

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

MANUAL OF PROCEDURES



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CT Surgery Network Research Group

Data Coordinating Center:
International Center for Health Outcomes and Innovation Research
Department of Health Evidence & Policy
Mount Sinai School of Medicine
New York

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Table of Changes

Revision	Section	Change	Reason	Page
3.2	Entire Document	Updated the trial name to patients with persistent or longstanding persistent AF	Per request of the FDA	All
3.2	Entire Document	Added ERB to all IRB-related sections	MOP refinement for clarity	All
3.2	Table of Contents	Added Appendix II-VII	MOP update	3
3.2	Clinical Centers	Clarified the documents to be sent to study monitor	MOP refinement for clarity	8
3.2	Training Plan	Clarified the site initiation process	MOP update for clarity	8
3.2	EDC System Training	Clarified process for training and gaining access to the web-based training site	MOP update for clarity	9
3.2	QoL Training	Added clarification the completion of QoL forms and that inability to participate in QoL due to language barriers does not preclude a patient from enrollment	MOP update for clarity	9
3.2	TTM	Added technical support contact information for Medicomp	MOP update for clarity	9
3.2	Screening and Eligibility Criteria	Updated the screening and eligibility criteria for the trail	MOP update	10
3.2	Informed Consent Form	Clarified the process for reviewing informed consents	MOP refinement for clarify	11
3.2	Obtaining Informed Consent	Clarified that any patient unable to sign the informed consent is excluded form the trial	MOP refinement for clarity	12
3.2	Screening Activity Prior to Informed Consent	Clarified the pre-screening process	MOP refinement for clarity	12
3.2	HIPPA and Release of Medical Information Forms	Replaced “Privacy Board” with ERB	MOP refinement for clarity	12
3.2	Randomization	Updated the randomization process	MOP update	12
3.2	Study Intervention	Added the PVI and Pacing Protocol Video training	MOP update	13
3.2	Masking	Added clarification of masking procedures	MOP refinement for clarity	13
3.2	Participant Evaluations and Follow-Up	Clarified the telephone follow-up process	MOP refinement for clarity	14
3.2	Participant Evaluations and Follow-Up	Added symptomatic rhythm records to second bullet point	MOP refinement for clarity	14
3.2	Safety Reporting	Clarified the process for reporting AEs and added UPs and UADEs	MOP update	14
3.2	Medicomp Treating	Clarified the process for notifying treating	MOP update	15

	Physician Notification	physicians of symptomatic arrhythmia notification		
3.2	Event Adjudication Committee	Clarified that the EAC will adjudicate the relatedness to the surgical procedure, investigational intervention, and investigational device	MOP update	16
3.2	Study Compliance	Updated the reporting of violations	MOP update	16
3.2	Data Collection Schedule	Added Pre-Screening Failure form, Demographics Form, Eligibility Evaluation Form, and Follow-Up Surgical Procedure form, deleted the Screening Outcome form, and added assessment points to the Surgical Procedures form, 12-lead ECG, and patient diaries	MOP update	17
3.2	Screening and Baseline	Updated the name of the Pre-Screening Failure Form and clarified this process	MOP update	18
3.2	Screening and Baseline	Updated the Screening Log and Registration form to the Demographics Form and clarified this process	MOP update	18
3.2	QoL	Added clarification that inability to participate in QoL due to language barriers does not preclude a patient from enrollment	MOP update for clarity	20
3.2	Eligibility Criteria	Updated the title and clarified the eligibility process	MOP update for clarity	20
3.2	Cardiovascular Rhythm Assessment	Revised AF documentation	Per request of FDA	21
3.2	TTE	Added echo core lab's mailing address	MOP update	21
3.2	Cardioversion	Deleted section on cardioversion	MOP update	21
3.2	Screening Outcome	Deleted section on Screening Outcome	MOP update	21
3.2	Randomization	Clarified the randomization process	MOP update	21
3.2	Surgical Procedures	Clarified process for forwarding the surgical procedure form to the DCC	MOP refinement for clarity	22
3.2	Blood, Urine, and Tissue Sample Collection	Clarified collection process and deleted the Biorepository Specimen Collection Schedule	MOP refinement for clarity	22
3.2	Adverse Events	Clarified the process for assessing AEs	MOP update	23
3.2	Patient Diaries	Updated the section on patient diaries	MOP update	23
3.2	Transtelephonic Monitoring	Updated the TTM initiation, reporting, and training processes	MOP update	24
3.2	Transtelephonic Monitoring	Updated the TTM device kit contents	MOP update	25
3.2	Transtelephonic Monitoring	Updated the weekly transmission process	MOP update	26
3.2	Transtelephonic Monitoring	Updated the symptomatic transmission process	MOP update	28

3.2	Transtelephonic Monitoring	Updated the 72-Hour Holter transmission process	MOP update	28
3.2	Telephone Follow-up	Clarified the telephone follow-up process	MOP update	28
3.2	Post-Discharge Study Visit	Updated the description of the 12-month return in-person visit	MOP update	29
3.2	Remote Echo Assessments	Clarified the process for remote image acquisition	MOP update	30
3.2	QoL	Added clarification that inability to participate in QoL due to language barriers does not preclude a patient from enrollment	MOP update for clarity	31
3.2	Event Driven Data Collection	Added “Follow-Up” to Surgical Procedures section	MOP refinement for clarity	32
3.2	Adverse Events	Clarified the AE assessment and reporting process	MOP refinement for clarity	32
3.2	Anti-arrhythmic Interventions	Clarified the process for reporting arrhythmias	MOP refinement for clarity	32
3.2	Regulatory Documents	Updated the manner for storing regulatory documents at the clinical sites and added the SAVI cardiac monitor training certificate and Investigator PVI and Pacing Protocol Training form	MOP update	33
3.2	Quality Control Procedures	Clarified and updated the site initiation process	MOP refinement for clarity	35
3.2	Appendices	Added Appendix II – VII	MOP update	43
3.2.1	Appendices	Updated Medicomp’s website	MOP update	47
4.2	Title Page	Updated MOP rev # and date	MOP update	All
4.2	Table of Contents	Added Appendix VIII-X	MOP update	2
4.2	Study Team Roster	Updated Contact Information	MOP update	7-8
4.2	Clinical Centers	Added “23 clinical centers including” and listed the 3 new sites	MOP update	9
4.2	Transtelephonic Monitoring	Updated contact information	MOP update	10
4.2	Communications Plan	Updated communication processes description	MOP update	11
4.2	Safety reporting	Defined Unanticipated Adverse Effects (UADE) and unanticipated problems	MOP refinement for clarity	15
4.2	Safety Reporting	Clarified the process for reporting timelines for SAEs, UADEs and Deaths	MOP refinement for clarity	18
4.2	Study Compliance	Clarification that protocol violations will be reported to local IRBs	MOP refinement for clarity	18
4.2	NYHA	Changed to unblinded coordinator	MOP update	21
4.2	Laboratory Assessment	Expanded the baseline laboratory assessment window	MOP update	22
4.2	Transthoracic Doppler Echocardiogram	Expanded the baseline echocardiogram window	MOP update	23
4.2	Patient Post-Discharge	Reorganized and added section sub-	MOP clarification for	26

	Assessments	headings to entire section for ease of review	refinement	
4.2	Ordering and Storage of TTM Devices	Clarified Medcomp's process for providing replacement devices to the clinical site	MOP update	26
4.2	Online Patient Enrollment	Instructed clinical site coordinators to reference the Arrhythmia Access Tutorial for instructions on enrolling patients	MOP refinement for clarity	27
4.2	Notification of Treating Physician	Referenced MOP Appendix VIII	MOP update	27
4.2	Patient Training Pre-Discharge	Deleted the section on sending patients home with the CardioPAL SAVI guide and DVD	MOP refinement for clarity	28
4.2	Weekly Transmissions	Clarified the process for initiating the weekly TTM process	MOP refinement for clarity	28
4.2	Weekly Transmissions	Updated TTM Schedule to include all weekdays	MOP update	29
4.2	Weekly Transmissions	Updated the process for monitoring patient compliance with weekly TTMs	MOP update	29
4.2	Telephone Follow-Up	Referenced Appendix VIII in the Anti-arrhythmic drug termination section	MOP update	31
4.2	Telephone Follow-Up	Added Patient Contact Log	MOP Update	32
4.2	NYHA	Changed to blinded rater	MOP update	33
4.2	Study Completion/Early Termination	Updated language	MOP clarification	35
4.2	Ongoing Study Requirements	Added Device Accountability Log	MOP Update	36
4.2	Changes in CTSN personnel	Updated procedures for notifying the DCC of changes in personnel	MOP Update	37
4.2	Appendix VIII	Added Follow-Up Letter to the Referring Cardiologist at 3 Months Post-Discharge Template	MOP Update	72
4.2	Appendix IX	Added Patient Contact Log	MOP Update	73
4.2	Appendix X	Added Device Accountability Log	MOP Update	74

1. STUDY TEAM ROSTER

A complete directory for the Cardiothoracic Surgery Network (CTSN) and all documents approved for the network may be found at the following website address:

<http://www.ctsurgerynet.org/>

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2. CLINICAL CENTERS

The study will be conducted in 23 clinical sites including the following highly experienced clinical centers participating in the CT Surgery Network:

Cleveland Clinical Foundation (Eugene Blackstone, MD)
Columbia University Medical Center (Michael Argenziano, MD)
Duke University (Peter Smith, MD)
East Carolina Heart Institute (T. Bruce Ferguson, MD)
Emory University (John Puskas, MD)
Montefiore-Einstein Heart Center (Robert Michler, MD)
Montreal Heart Institute (Louis Perrault, MD)
NIH Heart Center at Suburban Hospital (Keith Horvath, MD)
University of Pennsylvania (Michael Acker, MD)
University of Virginia Health Systems (Irving L. Kron, MD)
Baylor Research Institute (Michael Mack, MD)
University of Maryland (James Gammie, MD)
Hopital Laval (Pierre Voisine, MD)

Each clinical center will be required to obtain IRB/Ethics Review Board (ERB) approval for the protocol and consent revisions in a timely fashion, recruit patients, obtain informed consent from each subject and protect their rights, collect data and enter it accurately in the electronic data capture (EDC) system, faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP)/Human Subjects Research. In addition, centers will be required to provide the Data Coordinating Center (DCC) the information necessary for interim, annual, and final reports, provide source and regulatory documents to study monitors, respond promptly to DCC inquiries, and participate in analyses and reporting of study results.

A trial roster for all surgeons, cardiologists, coordinators and other investigators in the study, including hospital affiliation, address, telephone, fax, beeper and email information will be maintained by the DCC. The principal investigator and co-investigator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, Institutional Health Insurance Portability and Accountability Act (HIPAA) and Institutional GCP/Human Subjects Certificates when available to the DCC. All surgical investigators must complete a Surgical Certification form signed by the surgical Principal Investigator at their site. FWA (Federal Wide Assurance) number for the local governing IRB/ERB must be provided to the DCC along with the DUNS numbers for relevant investigators.

3. TRAINING PLAN

All clinical site investigators and coordinators must be trained by the DCC in the specifics of the protocol at a site initiation visit, via teleconference, and/or at in-person coordinators meetings in advance of patient enrollment. All participants must review the training slides and sign the attestation that they completed training. This document should be filed in the site regulatory binder, and a copy should be forwarded to the DCC.

Electronic Data Capture System Training

All site coordinators will be trained to input the data for the protocol into the web-based electronic data capture system (EDC). This training will consist of either in-person demonstrations or a web-based teleconference demonstrations and a web-based training site: (<https://www.inchoir.org/ctsn-train/main>). To gain access to the web-based training site, please contact the Clinical Trials Manager at the DCC. Upon completion of web-based training, all site coordinators will complete the CTSN Afib EDC Training Attestation form and fax it back to the Clinical Trials Manager at the DCC.

National Institute of Health Stroke Scale (NIHSS) Training

The NIHSS must be administered at the time of a neurological adverse event (within 72 hours following the event) and 90 days following the event to document the presence and severity of neurological deficits. The study coordinators must receive on-line training in the NIHSS in order to administer this scale. A certificate can be printed and should be filed in the site regulatory binder at the completion of the training. A copy should be forwarded to the DCC. The certification program can be found at:

<http://www.nihstrokescale.org/>

Quality of Life Training

The study coordinators will be instructed during the protocol training to teach the study subject to complete the quality of life questionnaires independently. The quality of life measures selected for this study are to be self-administered. In the event a study subject is unable to read the questionnaires, the coordinator may read the documents, word for word, to them. It is important that the coordinator not add any description or explanation to the questions being asked. 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.

Trans-Telephonic Monitoring

Medicomp will provide the training for the study coordinators in the use of the trans-telephonic monitoring system (TTM). The training will include how to enroll a patient, the use of the monitor, basic troubleshooting of the device and how to train the patients in the use of the device. A certificate will be issued following completion of training to be filled in the Site Regulatory Binder. Medicomp will provide in-person training, training videos for both coordinator and patient and 24/7 technical support. For technical support with the monitors, please contact Medicomp at the number specified in the CardioPAL SAVI Patient Guide. For all other assistance, please contact Anne Shering at 1-800-234-3278, ext. 2162 or asherling@medicompinc.com.

Echocardiographic Training

The Echocardiography Core lab will train a designated echocardiographer at each site participating in the protocol, according to the Echocardiographic Image Acquisition Protocol (MOP Appendix I). Training will include image acquisition for the full and

limited image collection (see Appendix I for limited image acquisition) and transmission of data.

4. COMMUNICATIONS PLAN

The DCC will coordinate and facilitate communication amongst all participating clinical centers, committees, and governing bodies via email, telephone conference calls, and the study website. Such communications will include monthly Steering Committee and monthly PI calls, bi-weekly Coordinator Conference calls, and ad hoc trial-specific meetings related to recruitment, protocol/development/refinement, and publications.

5. STUDY ORGANIZATION AND RESPONSIBILITIES

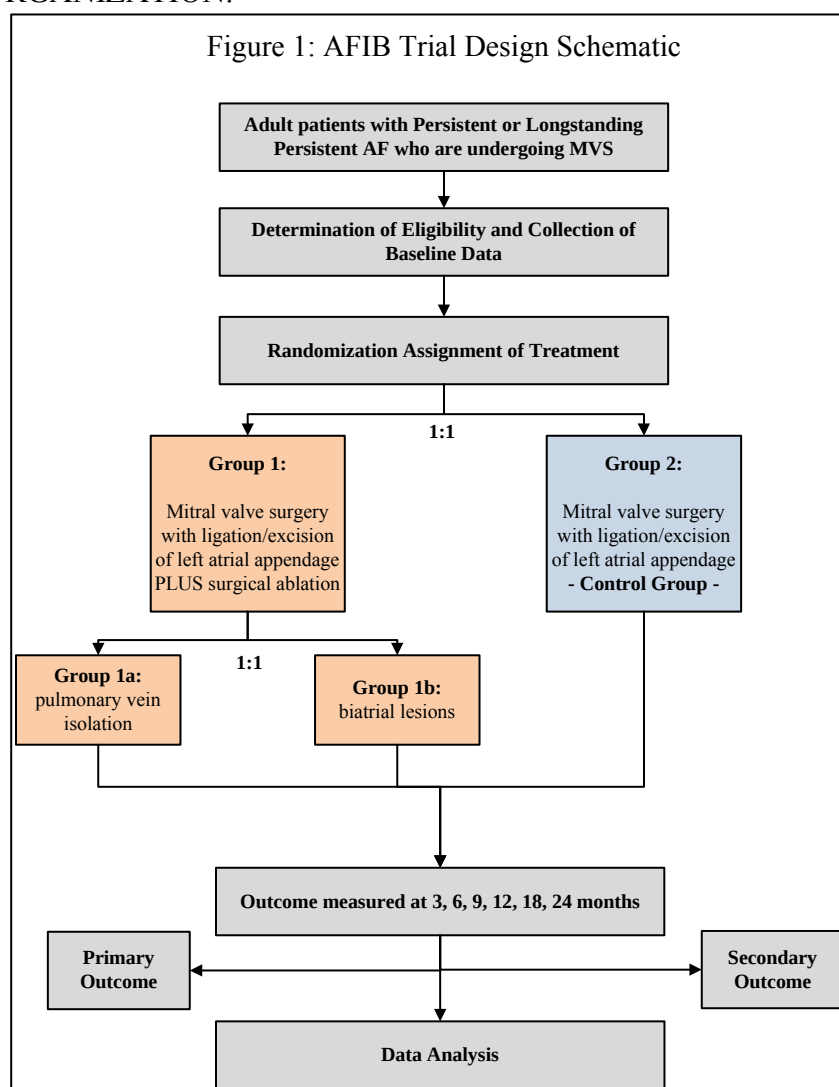
Please refer to the Network for CT Surgical Investigations Administrative Manual of Procedures (MOP) Section I: CTSN ORGANIZATION.

6. RECRUITMENT

Please refer to the protocol sections “Recruitment Strategies” and “Inclusion of Women and Minorities” and/or to the Network for CT Surgical Investigations Administrative Manual of Procedures, Section 9.4, “Inclusion of Women and Minorities as Subjects”. Investigators will be required: (1) to document the number of women and minorities screened and enrolled via screening/exclusion logs, which will be monitored monthly by the DCC; and (2) if necessary, participate in the implementation of outreach programs designed to recruit adequate numbers of women or minorities.

7. STUDY FLOW

See diagram to the right.



8. SCREENING AND ELIGIBILITY CRITERIA

All patients with mitral valve disease requiring surgical intervention 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 and 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 (defined as continuous AF of greater than one year duration) who meet the eligibility criteria may be included in the study regardless of gender, race or ethnicity.

- o The judgment of the investigator is critical for identifying those subjects suitable for study enrollment.
- o The 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 (for persistent AF) and/or upon arrival in the OR (for both persistent and longstanding persistent AF).
- o Investigators may include patients with a 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.
- o Eligibility for this trial is not determined until the patient is in the OR and the TEE has been performed.
- o All patients are ineligible for the trial if atrial thrombus is documented on the intra-operative TEE.

9. INFORMED CONSENT, HIPAA, RELEASE OF MEDICAL INFORMATION

Informed consent is a process that involves:

- o Providing participants with adequate information concerning the study procedures and purpose of the research study, expected duration of participation, and the risks and benefits of participation;
- o Providing opportunity for a potential participant to consider all available treatment options which include information about any appropriate alternative treatments that could possibly benefit the subject;
- o Responding to an individual's questions and concerns;
- o Ensuring that all information provided is understood by the potential study subject;
- o Obtaining the individual's written voluntary consent.

Informed Consent Form

The consent form documents the willingness of the individual to participate in the study. It contains the signature of the subject and the signature of the investigator giving information on the research. The CTSN informed consent template provides the essential elements to ensure that a patient participating in the study is appropriately informed of the risks and potential benefits of study participation. Site investigators may modify the

sample consent form to meet the individual Institutional Review Board (IRB) or ERB requirements, with approval from the DCC.

Obtaining Informed Consent

Informed consent will be obtained according to individual institutional guidelines. Patients should be encouraged to have family or other support available during the informed consent process. They should be assured that declining to sign an informed consent document will in no way compromise their care, and that should they consent to participate in the study, they may revoke that consent at any time. All patients will be required to sign informed consent to participate in this study. Any patient unable to sign the informed consent will be excluded from the trial. (Please see the protocol inclusion criteria #1.) As part of the informed consent process, all patients will be given the opportunity to opt in or out of the biological specimen collection process.

Timing for the informed consent process must be consistent with the center's institutional IRB or ERB policies, and in accordance with the CTSN guidelines. *The consent process (and its documentation) must begin at least the day before the surgical procedure.* This is to ensure that all subjects will be given adequate time to review the informed consent document and consider participation in the trial.

As part of the informed consent process, the investigator must:

- o Obtain informed consent before screening studies are performed
- o Document any questions addressed with the patient and/or family during the informed consent process in the medical chart
- o Confirm that all signatures on the informed consent are complete and dated
- o Place one copy of the signed informed consent in the medical chart
- o Provide one copy of the signed informed consent to the patient
- o File the original signed informed consent in the Case Report Binder

Screening Activity Prior to Informed Consent

In preparation for participation in the study, with local IRB/ ERB approval, the investigator can review patient charts for the purpose of identifying potential research candidates and will record HIPAA compliant data on all pre-screened patients who are not enrolled in the Pre-Screening Failure form. *HIPAA sensitive data cannot be extracted or screening studies performed until written informed consent is obtained.*

HIPAA and Release of Medical Information Forms

- o The HIPAA Clinical Research Authorization and Release of Medical Information forms may either be incorporated into the consent form as separate documents or as dictated by institutional requirements.
- o The HIPAA Clinical Research Authorization form, approved by the IRB or ERB, allows investigators to approach, screen, and enroll patients in the study.
- o The Release of Medical Information form authorizes release of medical records to the study investigators, monitors, FDA, NHLBI, NINDS, CIHR, local IRBs and the DCC.

10. RANDOMIZATION

Randomization will be performed intra-operatively following anesthesia and TEE. Atrial thrombus must be ruled out by intra-operative TEE prior to randomization.

Randomization Procedure

- Randomization will be performed through the web-based electronic data capture (EDC) system that automates the delivery of the randomization codes. This code will be generated once the patient's demographic information and the checklist of inclusion and exclusion criteria have been completed and verified.
- The treatment assignment will be immediately visible to the coordinator in the EDC.
- Electronic verification (signature) of the treatment assignment via the EDC will be required before proceeding with the treatment intervention.
- A printed version of the randomization form should be signed and kept in the clinical center Patient Study Binder.
- From the time of randomization on, the primary efficacy endpoint will be analyzed by intention-to-treat; that is, the patients will be grouped by their assignment at randomization whether or not they actually received the treatment to which they were assigned.

11. STUDY INTERVENTION

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

All surgeons participating in this trial must view the Pulmonary Vein Isolation and Pacing Protocol video and sign the PVI and Pacing Protocol Attestation form. A copy of this video will be sent to each of the clinical sites and will be available on the CTSN website (<http://www.ctsurgery.net/org/>). (Please refer to the Protocol section 11, "Treatment Interventions".

12. MASKING

Neither patients nor investigators will be blinded to treatment assignment due to the nature of treatment intervention. Investigators will, however, be blinded to all data from other clinical sites, except serious unexpected AEs for IRB or ERB reporting purposes. All weekly rhythm strips, event recordings and Holter results will be analyzed by core laboratory personnel who will be blinded to treatment assignment and clinical outcomes.

13. PARTICIPANT EVALUATIONS AND FOLLOW-UP

All patients who meet the eligibility criteria and are enrolled in the study will follow the same study visit schedule.

- Telephone follow-up will occur at 3, 6, 9, 18 and 24 months. In addition, patients who are unable to return to the clinical site for the 12 month assessment will also have a telephone follow-up at 12 months. (Please see the “Patient Post-Discharge Assessment” section.)
- TTM will enable remote weekly and symptomatic recordings and a continuous 72-hour Holter assessment will be performed at 6 and 12 months.
- A single in-person study visit is scheduled at 12 months post randomization.
- *Remote Follow-up:* Patients who are unable to return to the clinical site for the 12 month assessment because of extreme geographic distance can obtain a limited echo at a remote site (see Limited Echocardiographic Image Acquisition Protocol, Appendix I). ***However, this should be avoided whenever possible, and the clinical coordinator should strongly encourage patients to return to a CTSN clinical site for the follow-up echos.*** (Please see the “Remote Echo Assessment” section in the “Patient Post-Discharge Assessment” section.)

14. PARTICIPANT RETENTION

Every effort will be made by all Clinical Investigators to have each randomized subject complete all aspects of the study to study completion.

15. CONCOMITANT INVESTIGATIONAL MODALITIES

Medications and medical substances and devices not approved by the FDA for study subjects are prohibited while the subject is on the study.

16. SAFETY REPORTING

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, 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.

Adverse Events

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.

All investigators conducting clinical studies supported by the NHLBI must report both expected (protocol-defined) and unexpected serious adverse events. All AE reporting should proceed as follows:

Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects

- o 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.
- o 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.

Medicomp Treating Physician Notification

Medicomp will provide notifications of arrhythmias directly to the treating physician for any patient-triggered Symptomatic Transmission (See Post Discharge Assessments, TTM section). The notification criteria are detailed in Appendix III. Prior to patient discharge, the clinical site should identify the patient's treating physician and complete and fax the Event Notification Criteria form (Appendix III) to Medicomp. A copy of this form will be maintained in the Study Binder. In addition, a letter will be mailed to the treating

physician to notify him/her of the patient's participation in the trial and the possibility of receiving symptomatic event notifications from Medcomp (Appendix IV). The clinical site will include a copy of the Event Notification Criteria guidelines in this letter.

17. EVENT ADJUDICATION COMMITTEE

All mortalities and protocol defined and serious adverse events will be adjudicated by an independent Event Adjudication Committee (EAC). The committee will adjudicate adverse event classifications, seriousness and relatedness to the surgical procedure (mitral valve surgery with ligation/excision of left atrial appendage), the investigational intervention (surgical ablation), and the investigational device as reported by the site PI, as well as the reported primary and underlying causes of mortality events. The DCC will provide de-identified source documentation supplied by the clinical sites to the committee to support each event and mortality to be adjudicated. The optimal procedure for the clinical site personnel in this process is to file source documentation supporting each reported AE in the Patient Source Binder as the events are reported. All events will be fully monitored prior to presentation to the EAC for adjudication.

18. DATA AND SAFETY MONITORING RESPONSIBILITIES

The conduct of the study will be overseen by an independent Data and Safety Monitoring Board (DSMB) appointed by NHLBI. Please refer to the Network for CT Surgical Investigations Administrative Manual of Procedures, Section I, NETWORK ORGANIZATION.

19. STUDY COMPLIANCE

Efforts to maximize adherence to the study protocol will be made through careful and comprehensive training, early review of study data submitted via the EDC system, and routine communication with all site investigators. Protocol deviations and/or violations may occur despite the best efforts of the clinical investigators. They may include but are not limited to randomizing an ineligible study participant; failing to obtain informed consent; failing to maintain IRB/ERB and related study documents; or administering the wrong treatment. Clinical sites will report protocol violations to their IRBs according to local policy. Relevant violations will be reported to the DCC, who will notify appropriate parties, including the FDA, study site Principal Investigator, NHLBI, NINDS, CIHR, and/or DSMB. The DCC will instruct each Clinical Center to maintain a log of protocol deviations and/or violations and report them routinely to the Clinical Trial Manager.

20. 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								X
Telephone Follow-up					X	X	X	X	X	
Cardiac										
Echocardiogram	X	X ⁴						X		X
12-lead ECG	X	X	X							
Weekly TTM ⁵ /event recorder			X ⁶	X ⁷						X
72-hr Holter Monitoring						X		X		
Patient diary			X	X		X		X		X
Anti-arrhythmic interventions ⁸					X	X	X	X	X	X
Anti-arrhythmic drug termination					X					X
Biological Specimen Collection ⁹		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/NHSS										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 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 at baseline. In addition, if not collected at baseline, DNA may be collected at the patient's 12-month follow-up visit.

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.

Screening and Baseline

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 in accordance with the clinical site's IRB/ERB policies. Reasons for screening failure are collected.
- The data collected are HIPAA compliant and do not include patient identifiers.
- The data collected include screening quarter, screening year, age, gender and reason not eligible.

Informed Consent

Prior to screening data collection and protocol-defined procedures

- Prior to obtaining informed consent, a thorough explanation of the risks and benefits of the study will be outlined by the investigator or designee to the potential study subject.
- Study personnel will begin the informed consent process as soon as possible during the preoperative evaluation phase for each patient.
- Timing for the informed consent process must be consistent with the center's institutional IRB/ERB policies, and in accordance with the CTSN guidelines. *The consent process must begin at least the day before the surgical procedure.* This is to ensure that all subjects will be given adequate time to review the informed consent document, and consider participation in the trial.
- All questions will be answered to the satisfaction of the subject prior to signing the informed consent document.
- Site source records will include documentation of the informed consent process for each subject.
- No study specific procedures will be performed prior to signing the informed consent document.

HIPAA and Release of Medical Information Form

Prior to screening data collection and protocol defined procedures

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

Demographics Form

At initiation of screening

- A screened patient is defined as someone (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.

- o For all patients screened, the first, middle, and last initial, date of birth, sex, ethnic origin, racial category, health insurance, level of education, and handedness will be captured on the screening form.
- o The EDC will generate a unique 8 or 9-digit identification code (e.g., AAA-0-A-001) that will identify the patient throughout the course of the study. The code is composed of three patient initials (if no middle initial, a dash is acceptable), site number (auto-populated by the EDC), the trial, and the consecutive patient enrollment count at the site (also auto-populated).
- o All screened patients who are not randomized will have reasons for non-randomization documented in the Eligibility Evaluation Form.

Medical History

Within 7 days prior to randomization

- o This form captures the information pertaining to the study subject's cardiovascular history, cardiovascular procedure history, cerebrovascular history, history of "other" medical conditions, and current medical condition.

New York Heart Association Classification (NYHA)

Within 7 days prior to randomization

- o The presence of heart failure will be assessed, and when present, classified according to the NYHA classification criteria.
- o NYHA The 12- month New York Heart Association Classification/Functional Status will be completed in person, by a qualified clinical site coordinator or MD.
- o The NYHA classification scheme is detailed in Appendix II of the trial Protocol.

Medications

Within 7 days prior to randomization

- o This form captures all protocol-defined medications taken within 7 days prior to randomization.
- o This includes antiarrhythmics (Classes I, II, III and IV), CRF-defined cardiac, anticoagulation and anti-platelet medications.
- o "Other Medication" entered should include those that are clinically relevant in the judgment of the investigator (e.g., antibiotics, immunosuppressants, etc.).
 - o It is not necessary to list *all* non-clinically relevant medications (e.g., vitamins, stool softeners, GI prophylaxis, nutraceuticals, etc.).

Physical Examination

Within 7 days prior to randomization

- o This form captures the comprehensive physical examination including vital signs, anthropometrics (height, weight and BSA), cardiopulmonary examination, abdominal examination, and nutritional assessment.
- o The physician or his/her delegate (including another physician, PA, or NP) can perform this exam.

Quality of Life

Within 7 days prior to randomization

- o The Short Form (SF) 12 Health Questionnaire, Atrial Fibrillation Severity Score (AFSS), and Emory Living with Atrial Fibrillation (ELWAF) questionnaires will be completed by the patient to assess quality of life.
- o Data regarding completeness of QOL data collection and reasons for missing responses to questionnaires will be collected on the QOL Checklist.
- o *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.*

Laboratory Assessment

Within 30 days prior to randomization

Samples will be collected to assess the following:

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

Eligibility Criteria/Eligibility Evaluation From

Prior to randomization

- o The inclusion and exclusion criteria will be documented by the clinical site study coordinator and verified with the site Principal Investigator.
- o Verification of eligibility criteria cannot be completed until the intra-operative assessment of absence of atrial thrombus by TEE has been performed.
- o 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 non-randomization.
- o A screened patient may become ineligible for randomization if either a thrombus is seen during TEE or, for *longstanding persistent AF patients only*, if presence of AF is not documented by a direct electrocardiographic assessment upon arrival in the OR.
- o When a screened patient becomes ineligible for randomization, further data collection will end.

Cardiovascular Rhythm Assessment**Prior to randomization**

- For patients with a diagnosis of persistent AF: one ECG or other direct assessment of heart rhythm must be obtained within 6 months prior to randomization.
- For all patients (both those with a diagnosis of persistent and longstanding persistent AF): heart rhythm by a 12-lead ECG will be assessed on arrival to the operating room. ***This must be documented in the patient's clinical chart. Whenever possible, a rhythm strip should be included in the chart as well.***
- Copies of this source documentation should be placed in ***the Patient Study Binder.***

Transthoracic Doppler Echocardiogram**Within 3 months prior to randomization**

- The site echocardiography lab must be trained by the CTSN Echocardiography Core Lab in advance of performing any study echocardiograms. Each test must be performed by the trained technician within the lab.
- A complete transthoracic echocardiogram will be performed at the clinical center, according to the specifications defined in the Echocardiographic Image Acquisition Protocol at each of the designated time points.
- A trans-esophageal echocardiogram cannot serve as the baseline study echo.
- After this initial assessment, the study echo will be sent to the Echocardiography Core Lab for centralized reading by a blinded core lab investigator.
- Pre-labeled CDs for copying the echo and pre-labeled mailing slips for shipping studies to the core lab will be provided to the clinical sites by the core lab.
- Baseline echo studies will be batched at the site and shipped to the core lab on a monthly basis to the following address:
ATTN: Judy Hung, MD
55 Fruit Street
Massachusetts General Hospital
Echocardiography Blake 256
Boston, MA 02114

Transesophageal Echocardiography**Pre-randomization, Intraoperative**

- All patients will undergo an intraoperative TEE.
- The TEE will be performed according to the specifications defined in the Echocardiographic Image Acquisition Protocol.
- ***If a left atrial thrombus is detected, the patient is ineligible for the study.***

Randomization

- A representative from the DCC will be available to discuss any questions regarding patient eligibility.
- **Randomization will be performed intra-operatively following anesthesia and TEE (see section 10 above).**

Procedure***Surgical Procedure***

Patients will be randomized to either:

- 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

- o 50% of the patients will undergo ablation lesions (Group 1) and 50% will not (Group 2)
- o 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

All patients will undergo:

- o Left Atrial Appendage excision or exclusion
- o Mitral Valve Surgery (valve repair in the majority of cases)

See the trial Protocol for the complete surgical procedure guidelines.

Post-Randomization Data Collection***Surgical Procedures******Initial surgical intervention and event driven***

- o The initial surgical procedure and all subsequent operations must be reported on the surgical procedure form within 48 hours of knowledge of the event.
- o This form 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 *not including anesthesia medications*, and intra-operative blood transfusions.
- o 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 faxed or emailed to the Clinical Trials Manager at the DCC, and the original will be filed in the Patient Study Binder.

Blood, Urine, and Tissue Sample Collection***Intra-operative***

- o Patients must sign a separate consent for participation in the biological specimen collection portion of the trial. This discrete consent may be included in the trial consent form, but requires separate signature.

- For those patients that consent, the following will be collected as specified in the protocol:
 - Blood
 - Urine
 - Tissue
- The samples will be banked by the NHLBI Blood and Tissue Repository service (operated by SeraCare Bio Services, 217 Perry Parkway, Gaithersburg, Maryland 20877).
- See the CTSN Biological Specimen Manual of Procedures for detailed sample collection, handling and shipping procedures.

Hospitalizations

Index hospitalization and event driven

- The index (baseline) hospitalization and all subsequent hospital admissions (for any reason) must be reported. This includes any hospitalization that occurs at an outside hospital. All efforts should be made to collect the CRF-defined data and supporting documentation from outside hospital admissions.
- Limited information about hospital procedures, length of stay, days in intensive care, and discharge if applicable, as well as patient condition and disposition for each hospitalization will be collected.

PATIENT PRE-DISCHARGE ASSESSMENTS

Prior to discharge the following must be completed

- ***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 procedure (mitral valve surgery with ligation/excision of left atrial appendage), the investigational intervention (surgical ablation), and the investigational device.
- ***Patient Diaries***
Prior to discharge, each patient will receive a transtelephonic monitoring (TTM) device for use during the first six months post-discharge and will be instructed on its use. (Please see the “Transtelephonic Monitoring” section below.) Included with the device will be the patient dairies (a six months supply of Weekly and Symptomatic Recording Diaries and the six month 72-Hour Holter Diary). (See Appendix III).
 - Patients will be instructed to note the following information in their Weekly and Symptomatic Recording Diaries:
 - Symptoms at the time of Symptomatic TTM transmission

- Symptoms that occurred in the absence of a rhythm recording. For these symptoms, patients will be instructed to record the character of symptoms (e.g. rapid heart rate, irregular heart rhythm, etc.)
- Patients will be instructed to note any symptoms suggestive of dysrhythmia in their 72-Hour Holter Diaries.
- *Shipping Information:*
 - Prior to the patient's six month 72-Hour Holter, Medicomp will mail each patient a replacement TTM device with a new six months supply of Weekly and Symptomatic Recording Diaries and a new 72-Hour Holter Diary (for the patient's 12 month 72-Hour Holter).
 - After completion of the six month 72-Hour Holter, patients will be instructed to mail the first six months of Weekly and Symptomatic Recording Diaries, the six month 72-Hour Holter Diary, and old TTM device to Medicomp in the provided preaddressed, post-marked envelope.
 - After completion of the 12-month 72-Hour Holter, patients will be instructed to mail the last six months of Weekly and Symptomatic Recording Diaries, the 12 month 72-Hour Holter Diary, and TTM device to Medicomp in the provided preaddressed, post-marked envelope.

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.

PATIENT POST-DISCHARGE ASSESSMENTS

Transtelephonic Monitoring (TTM)

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

All TTM recordings (weekly recordings, 72-hour Holters and symptomatic transmissions) will be transmitted from Medicomp to the CTSN Electrophysiology Core Lab located at the University of Rochester, Rochester, NY.

Ordering and Storage of TTM Devices

- Based on expected enrollment, each clinical site will store a predetermined number of TTM devices at their institution, and as patients are enrolled on the Medicomp website, Medicomp will supply each clinical site with a replacement TTM device. *If a device has been stored at a CTSN clinical site for close to 6 months, Medicomp will contact the site to initiate the replacement process.*

- Prior to the patient's index hospital discharge, the site Investigator or research coordinator should ensure that a TTM device is available for the study-defined follow-up monitoring.
- If additional devices are needed or if a device is needed in an expedited fashion, please contact Anne Shering at Medicomp. (Please see Section 1 for her contact information.)
- The TTM device training for the coordinators can be found at the following site: <https://reports.medicompinc.com> (Log in: medicompm; Password: Access1)

Online Patient Enrollment

As part of the discharge process, online patient enrollment must be completed by the coordinator via the Medicomp website (<https://reports.medicompinc.com>). Individual logins will be provided by site. For instructions on how to enroll patients, please see the "CTSN Arrhythmia Access Tutorial".

Notification of Treating Physician (prior to discharge and at 3 months post-discharge)

- Notifications of arrhythmias associated with symptomatic TTM transmissions will be provided to the patient's local treating physician. Contact information for the treating physician is captured on the "Medicomp Event Notification Form" (Appendix III).
- The site Principal Investigator must contact the local treating physician to explain the follow-up monitoring and potential notifications for symptomatic transmission arrhythmias that meet criteria outlined in the "Medicomp Event Notification Criteria Form" (Appendix III).
- A letter detailing the trial and monitoring process should also be sent to the treating physician (Appendix IV).
- In advance of the 3 month visit, the site PI will contact the treating physician to reiterate the trial endpoints and discuss the clinical indications for continued AAD for each patient enrolled (MOP Appendix VIII).

Patient Training Pre-Discharge

The study coordinator will provide patient training on the Medicomp TTM and Holter procedures. Training should include reviewing the Patient Guide and CardioPAL SAVI Patient Training Video. Documentation of training should be recorded on the TTM Training Log (Appendix VI).

- Medicomp will include copies of the CardioPAL SAVI Patient Training Video with each TTM device.
- All patients will be discharged with a TTM device kit. The kit contains the following:
 - Savi Monitor with belt clip
 - 5-lead wire connector
 - Finger probe and alcohol prep pads
 - ECG stickers (Sufficient for the first three months of the trial. As explained in the Patient Guide, patients can contact Medicomp to request additional ECG stickers.)

- Skin prep materials
 - 8-unit, AA battery pack
 - Contact information for trans-telephonic transmission
 - CardioPAL SAVI Patient Guide
 - CardioPAL SAVI Patient Training Video
 - Six months supply of Weekly and Symptomatic Recording Diaries
 - 72-Hour Holter Diary
 - Pre-paid shipping mailer for device and diary return at 6 months. (Patient will receive replacement device and diaries prior to returning the device at 6 months).
 - Medicomp 24-7 technical support contact information for any issues or requests for additional materials
- The TTM Training Log form (Appendix VI) will be filed in the clinical site Patient Study Binder to document that patient education on the use of device has been completed.

Prior to discharge, each patient will be instructed on the following:

- **Weekly Transmissions**
 - *Initiation of Weekly TTM Process*
 - Patients will be instructed by the clinical site coordinator on the process for weekly transmission of rhythm strips. In addition, the CardioPAL SAVI Patient Training Video and the CardioPAL SAVI Patient Guide supplied in each TTM device kit will serve as a resource with instructions on the weekly transmission process.
 - Each investigative site has been given specific day/time slots for weekly TTM transmissions. Patients will select one of the day/time slots allotted to their site and will transmit one strip per week during their chosen day and window of time for the duration of the study.
 - The clinical site coordinator will notify Medicomp of the patient's chosen day/time slot during the test TTM transmission which should occur prior to patient discharge.

- Patients should sign up based on the following schedule:

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
7 – 9 a.m.	Cleveland Duke Montreal NIH Heart Ctr.	Columbia UVA East Carolina Cleveland Duke Montreal NIH Heart Ctr.	Montefiore Emory U Penn	Cleveland Duke Montreal NIH Heart Ctr.	Montefiore Emory U Penn	Cleveland Duke Montreal NIH Heart Ctr.	Montefiore Emory U Penn
9 – 11 a.m.	UVA East Carolina Columbia	Montefiore Emory U Penn Montreal NIH Heart Ctr. Columbia UVA	Cleveland Duke Montreal NIH Heart Ctr.	UVA East Carolina Columbia	Cleveland Duke Montreal NIH Heart Ctr.	UVA East Carolina Columbia	Cleveland Duke Montreal NIH Heart Ctr.
11 – 1 p.m.	Montefiore Emory U Penn	East Carolina Cleveland Duke Montefiore Emory U Penn	UVA East Carolina Columbia	Montefiore Emory U Penn	UVA East Carolina Columbia	Montefiore Emory U Penn	UVA East Carolina Columbia
1 – 3 p.m.	Montreal NIH Heart Ctr. UVA East Carolina Columbia		Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke
3 – 5 p.m.	Montefiore Emory U Penn Cleveland Duke		Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia
5 – 7 p.m.	Montreal NIH Heart Ctr. UVA East Carolina Columbia		Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke
7 – 9 p.m.	Montefiore Emory U Penn Cleveland Duke		Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia	Montefiore Emory U Penn Cleveland Duke	Montreal NIH Heart Ctr. UVA East Carolina Columbia

- *Weekly TTM Reminders and Monitoring*
 - All patients will receive automated reminder calls from Medicomp within 48 hours of their scheduled Weekly Recordings.
 - If a patient does not transmit their weekly recording, Medicomp will contact the patient to remind them to transmit their recording.

- For any missed transmissions during the first 4 weeks post-discharge, Medicomp will contact the clinical site coordinator so that he/she can assess the reasons for non-compliance. After the first 4 weeks post-discharge, the clinical site coordinator will be contacted according to the following algorithm:

In the event that a patient does not transmit a recording for two consecutive weeks or if a patient transmits a recording 24 hours after their designated time slot for four cumulative weeks, Medicomp will contact the clinical site coordinator so that he/she can follow-up with the patient and assess reasons for non-compliance.

- Once the coordinator has assessed the reasons for non-compliance, this should be documented in the EDC.

o **Symptomatic Transmissions**

- Patients with symptoms suggestive of an arrhythmia (rapid or irregular heart rhythm) will be instructed to transmit rhythm strips per Medicomp's guidelines at the time of symptom occurrence as explained in the CardioPAL SAVI Patient Guide (Appendix VII).

o **72-Hour Holter Transmissions** at 6 months (± 14 days) and 12 months (± 30 days) post-randomization

- *Initiation of Weekly TTM Process*
 - The TTM device will be used for 72-hour Holter monitoring at 6 and 12 months
 - Each TTM kit will include the CardioPAL SAVI Patient Training Video and the CardioPAL SAVI Patient Guide which will provide the patient with instructions on the 72-hour Holter monitoring
- *72-Hour Holter Reminders and Monitoring*
 - All patients will receive automated reminder calls from Medicomp within 48 hours of their scheduled 6 month 72-Hour Holter recording.
 - The 12-month 72-hour Holter will be initiated in person, at the post-discharge study visit; however, if the patient is unable to return to the CTSN investigative center for their 12-month follow-up visit, the clinical site coordinator should notify Anne Shering at Medicomp, and Medicomp will telephone the patient to remind them to complete the remote continuous 72-hour Holter assessment.
 - After the patient completes their 12-month 72-hour Holter, the patient should be instructed to return the TTM device along with their diaries to Medicomp in the provided preaddressed, post-marked envelope.
 - If the patient was too ill to undergo a Holter assessment, the coordinator should document this in the EDC.

Telephone Follow-up

3 months (Medications ± 7 days; AAD Termination +14 days); 6 and 9 months (± 14 days); 18 and 24 months (± 30 days) (For patients who will be completing their 12-month echo remotely, please see detailed information for remote follow-up in the “Post-discharge Study Visit” section below.)

Telephone follow-up assessments will be conducted by investigative site personnel to document the following:

- Survival status
- **72-hour Holter Monitoring (6 months; 12 months for patients receiving remote echos only)**
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 each scheduled telephone follow-up, and also as indicated at the time of associated adverse events.
 - Response to DC cardioversions (success or failure) will also be recorded.
- **Anti-arrhythmic Drug Termination (3 months only)**
An AAD termination form will be completed at the 3-month follow-up assessment. In advance of the 3 month visit, the site PI will contact the clinical cardiologist to reiterate the trial endpoints and discuss the clinical indications for continued AAD for each patient enrolled (Appendix VIII).
- **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.
- The 18 and 24 month follow-up call will be used to specifically document any of the following since the previous contact:
 - Survival status
 - Stroke
 - Treatment with AADs and/or on medications for heart failure
 - Undergone cardiac ablation, insertion of a pacemaker or cardioversion

- The patient's response to any DC cardioversions (success or failure) should be recorded at each phone follow-up.

All telephone follow-up calls will be documented in the Trial Patient Contact Log (Appendix IX).

Post-discharge Study Visit

12 months (± 30 days) post randomization

After discharge, a return in-person visit is planned at 12 months. *For patients unable to return to the CTSN investigative center for the 12-month follow-up for extreme geographic distance can obtain a limited echo at a remote site (e.g., performed by the treating cardiologist). However, this should be avoided whenever possible, and the clinical coordinator should strongly encourage patients to return to a CTSN clinical site for follow-up.*

The following assessments are scheduled at this visit:

Transthoracic Doppler Echocardiogram

12 months (± 30 days) post randomization

- A complete transthoracic echocardiogram will be performed, according to the specifications defined in the Echocardiographic Image Acquisition Protocol (MOP Appendix I).

Remote Echo Assessments:

- *The remote clinical site must be identified by the coordinator in advance of discharge from the index hospitalization.*
- The remote image acquisition site contact information, including primary contact person, must be documented on the Remote Image Acquisition Contact form (Appendix II). The form must be faxed to the DCC prior to patient discharge and filed in the Patient Study Binder.
- 30 days prior to the image acquisition assessment date the clinical site coordinator will:
 - Contact the patient and the remote image acquisition center to confirm that the echo is scheduled
 - Send (1) the limited echo acquisition protocol (See Echocardiographic Image Acquisition Protocol (MOP Appendix I)), (2) pre-labeled recording material for copying the echo, and (3) pre-labeled mailing slips for shipping studies to the core lab to the remote acquisition center contact person.
- The coordinator must obtain the following information from the remote image acquisition site and document it in the EDC: test date, patient blood pressure, patient height and weight, date images sent to the core lab, and the FedEx tracking number.
- All study echos will be sent to the Echocardiography Core Lab for centralized reading by a blinded investigator. Please send all study echos to:
ATTN: Judy Hung, MD

55 Fruit Street
Massachusetts General Hospital
Echocardiography Blake 256
Boston, MA 02114

72-hour Holter Monitoring

- The TTM device provided to patients prior to discharge will be used for this assessment.
- Medicomp will contact the patient within 48 hours prior to the scheduled 6 and 12 month Holter assessments to remind them to perform the recording.
- Medicomp will provide 24-7 technical support to answer any questions or provide any additional necessary materials.

Medications

- All cardiovascular, inotropic, antiplatelet agents, and anticoagulants will be recorded.
- Medications, including AADs, will be recorded at each scheduled telephone follow-up, 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**12 months (± 30 days) post randomization**

- The 12- month QoL questionnaires will be completed in person, at the 12-month post-discharge study visit.
- The SF-12, AFSS and ELWAF questionnaires will be completed by the patient to assess quality of life.
- *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.*
- Data regarding completeness of QOL data collection and reasons for missing responses to questionnaires will be collected on the QOL Checklist.
- If the patient is unable to return to the CTSN investigative center for their 12-month follow-up visit:
 - The coordinator will send the QoL questionnaires to the patient with a postage paid, self addressed return envelope.
 - The coordinator will telephone the patient to remind them to complete and return the QoL questionnaires.

New York Heart Association Classification/Functional Status**12 months (± 30 days) post randomization**

- The 12- month New York Heart Association Classification (Appendix I) will be determined by a coordinator or physician not otherwise involved in this trial and blinded to treatment assignment. The NYHA class will be documented on the New York Heart Association Classification form.

- If the patient is unable to return to the CTSN investigative center for their 12-month follow-up visit, the coordinator will telephone the patient and treating cardiologist to obtain the New York heart Association Classification.

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.

Cost

- Direct costing data from UB-92 forms and hospital billing sheets for all patients will be obtained by the DCC on a quarterly basis through 12 months post-randomization.
- The coordinator will provide a list of medical record numbers to the financial data administrator, at their institution, who will generate the UB-92 forms and hospital bills.
- For Medicare-eligible enrollees, CMS billing data will also be collected.

Event Driven Data Collection

Follow-Up Surgical Procedures

Event Driven

- All operations must be reported on the surgical procedure form within 48 hours of 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 must classify the events according to the seriousness and relationship of the event to the surgical procedure (mitral valve surgery with ligation/excision of left atrial appendage), the investigational intervention (surgical ablation), and the investigational device.
 - If a patient did not receive an investigational intervention (i.e. mitral valve surgery with ligation/excision of left atrial appendage), please indicate this in the EDC (i.e. Adverse Events Form). In this case, an event could not be classified as related to the investigational intervention.
- For more information on the reporting of AEs, please see the “CTSN Adverse Event Procedures” document.
- All adverse events will be recorded until completion of the trial.

Missed Phone/Visit Assessment***Event Driven***

- A missed visit form must be completed if a patient is unable to return for an in-person visit, or be contacted for phone follow-up before the closure of a study visit window.
- The reasons for missing the visit must be documented.

Anti-arrhythmic Interventions***Event Driven***

- Detailed information regarding arrhythmias will be recorded at the time an intervention occurs.
- If related to an AE, investigators must classify the events according to the seriousness and relationship of the event to the surgical intervention.

National Institute of Health Stroke Scale and Modified Rankin Scale***Event Driven***

- NIHSS and Modified Rankin Scale must be administered within 72 hours of a neurological event (as defined in the protocol) and 90 days following the event to document the severity of neurological deficits.

Mortality***Event Driven within 24 hours of knowledge of event***

- The following information must be collected:
 - Date of death
 - Immediate cause of death
 - Primary underlying cause of death
 - Notation of autopsy being performed
 - Clinical narrative of the event

Study Completion/Early Termination***Event Driven***

- The date and reason for study completion or early termination will be recorded.
- The reason for a patient withdrawal from this study will be recorded on the Study Completion/Early Termination Form; examples of reasons for termination included patient request and physician discretion. The site must notify the DCC within 72 hours and their institutional IRB as per institutional policy of any early terminations.

Investigator's Statement***End of study***

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

21. REGULATORY DOCUMENTATION

Regulatory requirements:

Each site will maintain a regulatory binder on paper, CD, DVD, or other secured data storage device for each protocol. The DCC must have the following documents on file prior to site approval and initiation of the study:

- o Clinical study agreement with Mount Sinai School of Medicine
- o Nondisclosure agreement with Mount Sinai School of Medicine and the DCC
- o Copy of IRB/ERB approval for protocol, informed consent, HIPAA, and Release of Medical Information forms
- o Investigator and Co-Investigator Curriculum Vitae (CVs)
- o Conflict of Interest Statement and Financial Disclosure Certification
- o GCP and HIPAA certification for all study personnel
- o IRB or ERB roster/IRB or ERB verification
- o FWA and DUNS numbers
- o Clinical site laboratory certification and laboratory normal values
- o Clinical site echocardiography laboratory accreditation
- o Medcomp SAVI Cardiac Monitor Training Program Certificate of Completion (at least one must be on file per site)
- o Specialized Training Certifications:
 - Surgical Certification Form
 - NIHSS Training Certificate
 - Investigator PVI and Pacing Protocol Training Form

Ongoing study documents:

All sites must retain a regulatory binder that must be updated as new revisions of study documents are made and approvals are renewed. Study documents include:

- o All IRB(US)/ERB (non-US) approvals for the protocol and informed consent
- o All IRB/ERB correspondence
- o Copies of all revisions of the protocol
- o Copies of all revisions of the informed consent
- o Printed copies of blank electronic case report forms
- o New Investigator and Co-Investigator CVs
- o Monitor site visit log
- o Site signature and delegation log
- o Correspondence with DCC
- o Device Accountability Log (Appendix X)

Ongoing IRB/ERB requirements:

- o The DCC will send clinical centers a reminder letter 90 days prior to IRB/ERB approval expiration date.
- o The DCC will provide the sites with DSMB protocol approval letters.
- o The protocol must be reviewed annually by the IRB/ERB.

- o Informed consent must be re-approved in accordance with the clinical center's IRB/ERB, or at least annually.
- o A copy of the IRB/ERB letter of re-approval must be forwarded to the DCC.

Changes in CTSN personnel:

The DCC should be informed of any personnel changes in Principal Investigator, Co-Investigator, and/or coordinators within 15 business days of any change.

Complete documentation for the new study personnel should be sent to the Clinical Trial Manager at the DCC. This should include:

- o Role in CTSN Study
- o Complete contact information including telephone, fax, email address, and beeper number
- o Curriculum vitae
- o Conflict of Interest Statement and Financial Disclosure Certification
- o GCP and HIPAA certification
- o Clinical Study agreement, as applicable
- o Specialized Training Certification, as applicable (e.g. Neurocognitive, NIHSS)
- o An updated copy of the Delegation of Authority Log

22. ELECTRONIC DATA MANAGEMENT

The primary data collection tool within the Network for forms-based data is a web-based forms management system that has been developed by the DCC's system development team. The system design is based on an industry-standard three-tier architecture consisting of the user's web browser, an SSL-enabled application server with the Apache web server, the Java-based Tomcat servlet engine, and a relational database server.

23. QUALITY CONTROL PROCEDURES

The training of investigators/coordinators will occur at site initiation, via teleconference and/or at investigator meetings held three times each year. Every effort will be made to implement quality control measures for all procedures, diagnostic tests, and samples obtained. To this end, documents specific to the CTSN have been created and should be referenced as applicable.

These materials and documents include:

- o Medcomp patient/coordinator training (SAVI Patient Training Video [available on the CTSN website and included in each TTM device kit]) and the CardioPAL SAVI Patient Guide [Appendix VII]
- o Biological Specimen Manual of Procedures
- o IATA Shipping Certification
- o Echocardiographic Image Acquisition Protocol (MOP Appendix I)
- o Investigator PVI and Pacing Protocol
- o Surgical Certification Form: All surgical investigators will complete a surgical certification form which will be reviewed and signed by each site PI. The site PI

will be responsible for overseeing the performance of each participating surgeon at their site over the course of the trial. (This form can be found on the CTSN website.)

24. STUDY COMPLETION AND CLOSEOUT PROCEDURES

The monitoring team will determine the study completion status following the study close-out visit. This visit will occur once the study is completed and all data and finalized CRFs are submitted. At this time the DCC policy for maintaining records will be reviewed with the clinical site. Additionally, the return of study supplies and/or medications (as applicable) is completed. Following this visit, a final report indicating the completion of the study will be prepared by the DCC.

25. POLICIES

Confidentiality Procedure (See the Certificate of Confidentiality on the CTSN Website)

26. MOP MAINTENANCE

The DCC will review the MOP annually for updated information and communicate these changes with the sites.

APPENDIX I: Echocardiographic Image Acquisition Protocol

I. AFIB TRIAL TRANSESOPHAGEAL ECHO IMAGE ACQUISITION

Pre-Procedure Imaging

Mid and High esophageal views

- LV (Mid-Esophageal views at 0 and 90 degrees)
- LA (at 0, 60, 90, 120~140 degrees)
- Mitral Valve and chordal (at 0, 60, 90, 120~140 degrees)
 - o 2D and color Doppler (MR jet and vena contracta)
 - o PISA (baseline shifting to Nyquist of 30 to 40 cm/s with Zoom): at least one view
 - o CW of MR jet: at least one view
- LA appendage
 - o 2D
 - o PW with sample volume at the orifice of LA appendage
- Pulmonary vein (one left and one right PV): PW in the PV, 1 cm from the orifice
- RA/TV/IAS:
 - o 4 Ch view (all of RV)
 - o TV rotation (0, 60, 90) with color Doppler (for jet area); include entire TV annulus
 - o IAS: PFO view and Bicaval view (90-110°) with Color Doppler
- LVOT/AV/Aorta
 - o Long-axis view (120-140°) with color Doppler
 - o AV SAX (30°, mid esophageal) with color Doppler
 - o Ascending aorta (mid to high esophageal view) (90° to 110)
 - o Ascending aorta SAX views (0°, high esophageal)
- RVOT/PA (50-70°, mid esophageal)

Transgastric views

- 2D short axis views
 - o Mitral valve level
 - o Mid papillary muscle
 - o Apical level.
- Deep Gastric views : 5Ch view Aortic valve (with color, PW and CW Doppler)

Post-procedure Imaging

A full post-procedure TEE should be obtained if time permits. Otherwise, the study should be tailored to the procedure performed, including a minimum of the following:

- LV (Mid-Esophageal views at 0 and 90 degrees)
- LA (Mid-Esophageal views at 0, 60, 90, 120~140 degrees)
- Full rotation on mitral valve with attention to:
 - o MR jet area and vena contracta
 - o CW Doppler to assess post-procedure mitral gradients

- o PISA and CW of MR jet velocity (if MR is >mild by semi qualitative assessment)
- PW Doppler in Pulmonary vein (one left and one right PV): 1 cm from the orifice
- RA/TV
 - o TV rotation (0, 60) with color Doppler (for jet area); please include entire TV annulus
 - o IAS: PFO view (50 to 70-with aortic rim in view) and Bicaval view (90-110°) with Color Doppler
- Deep gastric 2D SAX views of LV
 - o Mitral valve level
 - o Mid papillary muscle
 - o Apical level.

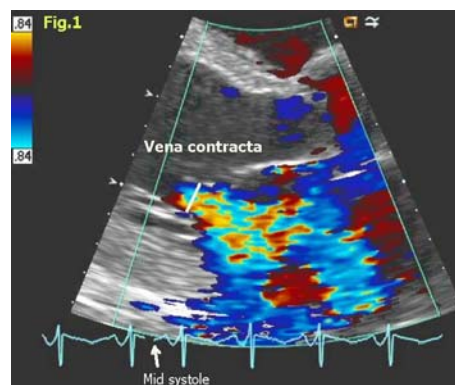
II. TRANSTHORACIC ECHOCARDIOGRAM (TTE)

- o All images should be acquired during quiet respiration.
- o At least 5 cardiac cycles are requested for 2D imaging, spectral pulsed wave (PW) and continuous wave (CW) Doppler.
- o Harmonic imaging should be employed to optimize visualization of endocardial borders.
- o A sweep speed of 100 mm/sec is required for PW, CW Doppler and M-mode recordings.
- o Color Doppler Nyquist limits will be adjusted to the range of 50 –70 cm/sec.

A. Complete TTE Image Acquisition

The following images should be acquired by the Core Lab certified personnel for studies performed at the CTSN clinical site.

1. PLAX with and without magnification of the left ventricular (LV) outflow tract; with and without color flow Doppler interrogation of the aortic and mitral valves. Careful attention should be paid to identifying the vena contracta of the mitral regurgitant jet using zoom views (Fig.1).

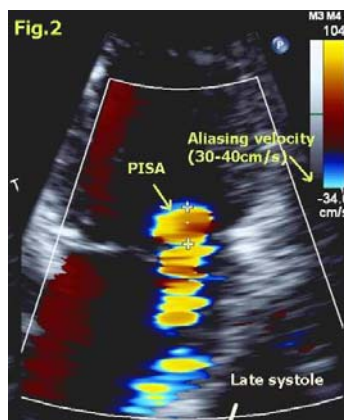


2. An M-mode recording of the LV just below the tips of the mitral leaflets.
3. Parasternal inflow view of the tricuspid valve; with and without color flow Doppler (CW if jet imaged parallel to beam).
4. Parasternal outflow view of the pulmonic valve (PV); with and without color flow Doppler and PW and CW of the PV.
5. PSAX (ensure on-axis views)
 - i. Apex
 - ii. Mid-papillary muscle level
 - iii. Level of the mitral valve when both anterior and posterior leaflets are visualized. Position the Color Doppler scan box over the mitral orifice to visualize the regurgitant jet origin.
 - iv. Tips of the mitral valve leaflets (identify minimum diastolic orifice)
6. Basal PSAX (at the aortic valve level). Evaluation of PV and TV performed with and without color flow Doppler. Pulsed Doppler sample of pulmonary flow at the level of the pulmonary valve to measure pulmonary velocity time interval (VTI) opening and closing transients of the pulmonary valve should be recorded.
7. Optimize the pulmonary valve annulus for measurement of the pulmonary annular diameter.

Apical 4-chamber view

- A. Full sector and zoom/res of individual valves with and without color flow interrogation of mitral and tricuspid valves. The color flow Doppler interrogation should include the entire left atrium taking care to include wall impinging eccentric jets in the region of interest. Gain should be adjusted to reduce excess noise. Spectral Doppler interrogation in this view includes:
 - i. PW Doppler of mitral inflow at mitral leaflet tips.
 - ii. PW Doppler of mitral inflow at the level of the mitral annulus at end diastole with a small sample volume.
 - iii. CW of the mitral inflow signal.
 - iv. CW of the mitral regurgitant jet with care to record a complete signal and maximize the peak velocity. Contrast should be used to enhance this signal when incomplete and when a peak velocity cannot be determined. NOTE: Occasionally eccentric CW jets may require interrogation of additional views (e.g., PLAX, Apical 2C view) to obtain the true maximal jet velocity.
 - v. PW Doppler of tricuspid inflow, with sample volume placed between the tips of the tricuspid leaflets
 - vi. CW of the tricuspid inflow signal to detect tricuspid valve stenosis.
 - vii. CW of tricuspid regurgitant jet for estimation of pulmonary artery systolic pressure. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).

- viii. PW Doppler of right pulmonary vein flow. The sample volume should be placed at least 1 cm within the pulmonary vein, if possible.
- ix. Color flow Doppler visualization of regurgitant jets (mitral and tricuspid).
- x. PISA (proximal isovelocity surface area) for mitral regurgitation (Fig.2)
 - o Using zoomed views
 - o The PISA aliasing velocity should be set between 30-40 cm/sec.
 - o The baseline will be shifted in the direction of flow (toward LA) to maximize the PISA signal.
 - o Record at least 5 cycle clip of PISA as well as still frame of maximum PISA radius.

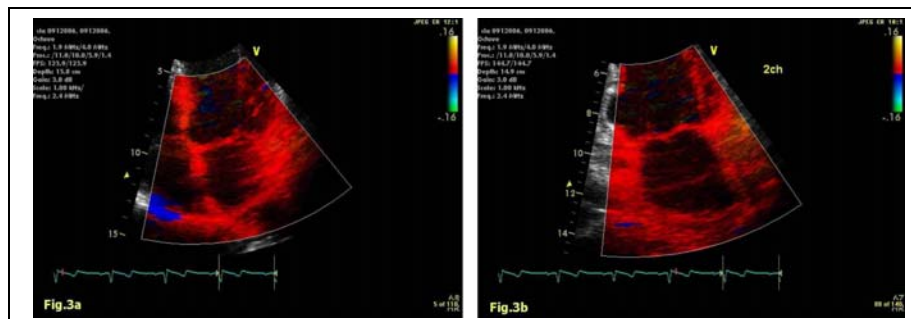


- xi. Pulsed wave tissue Doppler of the mitral annulus (lateral and septal)

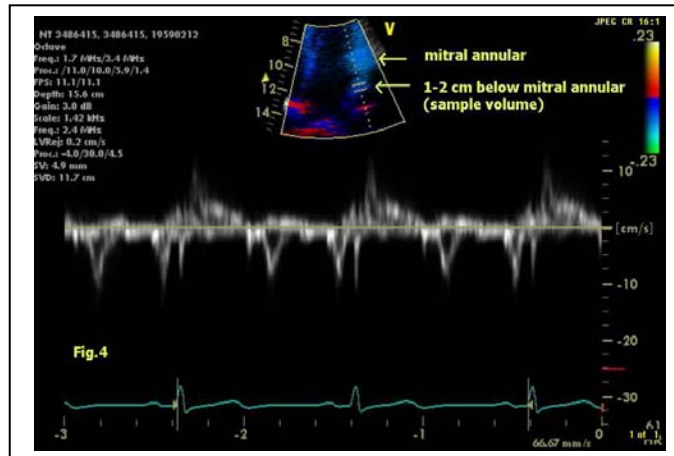
B. Apical 4-chamber zoom/res images of the LV.

C. Apical 4-chamber zoom/res image of the left atrium (LA).

D. Color-coded tissue Doppler imaging of LA with frame rate >110fps (Fig.3a).



- E. PW tissue Doppler image with the sample volume placed in the basal lateral wall of left atrium (1 to 2 cm below mitral annulus) (Fig. 4)



Anteriorly angulated 4-chamber view

- Color flow Doppler to exclude aortic insufficiency
- PW Doppler in left ventricular outflow tract positioned such that closing artifact but not opening artifact of the valve is visible
- CW Doppler through the aortic valve

Apical 2-chamber view

- Mitral valve with and without color Doppler
- Zoom/res images of the LV
- Zoom/res images of the LA
- Color-coded tissue Doppler imaging of LA with frame rate >110fps (Fig.3b)

Apical 3-chamber view

- Mitral valve and aortic valve with and without color Doppler
- Apical 3-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus)

Subcostal imaging

- Inferior vena cava with and without a “sniff”
- Color Doppler of inter-atrial septum to interrogate presence of ASD
- 4-chamber and SAX views (particularly if parasternal evaluation was limited)

Contrast

Contrast will be used for endocardial border delineation when less than 80% of the endocardium can be visualized on the harmonic image. Contrast can also be employed for enhancement of the tricuspid regurgitant and pulmonary venous flow signals. During the contrast imaging, the mechanical index (MI) should be adjusted according to manufacturer recommendations.

Note: Addition of any non-standard imaging will be coordinated in collaboration with the selected Core Laboratory under a protocol amendment and should be obtained at the

discretion of the sonographer/physician.

B. Limited TTE Image Acquisition

The following images should be acquired for follow-up echocardiograms performed outside the CTSN clinical site.

- o All images should be acquired during quiet respiration.
- o At least 3 cardiac cycles are requested for 2D imaging, spectral pulsed wave (PW) and continuous wave (CW) Doppler.
- o For patients in atrial fibrillation, a minimum of 2 captures of 3 consecutive cardiac cycles are required.
- o Harmonic imaging should be employed to optimize visualization of endocardial borders.
- o A sweep speed of 100 mm/sec is required for PW, CW Doppler and M-mode recordings.
- o Color Doppler Nyquist limits will be adjusted to the range of 50 –70cm/sec.

I. Protocol for Transthoracic Echocardiogram (TTE)

1. PLAX

- a. 2D image for measurements of LV, LA, LVOT and Ao dimension
- b. Color Doppler at MV with Zoom (for MR vena contracta assessment)
- c. Color Doppler at AV

2. RV inflow

- a. 2D
- b. Color Doppler at TV
- c. CW of TR jet (if jet imaged parallel to beam)

3. PSAX

- a. 2D images at the AV level, MV level, papillary muscle level and apex of LV
- b. Color Doppler at PV and TV
- c. PW at PV at AV level

4. Apical 4 chamber

- a. Full sector (including the entire LA, LV, RA, RV)
- b. Zoom of the LV
- c. Zoom of the LA
- d. Color Doppler of MV
- e. Zoom of the MV with color, shift baseline between 30-40 cm/sec to maximum
 - i. PISA radius, record 3-5 cardiac cycles as well as still frame of maximum PISA
 - ii. radius. **(Apply to patients with mitral valve repair only).**

- f. CW of MR jet with the maximal peak velocity (**Apply to patients with mitral valve repair only**).
 - g. CW at the tip of MV
 - h. PW at the tip of MV
 - i. PW at 1 cm within one pulmonary vein
 - j. PW-tissue Doppler imaging of mitral annulus (septal and lateral)
 - k. Color Doppler of TV
 - l. PW at the tip of TV
 - m. CW of TR jet
- 5. Apical 5 chamber**
- n. Color Doppler at AV
 - o. CW at AV
 - p. PW at LVOT
- 6. Apical 2 chamber**
- q. Full sector (including the entire LA and LV)
 - r. Zoom the LV
 - s. Zoom the LA
 - t. Color Doppler at MV
- 7. Apical long-axis**
- u. Full sector (including the entire LA and LV)
 - v. Color Doppler at MV and AV

NOTE: Occasionally eccentric CW jets may require interrogation of additional views (e.g., PLAX, Apical 2C view) to obtain the true maximal jet velocity.

ABBREVIATIONS

AV	Aortic valve
LA	Left atrium
LV	Left ventricular
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
MV	Mitral valve
PV	Pulmonary valve
TDI	Tissue Doppler imaging
TR	Tricuspid regurgitation
TV	Tricuspid valve

APPENDIX II: CTSN Remote Image Acquisition Contact Form

Patient ID: _____



CTSN Remote Image Acquisition Contact Form

Remote Image Acquisition Site: _____

Contact Information: _____

Shipping Address: _____

Form Completed By: _____

Date Completed: _____

Rev 1.0, dated 12-12-09

APPENDIX III: Medicomp Event Notification Form**Cardiothoracic Surgical Trials Network (CTSN)
Dysrhythmia Notification Criteria**

Please review this form carefully. The information contained in this document defines the criteria that Medicomp, Inc. will use to notify you of dysrhythmias detected during a symptomatic event recording scan.

It is our policy to take the following actions when physician notification is warranted:

1. Notify the treating physician of the patient's name and reason for contact as specified on this Notification Criteria form.
2. Document name of person notified and date and time of notification. The mode of notification will be included where necessary, e.g. message left on answering machine.
3. A rhythm strip may be printed and sent to the treating physician, if requested.

The criteria listed on page 3 will be used for notification.

Medicomp, Inc. • 7845 Ellis Road • Melbourne, FL 32904 • Phone: (321) 676-0010 • Fax: (253) 276-4400

Rev 1.0, dated 12-17-09

A United Therapeutics Company

Date Controlled Document: EventCriteria 091807



CTSN Notification Contacts

page 2 of 3

PLEASE FAX OR EMAIL THIS TWO-PAGE FORM TO: (253) 276-4400 OR MWILSON@UNITHER.COM

SITE NAME: _____

ADDRESS: _____

TREATING PHYSICIAN
(PLEASE PRINT): _____

For the Cardiac Monitoring Center:
cc: mwilson@unither.com for all
CTSN email communication

ONLY TREATING PHYSICIAN RECEIVES NOTIFICATIONS.

DURING BUSINESS HOURS

TREATING PHYSICIAN BUSINESS HOURS (SPECIFY; include weekends and holidays)

CONTACT PERSON AND/OR DEPARTMENT _____

PHONE NUMBER _____ ALTERNATIVE NUMBER _____

FAX NUMBER _____

IS MESSAGE LEFT ON ANSWERING MACHINE/VOICE MAIL ACCEPTABLE? YES ☐ NO ☐
IF "NO", PLEASE SPECIFY ALTERNATE CONTACTS (Name, area code, phone no.):

1. _____ 3. _____
2. _____ 4. _____

AFTER HOURS NOTIFICATION

Medicomp's policy when an answering service is contacted: We will inform the service of specific details (i.e. patient name, dysrhythmia(s), pertinent symptoms) and also leave a direct phone number where the person responsible for the scan can be reached, if desired.

CONTACT PERSON AND/OR DEPARTMENT _____

PHONE NUMBER _____ ALTERNATIVE NUMBER _____

ADDITIONAL INSTRUCTIONS _____

NOTE: Medicomp must be informed immediately of any updates or changes in notification criteria and/or contact information. Failure to do so may result in a delay in notification of critical dysrhythmias.

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Rev 1.0, dated 12-17-09

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Date Controlled Document: CTSN NotifCriteria 091208



CTSN Notification Criteria

page 3 of 3



All arrhythmias marked with an asterisk (*) will be triaged until we have followed the patient with one or two follow-up transmissions (depending on the severity of symptoms) with intervals between 5 and 20 minutes apart. If these arrhythmias/symptoms occur after business hours and the follow-up ECG is normal, you will be notified the next business day. *Note:* If severe or life-threatening conditions are seen, or the patient is highly symptomatic, we will triage the patient first, then notify the physician. "Highly symptomatic" refers to the following symptoms: nausea, SOB, chest pressure, diaphoresis, numbness of the neck or jaw, radiation of pain, numbness to an extremity or unable to speak.

(^)*Sustained Arrhythmias are defined as a duration of 30 seconds or greater. Triage actions will not be taken if we have been notified on a patient by patient basis that certain arrhythmias are chronic for that patient.

ARRHYTHMIAS		
1.	Sustained (^) Supraventricular Tachycardia (SVT in which the P wave has changed Morphology or is Absent) (*)	HR > 150
2.	Sustained (^) Atrial Fibrillation w/RVR (*)	HR > 150
3.	Sustained (^) Sinus Tachycardia, non-exercise related (*)	HR > 180
4.	New onset of Atrial Fibrillation (any rate)	YES
5.	Sustained (^) Marked Bradycardia, IVR or A-fib with SVR (*)	HR < 36
6.	SA Block 3:1, Sinus Arrest, pause of uncertain origin	> 3.0 sec
7.	Second degree AV block, type 2, high grade AVB, or Complete Heart Block	YES
8.	Atrial Fibrillation with WPW, R on T PVC	YES
9.	Ventricular Standstill	YES
10.	Ventricular Tachycardia/Wide QRS Tachycardia (all types) of more than 6 beats	YES
11.	Frequent ventricular couplets/triplets, frequent Ventricular runs of 3-5 beats, frequent PVCs > 6/min, and sustained Bigeminy or Trigeminy: <u>if highly SX</u>	YES
12.	Exercise Related Sinus Tachycardia	> APMHR (220-age)
13.	Ventricular Escape Rhythm/Accelerated IVR	> 6 beats
14.	Ventricular Fibrillation or Torsades de Pointes	YES
15.	Highly SX Intermittent IVCD/Progressive IVCD	YES
16.	SX with ST depression > 2 mm	YES
17.	SX with ST elevation > 1.5 mm	YES

**FOR THE FOLLOWING SYMPTOMS, SEND PATIENT TO EMERGENCY DEPT OR EMS;
PATIENTS SHOULD BE INSTRUCTED TO NOTIFY THEIR PRIVATE PHYSICIAN.**

1. Syncope/Blackouts – any episode (*)
2. Chest pain/Angina – associated with ischemic changes in ECG and/or sustained for 2 minutes in duration
3. Seizure – any episode
4. Shortness of breath, unprovoked or with ECG changes
5. Pacemaker failure

Physician signature: _____ Date: _____

Physician Name (Please Print): _____

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Date Controlled Document: CTSN NotifCriteria 091208

Rev 1.0, dated 12-17-09

APPENDIX IV: Draft Letter to the Treating Physician

CTSN Draft Letter to the Referring Cardiologist



[Referring Cardiologist]

[Address]

[Date]

Dear [Referring Cardiologist]:

Your patient, XXX, was enrolled on xx/xx/2010 in the National Heart, Lung, and Blood Institute-supported Cardiothoracic Surgery Network trial: *Surgical Ablation versus No Surgical Ablation for Patients with Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Mitral Valve Surgery*. The purpose of the trial is to assess the effectiveness of adding ablation to mitral valve surgery for treating your patient's atrial fibrillation. The trial's primary outcome is freedom from atrial fibrillation at 6 and 12 months after surgery, assessed with 3-day continuous (Holter) monitoring. In addition, 2 different techniques for heart rhythm monitoring will be compared: the 3-day monitoring at 6 and 12 months vs. weekly rhythm strips. Results of this comparison will guide follow-up strategies for future studies of rhythm control in AF patients.

Medicomp (<http://www.medicompinc.com/index.html>) will be providing rhythm monitoring services for the trial. The protocol-defined recordings will be sent for analysis to our core lab. In the event that your patient experiences symptoms, [he or she] has been instructed to transmit a recording during the symptoms. The symptomatic recordings will be triaged by Medicomp according to their policy, and you will be notified if there is a dysrhythmia meeting notification criteria. We have attached the notification criteria that have been developed by the trial clinical leadership. Thank you for your support of this important trial.

Please do not hesitate to contact me with any questions.

Sincerely,

[Principal Investigator]
[Site Contact Information]

Afib Ablation Trial
Rev 1.1, dated 01-12-10

APPENDIX V: Medicomp Patient Diaries

1. 72-Hour Holter Diary



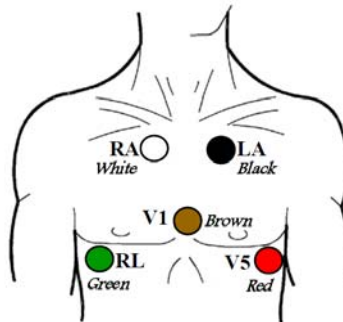
72-Hour Holter Diary

Preparing for the Holter Test:

Wear comfortable clothing that will not interfere with your normal daily activities. A button down shirt works best since wires must be brought out to connect to the monitor.

Depending on your activity, you will be able to choose the belt or lanyard to secure the monitor. **There should be no tension on the patches from the wires connected to the monitor.**

If Electrode Patches or Wires Fall off....



Here's how to replace them:

Look at the picture above to find out where to place the adhesive patches. Press the patches onto your skin firmly so that there is no air space in between your skin and the gel cup on the patch. **It is very important that the patches remain intact during the test.** It's okay to apply extra tape to the patches, but try not to tape across the snap where the lead wires attach.

If the wires are accidentally pulled off, just snap them back on in the proper locations.

Things to remember while wearing the monitor:

- Don't use an electric blanket.
- Don't expose the monitor to "industrial" microwave equipment.
- Don't expose the monitor to severe cold temperatures.
- Avoid touching or lying on the patches.
- If a wire comes off, snap it back on the patch and record this in your diary.

If any errors appear on the monitor's display, call:

1-877-996-5553

Remove the monitor before bathing. *Be sure to disconnect the cable from the monitor before removing the lead wires from your chest.*

At the end of the Holter Test....

The monitor will turn off automatically. The display will go blank. **Only after this occurs is it safe to remove the patches.** Unsnap the lead wires, peel off the patches and throw the patches away. You may wish to apply a skin care product to soothe any skin irritation.



72-Hour Holter Diary

PATIENT NAME:	PHYSICIAN NAME:		
DATE:	PACEMAKER?:	YES	NO

Please record the activity and time of any symptoms you experience during this testing period. In addition, please refer to the time on the patient monitor when recording your entries, and use blue or black ink.

[illegible]



72-Hour Holter Diary

[illegible]

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Page 3 of 4



Medicomp, Inc...#1 in Holter and Event Solutions

72-Hour Holter Diary

[illegible]

**If you need more space, please continue to record the activity and time of any symptoms you experience during this testing period in the above format on a blank sheet of paper.*

After your 72-Hour Holter has been completed, please be sure to enclose this diary in the monitor kit that you will be shipping back to Medicomp in the large, pre-addressed, post-marked envelope.

Thank you for your cooperation.

DC: CTSN HD09110
Rev 1.0, dated 12-17-09

Page 4 of 4

2. Weekly and Symptomatic Recording Diary



Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

PATIENT NAME:	PHYSICIAN NAME:		
DATE:	PACEMAKER?:	YES	NO

Please record the following activities and dates/times in this diary: (1) the transmission of symptomatic rhythm strips and (2) any symptoms that occurred in the absence of a rhythm recording. In addition, please document the character and the duration of any symptoms that you experience (whether a rhythm recording occurred or not) that you perceive to have been related to heart rate or rhythm. Please refer to the time on the patient monitor when recording your entries and use blue or black ink.

[illegible]

DC: CTSN WRL091106
Rev 1.0, dated 12-17-09

1



Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Rev 1.0, dated 12-17-09

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Rev 1.0, dated 12-17-09

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Rev 1.0, dated 12-17-09

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

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Rev 1.0, dated 12-17-09

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Medicomp, Inc...#1 in Holter and Event Solutions

Weekly and Symptomatic Recording Diary

[illegible]

**If you need more space, please continue to record the transmission of symptomatic rhythm strips and any symptoms that occurred in the absence of a rhythm recording in the above format on a blank sheet of paper.*

Please be sure to mail this diary in the monitor kit that you will be shipping back to Medicomp in the large, pre-addressed, post-marked envelope after completion of your 72-Hour Holter.

Thank you for your cooperation.

DC: CTSN WRL091106
Rev 1.0, dated 12-17-09

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APPENDIX VI: TTM Training Log

Cardiothoracic Surgical Trials Network



TTM Training Log

Surgical Ablation Versus No Surgical Ablation for Patients with Persistent Atrial Fibrillation Undergoing Mitral Valve Surgery

Patient Study ID #: _____

SAVI Patient Training Video:

(1) *To be completed by the patient:*

I have watched the SAVI Patient Training Video and all of my questions have been answered.

Patient Signature: _____

Date: _____

(2) *To be completed by the coordinator:*

- Did the patient receive a copy of the training video? (Please circle one.) **Yes** **No**
 - If no, please indicate the reason why: _____

- If the patient was unable to watch the SAVI Patient Training Video, please indicate the reason why: _____

Coordinator Signature: _____

Date: _____

CardioPAL SAVI Cardiac Monitor Patient Guide:

I have received the CardioPAL SAVI Cardiac Monitor Patient Guide. The contents in this guide have been fully explained to me, and all of my questions have been answered.

Patient Signature: _____

Date: _____

Coordinator Signature: _____

Date: _____

Rev 1.0, dated 12-17-09

APPENDIX VII: CardioPAL SAVI Patient Guide

☐ Section 8: PRECAUTIONS

A. CHOKING HAZARD

A lanyard is provided with the CardioPAL SAVI as an optional accessory. However, this should be worn by adults only, and should not be worn during sleep. People working with machinery or working in environments where loosely-hanging, rope-like objects can pose a potential threat or harm to themselves and/or the machinery are advised to use the carrying case.

- B.** The CardioPAL SAVI should be worn outside your clothing if there is any chance that perspiration might come in contact with the monitor. The unit should be worn beneath outer wear, such as raincoats or jackets, for protection during wet or cold conditions.

☐ Section 9: Ordering Supplies

Your SAVI kit comes with enough supplies to last about 3 months. Prior to the 3- and 9-month anniversary dates, extra supplies will be shipped to you. If you find that you need more supplies during the course of the procedure, call **1-877-996-5553**.

*Supplies will be shipped via Priority Mail.
Please allow 2-3 business days for delivery.*

☐ Section 10: Returning the CardioPAL SAVI to Medicomp

- A.** First, check the monitor for recordings that you may not have transmitted yet.

 To do this, press the **YES** button. If transmission tones begin, there are still recordings to be sent to the CMC. Next, press the **NO** button to stop the transmission and then call the CMC to send the recordings. After transmitting the recordings, proceed to Part B.

 If you do not hear a transmission tone, then all recordings have been sent to the CMC. Proceed to Part B.

- B.** Place the CardioPAL SAVI* in its case, along with the cable, finger-electrode accessory, this card and any unused electrodes. Properly dispose of used batteries (you may keep any unused batteries for your personal use).

**If the monitor has been submerged in any liquid, seal it in a plastic bag prior to putting it in the case.*

- C.** Place the case into the pre-paid shipping envelope provided.
D. Seal the envelope and drop it in any U.S. Mailbox.

FEDERAL LAW RESTRICTS THIS DEVICE TO
SALE OR USE BY, OR ON THE ORDER OF, A LICENSED PHYSICIAN.

8 *Medicomp is a United Therapeutics Company* CTSN090824



CardioPAL SAVI™

Cardiac Monitor

Patient Guide

**To TRANSMIT RECORDINGS, CALL
1-877-996-5553
(TOLL-FREE)**

PLEASE REMEMBER:

**RETURN THE CardioPAL SAVI MONITOR,
ALONG WITH ALL UNUSED ELECTRODES
(PATCHES) TO MEDICOMP IN THE CASE
AND ENVELOPE PROVIDED.
(Please do not return any batteries.)**

*Should you have any questions regarding
any information in this patient guide, please
contact the Cardiac Monitoring Center at
1-877-996-5553.*

Medicomp, Inc.
7845 Ellis Road
Melbourne, FL 32904



☐ Section 1: Instructions for Using Your Monitor

As a participant in this research protocol, you will make recordings of your heart's electrical activity over the next year. The recordings are divided into three types:

- A. Weekly Recordings
- B. Symptomatic Recordings
- C. 3-Day Continuous Recording (Holter Procedure)

You will receive automated reminder calls from the Cardiac Monitoring Center (CMC) at Medcomp within 24 hours of your scheduled Weekly Recordings.

A. Weekly Recordings

You have selected the following day and time for your weekly recording and transmission:

Saturday Sunday Monday

Time block: _____

(Please see Section 2 for instructions on connecting yourself to the CardioPAL SAVI monitor in preparation for this recording, and Section 4 for instructions on transmitting your recording.)

B. Symptomatic Recordings

You have also been asked to transmit a recording when you feel symptoms of an abnormal heart rhythm. In order to make these recordings, you will need the finger-electrode accessory. (Please see Section 3 for instructions on how to use this accessory and Section 4 for instructions on transmitting your recording.)

C. 3-Day, Continuous Recording (Holter Procedure)

You will complete a 3-day, continuous recording/Holter procedure about 6 and 12 months after your hospital discharge. In order to perform this procedure, you will need to apply chest electrodes. (Please see Section 2 for instructions on connecting yourself to the monitor in preparation for this procedure, and Section 4 for instructions on transmitting the recordings that you make during the procedure.) A representative from the CMC will contact you to remind you to apply your electrodes, and to wear the monitor for 3 consecutive days.

During this 3-day procedure, you can wear the monitor on a belt, around your neck using the cord provided, or in a pocket that is readily accessible. If you feel any symptoms of an abnormal heart rhythm during this time, you will press the **SYMPTOM** button and transmit your recording (Please see Section 4).

3-Day Continuous Recording Dates: _____

Before the end of the first 6 months, you will receive a replacement monitor and kit. After you have completed the first, 3-day Holter procedure, you will return the first monitor to Medcomp. Please refer to Section 10 for the instructions on returning the CardioPAL SAVI monitor to Medcomp.

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☐ Section 5: Resetting the CardioPAL SAVI

Your monitor may require a "reset" periodically to start another round of weekly recordings. The monitor will beep and display, "Procedure Complete/Please return SAVI monitor in the prepaid envelope." **Do not return the monitor.** Call the CMC to help you restart your procedure.

☐ Section 6: Replacing the Battery

The monitor will alert you when the battery needs to be changed. Please follow the steps below when changing the battery:

-  The CardioPAL SAVI is designed to operate with one, AA alkaline battery **ONLY**.

The location of the battery compartment is on the back of the monitor, at the bottom of the case.



Battery Compartment

- A. Slide the battery-door panel in the direction of the embossed arrow to remove the panel completely from the unit. Pop out the old battery from the compartment using the ribbon attached to the inside, if needed.
- B. Insert the new battery over the ribbon, using the picture inside the compartment as your guide.
- C. Align the cover to the compartment and slide the door back into position.

☐ Section 7: Cleaning the CardioPAL SAVI

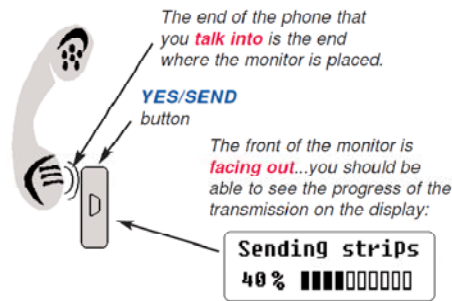
If needed, clean the monitor with alcohol prep pads, or a soft cloth slightly moistened with isopropyl alcohol.

-  Do not submerge the monitor in any liquid. If the unit does get wet, you should notify the CMC as soon as possible, so that a replacement can be shipped to you. You should return the damaged monitor after allowing it to air-dry. **Seal it in a plastic bag prior to shipping.**

7

+

Section 4: Transmitting Your ECG Recording(s) - Cont'



- 4) Press and release the **YES/SEND** button on the side of the unit to begin transmitting the ECG. You'll hear a continuous tone. To insure quality transmission, please do not bump the flat surface, talk, make loud noises or touch the monitor while the transmission is in progress.

What does the Cardiac Monitoring Center see when you transmit? ...something like this:



CMC policy prohibits the staff from releasing information to you about the content of your ECG recordings.

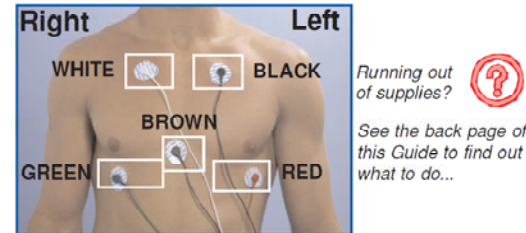
- 5) When the tones stop, transmission is complete. **ALWAYS** pick up the handset and wait for further instructions from the technician at the CMC.
- C.** If you just transmitted a
- 1) Weekly Recording, insert the finger electrode into the top of the monitor, and place the unit in a location where you can reach the **SYMPTOM** button easily. Unsnap the patient cable wires from the electrodes and then remove them from your chest. (Tip for easy removal: First soak the electrodes with soapy water.)
 - 2) Symptomatic Recording using the finger electrode, leave the accessory in the top of the monitor and place the unit in a convenient location.
 - 3) Symptomatic Recording during the 3-Day Procedure, connect the patient cable back to the monitor and continue to wear the unit as instructed.

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Section 2: Connecting Yourself to the Monitor

Try to take care in preparing your skin for electrode (adhesive skin patches) application. Good skin preparation means better Electrocardiogram (ECG) signal traces that in turn are easier for your doctor to review and evaluate.

The center of the patch should be within the areas indicated by the boxes in the figure below.



How to Prepare Your Skin

- A.** Choose areas of your chest that are flat and not very muscular; avoid skin folds or creases, irritated skin or scar tissue.
 - B.** Shave hairy areas using the skin patch (electrode) as a guide for the size of the area to shave. This insures good contact and makes electrode removal much easier and a lot less painful.
 - C.** Wash each site thoroughly with **PLAIN** soap and water. Do not use soap that contains lotion or oil. Dry well.
- If you are starting the 3-Day Holter Procedure, the skin prep is slightly different. You'll be using the skin prep gel that was sent in your kit. The CMC will help you with this.*
- D.** Snap the wires of the patient cable onto the electrodes and apply them to your chest using the illustration above.
 - E.** Plug the connector end of the patient cable into the monitor. The unit will automatically turn on, and the display will show, "Ready" on the top line.
 - F.** Relax in a comfortable position and limit your movement. Wait one minute to allow the monitor to gather your ECG data. Then, press and release the **SYMPTOM** button. Listen for a beep indicating that the recording of your heart rhythm has begun. The unit displays a countdown message while it is recording.
 - G.** When the recording is finished, the unit beeps and displays, "Recording Complete." Then the monitor displays, **"To TRANSMIT CALL / 1-877-996-5553."** (Please see Section 4 for instructions on transmitting your recordings).

If you experience excessive skin irritation from the adhesive electrodes patches during your procedure, please call the CMC at 1-877-996-5553.

3

□ Section 3: Using the Finger Electrode Accessory

Please carry the monitor with you at all times with the finger electrode accessory attached.



Correct Finger Placement

Do not allow fingers of the opposite hands to come in contact with each other while the recording is taking place.

- A. When you have a symptom, pull the monitor from its location, press and release the **SYMPTOM** button, and listen for the beep.
- B. Moisten fingers from each hand with an alcohol prep pad, and quickly place them on the finger electrode as shown in the photograph.
- C. Rest your arms on a solid surface to minimize movement of your fingers and hands. Press down firmly on the contacts, but do not use excessive pressure.
- D. Wait until the CardioPAL SAVI emits a second beep and displays, "Recording Complete," before removing your fingers. The monitor will display, **"To TRANSMIT CALL / 1-877-996-5553."** Continue with Section 4.

Make a habit of carrying a few alcohol prep pads with you at all times, as they are used with the finger electrode accessory.

□ Section 4: Transmitting Your ECG Recording(s)

A. When to Transmit Your Recording(s):

1) Weekly Recordings

Please submit your weekly recordings according to the day/time that you selected. (Please see Section 1.)

What to do if you are unable, or forget to transmit during your transmission time:

If you miss your transmission time for any reason, please transmit your recordings as soon as possible. If it has been more than 4 days, please call:

2) Symptomatic Recordings

Although the monitor can hold multiple recordings, you should transmit these recordings after each episode.

3) 3-Day, Continuous Recording Procedure

If you experience any symptoms of an abnormal heart rhythm during this 3-Day Procedure, please press the **Symptom** button and transmit the recording(s) after each episode. (See Part B below.) You will not be transmitting the full, 3-Day Continuous Recording. When the monitor displays, "Procedure Complete," please remove the monitor and ship it back to Medicomp. (Please see Section 10 for instructions on how to do this.)

*At times, you may hear the monitor emit a beep and display, **"MEMORY FULL! TRANSMIT STRIPS."** This means that you have filled the monitor's memory with ECG recordings, and it is time to call the CMC. Please see Part B below.*

B. How to Transmit Your Recordings:

- 1) Call the CMC (toll-free at 1-877-996-5553). Give the technician your name, city, and any symptoms that you felt while making the recording(s).
- 2) Disconnect the cable from the monitor and stand the unit upright on a flat surface near the telephone. If you are using the finger electrode accessory, it is not necessary that this part be removed while transmitting.
- 3) Place the mouthpiece of the phone handset about half an inch (1/2") **behind**, but not touching, the unit.



DO NOT USE CELLULAR OR CORDLESS PHONES.

(Section 4 is continued on the next page.)

Appendix VIII: Follow-up Letter to Referring Cardiologist

[Referring Cardiologist]
[Address]
[Date]



Dear [Referring Cardiologist]:

Your patient, XXX, was enrolled on xx/xx/2010 in the National Heart, Lung, and Blood Institute-supported Cardiothoracic Surgery Network trial: ***Surgical Ablation versus No Surgical Ablation for Patients with Persistent or Longstanding Persistent Atrial Fibrillation Undergoing Mitral Valve Surgery.*** The purpose of the trial is to assess the effectiveness of adding ablation to mitral valve surgery for treating your patient's atrial fibrillation. The trial's primary outcome is freedom from atrial fibrillation at 6 and 12 months after surgery, assessed with 3-day continuous (Holter) monitoring. In addition, 2 different techniques for heart rhythm monitoring will be compared: the 3-day monitoring at 6 and 12 months vs. weekly rhythm strips. Results of this comparison will guide follow-up strategies for future studies of rhythm control in AF patients.

The protocol recommends stopping anti-arrhythmic agents at three months after discharge. Your patient, XXX, [reached/will reach] this date on [date]. We would like to confirm with you at this time that [he/she] can come off anti-arrhythmic agents. A member of the study team will be contacting you to discuss further.

Thank you for your support of this important trial. Please do not hesitate to contact me with any questions.

Sincerely,

[Principal Investigator]
[Site Contact Information]

Appendix IX: AFib Trial Patient Contact Log



Subject ID	Person Initiating Contact	Date	Time	Method of Contact (e.g. in-person visit, phone call, email, certified letter w/ return receipt, etc.)	Issue Discussed	Comments

Rev 2.0
Dated 6/8/10

CTSN DEVICE ACCOUNTABILITY LOG

Study Site: _____

[illegible]

Principal Investigator Signature: _____

Date:_____

April 2011
Rev. 4.2