ¹⁰					X	X	X	X		

¹Scheduled study visit. If in-person visit is not possible for 12-month assessment, then participating local cardiologist will perform echocardiogram, TTM will allow for a remote continuous 72-hour Holter assessment, and a telephone follow-up assessment by investigative center personnel will be performed.

²The Eligibility Evaluation Form will be completed in the OR following ECG and TEE.

³Surgical procedures include: primary procedure, operative parameters, device used for ablation, lesion sets created, and additional procedures performed at time of initial operation.

⁴Intra-operative trans-esophageal echocardiogram (TEE)

⁵Trans-telephonic monitoring (TTM)

⁶Patients receive a TTM device and are instructed in its use prior to discharge.

⁷Weekly and symptomatic arrhythmia driven TTM monitoring occurs between discharge and 12 months.

⁸Anti-arrhythmic interventions include: cardioversion, permanent pacemaker placement, and subsequent ablation.

⁹Biological specimen collection includes: blood, urine, and tissue collections.

¹⁰Investigative center coordinators must provide patient MR numbers to their center's financial administrators who then provide cost data to the Data Coordinating Center (DCC) directly.

* 12-Lead ECG

Δ Rhythm Strip

4. OBJECTIVES

Purpose of the Study

The primary aim of this proof-of-concept trial is to determine if surgical ablation for persistent or longstanding persistent AF is more effective than MVS alone in reducing occurrence of post-MVS AF at 6 months and 1 year. Inclusion of 2 different lesion sets in the ablation group (pulmonary vein isolation only [PVI] and a biatrial Maze lesion set) will provide preliminary data to guide development of a follow-up study comparing effectiveness of these 2 lesion sets. In addition to 72-hour continuous rhythm assessment at 6 months and 1 year (Holter), we will employ weekly transtelephonic monitoring to inform follow-up strategies for future trials of rhythm control in AF.

4.1 Primary Hypothesis

In patients with mitral valve disease requiring surgical intervention and persistent or longstanding persistent AF within 6 months prior to randomization, the proportion of patients free of AF (at both the 6 and 12 month assessments) will be greater after surgical ablation for AF than after MVS alone.

4.2 Secondary Aims

- (a) Obtain preliminary estimates of the relative benefit of a biatrial maze lesion set compared to PVI alone for ablation in MVS patients, to inform the design of a subsequent trial.
- (b) Compare 2 different techniques for post-ablation heart rhythm monitoring (long-term monitor at 12 months vs. weekly rhythm strips) to guide follow-up strategies for future studies of rhythm control in AF patients.
- (c) Compare QoL in persistent or longstanding persistent AF patients who undergo surgery for mitral valve disease and receive surgical ablation for AF to those who receive MVS alone.

5. BACKGROUND

Epidemiology

AF is the most common cardiac arrhythmia, and with a prevalence of nearly 0.5%, affects over 2 million Americans [1]. Patients with AF may suffer from symptomatic tachycardia or low cardiac output secondary to loss of atrial mechanical function, and have a 5-10% risk of thromboembolic complications [2]. As a result, conventional wisdom suggests that the risk of mortality is increased by AF [3]. These factors have led to great enthusiasm for catheter and surgical ablation in AF patients.

AF is present in 30% to 50% of patients presenting for MVS. In such patients, AF is associated with reduced survival and increased risk of stroke. It is hypothesized that long-term outcomes—stroke, mortality—can be improved by an ablation procedure for

preoperatively existing persistent AF in patients undergoing MVS. Successful ablation might free many patients from need for long-term warfarin therapy and its associated risks. However, demonstration of the true efficacy of surgical ablation techniques has been incomplete at best, due to the heterogeneity of lesion sets created and technologies employed and because of the challenges of long-term monitoring of recurrent AF.

Current Practices

The cut-and-sew Cox-Maze III procedure has been reported to cure AF in more than 90% of MVS patients [4-7]. However, this complex operation, with its biatrial lesion set, represents an empiric approach based on the understanding of AF in the late 1980s. Furthermore, sporadic and inconsistent monitoring of post-ablation heart rhythm, variable intensity of monitoring (rarely continuously for duration of follow-up), and inadequate data analysis methodology make it impossible to state with certainty the true results of this operation [8].

Today, more detailed understanding of the pathogenesis of AF and new tissue ablation technologies to create lines of conduction block have laid the foundation for widespread attempts at AF ablation during heart surgery. The pulmonary veins and left atrium house the triggers, drivers, and substrate for AF in most patients, and ablation strategies are directed to these structures, frequently leaving the right atrium untreated [9-12]. New ablation energy sources (radiofrequency, microwave, laser, high-frequency ultrasound, argon-based cryothermia) facilitate procedures and reduce operative time to 10–20 minutes [8, 13]. These factors have led to a large increase in the number of surgical ablations performed over the last 5 years, with MVS patients representing the majority of those treated.

Almost all current approaches to surgical ablation for AF include PVI. PVI is the simplest, most rapidly completed lesion set, and can be performed epicardially and off pump [14, 15]. In contrast, the biatrial Maze lesion set, performed with contemporary ablation devices, requires right and left atriotomies, cardiopulmonary bypass (CPB), and endocardial lesion location for the mitral and tricuspid annuli connecting lesions [16]. Consequently, the PVI lesion set is used more frequently in cardiac surgery than the biatrial Maze lesion set. Although surgical PVI is widely employed, several lines of evidence suggest that a more extensive lesion set, may enhance ablation effectiveness [6, 7, 11, 12, 17]. In the electrophysiology laboratory, higher freedom from AF correlates with a greater volume of ablated left atrial tissue [18]. Thus, a lesion set that ablates more of the posterior left atrium may be more effective than simple PVI [12, 18], as may ones that include right atrial lesions and a connecting lesion to the mitral annulus [16, 19-21].

Methods for assessing post-ablation heart rhythm and data analysis and depiction vary widely. Current guidelines suggest that ablation success should be quantified by ascertaining freedom from AF at 12 months (or longer) post-ablation; such assessment may be achieved by a 3-day continuous monitor applied at the 12 month point. Others suggest that ablation outcomes should be assessed by regular and periodic rhythm strips (e.g. weekly transtelephonic strips) and that these data may be analyzed to depict AF

incidence over time and AF load, defined as the proportion of days on which a patient has documented AF. The primary end point of this study is freedom from AF on a 3-day continuous monitor at 6 and 12 months post-ablation; however, we will also collect weekly rhythm strips to depict AF load. This strategy of intense rhythm monitoring using 2 different techniques will enable us to compare these 2 methods for ascertaining results, providing important guidance for the design of future trials of rhythm control strategies for AF.

Current Studies

Several factors contribute to the weakness of available data on outcomes after concomitant modified Maze procedures in patients undergoing mitral valve surgery. First, the majority of studies are limited to **retrospective, single center studies**, with few studies offering controlled subjects as a point of reference. Second, significant **procedural variations** exist both within and across studies, with variation typically resulting from surgeon preferences that are not restricted by a defined set of predetermined guidelines. Third, because indications and contraindications for surgical ablation are frequently loosely determined and vary significantly between institutions and studies, **patient populations are heterogeneous** and therefore difficult to compare due to variations in patient characteristics such as type of AF, duration of AF, degree of left atrial enlargement, pre-operative therapies and existence/severity of underlying cardiac disease or other major co-morbid medical conditions. Fourth, **outcomes have not been standardized**. In some reports, success is defined only as “freedom from atrial fibrillation” at a single postoperative time point (e.g. 3 months), while in others, a successful outcome requires documentation of a normal rhythm that is sustained over a period of time; in yet other institutions, success is defined more stringently as absence of atrial fibrillation after discontinuation of all antiarrhythmic medications. Furthermore, few reports have addressed measures of success apart from restoration of sinus rhythm, such as restoration of normal atrial contraction, ventricular function, incidence of stroke or other thromboembolic events, overall QoL, ability to discontinue or reduce poorly tolerated antiarrhythmic or anticoagulant medications, or long-term survival. And lastly, in most surgical series, there is no electrical confirmation of PVI. All of these factors likely explain the wide variability of results [8, 13, 16, 17].

To date there have been 6 randomized clinical trials examining outcome in MVS patients with AF. All trials included a control group of patients who did not have ablation. Treatment groups included MVS with biatrial ablation (3 trials), left atrial ablation (2 trials), and left atrial reduction without ablation (1 trial). These trials were small (none enrolled more than 100 patients) and it is not clear that they were powered to document the effectiveness of ablation compared to MVS alone. They included a variety of lesion sets and generally had poor post-procedure documentation of heart rhythm. None assessed acute procedural success (conduction block). Although a crude meta-analysis of 4 of these trials performed by the Data Coordinating Center (DCC) suggested that the relative risk of success for patients treated with ablation compared to patients treated without ablation is 2.97 (95% CI 1.88 to 4.80), there is general agreement that these trials are not conclusive. With these serious limitations, the published trials fail to answer the key question addressed by the current proposal.

Rationale for this Study

Despite its reported success, the true clinical efficacy of surgical ablation for the treatment of AF in patients with mitral valve disease has been difficult to quantify for numerous reasons. These include: (1) lack of randomized studies, (2) patient heterogeneity across published studies, (3) operator learning curves, (4) procedural variations, (5) lack of standardized outcome measures, and (6) difficulty in patient monitoring and follow-up. Large-scale, pivotal trials designed to assess the clinical benefit of surgical ablation for AF in MVS patients are needed; however, before such trials can be conducted, it is necessary to perform proof-of-concept trials to generate data that will document the effectiveness of surgical ablation and guide the choice of ablation procedure (ie, lesion set) in individual patients presenting for MVS. Clinical practice has outpaced data in this field; physicians and their patients need data from well-designed clinical trials to choose the best treatment options. Furthermore, effectiveness is only presumed to translate into reducing strokes and mortality.

This proof-of-concept trial takes the first in a series of steps toward building an evidence basis for surgical ablation therapies for persistent or longstanding persistent AF ablation. Results from this trial, if ablation is effective over MVS alone, will inform the design of subsequent trials comparing specific lesion sets and ablation devices. The decision to study MVS patients with persistent or longstanding persistent AF addresses safety concerns, improves our ability to determine the impact of ablation procedures, and should facilitate enrollment. Because the left atrium is routinely opened for MVS, ablation adds little time or risk to the surgical procedure; the surgeon is “already there” for the mitral valve procedure. By choosing patients with persistent or longstanding persistent AF, we exclude those patients who move between AF and sinus rhythm sporadically and without intervention, enabling us to attribute elimination of AF to the assigned treatment. Finally, we propose to manage the left atrial appendage (LAA) in all MVS patients in this study. This strategy, which is consistent with current guidelines for MVS, ensures that all patients will receive some treatment related to their AF - which may facilitate study enrollment¹.

¹ ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society. Journal of the American College of Cardiology, Volume 48, Issue 4, Pages 854 – 906. V. Fuster, L. Rydén, D. Cannom, H. Crijns, A. Curtis, K. Ellenbogen, J. Halperin, J. Le Heuzey, G. Kay, J. Lowe. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and Approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. Heart Rhythm, Volume 4, Issue 6, Pages 816 - 861 H. Calkins, J.

6. SPECIFIC AIMS

6.1 Primary Endpoints

Efficacy

Freedom from AF in patients with mitral valve disease and persistent or longstanding persistent AF. AF will be measured by 3-day continuous monitoring at 6 and 12 months post-ablation; and freedom of AF will be defined by absence of AF lasting > 30 seconds at both time points.

Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF assessment, will be considered as treatment failures (not free of AF). In the primary analysis, patients in both treatment arms who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure will be considered treatment failures (not free of AF).

Safety

A composite of death, stroke, serious cardiac events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism, peripheral embolism, excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, damage to peripheral structures, such as the esophagus, within 30 days post-procedure or hospital discharge (whichever is later).

6.2 Secondary and Tertiary Endpoints

Secondary Endpoints

AF load

The proportion of recordings documenting AF, atrial flutter or atrial tachyarrhythmia in a given patient during spot recordings (trans-telephonic monitoring, TTM) between 3 and 12 months.

Freedom from Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences

Freedom from AF, atrial flutter or atrial tachycardia (in patients with mitral valve disease and persistent or longstanding persistent AF) will be defined by absence of any electrocardiographically documented (TTM, including rhythm strips and Holter monitoring) AF, atrial flutter or atrial tachycardia lasting > 30 seconds.

- Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF assessment, will be considered as treatment failures (not free from AF).

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- In both treatment arms, patients who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure will be considered treatment failures.
- Patients in both treatment arms will be considered treatment failures if they take class I or class III anti-arrhythmic drugs (AADs) or undergo cardioversion for AF following 3 months post-randomization.

Anti-Arrhythmic Interventions

- Need for permanent pacemaker or electrical cardioversion
- Use of anti-arrhythmic drugs
- Subsequent AF ablations

Survival (All-cause Mortality)

All-cause mortality at 12 months post-randomization

Safety

- Major adverse cardiac events (MACE) defined as a non-weighted composite score of: death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, and mitral valve [MV] re-intervention within 12 months of randomization
- Incidence of protocol-defined and serious adverse events (especially thrombo-embolic and hemorrhagic events) within 12 months of randomization

Quality of Life

- Short Form – 12 (SF-12)
- Atrial Fibrillation Severity Scale (AFSS)
- Emory Living With Atrial Fibrillation (ELWAF) Scale

Tertiary Endpoints

Functional Status

- Assessed by NYHA class

Hospitalizations

- Length of index hospitalization
- Readmission

Inpatient Costs

- Inpatient costs for all admissions from baseline to 12 months

7. STUDY DESIGN

This is a prospective, multi-center, randomized, controlled clinical trial. The trial will be conducted in up to 24 clinical sites. Two hundred and sixty (260) patients will be

randomized. Accrual is expected to take 21 months, and all patients will be followed for 12 months post randomization.

8. RANDOMIZATION

Patients will be randomized to one of two treatment groups:

- Group 1: mitral valve surgery with ligation/excision of left atrial appendage PLUS surgical ablation
- Group 2: mitral valve surgery with ligation/excision of left atrial appendage (control group)

Patients will be randomized in a 1:1 fashion. By this arrangement, 50% of the patients will undergo ablation lesions (Group 1) and 50% will not (Group 2). All patients will undergo ligation or excision of LAA.

Patients randomized to the ablation (Group 1) will be further randomized (1:1) to one of two lesion sets:

- Group 1a: pulmonary vein isolation
- Group 1b: biatrial lesions

Randomization will be performed intra-operatively following anesthesia and TEE.

9. MASKING

Neither patients nor investigators will be blinded to treatment. Investigators will, however, be blinded to all data from other clinical sites except serious unexpected AEs for IRB reporting purposes. Core labs will also be blinded to clinical outcomes and treatment assignment. Adverse events will be adjudicated by an Event Adjudication Committee and trial oversight will be provided by an independent DSMB. Those assessing the primary outcome will be blinded to patients' treatment assignment.

10. STUDY POPULATION

Characterization of Patient Population

The patient population for this trial consists of adult patients with mitral valve disease requiring surgical intervention and persistent or longstanding persistent atrial fibrillation. Persistent AF is defined as in the 2007 report of the Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation as non self-terminating AF lasting greater than 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion. Longstanding persistent AF is defined as continuous AF of greater than one year duration. This definition applies only to AF episodes that are of at

least 30 seconds' duration and do not have a reversible cause such as acute pulmonary disease or hyperthyroidism.² All patients who meet the eligibility criteria may be included in the study regardless of gender, race or ethnicity.

Inclusion Criteria

1. Able to sign Informed Consent and Release of Medical Information forms
2. Age $\geq$ 18 years
3. Clinical indications for mitral valve surgery for the following:
 - Organic mitral valve disease; *or*
 - Functional non-ischemic mitral regurgitation; *or*
 - Ischemic mitral regurgitation with evidence of concomitant structural mitral valve disease

Note: May include need for surgical management of functional tricuspid regurgitation or patent foramen ovale. May also include concomitant CABG, aortic arch or aortic valve procedure. Surgical intervention may be performed via sternotomy or minimally invasive procedure.

4. a) Persistent AF within 6 months prior to randomization, defined as non self-terminating AF lasting greater than 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion.
 - Duration of AF must be documented by medical history and
 - Presence of AF must be documented by a direct electrocardiographic assessment within 6 months prior to randomization.
- b) Longstanding persistent AF is defined as continuous AF of greater than one year duration.
 - Duration of AF must be documented by medical history and
 - Presence of AF must be documented by a direct electrocardiographic assessment upon arrival in the OR.
5. Able to use heart rhythm monitor

Exclusion Criteria

1. AF without indication for mitral valve surgery
2. AF is paroxysmal³
3. Evidence of active infection
4. Mental impairment or other conditions that may not allow subject to understand the nature, significance, and scope of study

² Calkins, H., et al., *HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up*. European Society of Medicine, 2007; 9: p. 819.

³ Paroxysmal AF is defined as recurrent AF (2 or more episodes) that terminates spontaneously within 7 days of onset.

5. Surgical management of hypertrophic obstructive cardiomyopathy
6. Previous catheter ablation for AF
7. Life expectancy of less than one year
8. Absolute contraindications for anticoagulation therapy
9. Enrollment in concomitant drug or device trials
10. Uncontrolled hypo- or hyperthyroidism
11. FEV1 < 30% of predicted value
12. Women who are pregnant as evidenced by positive pregnancy test
13. Women of childbearing age who do not agree to be on adequate birth control throughout the period of the trial.

Recruitment Strategies

Based on a survey of the clinical sites, it is estimated that approximately 260 patients could be enrolled annually through active screening and recruitment by up to 24 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, 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 CT Surgery Network intends to recruit 50% women and 25% minorities. The following measures will be employed to ensure adequate representation of these groups: (1) documentation of the number of women and minorities screened and enrolled via screening/exclusion logs; (2) monitoring of such logs from each clinical center on a monthly basis; and (3) if necessary, the development and implementation of outreach programs designed to recruit adequate numbers of women or minorities.

11. TREATMENT INTERVENTIONS

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) will be used to measure left atrial size and volumes, quantify mitral valve function, detect intracardiac thrombi, and to assess pulmonary vein anatomy/flows and left atrial and left ventricular function. TEE will be used to measure LA size in the mid esophageal view with images obtained at zero degrees and 90 degrees. From these 2 views, LA length, width, area and volume can be ascertained.

Transthoracic Doppler-Echocardiography

The baseline transthoracic doppler echocardiography will be used to measure LA function (a. atrial filling function, b. LA ejection fraction, c. atrial systolic mitral annular velocity (TDI)).

Electrocardiogram (ECG)

An ECG will be done upon arrival in the operating room. This tracing will be used to assess heart rhythm on all patients and provide part of the documentation needed to establish the diagnosis of longstanding persistent AF.

Left Atrial Appendage

All patients will have their LAA excised or excluded.

Mitral Valve Surgery

For mitral regurgitation, the procedures will be a valve repair in the majority of cases. For valves that are not amenable to repair, and for most cases of mitral stenosis, a valve replacement will be performed.

Surgical Ablation and Pacing Procedures

After randomization, general anesthesia induction and TEE, but before ablation, patients will undergo chest wall incision (usually median sternotomy), cannulation, and institution of CPB. Then, a pacing protocol will be conducted to assess conduction before and after PVI.

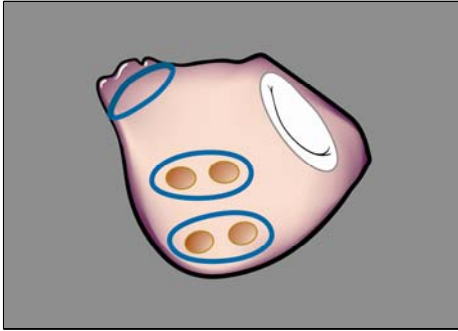
Pre-PVI Pacing Protocol: The pacing protocol (before and after PVI) will confirm acute conduction block at the pulmonary vein level.

The pacing protocol will not be performed in patients undergoing unilateral minithoracotomy, in patients with left atrial thrombus or suspected left atrial thrombus, or in patients who underwent previous cardiac surgery. For those patients not meeting the above exclusion criteria and who present to the OR in AF, the surgeon will attempt a synchronized cardioversion following institution of CPB but before cardioplegic arrest. If the patient does not present to the OR in AF or if the cardioversion is successful, a standard 6F bipolar pacing electrode (or other apparatus for direct epicardial pacing) will be placed directly on the right pulmonary veins and the pacing threshold established. Pacing will be initiated at 5 MA, 20 beats per minute above the intrinsic rate. With these settings, it will be noted whether or not the heart is entrained. If entrainment fails, threshold will be established and recorded after attempting capture at progressively higher pacer outputs (10, 15, 20 MA). This pre-PVI pacing protocol will be repeated for the left pulmonary veins. If the patient presents to the OR in AF and cardioversion is unsuccessful, the pacing protocol will not be attempted and the surgeon will conduct the ablation according to the lesion set specified. In such instances, it is recommended that bipolar ablation devices be applied three times and that unipolar devices be applied one time in performing PVI.

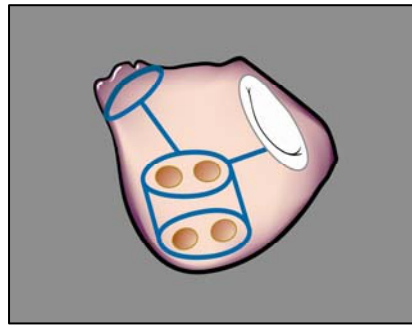
This trial will use bipolar and unipolar devices, based on a radiofrequency [RF] energy source: (1) Medtronic Cardioblate LP (bipolar RF), (2) Medtronic Standard or XL Surgical Ablation Pens (unipolar RF), (3) Medtronic Cardioblate Surgical Ablation Pen 60813; (4) Medtronic Cardioblate XL Surgical Ablation Pen 60814; (5) Medtronic Cardioblate BP2 Surgical Ablation Clamp/Cardioblate LP Surgical Ablation Clamp 60831/60841; (6) Medtronic Dispersive Electrode 60882; (7) Medtronic MAPS, Ablation Pen with Pacing 49205; (8) Medtronic Cardioblate Cryoablation Probe and Clamp 60SF2/60SF3/60SF7/60CM1; (9) AtriCure OLL2 Bipolar Handpiece (Bipolar RF), (10) Atricure MAX1 Transpolar Pen (Unipolar RF), AtriCure LAA Exclusion System—LAA035, LAA040, LAA045 and LAA050; (11) AtriCure Isolator Synergy—OLL2, EMR2, EML2 and OSL2; (12) AtriCure Isolator Synergy Access—EMT1; (13) AtriCure Coolrail Linear Pen—MCR1 and MLP1; (14) AtriCure Isolator Transpolar Pen—MAX3 AtriCure Isolator Long Pen TT—MAX5; (15) AtriCure Cryo 1Cryo-ablation Probe—CRY01; (16) AtriCure CryoICE Cryo-ablation Probe—CRY02; (17) Estech COBRA Cooled Surgical Probe (Unipolar RF) and Bipolar Straight and Parallel Clamps (Bipolar RF).

In addition to the linear lesions created by unipolar or bipolar radiofrequency, additional spot lesions will be created at the mitral annulus and isthmus using either unipolar radiofrequency or cryotherapy. The ATS Cryomaze or AtriCure Frigitrionics device will be used for the creation of cryo lesions. The cryoprobe is recommended for lesions approaching the mitral or tricuspid annulus; this enables incorporation of the coronary sinus.

PVI alone or with Biattrial Maze Lesion Set Using Bipolar Energy Source: Bipolar energy sources are preferred for PVI alone and for the pulmonary vein isolation component of the biatrial maze lesion set. For patients randomized to PVI alone, two separate encircling lesions will be made around the left and right pulmonary veins. For patients randomized to the biatrial maze lesion set, the left atrial lesions will include; the two encircling lesions, as well as connecting lesions to the pulmonary veins, from the pulmonary veins to the mitral valve annulus, and from the pulmonary veins to the LAA. The right pulmonary veins will be isolated first. Isolation will be confirmed by pacing the pulmonary veins at the previously identified threshold for capture. If no atrial capture is noted, it will be inferred that the right pulmonary veins were isolated. If atrial capture is noted, additional ablations on the atrial cuff will be performed until isolation is confirmed. This protocol will be repeated on the left pulmonary veins.

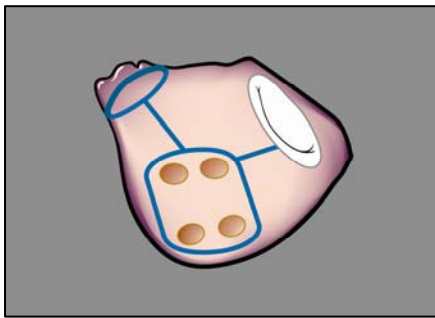


PVI Lesion set with bipolar device



Left Atrial Component of Biatrial Lesion set with bipolar device

PVI alone or with Biatrial Maze Lesion Set Using Unipolar Energy Source:



Pulmonary vein isolation should be achieved with a bipolar ablation device. However, if patient anatomy, a minimally invasive approach, or surgeon preference dictates use of a unipolar device, such device may be employed to create a "box lesion" to encircle the pulmonary veins and other connecting lesions. If the patient is randomized to the PVI alone or biatrial Maze lesion set and a unipolar energy source is employed to create an epicardial box lesion, ablation

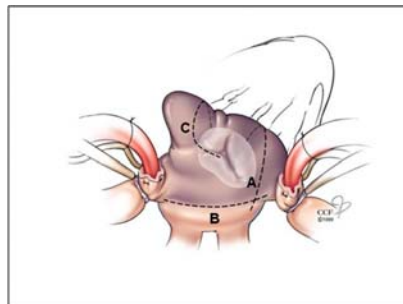
will be performed on the arrested heart from the endocardial aspect. A box lesion will be created around all four pulmonary veins on the arrested heart from the endocardial aspect. The connecting lesions from the pulmonary veins to the mitral valve annulus, and from the pulmonary veins to the LAA will be made next. It is recommended that the Estech Cooled Cobra device be used for this lesion, as its conformation ensures that this larger lesion can be made linearly and contiguously. If a unipolar energy source is used as noted above, the surgeon will attempt to confirm conduction block at the pulmonary vein level after reperfusion of the heart but before separation from bypass. If the surgical approach is minimally invasive via the right chest, the pacing protocol will be followed for the right pulmonary veins. If the surgical approach is sternotomy, the pacing protocol will be followed for the right pulmonary veins and then for the left pulmonary veins. In confirming conduction block, pacing from the pulmonary veins will be attempted at a rate 20 beats per minute greater than the intrinsic heart rate at outputs of 5, 10, 15 and 20 MA.

Remaining Lesions: After PVI, the heart will be arrested and LAA excised or excluded. The remainder of the procedure for patients randomized to the biatrial Maze lesion set will be performed at a point in the operation dictated by the surgeon's standard practice. Components of this biatrial Maze lesion set will include:

- *Left atriotomy:* The left atrium will be opened adjacent to the interatrial groove, anterior to the right pulmonary veins.
- *Connecting lesions from right to left pulmonary veins:* This applies to patients in whom a bipolar energy source was used for PVI. A bipolar device will be used to

create separate lesions between superior pulmonary veins and between inferior pulmonary veins.

- *Connecting lesion to mitral annulus:* A cryosurgical device or unipolar heat-based device will be used to create a connection from the “box” lesion to the mitral annulus. This lesion will be directed toward the P3 segment of the mitral valve.
- *Connecting lesion to left atrial appendage:* After excising or excluding the appendage, a unipolar or bipolar energy source will be used to create a connecting lesion from its orifice to the “box” lesion.
- *Right atrial lesions:* A vertical right atriotomy will be made beginning from the AV groove and extending toward the fossa ovalis. A unipolar energy source will be used to connect this lesion to the tricuspid annulus at the 2 o’clock position as viewed by the surgeon (A). A unipolar or bipolar energy source will be used to connect the posterior aspect of this atriotomy to the superior and inferior vena cavae (B). An incision will be created in the body of the right atrial appendage and a unipolar energy source used to connect the incision to the tricuspid annulus at the 10 o’clock position as viewed by the surgeon (C). At the discretion of the surgeon, patients with a history of atrial flutter are candidates for the right atrial isthmus lesion.



Left atrial appendage amputation, ligation, or occlusion

Amputation of the LAA may be achieved by cut-and-sew technique or by application of a surgical stapler. Ligation of the LAA may be accomplished by oversewing or stapling across the base of the LAA.

Standardization of Anti-arrhythmic Drug Use during Follow-up

Unless contraindicated (hypotension or bradycardia defined as heart rate less than 60 beats per minute), all ablation and non-ablation patients will receive prophylactic Class I/III anti-arrhythmic agents (amiodarone, sotalol, propafenone, procainamide) beginning within 24 hours of randomization. Patients will be discharged on the anti-arrhythmic agent. At the 3-month point, antiarrhythmic agents will be terminated in all patients and this recommendation communicated by study personnel to the managing physician. Direct current cardioversion will be performed as clinically indicated by managing physicians and recorded by study personnel for the duration of follow-up.

Suggested Antiarrhythmic agents

Agent	Dose	Notes
Amiodarone	400 mg TID for 4 days 400 mg QD for 7 days 200 mg QD for 11 weeks	Contraindicated in patients with untreated thyroid disorder, sinus bradycardia, PR>240 ms, 2 nd or 3 rd degree AV block, QTc>480 ms,

		AST>2x upper limits, cirrhosis.
Sotalol	120 mg BID for 12 weeks	Contraindicated in patients with significantly reduced renal filtration (Clcr <40 mL/minute). Must remain monitored for first 6 doses following QT interval. If increase in QT >20% or over 500ms decrease dose or discontinue.
	80 mg BID for 12 weeks	For patients with smaller BSA.
Propafenone	150 mg TID for 3-4 days may titrate to 225mg TID if necessary	Contraindicated in patients with CAD and septal hypertrophy (>1.5cm). Use cautiously in patients with sinus bradycardia and LV dysfunction.
Procainamide	750 mg BID for 12 weeks	Contraindicated in patients with significantly reduced renal filtration (Clcr <40 mL/minute) and patients with lupus. Check procainamide and NAPA levels.

Anticoagulation

Unless specifically contraindicated, warfarin will be prescribed for all patients (ablation and control group) at hospital discharge, with a target INR of 2.0. It is recommended that warfarin be continued in all patients for the entire duration of the study unless a specific contraindication to anticoagulation develops.

12. DEFINITIONS AND MEASUREMENT OF ENDPOINTS

12.1 Primary Endpoints

Efficacy

Freedom from AF in patients with mitral valve disease and persistent or longstanding persistent AF. The primary efficacy endpoint will be assessed with 3-day continuous monitoring at 6 and 12 months post-ablation (between weeks 50 and 54). Freedom from AF will be defined as the absence of any episodes of AF lasting >30 seconds at both the 6 and 12 month monitoring time points.

Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF assessment, will be considered as treatment failures (not free of AF). In the primary analysis, patients in both treatment arms who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure will be considered treatment failures (not free of AF).

Safety

A composite of death, stroke, serious cardiac events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism, peripheral

embolism, excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, damage to peripheral structures, such as the esophagus, within 30 days post-procedure or hospital discharge (whichever is later).

12.2 Secondary and Tertiary Endpoints

Secondary Endpoints

AF Load

The proportion of recordings documenting AF, atrial flutter or atrial tachyarrhythmia in a given patient during spot recording (including ECGs and TTM).

AF load will be measured with ECGs and weekly TTM. Atrial fibrillation, atrial flutter, and other atrial tachyarrhythmias will be recorded distinctly but combined as a single endpoint for analysis. In order to be included in analysis, an arrhythmia must be documented to last 30 or more seconds.

TTM favorably balances signal fidelity and patient compliance to obtain the highest yield of data for analysis. During hospitalization, patients will be given a TTM device and instructed in its use. The SAVI platform is capable of recording weekly rhythm strips (90 seconds in duration) and a 3 day assessment of heart rhythm at 6 and 12 months post-ablation. The weekly strips will be transmitted transtelephonically to a Core Laboratory for assessment and analysis of heart rhythm. Patients will be instructed to transmit one strip per week during the course of this study (see AF MOP). Specifying the day and time of transmission is necessary to ensure that the monitoring schedule is independent of all potential confounders, including patient rhythm status. In addition, patients with symptoms suggestive of an arrhythmia (rapid or irregular heart rhythm) will be instructed to transmit rhythm strips at the time of symptom occurrence. All patients will receive a diary in which they will note their regular transmissions and also transmissions associated with symptoms and symptoms in the absence of a rhythm recording; they will record the character of symptoms that they perceive to be related to heart rate or rhythm (rapid heart rate, irregular heart rhythm). At the 6 and 12 month points, patients will use the same device to monitor heart rhythm for 72 hours. The sites will then send the device to the Core Laboratory for analysis. On a quarterly basis, sites will receive a report of number of rhythms received for each patient over the number of rhythms expected to assess patient compliance.

All rhythm tracings from the event monitor will be evaluated by two collaborating electrophysiologists, blinded to the treatment received, in an Electrophysiologic Core Laboratory for assessment and analysis of heart rhythm, to be established by the Network and DCC. Rhythms will be classified (non-mutually exclusively) as AF, atrial flutter, other atrial tachycardia, sinus rhythm, junctional, atrial pacing, atrioventricular sequential pacing, or indeterminate. After surgery, patients will be followed for a minimum of 12 months.

Freedom from Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences

Freedom from AF, atrial flutter or atrial tachycardia (in patients with mitral valve disease and persistent or longstanding persistent AF) will be defined by absence of any electrocardiographically documented (TTM, including rhythm strips and Holter monitoring) AF, atrial flutter or atrial tachycardia lasting > 30 seconds.

- Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF assessment, will be considered as treatment failures (not free of AF).
- In both treatment arms, patients who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure will be considered treatment failures.
- Patients in both treatment arms will be considered treatment failures if they take class I or class III anti-arrhythmic drugs (AADs) or undergo cardioversion for AF following 3 months post-randomization.

Anti-Arrhythmic Interventions

- Requirement for permanent pacemaker implantation or electrical cardioversion at any point following the treatment intervention
- Use of anti-arrhythmic drugs (Class I or III anti-arrhythmics) after 3 months post-randomization will be measured
- Any ablation therapy for AF (surgical or percutaneous) at any point following the treatment intervention

Survival (All-cause Mortality)

- All-cause mortality will be assessed at 12 months post-randomization.

Safety

- Major Adverse Cardiac Events (MACE) within 12 months of randomization
MACE is defined as a non-weighted composite score comprised of the following components:
 - death
 - stroke
 - worsening heart failure (+1 NYHA Class)
 - CHF hospitalization
 - mitral valve re-intervention
- Incidence of protocol-defined and serious adverse events (refer to Section 12.3 Safety below) within 12 months of randomization

Quality of Life

The change in QoL from baseline to 12 months will be measured using three complementary instruments (SF-12, AFSS, ELWAF). The SF-12 is a general health status measure. This instrument examines 8 QoL dimensions (physical activity, social activity, role/physical, body pain, general mental health, role/emotional, vitality and general health perception). The AFSS is a 14-item disease-specific scale developed to

capture subjective and objective ratings of AF disease burden, including frequency, duration, and severity of episodes. The ELWAF is a disease-specific scale that measures the impact of AF disease and treatment burden on the patient. Specifically, physical, psychological and social consequences of the disease itself, as well as from the treatment, are assessed. SF-12, AFSS, and ELWAF questionnaires can be found in Appendix II. *For this trial, the SF-12 is available in English, Spanish and French. The AFSS and ELWAF are available in English and French. Inability to read and complete these instruments in the available languages does not preclude a patient from enrollment in the trial.*

Tertiary Endpoints

Functional Status

Functional status will be assessed by the New York Heart Association (NYHA) classification scale. Complete NYHA classification guidelines can be found in Appendix I.

Hospitalizations

- Length of 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).
- Readmission
Readmission rates will be calculated for the first 30 days following intervention and long term. Hospitalizations will be classified for all causes, including for cardiovascular readmissions.

Inpatient Costs

Inpatient costs for all admissions (index hospitalization and all subsequent re-hospitalizations) will be measured from baseline to 12 months. Costing data (obtained from UB-04 forms and hospital billing sheets) will be collected from investigative center financial administrators by the DCC for enrolled patients on a quarterly basis. For Medicare-eligible enrollees, we will also collect CMS billing data. NOTE: Investigative center coordinators are required to provide patient MR numbers to their center's financial administrators prior to any data transmissions to the DCC. All costing data will be cross-referenced against the clinical database to ensure that the available costing data are appropriate and complete.

12.3 Safety

Adverse Events

The incidence of serious adverse events over the course of the trial will be compared between the two treatment groups. All serious and all protocol-defined adverse events (AE) will be adjudicated by an Event Adjudication Committee (EAC). The endpoints for safety will be reported as the frequencies of occurrence of each adverse event, the rate of adverse events per patient/year and time to each event. In addition, the number of patients with each serious adverse event type will be recorded. Safety data will be collected throughout this study and the incidence of each event type will be computed along with the 95% confidence intervals.

An adverse event is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an AE unless there is a change in the nature, severity or degree of the condition.

Serious Adverse Event

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

Unanticipated Serious Adverse Event

An unanticipated (unexpected) serious adverse event is any serious adverse event that is not protocol-defined or documented in the patient consent form. Expedited reporting is required for serious adverse events that are unexpected.

Unanticipated Adverse Device Effects

An unanticipated adverse device effects (UADE) is any serious adverse effect on health or safety or any life-threatening problem caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

Unanticipated Problems

According to the Office for Human Research Protections ([OHRP](#)), an Unanticipated Problem (UP) generally includes any incident, experience, or outcome that meets **all** of

the following criteria: (1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; *and* (2) Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); *and* (3) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Based on the definitions above and as illustrated below (per OHRP guidance), many adverse events are not unanticipated problems, and many unanticipated problems are not adverse events. However, some adverse events are also unanticipated problems. For example, a serious adverse event that is unexpected and at least possibly related to study participation is also by definition an unanticipated problem. As stated above, an unanticipated problem may not necessarily be an adverse event, which is the case when the problem does not cause actual physical harm to participants. For example, if a laptop computer with sensitive, identifiable study data is stolen, this theft places the participants at greater *risk* of psychological or social harm; this is an unanticipated problem that is not an adverse event. Another example of an unanticipated problem that is not an adverse event is if the FDA announces that one of the study drugs is tainted (e.g., with paint chips), yet no participant experiences any adverse effects.

Event Recording

The following adverse events will be captured throughout the period of trial participation:

- o Protocol-defined (as described below)
- o Serious unanticipated events (serious “*Other*” adverse events)

Causality

The investigator will assess the relationship of an adverse event to the surgical intervention. The investigator should distinguish the relationship between the event and (a) surgical procedure (i.e. MV procedure or other concomitant procedures), and (b) surgical ablation. Causality will be defined as follows:

Probable

Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the surgical intervention (MV procedure ± surgical ablation). The following characteristics will apply:

- o A reasonable temporal relationship exists between the event and the surgical intervention, and
- o The event is a known reaction to the surgical intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

Possible

Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the surgical intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after surgical intervention, and
- The event is not a known reaction to surgical intervention, but cannot be explained by a commonly occurring alternative etiology

Unlikely

Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to surgical intervention and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the surgical intervention, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the surgical intervention.

Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects

All investigators conducting clinical studies supported by the NHLBI must report both expected (protocol-defined) and unexpected SAEs. All protocol defined SAEs must be reported directly to the clinical center's IRB and the DCC within 10 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths, UADEs, and unexpected SAEs that are possibly or probably related to the surgical ablation must be reported to the DCC and the clinical center's IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All *unexpected SAEs* that are **unlikely related to the study intervention** must be reported to the DCC and the clinical center's IRB within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

The DCC will notify the NHLBI program officer of any unexpected SAEs (including UADEs) that are possibly or probably related to the intervention and all deaths (regardless of relatedness and expectedness) via e-mail within 24 hours of receipt of the event. The program officer will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

Reporting of Unanticipated Problems

All *UPs* that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All *UPs* that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

DCC Reporting to FDA

The DCC will report unexpected SAEs that are possibly or probably related to the investigational device or UADEs to FDA as appropriate. The DCC will send an initial IDE safety report communication to the FDA within 2 business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of a UADE for this IDE trial.

Specific Adverse Event Definitions

Bleeding

A bleeding event is defined by any one of the following:

- o Transfusion of > 2 units RBC within the first 24 hours following surgery
- o Death due to hemorrhage
- o Re-operation for hemorrhage or tamponade

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias

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

1. Sustained ventricular arrhythmia requiring defibrillation or cardioversion
2. Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
3. Cardiac conduction abnormalities requiring permanent pacemaker

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.

Atrial Rupture

Disruption in the integrity of the left or right atrial wall, documented by direct inspection or diagnostic testing, that necessitates surgical repair.

Valvular Injury

Injury to a cardiac valve (excluding the mitral valve), as evidenced by new regurgitation or stenosis following the treatment intervention. This definition excludes changes to the mitral valve because it will be surgically repaired at the time of the treatment intervention.

Non-infectious Pericarditis

Signs and symptoms of pericardial inflammation, with or without electrocardiographic evidence, requiring pharmacologic anti-inflammatory therapy. This definition excludes infectious pericarditis (see Major Infection infectious pericarditis definition below).

Esophageal Injury

Disruption in the integrity of the esophagus documented by diagnostic imaging, such as contrast radiography or chest CT, that requires surgical intervention.

Pulmonary Vein Stenosis

A $\geq 50\%$ decrease in the diameter of the pulmonic vein as documented by chest CT or echocardiography.

Diaphragmatic Paralysis

Phrenic nerve injury as evidenced by new elevation of a hemi-diaphragm on chest radiogram.

Pneumothorax

Presence of gas in the pleural space, documented by chest radiogram or chest CT, that requires evacuation or prolongs the duration of chest tube drainage.

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, (or if hepatic dysfunction is the primary cause of death).

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 $\geq 38.0^\circ\text{C}$, 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 infarction⁴:

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:

⁴ Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*.2007;116:0-0.

- o Symptoms of ischemia;
- o ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- o Development of pathological Q waves in the ECG;
- o 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 $> 5 \times 99^{\text{th}}$ percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

Peri-Percutaneous Intervention (PCI) Myocardial Infarction

For PCI 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 $> 3 \times 99^{\text{th}}$ percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

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.

Neurologic Dysfunction

Any 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 evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The Modified Rankin Scale and the NIH Stroke Scale (NIHSS) must be administered at time of event (within 72 hours following the event) and 90 days following the event to document the presence and severity of neurological deficits. The Modified Rankin Scale and NIHSS can be found in Appendix III.

Each neurological event must be subcategorized as:

Transient Ischemic Attack

Defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.

Ischemic or Hemorrhagic Stroke (Cerebrovascular Accident)

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

Toxic Metabolic Encephalopathy

Defined as a disorder of the brain function that arises from abnormal systemic metabolism or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.

Other Neurologic Dysfunction***Renal Events***

Two categories of renal events will be identified:

Renal Dysfunction

Abnormal kidney function defined by > 100% rise in serum creatinine (Cr) from baseline, and Cr > 2.0

Renal Failure

New requirement for hemodialysis related to renal dysfunction. This definition excludes aquapheresis for volume removal alone.

Respiratory Failure

Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue ventilatory support within 48 hours post-surgical intervention. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m² in the absence of elevated left atrial/pulmonary capillary wedge pressure (> 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation, inhaled nitric oxide or inotropic therapy, for a duration of > 7 days.

Arterial Non-CNS Thromboembolism

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

- o Standard clinical and laboratory testing
- o Operative findings

- o Autopsy findings

This definition excludes neurological events.

Venous Thromboembolic Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

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.

13. CLINICAL CENTERS

The study will be conducted in up to 24 of the clinical centers participating in the NIH-supported Cardiothoracic Surgery Network. Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) 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 DCC 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 NHLBI and DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile

All surgeons, cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The surgeon, cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in atrial fibrillation surgery and cardiologists with experience in caring for patients with arrhythmias. To qualify as a participating surgeon, the surgical investigators must have performed at least 10 surgical AF ablation and 10 mitral valve procedures over a 2 year period. The certified surgeon will either perform the ablation and mitral procedure on their own patient, or participate in the ablation and mitral procedure of an enrolled patient whose

surgeon is not certified. Surgical qualifications for all participating surgical investigators will be collected on the Surgical Certification Form and faxed to the DCC prior to accreditation. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating surgical investigators at that site over the course of the study. In addition, each surgical investigator will participate in at least one of the bi-annual meetings of the Clinical Management Committee.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

Signature Verification

Investigators will input an electronic signature into the electronic data capture system (EDC). It will be updated throughout the study as new site personnel are approved.

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
- Clinical Center Laboratory Certification

A signed agreement between the clinical site and the DCC (Mount Sinai School of Medicine) 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 (e.g. engineers, social workers).

Patient Confidentiality

All patients' records will be kept confidential according to HIPAA guidelines. Study Investigators, site Institutional Review Boards (IRBs), the DCC and the NHLBI 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.

14. SCREENING AND BASELINE DATA COLLECTION

Pre-Screening Failure Form

Prior to informed consent

Prior to approaching a patient to begin the informed consent process, the study personnel will review data on prospective patients to determine eligibility for inclusion in the trial. All pre-screened patients (patients who are not consented) who are not enrolled are recorded in the Pre-Screening Failure form. For these patients, reasons for failing the pre-screening process are documented. The data collected is HIPAA compliant and does not include patient identifiers but only includes screening quarter, screening year, age, gender and reason for not being eligible. The reasons for screening failure for patients who were consented are collected on the Eligibility Evaluation Form.

Consent

Prior to screening data collection and protocol-defined procedures (initiated ≥ 24 hours prior to randomization)

Prior to screening, a thorough explanation of the risks and benefits of the study will be outlined by the investigator to the patient and the patient will be asked to sign a consent form.

Release of Medical Information

Prior to screening data collection and protocol defined procedures

The patient must sign the Release of Medical Information form or equivalent that authorizes release of medical records, including hospital costing data, to the study NHLBIs, investigators, monitors, and the FDA.

Demographics Form

At initiation of screening

A screened patient is defined as an individual (a consented patient) who was referred to, or identified at a clinical site for consideration of entry into the study, and for whom some preliminary (i.e. medical record) data have been collected and/or reviewed. For all patients screened, the first, middle, and last initial, date of birth, ethnic origin, and sex will be captured on the screening log and registration form. The EDC will generate a unique 8-digit identification code that will identify the patient throughout the course of the study.

Medical History

Within 30 days prior to randomization

This form captures the information pertaining to the medical history, including but not limited to previous myocardial infarction, myocardial revascularization, arrhythmias, automatic implantable cardioverter-defibrillator, permanent right ventricular or biventricular pacemaker, stroke and other comorbidities such as diabetes and peripheral vascular disease. Information regarding the current medical condition is also captured, including but not limited to disposition at time of screening (outpatient, inpatient, ICU monitoring, etc) and intra-aortic balloon pump use.

New York Heart Association Classification

Within 30 days prior to randomization

Functional status will be assessed using the NYHA classification. NYHA classification will be determined by investigative center personnel and documented on the “New York Association Classification” form. The NYHA classification scheme is detailed in Appendix I.

Medications

Within 30 days prior to randomization

This form captures all protocol-defined medications taken within 7 days prior to randomization.

Physical Examination

Within 30 days prior to randomization

This form captures the comprehensive physical examination including vital signs, cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight and BSA).

Quality of Life

Within 30 days prior to randomization

SF-12, AFSS, ELWAF (Appendix II) Questionnaires will be completed by the patient and used to assess QoL. Data regarding completeness of QoL data collection and reasons for missing responses to questionnaires will be collected on the QoL Checklist.

Laboratory Assessment

Within 30 days prior to randomization

- White blood cell ($10^3/\mu\text{L}$)
- Hemoglobin (g/dL)
- Hematocrit (%)
- Platelet count ($10^3/\mu\text{L}$)
- Prothrombin time (PT/sec), partial thromboplastin time (PTT/sec)
- International Normalized Ratio (INR)
- Blood chemistries, including sodium (mM/L), potassium (mM/L), blood urea nitrogen (mg/dL), creatinine (mg/dL).
- Liver function tests, including total bilirubin (mg/dL), alanine aminotransferase (ALT U/L), aspartate aminotransferase AST (U/L), albumin (g/dL), lactate dehydrogenase (LDH).
- Urine or serum beta HCG (IU/L) is required for women who have the potential to become pregnant

Eligibility Criteria/Eligibility Evaluation Form

Prior to randomization

The inclusion and exclusion criteria will be documented by the clinical site study coordinator and verified with the site Principal Investigator in the Eligibility Evaluation Form. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Eligibility

Evaluation Form. The data collected is HIPAA compliant and includes reason for not being randomized.

A representative from the DCC will be available to discuss any questions regarding patient eligibility.

Cardiovascular Rhythm Assessment

Prior to randomization, Intraoperative

Physicians must document in the Medical History Form the timing and duration of AF. For patients with persistent AF, the physician note must indicate that the episode of AF occurred within 6 months of randomization and lasted >7 days, or < 7 days but required pharmacological or DC cardioversion. For longstanding persistent AF, the physician note should indicate > 1 year of continuous AF. An **ECG** or other direct assessment of heart rhythm will be obtained within 6 months prior to randomization to document the presence of *persistent AF*. All patients, both those with persistent and longstanding persistent AF, will undergo an ECG upon arrival in the operating room (OR). Furthermore, there will be a baseline **transthoracic Doppler echocardiogram** performed within 3 months prior to randomization.

Transesophageal Echocardiography

Pre-randomization, Intraoperative

All patients will undergo intraoperative TEE, which is standard care during mitral valve surgery. TEE will be used to measure left atrial size and volumes, quantify mitral valve function, detect intracardiac thrombi, and to assess pulmonary vein anatomy/flows and left atrial and left ventricular function. For LA size, images will be obtained in the mid esophageal view at zero degrees and 90 degrees. From these measurements, LA length, width, area and volume will be ascertained.

15. POST-RANDOMIZATION DATA COLLECTION

Surgical Procedures

Initial surgical intervention and event driven

Includes information regarding specific primary procedure, operative variables, device used for ablation, lesion sets created, additional procedures performed at time of initial operation, intra-operative pharmacological agents, and intra-operative blood transfusions. The procedure form will also include a section where the investigator can depict the lesion set created by annotating a diagram; this form will be mailed to the DCC.

Blood, Urine and Tissue Specimen Collection

Intra-operative

For those patients that consent to participate in the biological specimen analysis program, blood, urine and tissue will be obtained and banked for future genetic, molecular and biomarker analyses. In brief, the samples will be collected and banked by using the NHLBI Blood and Tissue Repository service (operated by SeraCare Bio Services, 217 Perry Parkway, Gaithersburg, Maryland 20877). The repository only assists in the

collection and storage of samples; it does not conduct assays nor analyze samples. The samples will be available to the Network Investigators during the “proprietary period” which starts when the samples are collected and banked, and continues up to three (3) years beyond the last clinic visit or two (2) years after the main results paper is published (whichever is first). The “open period” begins when the proprietary period ends; during this open period Limited Access Data Sets (LAD) and biospecimens are made available to the wider scientific community. By using the NHLBI repository, it is expected that Network Investigators will not exhaust samples during the proprietary period and that aliquots will be available to the wider community during the open period. The following table shows the sample type, quantity and time of collection:

Type of Sample	Baseline/Intra-operative
Cardiac Tissue*	1cm ²
Urine	8mls
Whole Blood for Plasma	24mls
Whole Blood for DNA**	10mls
Whole Blood for RNA (PAX Gene)	5mls
Total	39mls

*1cm² of left atrial tissue from the left atrial incision suture remnant.

**Whole venous blood.

Instructions on collection methods and procedures (such as sample collection, specific collection tubes, packing materials, coding labels and preaddressed shipping labels) are detailed in the Biospecimens Operations Manual.

Hospitalizations

Index hospitalization and event driven

For all patients the index (baseline) hospitalization and all subsequent hospital admissions (for any reason) must be reported on the Hospitalization form.

Patient Pre-discharge

Prior to discharge

- **Medications**
All cardiovascular medications are recorded, including AADs given prophylactically since randomization.
- **Physical Examination (including vital signs and cardiopulmonary examination)**
- **Electrocardiogram (12-lead ECG)**
- **Adverse Events**
Detailed information regarding adverse events is recorded at the time an event occurs during hospitalization. Investigators are asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention.

- **Patient Diaries**

All patients will receive a diary prior to discharge and instructed as to how to complete it.

Patient Discharge

Patients clinically stable for discharge may be discharged to an affiliated rehabilitation center, intermediate care center, long-term care facility, step-down facility or home. All patients will be discharged with a transtelephonic heart rhythm monitoring device.

Transtelephonic Monitoring

Weekly (± 24 hours) and symptomatic arrhythmia driven transtelephonic monitoring between discharge and 12 months.

Prior to discharge, patients will be given a TTM device and instructed in its use. The weekly strips will be transmitted transtelephonically to a Core Laboratory for assessment and analysis of heart rhythm. Patients will be instructed to transmit one strip per week (preferably, at a regular time each week) from discharge to 12 months post-randomization. In addition, patients with symptoms suggestive of an arrhythmia (rapid or irregular heart rhythm) will be instructed to transmit rhythm strips at the time of symptom occurrence.

From discharge through 12 months post-randomization, patients will note the following information in their diaries: 1- their regular TTM transmissions, 2- TTM transmissions associated with symptoms and 3- symptoms in the absence of a rhythm recording. They will record the character of symptoms that they perceive to be related to heart rate or rhythm (rapid heart rate, irregular heart rhythm).

Telephone Follow-up

*3 months (Medications ± 7 days; AAD Termination $+14$ days); 6 and 9 months (± 14 days); 18 and 24 months (± 30 days)**

Telephone follow-up assessments will be conducted by investigative site personnel to document that the patient is alive and to assess the following:

- **72-hour Holter Monitoring (6 months only)**

The TTM device provided to patients prior to discharge will be used for this assessment. Because the capabilities of the TTM allow for a remote continuous 72-hour Holter assessment, an in-person study visit is not required at the 6-month assessment.

- **Medications**

All cardiovascular, inotropic, antiplatelet agents, and anticoagulants will be recorded. Medications (including AADs) will be recorded at each telephone follow-up, and also as indicated at the time of associated adverse events. We will also record response to DC cardioversions (success or failure).

- **Anti-arrhythmic Drug Termination (3 months $+14$ days only)**

An AAD termination form will be completed at the 3-month follow-up assessment.

- ***Adverse Events, Anti-arrhythmic Interventions, and Hospitalizations***
Patients will be asked to recall any adverse events (including stroke and bleeding) and the number of hospitalizations that occurred out of network since the previous contact. Patients will also be asked if they had a permanent pacemaker insertion, cardioversion or subsequent ablation since the last contact.

***NOTE:** The 18 and 24 month follow-up call will be used to specifically document that the patient is alive, whether the patient had a stroke, is on AADs and/or on medications for heart failure, and has undergone cardiac ablation, insertion of a pacemaker or cardioversion since the previous contact.

Post-discharge Study Visit*

12 months (± 30 days) post randomization

After discharge, a return in-person visit is planned at 12 months provided the patient is still alive. The following assessments are scheduled at this visit:

- ***Transthoracic Doppler Echocardiogram***
All patients will undergo follow-up transthoracic Doppler echocardiography at the investigative center*. Transthoracic Doppler echocardiography will be used to measure LA function (a) atrial filling, (b) LA ejection fraction, (c) atrial systolic mitral annular velocity (TDI). MV function, mitral regurgitation and LV function will be measured.
- ***72-hour Holter Monitoring***
The TTM device provided to patients prior to discharge will be used for this assessment.
- ***Medications***
All cardiovascular, inotropic, antiplatelet agents, and anticoagulants will be recorded. Medications (including AADs) will be recorded at the study visit, and also as indicated at the time of associated adverse events. Response to DC cardioversions (success or failure) will also be recorded.
- ***Quality of Life***
The SF-12, AFSS and ELWAF questionnaires (Appendix II) will be used to assess QoL. The patients themselves must complete these questionnaires and return them to the investigative center.
- ***Functional Status***
NYHA classification (Appendix I) will be determined by a coordinator or physician not otherwise involved in this trial and blinded to the treatment assignment. The NYHA class will be documented on the “New York Heart Association Classification” form.
- ***Adverse Events, Anti-arrhythmic Interventions, and Hospitalizations***
Patients will be asked to recall any adverse events (including stroke and bleeding) and the number of hospitalizations that occurred out of network since the last contact. Patients will also be asked if they had a permanent pacemaker insertion, cardioversion or subsequent ablation since the last contact.

***NOTE:** For patients unable to return to the CTSN investigative center for the 12-month follow-up, an echocardiogram will be performed by the treating cardiologist and sent to the Echocardiography Core Laboratory for analysis. In addition, the TTM will allow for a remote continuous 72-hour Holter assessment, and investigative center personnel will telephone the patient for additional follow-up assessment, which includes medications, functional status, adverse events, anti-arrhythmic interventions, and hospitalizations as described in this section. Investigative center personnel will also remind patients to complete and return QoL questionnaires.

Inpatient Costs

Quarterly through 12 months post-randomization

Inpatient costs for all admissions (index hospitalization and all subsequent re-hospitalizations) will be measured from baseline to 12 months. Costing data, obtained from UB-2 forms and hospital billing sheets, will be collected from investigative center financial administrators by the DCC for enrolled patients on a quarterly basis. For Medicare-eligible enrollees, we will also collect CMS billing data. NOTE: Investigative center coordinators are required to provide patient MR numbers to their center's financial administrators prior to any data transmissions to the DCC. All costing data will be cross-referenced against the clinical database to ensure that the available costing data are appropriate and complete.

Event Driven Data Collection

Follow-Up Surgical Procedures

Event Driven

All operations following the initial mitral valve surgery 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. All intra-operative transfusion requirements must be documented.

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 procedure using the guidance provided. All adverse events will be recorded until completion of the trial. All serious and all protocol-defined adverse events will be adjudicated by an EAC.

Missed Phone / Visit Assessment

Event Driven

If a patient is unable to have a phone follow-up before the closure of a study visit window, a missed visit assessment must be completed that captures the reason for missing the follow-up.

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.

Neurologic Dysfunction Assessment

Event Driven

The Modified Rankin Scale and NIHSS (Appendix III) should be administered by a certified evaluator at the time of a neurologic event (within 72 hours following the event) and 90 days following the event to document the presence and severity of neurological deficits.

Study Completion/Early Termination

Event Driven or End of Study

This form records the date and reason for study completion or early termination. The anticipated reasons for a patient to be withdrawn from this study is at a patient's request or at the physician's discretion, details of which will also 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 at that center. His/her electronic signatures will attest to the accuracy and completeness of the data collected.

16. 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 provides hierarchical user permission for data entry, viewing, and reporting options. For optimum security, the system operates Secure Socket Layer (SSL) 128-bit encryption protocol over Virtual Private Networks. 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).

16.1 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.

16.2 On-Site Monitoring

The DCC will perform on-site monitoring visits at each study site at least once a year. The monitoring visits will be an opportunity to verify a minimum of the following data points for all patients: initials, date of birth, sex, signed informed consent, eligibility criteria, medical history, date of enrollment, protocol-defined serious adverse events (SAEs) and mortalities. The monitors will also conduct a review of the regulatory documents for the study.

In addition to on-site monitoring, the DCC will perform centralized or remote monitoring of the EDC with a focus on safety, study endpoints, data completion and data outliers. The DCC will review data entered by the site into the EDC and may also request supporting documentation be provided by the coordinator. The DCC will generate performance metrics to analyze site characteristics such as screening and enrollment rates and timeliness and completeness of data entry. This will allow the DCC to identify trends across sites and to address low-performing sites appropriately.

The primary objectives of the DCC in monitoring clinical sites are to educate, support, identify and resolve issues related to the clinical trial. The monitors will discuss the protocol in detail, and clarify any areas of uncertainty. At initiation of the study, the monitors will conduct a tutorial on the EDC system. The coordinators will practice entering data so that the monitors can confirm that the coordinators are proficient in all aspects of data entry, query response, and communication with the data management team.

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 serious and protocol-defined 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. 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 (administrative) 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, CVs of all study personnel, institutional HIPAA certificates, monitor site visit log, telephone contact log, a study device log and correspondence with the DCC.

If a problem is identified during the visit (i.e., 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 issue. Some issues may require input from the Steering Committee or the Principal Investigator, as well as the sponsor.

The combination of yearly 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.

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 randomization, anticoagulation, serious and protocol-defined adverse events, mortality, NYHA Classifications and QoL. 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.

17. ANALYTICAL PLAN

17.1 Statistical Analysis Plan

General Design Issues

This study is a prospective, multi-center, parallel group, randomized clinical trial. Patients with MV disease and persistent or longstanding persistent AF will be randomly assigned using a 1:1 allocation to treatment with MVS plus surgical ablation (MVS plus ablation) or to MVS alone. The nature of the treatments precludes masking of patients and their treating clinicians to treatment assignment; however, outcomes will be assessed and recorded by study personnel masked to treatment assignment. The trial's primary aim is to compare the two randomization groups (MVS alone versus MVS plus ablation) with respect to freedom from AF (measured using a 72-hour Holter monitor) over one year. Patients are considered to be free of AF if they are observed not to be in AF at both the six month and one year assessments. The primary null hypothesis is that there is no difference in the proportion of patients free of AF between randomization arms (MVS alone versus MVS plus ablation). An important secondary aim of the trial is to obtain a preliminary estimate of the potential benefit of ablation with a biatrial Maze lesion set compared to ablation with PVI.

An additional analysis will also be performed to assess whether treatment with MVS plus ablation is not inferior to treatment with MVS alone in terms of safety, where safety is defined by the primary composite safety endpoint.

Sample size

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for surgical ablation. To date there have been six randomized clinical trials examining effect of ablation in treating AF in MVS patients [22-27]. All trials included a control group of patients who did not have ablation. Treatment groups included MVS with biatrial ablation (3 trials), left atrial ablation (2 trials), and left atrial reduction without ablation (1 trial). These trials were small (none enrolled more than 100 patients), included a variety of lesion sets and

generally had poor post-procedure documentation of heart rhythm. None assessed acute procedural success (conduction block). The reported absence of AF one year post MVS among control patients in these six previously executed randomized clinical trials ranges from approximately 15% to 35%. These trials all reported a relatively large but imprecise, benefit of ablation. For example, Doukas et. al., in their trial of 99 MVS patients found an absolute benefit of 35% for ablation in the proportion of patients free of AF at one year (95% confidence interval from 17% to 53%;), corresponding to a slightly more than 3-fold increase in the proportion of patients free of AF at one year [22].

For computing sample size, we assume that 25% of patients treated with MVS without ablation (the control group) will be free of AF. A total of 260 patients randomized with equal probability to MVS plus ablation or to MVS alone (i.e., 130 in each randomization group) provides 90% power to detect an absolute increase of 20% (25% versus 45%) in the proportion of patients free of AF, based on a two-tailed 0.05 level continuity corrected chi-squared test. The sample size takes account of a single interim analyses to be performed in addition to the final analysis. The single interim analysis, detailed below, requires that the alpha level used for the final analysis to be 0.049.

17.2 Randomization Design and Procedure

This trial will use a 1:1 ratio in randomizing patients to MVS plus ablation or to MVS alone. In addition, patients randomized to MVS plus ablation will be randomly assigned with equal probability to ablation with a biatrial Maze lesion set or to PVI. The randomization will be stratified by clinical center and use a random permuted block design, with blocks of size 4 or 8 chosen at random. Randomization will be implemented as previously described.

17.3 Data Monitoring and Analysis

Methods of Analysis

The primary efficacy outcome of this randomized clinical trial is freedom from AF over one year post randomization. Patients who die within 12 months will be considered treatment failures (not free of AF). The null hypothesis is that there is no difference in the proportion of patients meeting the primary outcome between patients randomized to MVS plus surgical ablation or to MVS alone. That is, we will test

$$H_0: \pi_0 = \pi_1 \text{ versus } H_1: \pi_0 \neq \pi_1$$

Where π_0 and π_1 represent the proportion free from AF at both the six month and one year assessment among patients randomized to receive MVS alone and MVS plus ablation respectively. The primary null hypothesis will be tested in an intent-to-treat analysis using a 0.05 level Mantel-Haenszel chi-squared test with stratification by clinical center, the factor upon which randomization is stratified. For simplicity, the benefit of MVS plus ablation compared to MVS alone will be quantified as a simple difference in the proportion of patients free of AF 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 ablation compared to patients randomized to no ablation will be reported as the simple relative risk and associated 95% confidence interval.

Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF measurement, will be considered as treatment failures (not free of AF). In the primary analysis, patients in both treatment arms who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure will be considered treatment failures (not free of AF). Patients missing either the 6- or the 12-month assessment, for reasons other than death or illness, will have their primary outcome imputed using a multiple imputation algorithm described below. Imputed data will be rounded to 0 (free of AF) or 1 (AF present).

An implicit assumption of the proposed primary analysis is that the results for all of the study centers can be pooled or combined. We will assess the validity of this assumption by a variety of means, recognizing that establishing poolability merits both clinical and statistical examination.

We do not anticipate that pooling of results across study centers will be threatened due to any clinically important differences in trial conduct. Centers involved in the CT Surgery Network have been selected because they are experienced cardiac surgery programs with a high volume of patients and demonstrated success in conduct of clinical trials and adherence to study protocols. Frequent site monitoring and regular contact including weekly teleconferences involving site coordinators and investigators, as well as quarterly in person meetings, ensure that all centers strictly follow trial protocols.

Additionally, we will conduct several statistical analyses to assess poolability of results across centers. These include center specific analyses of the primary endpoint to assess the consistency of results, and similarity of patient demographics and baseline characteristics across centers. In addition to uncovering potential poolability issues that would require further exploration, differences may indicate the need for additional, more complex, statistical analysis. The effect of center will be explicitly assessed by a secondary analysis testing the interaction of treatment with center via a logistic regression model incorporating centers through a series of indicator variables. Power for detecting an interaction may be low, so we will also consider the qualitative analysis of center specific results to assess the extent the heterogeneity of treatment by center.

The primary safety endpoint of this trial is a composite of death, stroke, serious cardiac adverse events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism, peripheral embolism, excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, damage to peripheral structures, such as the esophagus, within 30 days post-procedure or hospital discharge (whichever is later). The following null hypothesis, stating the non-inferiority of MVS plus ablation compared to MVS alone, with respect to safety will be tested

$$H_0: \pi_0 > \pi_1 + \delta \text{ versus } H_1: \pi_0 \leq \pi_1 + \delta;$$

where π_0 and π_1 represent the proportion of patients experiencing the composite safety endpoint within 30 days post-procedure or hospital discharge (whichever is later) for patients randomized to receive MVS alone and MVS plus ablation, respectively, and $\delta=0.125$ represent a clinically insignificant difference. The null hypothesis will be rejected at the 0.05 level if the 95% upper confidence bound for $\pi_1 - \pi_0 \geq 0.125$. With 130 patients in each treatment group, a one-sided 0.05 level test power to reject the primary safety null hypothesis is at least 80% assuming $\pi_0 = \pi_1 \leq 0.20$. The primary safety null hypothesis will be tested on both the intention to treat and the “as treated” analysis sets.

Interim Analysis

We plan to perform a single interim analysis with respect to the primary outcome to give the option of stopping early should results strongly favor one arm or the other. The proposed timing of this analysis is at 0.5 on the information scale, i.e., after half of the total expected patients (130) reach the primary endpoint. The utility of performing this analysis will depend on the rate of accrual of patients into the trial. We assume an accrual rate of twenty-two (22) patients per month, or an average of 2.75 patients per month per center. As the decision to terminate early would likely occur after most, if not all, patients were randomized, the principal benefit of early termination would be prompt dissemination of results and the possibility of cross-over from the no ablation arm, should ablation prove to be superior. A group sequential procedure allows for flexibility in the number and timing of interim analyses should the DSMB choose to modify the proposed plan, or should accrual mitigate the usefulness of an interim look. We will use the Lan-DeMets approach, implementing an O'Brien-Fleming-type spending function that allots most of the type I error to the final look [28]. The resulting alpha critical values to be used for each analysis are 0.0030 at the interim analysis, 0.049 at the final analysis.

In addition to the ethical concern of continuing a trial that shows a clear benefit in favor of one treatment, there is also a corresponding ethical concern of continuing a trial that has little chance of ever showing a benefit of one treatment compared to the other. We propose that the trial's conditional power, under the original alternative hypothesis, be computed at the interim look and that the DSMB use this as a basis to determine whether randomization, if not completed, be halted for futility. We propose that consideration be given to halting the trial for futility if, given the data up to the point of the interim analysis, the probability of detecting an absolute 20% benefit for patients randomized to MVS + ablation is less than 20%.

We do not propose any a priori stopping criteria based on adverse events. The treatments in this trial are widely used, and have well known adverse event profiles. Mortality is expected to be relatively low. Moreover, we believe that incident rates of adverse events and mortality must be interpreted along with information about the consistency of related measures, consistency across centers, data completeness, and any external factors, including scientific developments that might impact patient safety. In addition to considering the data generated by this trial, the DSMB will consider all relevant background knowledge about the treatment of atrial fibrillation. The DSMB would be capable, and uniquely suited, to make decisions for convening outside the schedule of

meetings, and to make determinations to suspend or terminate the trial. These decisions should be at the discretion of the DSMB alone. We therefore will defer to the DSMB, who should be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review.

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 such as age and ethnicity. As 260 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 all analyses.

Secondary Analyses

A number of secondary analyses are planned to supplement the primary analysis. All secondary analyses will be performed at a two-sided 0.01 level.

Analysis of other Atrial Fibrillation Endpoints

AF Load. Additional analyses of AF will include risk factor identification for mean AF load and ordinal AF load measurement [29]. We expect a subgroup of patients to be completely free of AF after surgery, their AF load being 0. The remaining patients will have their AF continuously distributed between 0 and 1, with more positioned near 0 than 1. Therefore, AF load may be considered as a semi-continuous variable with a cluster of values at 0, and perhaps a smaller cluster at 1. To study features of AF load that are not sufficiently represented by the sample mean, we propose, as our primary analysis of this secondary endpoint, a two-part regression model based on the idea of Olsen and Shafer [30]. This is a joint model of 1) an ordinal regression for AF load=0, AF load between 0 and 1, AF load=1, and 2) a mean regression when AF load is between 0 and 1. Treatment group and risk factors for AF load, including sites, will be incorporated into both parts of the model. Because the distribution of AF load can be viewed as a mixture of ordinal and continuous variables, the proposed model reveals how various predictors might affect different aspects of the distribution of AF load.

Additional analyses of AF load will be performed using a zero-inflated Poisson model with random effects as proposed by Hall [31]. This model allows an analysis of counts that are assumed to follow a Poisson distribution (e.g., the number of documented AF episodes) except for an excess frequency of observed zero counts. This model-based regression analysis affords an in-depth comparison between the two randomization arms through the ability to include additional baseline and risk factors and accounts for the clustering effect due to repeated measures from the same subject.

Freedom from Any Electrocardiographically Documented Atrial Tachyarrhythmia Recurrences. Freedom from AF, atrial flutter or atrial tachycardia (in patients with

mitral valve disease and persistent or longstanding persistent AF) will be defined by absence of any electrocardiographically documented AF, atrial flutter or atrial tachycardia lasting > 30 seconds. Additionally patients will be considered treatment failures if (1) they die prior to the 12-month assessment, (2) they are determined by an independent adjudicator to be too ill to undergo AF assessment, (3) they undergo ablation therapy, including catheter ablation, subsequent to the index procedure, (4) they undergo cardioversion or use AADs for AF following 3 months post-randomization. Differences between randomization arms on this expanded AF endpoint will be assessed similarly to the primary endpoint.

Anti-arrhythmic Interventions

In addition to use of AADs after 3 months post-randomization, anti-arrhythmic interventions include the requirement for permanent pacemaker placement, electrical cardioversion, and any AF ablations (surgical or percutaneous) at any point following the treatment intervention. We will compare the need for anti-arrhythmic interventions between treatment groups. We will compare the proportion of patients requiring anti-arrhythmic interventions among randomization groups using a chi-squared test.

Survival

Survival will be assessed by all-cause mortality at 12 months. The proportion of deaths between randomization groups will be primarily compared by a continuity-corrected chi-squared test. Time to death will also be described by Kaplan-Meier curves and differences between randomization groups assessed via the log-rank test.

Safety

The presence of a major adverse cardiac event (MACE) will be analyzed analogously to mortality. In addition, the differences in the incidence of individual protocol-defined and serious adverse events within 12 months of randomization 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 for treatment with ablation versus treatment with no ablation will be computed.

Quality of Life

QoL will be measured using the SF-12, AFSS and ELWAF. We will employ two approaches to the analysis of QoL. The primary analysis of QoL will be based on the SF-12 physical and mental health summary measure and will employ a mixed modeling approach, requiring an assumption that patient dropout is ignorable in that the probability of dropping out at any time is related only to previously observed data items. Of course, this assumption may not hold, and moreover it is impossible to test robustly from the data at hand. An alternative approach we will also use, not subject to this criticism, will be to separate the data into strata defined by the time of death or dropout. We will then

estimate a separate linear model, including a treatment effect, for the data in each stratum. This method, known as pattern-mixture modeling is not sensitive to un-testable assumptions about the dropout mechanism because it models the data directly in strata defined by dropout time. The method of Wu and Bailey is an instance of pattern-mixture modeling [32].

Tertiary Analyses

Functional Status

Functional status will be determined by NYHA classification. We will compare the distribution across categories among randomization groups using a chi-squared test.

Hospitalizations

Hospital length of stay and days in ICU. We will compare hospital length of stay for the index hospitalization and days spent in ICU between treatment groups using a Wilcoxon Rank-Sum test.

Readmissions. We will use a Poisson regression model to compare the frequency of readmissions between groups for any cause, and specifically for heart failure hospitalizations within 12 months of randomization.

Inpatient Costs

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.

Imputation Procedure for Missing Data

Randomized patients missing the primary efficacy endpoint is a potential problem in all clinical trials. Adherence to the intention-to-treat principle requires that all randomized patients be included in the primary analysis. We will report reasons for missing data for each randomization group and compare the reasons qualitatively. The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets (for example, best-case or worst-case scenarios). Patients missing the trial's primary endpoint will be included in the analysis by modern imputation methods for missing data.

Data imputation methods generally require several assumptions to support their validity theory. One such assumption is that data are missing at random [33], i.e., the missing nature of the variable is independent of value of the variable given the observed data. While it is not possible to explicitly verify assumptions about the missing data mechanism, it may be possible to detect when data are not missing at random. If there is no evidence that the data are not missing at random, the imputation method described below will be implemented. If the assumption of missing at random appears untenable,

then additional procedures including selection modeling and pattern mixture modeling will be considered.

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for the respective outcome for each dropout. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. The imputation models will reflect uncertainty in the modeling process and inherent variability in patient outcomes, as reflected in the complete data. The specific imputation model to be used will be specified prior to the examination of any outcome data.

After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis performed for each imputed-and-completed dataset. Rubin's method of multiple (i.e., repeated) imputation will be used to estimate treatment effect. We propose to use 15 datasets (an odd number to allow use of one of the datasets to represent the median analytic result).

These methods are preferable to simple mean imputation, or simple "best-worst" or "worst-worst" imputation, because the categorization of patients into clinically meaningful subgroups, and the imputation of their missing data by appropriately different models, accords well with best clinical judgment concerning the likely outcomes of the dropouts, and therefore will enhance the trial's results.

Crossovers

Crossovers (patients who after randomization switch from the allocated treatment to the non-allocated treatment) are expected to be few in this trial. Patients randomized to ablation who do not receive it during the trial can be considered crossovers. In addition, patients who are randomized to no ablation and subsequently receive ablation therapy **during their index mitral valve surgical repair** are considered to have crossed over. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect of on trial outcome.

Analysis of pulmonary vein isolation versus ablation with biatrial lesion sets

An important aim of this trial is to provide comparative information on the relative benefit of ablation with biatrial lesion sets compared to ablation with PVI. To address this aim, the analyses specified above will be repeated among only patients receiving ablation comparing the different ablation methods.

18. ORGANIZATION OF THE STUDY

Event Adjudication Committee

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all adverse events and causes of mortality.

Data and Safety Monitoring Board

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, or the DCC, 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 (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. 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

A university-based DCC (InCHOIR) bears responsibility for study design, monitoring interim data, and analyzing the study's results in conjunction with the investigators and the NHLBI. In collaboration with the NHLBI, the DCC will coordinate and monitor the trial. The DCC will administrate the DSMB and EAC.

Echocardiography Core Lab

All echocardiograms will be performed according to a standardized protocol (Afib MOP Appendix I) and will be centrally analyzed by the Network Echo Core Lab directed by Judy W. Hung, MD, located at the Massachusetts General Hospital, Boston, MA.

Electrophysiology Core Lab

All transtelephonic rhythms will be centrally analyzed by the Network Electrophysiology Core Lab directed by Jean-Philippe Couderc, PhD, located at the University of Rochester, Rochester, NY.

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.

Clinical Management Committee

The CMC will be comprised of cardiothoracic surgical and cardiology investigators with extensive expertise in the management of cardiac arrhythmias and valvular heart disease. The charge to the CMC is to update guidelines for the medical management group, and guidelines for management as needed. They will monitor the implementation of these guidelines for patients in the trial.

19. REFERENCES

- [1] Feinberg, W.M., et al., *Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications.* Arch Intern Med, 1995. 155(5): p. 469-73.
- [2] Wolf, P.A., R.D. Abbott, and W.B. Kannel, *Atrial fibrillation as an independent risk factor for stroke: the Framingham Study.* Stroke, 1991. 22(8): p. 983-8.
- [3] Kannel, W.B., et al., *Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates.* Am J Cardiol, 1998. 82(8A): p. 2N-9N.
- [4] Cox JL. Intraoperative options for treating atrial fibrillation associated with mitral valve disease. J Thorac Cardiovasc Surg. 2001;122:212-5.
- [5] Ad N, Cox JL. Combined mitral valve surgery and the Maze III procedure. Semin Thorac Cardiovasc Surg. 2002;14:206-9.
- [6] McCarthy PM, Gillinov AM, Castle L, Chung M, Cosgrove D, 3rd. The Cox-Maze procedure: the Cleveland Clinic experience. Semin Thorac Cardiovasc Surg. 2000;12:25-9.
- [7] Schaff HV, Dearani JA, Daly RC, Orszulak TA, Danielson GK. Cox-Maze procedure for atrial fibrillation: Mayo Clinic experience. Semin Thorac Cardiovasc Surg. 2000;12:30-7.
- [8] Gillinov AM, Blackstone EH, McCarthy PM. Atrial fibrillation: current surgical options and their assessment. Ann Thorac Surg. 2002;74:2210-7.
- [9] Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659-66.
- [10] Todd DM, Skanes AC, Guiraudon G, et al. Role of the posterior left atrium and pulmonary veins in human lone atrial fibrillation: electrophysiological and pathological data from patients undergoing atrial fibrillation surgery. Circulation. 2003;108:3108-14.
- [11] Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N Engl J Med. 2006;354:934-41.
- [12] Oral H, Chugh A, Good E, et al. A tailored approach to catheter ablation of paroxysmal atrial fibrillation. Circulation. 2006;113:1824-31.
- [13] Jahangiri M, Weir G, Mandal K, Savelieva I, Camm J. Current strategies in the management of atrial fibrillation. Ann Thorac Surg. 2006;82:357-64.
- [14] Gillinov AM, McCarthy PM. AtriCure bipolar radiofrequency clamp for intraoperative ablation of atrial fibrillation. Ann Thorac Surg. 2002;74:2165-8.
- [15] Wolf RK, Schneeberger EW, Osterday R, et al. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation. J Thorac Cardiovasc Surg. 2005;130:797-802.
- [16] Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. J Thorac Cardiovasc Surg. 2006;131:1029-35.
- [17] Gillinov AM, McCarthy PM, Blackstone EH, et al. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. J Thorac Cardiovasc Surg. 2005;129:1322-9.

- [18] Pappone C, Santinelli V, Manguso F, et al. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation*. 2004;109:327-34.
- [19] Gillinov AM, Bhavani S, Blackstone EH, et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. *Ann Thorac Surg*. 2006;82:502-14.
- [20] Cox JL. Atrial fibrillation I: a new classification system. *J Thorac Cardiovasc Surg*. 2003;126:1686-92.
- [21] Cox JL, Ad N. The importance of cryoablation of the coronary sinus during the Maze procedure. *Semin Thorac Cardiovasc Surg*. 2000;12:20-4.
- [22] Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, Ng LL, Spyt TJ. Left atrial radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation: a randomized controlled trial. *JAMA*. 2005 Nov 9;294(18):2323-9.
- [23] de Lima GG, Kalil RA, Leiria TL, Hatem DM, Kruse CL, Abrahão R, Sant'anna JR, Prates PR, Nesralla IA. Randomized study of surgery for patients with permanent atrial fibrillation as a result of mitral valve disease. *Ann Thorac Surg*. 2004 Jun;77(6):2089-94; discussion 2094-5.
- [24] Schuetz A, Schulze CJ, Sarvanakis KK, Mair H, Plazer H, Kilger E, Reichart B, Wildhirt SM. Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective randomized clinical trial. *Eur J Cardiothorac Surg*. 2003 Oct;24(4):475-80; discussion 480.
- [25] Hornero F, Rodriguez I, Buendía J, Bueno M, Dalmau MJ, Canovas S, Gil O, Garcia R, Montero JA. Atrial remodeling after mitral valve surgery in patients with permanent atrial fibrillation. *J Card Surg*. 2004 Sep-Oct;19(5):376-82.
- [26] Abreu Filho CA, Lisboa LA, Dallan LA, Spina GS, Grinberg M, Scanavacca M, Sosa EA, Ramires JA, Oliveira SA. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. *Circulation*. 2005 Aug 30;112(9 Suppl):I20-5.
- [27] Deneke T, Khargi K, Grewe PH, Laczkovics A, von Dryander S, Lawo T, Müller KM, Lemke B. Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *Eur Heart J*. 2002 Apr;23(7):558-66.
- [28] Lan, K.K.G.; DeMets, D.L. Discrete sequential boundaries for clinical trials. *Biometrika* 1983, 70(3), 659-663..
- [29] Purerfellner H, Aichinger J, Martinek M, et al. Quantification of atrial tachyarrhythmia burden with an implantable pacemaker before and after pulmonary vein isolation. *Pacing Clin Electrophysiol*. 2004;27:1277-83.
- [30] Olsen MK, Schafer JL. A two-part random-effects model for semicontinuous longitudinal data. *J Am Stat Assoc*. 2001;96:730-45.
- [31] Hall DB. Zero-inflated Poisson and binomial regression with random effects: a case study. *Biometrics*. 2000 Dec;56(4):1030-9.
- [32] Wu, M. C. and Bailey, K. (1989). Estimation and comparison of changes in the presence of informative right censoring: Conditional linear model. *Biometrics* 45, 939-955.
- [33] Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health*. 2000;21:121-45.

Appendix I: New York Heart Association Classification (NYHA)

Class	Patient Symptoms
Class I (Asymptomatic)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

References:

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix II: Quality of Life Measures

SHORT FORM – 12 (SF-12)

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. In general, would you say your health is:

Excellent

☐

Very good

☐

Good

☐

Fair

☐

Poor

☐

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
3. Climbing several flights of stairs	☐	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. Accomplished less than you would like	☐	☐
5. Were limited in the kind of work or other activities	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. Accomplished less than you would like	☐	☐
7. Didn't do work or other activities as carefully as usual	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
10. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11. Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

ATRIAL FIBRILLATION SEVERITY SCORE (AFSS)

Atrial Fibrillation Severity Scale		Visit
office use only	Patient's Initials	J Number
	Nurse/physician's Initials	Date: - -
		Day Month (eg. "Jan") Year

The following section is for patients to complete. Please answer the following questions as accurately as possible.

1. Sex ☐ M ☐ F
2. Date of Birth / /
Day Month (eg. "Jan") Year
3. Are you in atrial fibrillation currently?
☐ Yes
☐ No
☐ I don't know

4. How do you feel about your life at the present time?

Worst possible life	Best possible life
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10	

5. How often on average, does your irregular heart rhythm (atrial fibrillation) occur?

- ☐ Continuously
- ☐ More than twice a day
- ☐ Daily or almost daily
- ☐ 4-6 times a week
- ☐ 2-3 times a week
- ☐ About once a week
- ☐ About twice a month
- ☐ About once a month
- ☐ About 2-4 times a year
- ☐ About once a year
- ☐ Less than once a year
- ☐ Not applicable, I have never had an irregular heart rhythm

6. How long on average, do the episodes of the irregular heart rhythm last?

- ☐ Continuously
- ☐ Several days or more
- ☐ All day
- ☐ Several hours, but less than a day
- ☐ About an hour
- ☐ 30-45 minutes
- ☐ < 30 minutes
- ☐ A few minutes
- ☐ Not applicable, I have never had an irregular heart rhythm

Atrial Fibrillation Severity Scale

Atrial Fibrillation Severity Scale		Visit
7. How severe was your most recent episode of irregular heart rhythm?		
Not at all severe	Extremely severe	
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10		

8. How severe was your first episode of irregular heart rhythm?

Not at all severe	Extremely severe
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10	

9. Have you ever been cardioverted (i.e. been put to sleep and electrically shocked)?

- ☐ Yes
☐ No
- If yes, how many times?

10. How many times did you visit the emergency room within the past year because of an irregular heart rhythm?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ more than 5 times → times

11. How many times were you hospitalized within the past year because of an irregular heart rhythm?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ more than 5 times → times

12. How many times did you visit your specialist within the past year because of an irregular heart rhythm?

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ more than 5 times → times

Atrial Fibrillation Severity Scale

EMORY LIVING WITH ATRIAL FIBRILLATION (ELWAF) SCALE: PARTS A and B

Emory Living with Atrial Fibrillation (ELWAF) Scale: Part A Quality of Life Impact Questionnaire

Patient Name _____

MRN _____

Date of Survey Completion ____/____/____

Name of Person Administering Survey _____

Select One: BASELINE 3 MO. F/U 6 MO. F/U 12 MO. F/U Other _____

The following questions refer to your irregular heart rhythm atrial fibrillation and how it affects your life. Please read each question carefully and fill in the circle of the answer that best applies to you.

1. Please indicate how much your ability to do the following activities has been limited over the past 4 weeks by your atrial fibrillation.

Activity	Extremely limited	Quite limited	Moderately limited	Slightly limited	Not limited at all	Limited for other reasons or did not do the activity
Walking one block on level ground	☐	☐	☐	☐	☐	☐
Climbing one or more flights of stairs	☐	☐	☐	☐	☐	☐
Doing strenuous yard work or housework (such as mowing the lawn, or vacuuming)	☐	☐	☐	☐	☐	☐
Dressing yourself, showering, or bathing	☐	☐	☐	☐	☐	☐
Running or playing competitive sports	☐	☐	☐	☐	☐	☐

2. Over the past 4 weeks, on average, how often did your symptoms of atrial fibrillation interfere with your falling asleep?

Every night	3 or more nights a week, but not every night	1-2 nights a week	Less than one night a week	Never over the past 4 weeks
☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how often did your symptoms of atrial fibrillation wake you after you had fallen asleep?

Every night	3 or more nights a week, but not every night	1-2 nights a week	Less than one night a week	Never over the past 4 weeks
☐	☐	☐	☐	☐

4. Please indicate how the following common symptoms of atrial fibrillation have **limited your ability to do what you wanted** over the past 4 weeks.

Symptom	All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 4 weeks
Palpitations, irregular heartbeats, or a feeling of your heart racing	☐	☐	☐	☐	☐	☐	☐
Chest pain or discomfort	☐	☐	☐	☐	☐	☐	☐
Shortness of breath	☐	☐	☐	☐	☐	☐	☐
Dizziness, feeling lightheaded, or fainting (passing out)	☐	☐	☐	☐	☐	☐	☐
Fatigue or weakness	☐	☐	☐	☐	☐	☐	☐

5. Over the past 4 weeks, how often have you felt **sad or discouraged** because of your atrial fibrillation?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way
☐	☐	☐	☐	☐

6. Over the past 4 weeks, how often have you felt **anxious or frightened** because of your atrial fibrillation?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way
☐	☐	☐	☐	☐

7. Over the past 4 weeks, how often have you had **difficulty concentrating or paying attention** because of your atrial fibrillation?

All of the time	Most of the time	Occasionally	Rarely	Never
☐	☐	☐	☐	☐

8. In general, compared to other people you know that are your age, how would you rate your **current health**?

Much worse than other people my age	Slightly worse than other people my age	The same as other people my age	Slightly better than other people my age	Much better than other people my age
☐	☐	☐	☐	☐

9. Please indicate how much your atrial fibrillation has **interfered** with the following aspects of your life over the past 4 weeks.

Activity	A great deal	Quite a bit	Moderately	Slightly	Not at all	Not Applicable
Participation in your normal social activities with family, friends, or social groups	☐	☐	☐	☐	☐	
Participation in your normal hobbies or recreational activities	☐	☐	☐	☐	☐	
Participation in your usual daily activities, such as doing household chores or running errands	☐	☐	☐	☐	☐	
Attendance or performance at work, or school, or volunteer activities	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

10. If you had to spend **the rest of your life** with your atrial fibrillation the way it is right now, how would you feel?

Completely dissatisfied	Mostly dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐	☐

Thank you!

Emory Living with Atrial Fibrillation (ELWAF) Scale: Part B Treatment Impact Questionnaire

Patient Name _____

MRN _____

Date of Survey Completion ____ / ____ / ____

Name of Person Administering Survey _____

Select One: **BASELINE** **3 MO. F/U** **6 MO. F/U** **12 MO. F/U** **Other** _____

The following questions are about **treatments, therapies, or procedures** that you have had for your **irregular heart rhythm, atrial fibrillation**. Please read each question carefully and answer each question to the best of your knowledge by filling in the circle below the answer you choose.

1. Compared with 4 weeks ago, how have your **symptoms of atrial fibrillation **changed**?**

Much worse	Slightly worse	Not changed at all	Slightly better	Much better
☐	☐	☐	☐	☐

2. Are you currently taking, or have you ever taken, **medicines or pills (including heart rhythm pills or blood-thinner pills) for the treatment of **atrial fibrillation**?**

Yes	No
☐	☐

If Yes, please answer questions 2a-2e
If No, please skip to question 3

2a. Have you found taking medicines for atrial fibrillation **inconvenient?**

Very inconvenient	Quite inconvenient	Moderately inconvenient	Slightly inconvenient	Not at all inconvenient
☐	☐	☐	☐	☐

2b. Have you found taking medicines for atrial fibrillation **expensive to you personally?**

Very expensive	Quite expensive	Moderately expensive	Slightly expensive	Not at all expensive
☐	☐	☐	☐	☐

2c. How much have you **worried about potential side effects from medicines taken for atrial fibrillation?**

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

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[Emory Living with Atrial Fibrillation: B]

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2d. How much have you **experienced actual side effects** from medicines taken for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

2e. Have you found taking medicines for atrial fibrillation **physically painful**?

Very painful	Quite painful	Moderately painful	Slightly painful	Not at all painful
☐	☐	☐	☐	☐

Please continue to the next page →

3. Have you had **blood tests** such as PT or INR tests (blood tests that measure the effect of Coumadin® or warfarin on blood clotting) during treatment for your **atrial fibrillation**?

Yes	No
☐	☐

If Yes, please answer questions 3a-3e

If No, please skip to question 4

3a. Have you found the blood tests for atrial fibrillation **inconvenient**?

Very inconvenient	Quite inconvenient	Moderately inconvenient	Slightly inconvenient	Not at all inconvenient
☐	☐	☐	☐	☐

3b. Have you found the blood tests for atrial fibrillation **expensive to you personally**?

Very expensive	Quite expensive	Moderately expensive	Slightly expensive	Not at all expensive
☐	☐	☐	☐	☐

3c. How much have you **worried about potential side effects** from blood tests done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

3d. How much have you **experienced actual side effects** from blood tests done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

3e. Have you found the blood tests for atrial fibrillation **physically painful**?

Very painful	Quite painful	Moderately painful	Slightly painful	Not at all painful
☐	☐	☐	☐	☐

Please continue to the next page →

4. Have you had cardioversion or shock therapy for treatment of your atrial fibrillation?

Yes	No
☐	☐

If Yes, please answer questions 4a-4e
If No, please skip to question 5

4a. Did you find the cardioversion or shock therapy inconvenient?

Very inconvenient	Quite inconvenient	Moderately inconvenient	Slightly inconvenient	Not at all inconvenient
☐	☐	☐	☐	☐

4b. Did you find the cardioversion or shock therapy expensive to you personally?

Very expensive	Quite expensive	Moderately expensive	Slightly expensive	Not at all expensive
☐	☐	☐	☐	☐

4c. How much have you worried about potential side effects from cardioversion or shock therapy done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

4d. How much have you experienced actual side effects from cardioversion or shock therapy done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

4e. Did you find the cardioversion or shock therapy physically painful?

Very painful	Quite painful	Moderately painful	Slightly painful	Not at all painful
☐	☐	☐	☐	☐

Please continue to the next page →

5. Have you had a catheter ablation procedure for treatment of your atrial fibrillation?

Yes	No
☐	☐

If Yes, please answer questions 5a-5e

If No, please skip to question 6

5a. Did you find the catheter ablation inconvenient?

Very inconvenient	Quite inconvenient	Moderately inconvenient	Slightly inconvenient	Not at all inconvenient
☐	☐	☐	☐	☐

5b. Did you find the catheter ablation expensive to you personally?

Very expensive	Quite expensive	Moderately expensive	Slightly expensive	Not at all expensive
☐	☐	☐	☐	☐

5c. How much have you worried about potential side effects from a catheter ablation procedure done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

5d. How much have you experienced actual side effects from a catheter ablation procedure done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

5e. Did you find the catheter ablation physically painful?

Very painful	Quite painful	Moderately painful	Slightly painful	Not at all painful
☐	☐	☐	☐	☐

Please continue to the next page →

6. Have you had a surgical ablation procedure (often called a MAZE procedure) for treatment of your atrial fibrillation?

Yes	No
☐	☐

If Yes, please answer questions 6a-6e
If No, please stop and return the questionnaire

6a. Did you find the surgical ablation inconvenient?

Very inconvenient	Quite inconvenient	Moderately inconvenient	Slightly inconvenient	Not at all inconvenient
☐	☐	☐	☐	☐

6b. Did you find the surgical ablation expensive to you personally?

Very expensive	Quite expensive	Moderately expensive	Slightly expensive	Not at all expensive
☐	☐	☐	☐	☐

6c. How much have you worried about potential side effects from a surgical ablation done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

6d. How much have you experienced actual side effects from a surgical ablation done for atrial fibrillation?

A great deal	Quite a bit	Moderately	Slightly	Not at all
☐	☐	☐	☐	☐

6e. Did you find the surgical ablation physically painful?

Very painful	Quite painful	Moderately painful	Slightly painful	Not at all painful
☐	☐	☐	☐	☐

THANK YOU!

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[Emory Living with Atrial Fibrillation: B]

[version 2.25.08]

References:

Melville MR, Lari MA, Brown N, Young T, and Gray D. Quality of life assessment using the short form 12 questionnaire is as reliable and sensitive as the short form 36 in distinguishing symptom severity in myocardial infarction survivors. *Heart* 2003 Dec;89(12):1445-6.

Newman D. Quality of life as an endpoint for atrial fibrillation research: Pitfalls and practice. *Heart Rhythm* 2004; 1:B20-6.

Puskas J. Emory Living with Atrial Fibrillation (ELWAF), Parts A and B. Personal communication

Appendix III: Neurologic Dysfunction Assessments

Modified Rankin Scale

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

References for Modified Rankin Scale

Rankin J. "Cerebral vascular accidents in patients over the age of 60." *Scott Med J* 1957;2:200-15.

Bonita R, Beaglehole R. "Modification of Rankin Scale: Recovery of motor function after stroke." *Stroke* 1988 Dec;19(12):1497-1500.

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients." *Stroke* 1988;19(5):604-7.

NIH Stroke Scale

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 patients 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 oculcephalic 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 oculcephalic 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	8. MOTOR LEFT LEG
☐ 0 Alert	☐ 0 No drift
☐ 1 Drowsy	☐ 1 Drift
☐ 2 Stuporous	☐ 2 Some effort against gravity
☐ 3 Coma	☐ 3 No effort against gravity
1b. LOC – QUESTIONS	☐ 4 No movement
☐ 0 Answers both correctly	☐ 9 Untestable
☐ 1 Answers one correctly	9. LIMB ATAXIA
☐ 2 Both incorrect	☐ 0 Absent
☐ 9 Untestable	☐ 1 Present unilaterally in either arm or leg
1c. LOC – COMMANDS	☐ 2 Present unilaterally in both arm & leg or bilaterally
☐ 0 Obeys both correctly	☐ 9 Untestable
☐ 1 Obeys one correctly	10. SENSORY
☐ 2 Both incorrect	☐ 0 Normal
☐ 9 Untestable	☐ 1 Partial loss
2. GAZE	☐ 2 Dense loss
☐ 0 Normal	☐ 9 Untestable
☐ 1 Partial gaze palsy	11. BEST LANGUAGE
☐ 2 Forced deviation	☐ 0 No aphasia
3. VISUAL FIELDS	☐ 1 Mild to moderate aphasia
☐ 0 No visual loss	☐ 2 Severe aphasia
☐ 1 Partial hemianopia	☐ 3 Mute
☐ 2 Complete hemianopia	☐ 9 Untestable
☐ 3 Bilateral hemianopia	12. DYSARTHRIA
☐ 9 Untestable	☐ 0 Normal articulation
4. FACIAL MOVEMENT (FACIAL PARESIS)	☐ 1 Mild to moderate dysarthria
☐ 0 Normal facial movement	☐ 2 Near unintelligible or worse
☐ 1 Minor paresis	☐ 9 Untestable
☐ 2 Partial paresis	13. EXTINCTION AND INATTENTION (formerly NEGLECT)
☐ 3 Complete palsy	☐ 0 No neglect
5. MOTOR RIGHT ARM	☐ 1 Partial neglect
☐ 0 No drift	☐ 2 Complete neglect
☐ 1 Drift	☐ 9 Untestable
☐ 2 Some effort against gravity	
☐ 3 No effort against gravity	
☐ 4 No movement	
☐ 9 Untestable	
6. MOTOR LEFT ARM	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