AtriCure

AtriCure, Inc.
7555 Innovation Way
Mason, Ohio 45040

ATLAS Study
CLINICAL STUDY PROTOCOL

Study Number: CP2015-2

Version date: 15Feb2017 / **Rev:** H

Regulatory Classification:	Check One: ☐ IDE ☒ Exempt ☐ Post-Market Surveillance ☐ Other _____
Name of Finished Product(s):	AtriClip® Gillinov-Cosgrove™ LAA Exclusion Systems [AtriClip FLEX (ACH2), AtriClip Long (LAA), or AtriClip Standard (ACH1)]
Sponsor's Medical Monitor:	[redacted]

This study will be performed in compliance with the 21 CFR Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 803 (Medical Device Reporting), International Conference on Harmonization (ICH) Guideline E6 for Good Clinical Practice (GCP); Declaration of Helsinki; Health Insurance Portability and Accountability Act (HIPAA) regulations; and Applicable state and local laws and regulations.

CONFIDENTIALITY STATEMENT

This document is a confidential communication of AtriCure, Inc. The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written approval of AtriCure, Inc. except that this document may be disclosed to appropriate IRB or Ethics Committees or duly authorized representatives of the U.S. Food and Drug Administration or other responsible regulatory authorities under the condition that they are requested to keep it confidential. It should be held confidential and maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

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INVESTIGATOR SIGNATURE PAGE

I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met;
- Conduct the clinical study in accordance with this protocol, including applicable local/state laws and regulations;
- Adhere to the publication policy of AtriCure, as stated in the Clinical Study Agreement (CSA), for data collected during this study;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments;
- Complete all Case Report Forms and study documentation and relevant imaging assessments (as required) promptly to the Sponsor, AtriCure, Inc., or its authorized representatives;

I will ensure that the IRB review complies with governmental requirements and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without sponsor and IRB approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the sponsor and government agencies.

Investigator Signature: I have read and understood the contents of this protocol. I agree to follow and abide by the guidelines set forth in this document.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Please scan, email or fax this signed off page to:

[redacted]

PLEASE RETAIN THE ORIGINAL IN YOUR STUDY RECORDS.

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SPONSOR SIGNATURES

Protocol Name:	ATLAS Study
Protocol Number:	CP2015-2
Protocol Title:	AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures (ATLAS)
Name of Finished Product(s):	AtriClip® Gillinov-Cosgrove® LAA Exclusion Systems [AtriClip FLEX (ACH2), AtriClip Long (LAA), or AtriClip Standard (ACH1)]

Approvals:

AtriCure

CLINICAL STUDY PROTOCOL SYNOPSIS

Protocol Name:	ATLAS Study
Protocol Number:	CP2015-2
Protocol Title:	AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures (ATLAS)
Name of Finished Product(s):	AtriClip® Gillinov-Cosgrove® LAA Exclusion Systems [AtriClip FLEX (ACH2), AtriClip Long (LAA), or AtriClip Standard (ACH1)]
Development Phase:	Exempt, post market
Study Design:	This is a prospective, multicenter, randomized (2:1), unblinded pilot study.
Indication of Device:	All medical devices used during this study are cleared for commercial distribution and are to be used in accordance with approved product labeling. The AtriClip LAA Exclusion System is indicated for the occlusion of the left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. Direct visualization, in this context, requires that the surgeon is able to see the heart directly, without assistance from a camera, endoscope, etc., or any other viewing technology. This includes procedures performed by sternotomy (full or partial) as well as thoracotomy (single or multiple).
Objective(s):	The objective(s) of this trial are to: 1. Compare impact of POAF among two randomized treatment arms; patients with POAF and surgical LAA closure (using AtriClip Gillinov-Cosgrove LAA Exclusion Systems) versus patients with POAF and no surgical LAA closure. 2. Evaluate Healthcare resource utilization [i.e. Hospital length of stay (LOS), emergency room and/or hospital re-admissions, and costs associated with specific adverse events that may be related to atrial fibrillation]. 3. Evaluate long-term outcomes of LAA closure with AtriClip in patients at risk of developing POAF.
Number of Subjects (Planned):	Up to 2000 subjects will be randomized into this study.
Sites:	Up to 40 sites
Patient Population:	Patients without a documented history of AF but who present with a CHA2DS2- VASc of $\geq$ 2 and HASBLED of $\geq$ 2 and will undergo a valve or CABG (structural heart) procedure with direct visual access to the LAA will be eligible to participate based upon the inclusion and exclusion criteria defined in this protocol.

Inclusion Criteria:	Patients satisfying the following criteria will be considered the screening population and will be eligible for participation: 1. Age ≥ 18 years male or female. 2. Scheduled for any non-mechanical valve and/or CABG (structural heart) procedure where direct access to the LAA is expected. 3. No documented preoperative AF. 4. CHA2DS2-VASc score of ≥ 2. 5. HASBLED score of ≥ 2. 6. Acceptable surgical candidate, including use of general anesthesia. 7. Willing and able to provide written informed consent. 8. Female patients must be of non-child bearing potential, or have a negative pregnancy test within 7 days prior to index procedure. 9. Must be willing and able to return for scheduled follow-up visits.
Exclusion Criteria:	Patients satisfying the following criteria will not be eligible for participation: 1. Redo cardiac surgery. 2. Mechanical heart valve or other anticipated or current requirement for anticoagulation therapy during the post-operative (30 day) period. 3. Hypercoagulability conditions that may confound the study. 4. Ejection Fraction < 30. 5. Left Atrium > 6 cm. 6. Severe Diastolic Dysfunction. 7. Requires anticoagulation therapy. 8. Any known reason that the patient would be unable to tolerate post-surgical anticoagulants. 9. Patient had a stroke/cerebrovascular accident (CVA) within previous 30 days prior to signing informed consent. 10. Any medical condition or finding for which the Investigator used medical discretion to determine the subject should be excluded. 11. Patient is currently or has participated in a clinical study in the last 30 days prior to signing informed consent. Participation in survey clinical studies with no treatment is not an exclusion criterion. 12. Patient has a condition that, in the opinion of the investigator, may jeopardize the patient's well-being, the soundness of this clinical study, or could interfere with provision of informed consent, completion of tests, therapy, or follow-up.
Intra-Operative Exclusion Criteria	Patients satisfying the following criteria will not be eligible for participation: 1. Presence of thrombus in the left atrium or LAA. 2. LAA tissue is deemed friable or has significant adhesions (as evaluated by the surgeon) near or on the LAA making AtriClip placement overly risky.

	3. Left atrial appendage is outside the range of manufacturer's recommendations - width < 29mm or > 50mm. 4. Direct visualization access is not available for AtriClip placement. 5. Any medical condition or finding for which the Investigator used medical discretion to determine the subject should be excluded.
Study Duration:	Anticipated subject duration will be approximately 365-days post index procedure (+/- 30 days).
Study Endpoints:	**Endpoints:** 1. Perioperative complications associated with AtriClip placement. [Defined as: stroke, major bleeding that requires re-operation and/or transfusion of > 2 U packed red blood cells (PRBC) within any 24-hour period during the first 2 days' post-index procedure, myocardial infarction (MI), or death.] 2. Intraoperative successful exclusion of LAA. [Defined as no (0 mm) flow between LAA and LA and ≤ 5 mm LAA remnant by intraoperative TEE with Doppler.] 3. Composite event rates between the group of subjects diagnosed with POAF (AtriClip vs no AtriClip) through 365-days post index procedure and between the group of subjects not diagnosed with POAF (AtriClip vs no AtriClip) through 30 days' post index procedure. Events to be evaluated include: Thromboembolic & Hemorrhagic Events such as cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral ischemia, hemorrhagic stroke, neurologic bleed, gastrointestinal (GI) bleeds, or other major bleeding event. 4. Composite event (listed above) rates through 365-days post index procedure for all AtriClip patients, regardless of whether the patient develops POAF. 5. Healthcare resource utilization variance between groups as related to the composite events above. [Specifically hospital length-of-stay (LOS), reoperation for bleeding, neurologic consults for stroke or TIA, emergency department (ED) visits, and hospital readmissions.]

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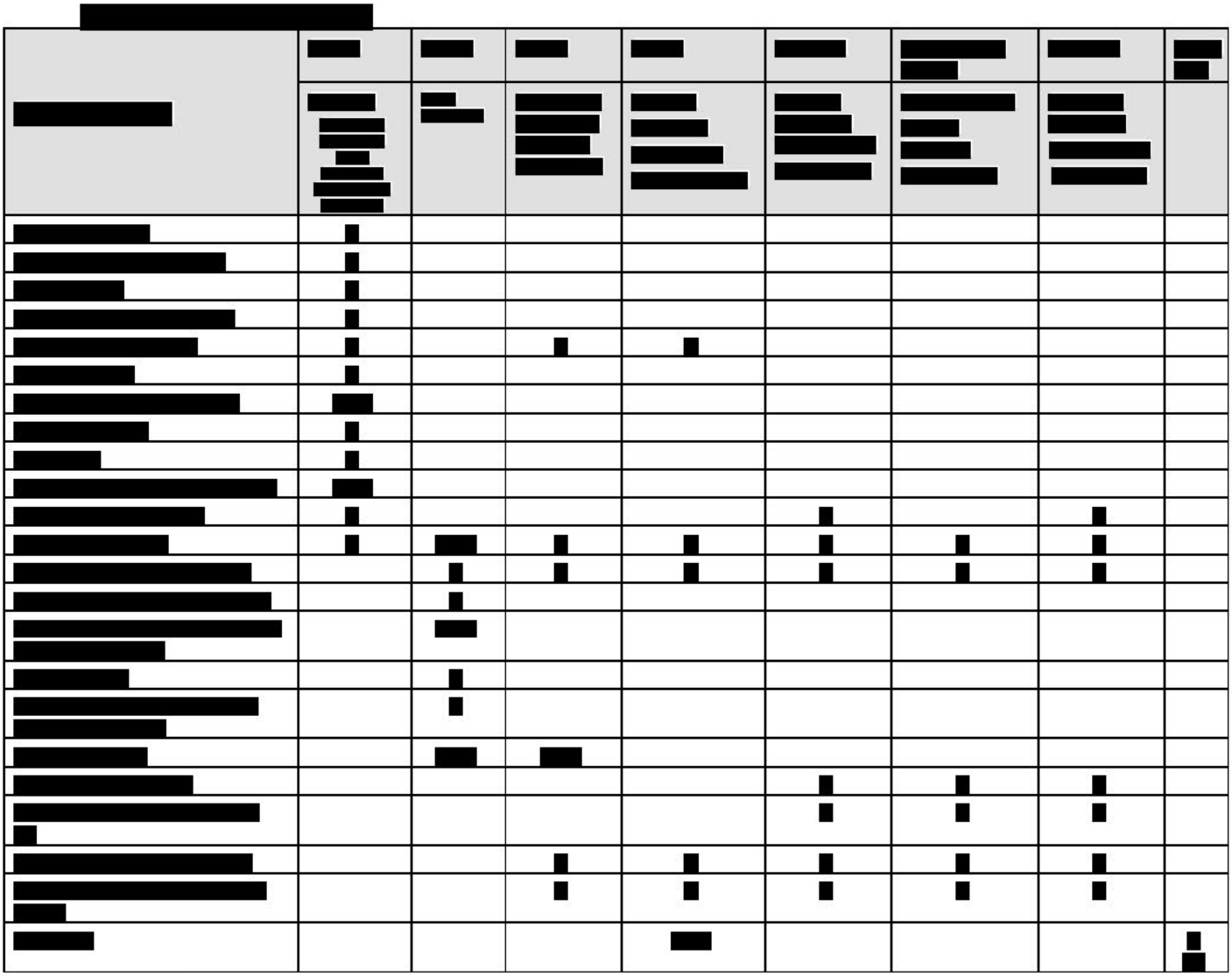
KEY PROTOCOL-SPECIFIC ACRONYMS AND ABBREVIATIONS

Acronyms/Abbreviation	Terms
AE	Adverse Event
AC	Anticoagulant
AF	Atrial Fibrillation
CPT	Current Procedural Terminology
CRA	Clinical Research Associate
CVA	Cerebrovascular Accident
CABG	Coronary Artery Bypass Graft
DRG	Diagnosis-related Group
eCRF	Electronic Case Report Form
ED	Emergency Department
EQ	EuroQol or European Quality of Life
LOS	Length of Stay
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Information for Use
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LAA	Left Atrial Appendage
MDR	Medical Device Reporting
OAC	Oral Anticoagulant
PI	Principal Investigator
POAF	Post-operative Atrial Fibrillation
PET	Polyethylene Terephthalate
PE	Physical Exam
PRBC	Packed Red Blood Cells
SAE	Serious Adverse Event
SAS	Science Analysis System
SOC	Standard of Care
SOP	Standard Operating Procedures
PHI	Protected Health Information
STS	Society of Thoracic Surgeons
PROM	Predicted Risk of Mortality
QS	Quality Systems
TEE	Transesophageal Echocardiogram (graphy)
TIA	Transient Ischemic Attack
VAS	Visual Analog Scale



ETHICS

Institutional Review Board

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

The study protocol, any protocol amendments, Informed Consent Form (ICF), any ICF amendments, and if applicable, any other written information provided to the subjects e.g., subject recruitment advertising, will be reviewed and approved by an or Institutional Review Board (IRB) prior to implementation of any procedures required solely for the purposes of this study. Each Investigator must obtain IRB approval prior to consent of the first subject.

Prior to site initiation, a signed copy of the IRB approval letter identifying the study and site is required to be submitted to the sponsor signifying study approval.

Each Investigator must also maintain continuous IRB approval. Documentation of approval and renewals must be provided to the Sponsor, and filed on site in the Investigator's Regulatory Binder. Additionally, amendments to the protocol will be submitted for review before implementation except when necessary to eliminate apparent immediate hazards to a subject. IRB approval is required to implement protocol amendments or to resume a suspended clinical investigation.

The occurrence of serious or unanticipated Adverse Events (AEs) during the study must be reported to the IRB.

Applicable Regulations

Regulations are to be followed as applicable including: 21 CFR Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 803 (Medical Device Reporting); All surgical products used in this study are commercially available and will be used within current labeling and indications for use. Consequently, this study is not investigational and is exempt from 21CFR Part 54 (Financial Disclosure by Clinical Investigators) and 21CFR Part 812 (Investigational Device Exemptions) with the exception of 21CFR812.119 (Disqualification of a Clinical Investigator); International Conference on Harmonization (ICH) Guideline E6 for Good Clinical Practice (GCP); Declaration of Helsinki; Health Insurance Portability and Accountability Act (HIPAA) regulations; and Applicable state and local laws and regulations.

Subject Information and Consent

This informed consent process applies to participation in the study only (i.e., this process does not include consent required for structural heart surgery). The surgeon will obtain the Institution's standard informed consent for surgery.

In compliance with FDA regulations, no subject shall be enrolled in an investigation without provision of adequate informed consent. The Principal Investigator is responsible for ensuring that each subject enrolled in the study is given adequate informed consent. Failure to obtain and properly document this process is in violation of the US Code of Federal Regulations, the Declaration of Helsinki, and this study protocol.
The ICF must have the approval of the IRB. While some institutions may request for modification of the ICF to satisfy specific institutional requirements, the use of a modified or unique ICF is permitted if it meets the requirement of 21 CFR Part 50 and is approved by the Sponsor. Informed consent of all subjects must be documented on an ICF in the primary language of the subject. All translated consent forms need IRB

approval. Eligible U.S. subjects should also sign the Health Insurance Portability & Accountability Act form, if not combined with the ICF.

The Investigator or designee shall carry out the Informed Consent process on those subjects meeting the eligibility criteria. The informed consent process involves the following: giving a subject adequate information concerning the study, providing adequate opportunity (time) for the subject to consider all available options, responding to the subject's questions, ensuring that the subject has comprehended this information and finally, obtaining the subject's consent to participate in this study. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the subject to participate, and does not waive or appear to waive the subject's legal rights. The ICF is presented in native, non-technical language that is understandable to the subject. The ICF ensures important new information is provided to new and existing subjects throughout the clinical investigation.

The Informed Consent process is finalized by completion of the ICF. Following the explanation of the study intent, the Investigator or designee shall offer to answer any of the subject's questions. If the subject then agrees to participate, his or her willingness must be documented via signatures of the ICF.

This document must be signed and dated by the subject prior to any study related procedures or enrollment. No dates should be pre-populated, or completed by someone other than the person providing the signature. The subject will be provided a copy of the signed informed consent document.

During a subject's participation in the study, the subject will sign and date any amendment(s) to the informed consent document and a copy of the signed document will be provided to them.

STUDY ADMINISTRATIVE STRUCTURE

This study is sponsored by AtriCure, Inc. and will be conducted in the US, under a single protocol approved by an IRB for each site prior to implementation at the study site.

The Principal Investigators (PI) at the study sites are board-certified cardiothoracic surgeons qualified by education, experience and training to assume responsibility for the conduct of this study.

An Electronic Data Capture (EDC) system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common electronic case report forms (eCRFs). The EDC system is a web-based, secure electronic software and is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements.

Serious Adverse Events (SAEs) and product quality problems (for products used during the index procedure), including potential and actual product use errors suspected to be associated with the use of a Food and Drug Administration (FDA) regulated drug, biologic, medical device or dietary supplement used during the course of this study will be reported by the PI to applicable authorities including the: 1) Sponsor (AtriCure); 2) IRB; 3) respective manufacturer(s); and/or 4) FDA via MedWatch Online Voluntary Reporting Process or Medical Device Reporting (MDR) as appropriate.

1.0 INTRODUCTION

The traditional standard of care for patients with POAF is oral anticoagulation (OAC) therapy as prophylaxis of thromboembolic events. Recent clinical literature from Gallego et al (Gallego, Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortatlity in anticoagulated patients with atrial fibrillation., 2012) suggests that the risk of major bleeding exceeds the risk of thromboembolic events in AF patients at a HAS-BLED score of > 3. Gallego et al. also reported that patients with low CHADS score (e.g., 0 – 1) have lower major bleeding risk than those patients with CHADS >=2. Although Gallego et al. focused on HAS-BLED > 3, the study recruited 800 (83%) and 740 (77%) patients with HASBLED>=2 and CHADS>=2, respectively. In fact, 472 (49%) of the patients recruited in the study had a HASBLED score of 2. Other peer-reviewed research from Tung et al (Tung, 2015) identifies that the highest risk for major bleeding occurs within the first 30 days of initiating OACs. Therefore, this study focuses entirely on a subset of patients that are vulnerable to both initiation of OACs as well overalls risks of OAC therapy.

Literature and current practice reinforce the fact that this subset of high risk AF patients are not routinely being started on OACs. In a recent meta-analysis from Lip et al (Lip, Underuse of Oral Anticoagulation in AF, A systematic review, 2010), looking at high risk patients (defined as those with a CHADS > 2) only 39% of AF patients in the U.S. were on OAC therapy.

This study intends to monitor a subset of patients with specific risk factors where both the risk of thromboembolic events and major bleeding intersect resulting in significant clinical equipoise both in literature and in current “real life” clinical practice.

Use of the AtriClip device may eliminate the nidus for AF-related thrombi originating in the Left Atrial Appendage. While not the focus of this study it is believed that this may contribute favorably to the primary composite endpoint of major bleeding, stroke and TIA. This research may begin to better inform clinical practice for those treating these high risk patients and continue to ascertain the risk of major bleeding vis-

à-vis the risk of thromboembolic events in AF patients at a HAS-BLED score >=2.

Need for Treatment in ATLAS

Postoperative atrial fibrillation (POAF) and related stroke/TIAs impact mortality, morbidity and QOL for patients undergoing structural heart disease procedures. Oral anticoagulation (OAC) therapy is typically indicated for stroke prophylaxis in patients with POAF. Risk factors identified by HAS-BLED scoring of ≥2 present an increased risk for bleeding creating clinical equipoise between the risk/benefit of stroke/TIA risk and clinically significant bleeding. Initiation of anticoagulation therapy for POAF patients is reported to increase hospital length of stay by 2-5 days. Exclusion of the Left Atrial Appendage in patients with Atrial Fibrillation is believed to reduce the potential for thrombus formation within the Left Atrial Appendage which is the site of a majority (90%) of all thrombi identified in patients examined with an AF related stroke (Blackshear, 1996).

The 2006 ACC/AHA Guidelines recommended removal of the Left Atrial Appendage to reduce the potential for stroke during cardiac (structural heart) procedures for any patient with risk factors for stroke or postoperative atrial fibrillation when it can be done without adding risk to the primary operation. Due to a lack of randomized controlled trials showing a reduction in stroke in patients with their LAA removed, prophylactic LAA exclusion is not routinely performed.

Postoperative Atrial Fibrillation (POAF) incidence is reported to be between 30-50% depending upon patient demographics, procedural variables and intensity of rhythm monitoring. Historically, POAF was considered to be self-terminating and confined to the postoperative hospital stay. A recent paper from Joung et al (Joung, 2014), published in the American Heart Journal suggests that new-onset POAF is associated with a five times higher risk of future long term AF than matched patients as well as a three times higher mortality.

In addition, POAF has been shown to have a strong association with perioperative stroke/TIA, increased length of hospital stay, decreased QOL and increased mortality. A 2014 Annals paper from LaPar et al. (LaPar, 2014) evaluated ~50,000 patients undergoing structural heart procedures. For patients with POAF, stroke incidence was 2.6% vs. 1.1% vs. in non-POAF patients at 30-day follow-up, increased ICU time of 48 hours longer, increased hospital LOS of 3 days, and a 25% higher 30-day readmission rate. The total incremental hospital costs associated with POAF was determined to be ~$9000. Yusuf et al (Yusuf, 2014), reviewed data on over 100,000 cardiac surgery patients in Ontario, Canada over 10 years to examine the rate and predictors of early and late stroke. New-onset POAF was one of the strongest predictors of early stroke with an Odd Ratio of 1.5. Age, history of TIA/stroke, PAD, CHF, and valve surgery were also predictors. The data also showed that increasing CHADS2 scores predicted increased risk of stroke or death among patients with AF vs. those without AF.

An October 2013 JTCVS paper by Chua et al. (Chua, 2013) validated the CHADS2 scoring system as highly predictive for risk of POAF in CABG patients without a history of preoperative AF. Specifically, patients with CHADS2 scores of ≥2 had a 36% risk of POAF (range of 27-100%).

A more refined scoring system, the CHA2DS2-VASc score, has been validated to define the risk of stroke in AF patients in numerous papers. A CHA2DS2-VASc of ≥2 estimates an annual risk of stroke of between 4.5-18.2% in patients with AF.

Risks Associated with Initiating Anticoagulation Therapy

Typical hospital protocol for stroke prophylaxis in patients with POAF is the initiation of anticoagulation therapy (AC) within 24 hours of diagnosis. A 2009 Annals paper from (Kasirajan, 2009) et al. identified isolated POAF as adding 2.2 days to hospital length of stay presumably associated with normalization of anticoagulation therapy within therapeutic range. The HASBLED scoring system has been validated in multiple studies to identify the risk of clinically significant bleeding. HASBLED scores of $\geq$2 have an associated risk of bleeding of between 4.1-19.6% annually.

A recent Circulation paper from Roldan (Rolden, 2013) et.al defined a strong correlation between bleeding and adverse cardiovascular events using the HASBLED scoring system. They concluded that crude bleeding rates exceeded thrombotic events at HAS-BLED scores of $\geq$3.

Azoulay (Azoulay, 2014) et al. reported that the initiation of Warfarin was associated with a 1.71 relative risk of AF-related stroke within the first 30 days suggesting a significant transient hypercoagulable state at the start of treatment. In a report from Ruiz-Nodar at al. (Ruiz-Nodar, 2012), they reported a major bleeding rate of 11.8% at one year in patients with a HAS-BLED score of $\geq$ 3 in their series of patients undergoing coronary artery stenting procedures.

Clinical equipoise exists regarding the initiation of anticoagulation therapy in patients with a significant risk of AF-related stroke as well as significant risk of bleeding related to OAC therapy.

Evidence suggests that the risk of major bleeding exceeds the risk of thromboembolic events in AF patients with a HAS-BLED $\geq$ 3 (Gallego, Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortatlity in anticoagulated patients with atrial fibrillation., 2012). Other peer-reviewed research identifies that the highest risk for major bleeding and ischemic stroke occurs within the first 30 days of initiating OACs (Tung, 2015) (Gomes, 2013). This study focuses on patients that are vulnerable to both risks identified by two well established scoring strata (CHADS and HASBLED) as well as significantly increased risks for patients initiating OAC therapy for a complication that will largely self-terminate within 30 days of onset.

Hypothesis Testing of LAA Closure in POAF

Dr. Cox (Cox, 1993) describes a large series of patients where a Maze procedure was performed including LAA surgical exclusion. At 90 day follow up only 2/306 (.6%) patients experienced a stroke/TIA although 37% had POAF in spite of a majority not receiving postoperative anticoagulation therapy.
In a 2013 paper from Kim et al. (Kim, 2013); describes a series of 631 matched patients with/without LAA exclusion concomitant to cardiac (structural heart) procedures. Using propensity analysis, 260 subjects with postoperative AF were analyzed evaluating incidence of stroke/TIA. In the LAA exclusion group there were zero (0%) stroke/TIAs in spite of a majority of these patients not receiving anticoagulation therapy. Conversely there were 6% stroke/TIAs in the no LAA exclusion group ($p = 0.003$). A second article (Viles-Gonzalez, 2012) et al.; showed a ~77% reduction in expected stroke rate in AF patients with a $\geq$2 CHADS2 score undergoing a percutaneous LAA closure device and contraindications to Warfarin.

These papers provide preliminary evidence that LAA exclusion may potentially reduce stroke/TIA complications associated with POAF and that its application to patients with a significant risk of bleeding on OACs may have a secondary benefit in reducing bleeding complications.

Published data suggests a risk of POAF in valve and CABG patients of between 32-66% (Creswell, 1993). The risk of a perioperative CVA event in the POAF patient population of up to 6% (Lee, 2014) and a 2-year rate of stroke or death of 21.2% for those with a CHADS2 score of greater than 3 (Whitlock, 2014). The decision to forgo placing an AtriClip in the treatment arm will be at the surgeon's perioperative discretion due to overall risk of the procedure or risk associated with accessing the LAA and documented with a rationale on the Case Report Form (for example, excessive adhesions in the vicinity of the LAA.).

The Role of ATLAS in Critically Ill Patients

Anticoagulation therapy is considered the standard of care for stroke prophylaxis in patients with Atrial Fibrillation but in patients with risk factors for bleeding the risk/benefit of medical management is elucidated. This study will evaluate a medical management arm vs. mechanical exclusion of the left appendage via an implantable device. It is believed that the left appendage is the source for a predominant number of stroke causing emboli in AF patients. It is postulated that patients receiving anticoagulation will incur a longer length of stay due to the initiation and normalization and maintenance of therapeutic levels associated with therapy. This will also be evaluated in the study.

2.0 STUDY OBJECTIVES

The objective(s) of this trial are to:

1. Compare impact of POAF among two randomized treatment arms; patients with POAF and surgical LAA closure (using AtriClip Gillinov-Cosgrove LAA Exclusion Systems) versus patients with POAF and no surgical LAA closure.
2. Evaluate Healthcare resource utilization [i.e. Hospital length of stay (LOS), emergency room and/or hospital re-admissions, and costs associated with specific adverse events that may be related to atrial fibrillation].
3. Evaluate long-term outcomes of LAA closure with AtriClip in patients at risk of developing POAF.

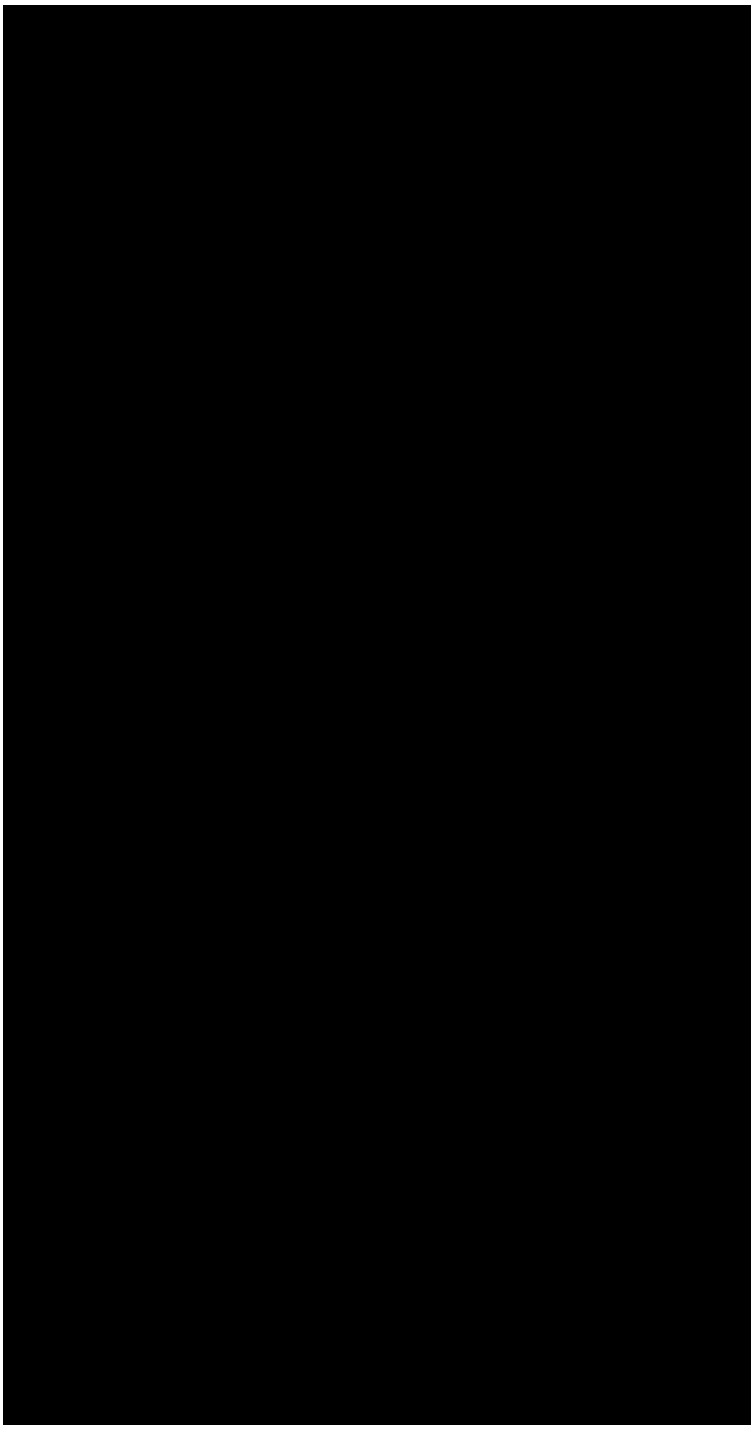
3.0 STUDY ENDPOINTS

Study Endpoints are as follows.

1. Perioperative complications associated with AtriClip placement. [Defined as: stroke, major bleeding that requires re-operation and/or transfusion of > 2 U packed red blood cells (PRBC) within any 24-hour period during the first 2 days' post-index procedure, myocardial infarction (MI), or death.]
2. Intraoperative successful exclusion of LAA. [Defined as no (0 mm) flow between LAA and LA and $\leq$ 5 mm LAA remnant by intraoperative TEE with Doppler.]
3. Composite event rates between the group of subjects diagnosed with POAF (AtriClip vs no AtriClip) through 365 days' post index procedure and between the group of subjects not diagnosed with POAF (AtriClip vs no AtriClip) through 30 days' post index procedure. Events to be evaluated include: Thromboembolic & Hemorrhagic Events such as cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral ischemia, hemorrhagic stroke, neurologic bleed, gastrointestinal (GI) bleeds, or other major bleeding event.
4. Composite event rates through 365-days post index procedure for all AtriClip patients, regardless of whether the patient develops POAF.
5. Healthcare resource utilization variance between groups as related to the composite events above. [Specifically hospital length-of-stay (LOS), reoperation for bleeding, neurologic consults for stroke or TIA, emergency department (ED) visits, and hospital readmissions.]

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study and Design – Subject Disposition Diagram



Overall Study and Design – Description
All patients who undergo a valve or CABG (structural heart) procedure with direct visual access to the LAA will be eligible to participate based upon consent and evaluation of the inclusion and exclusion criteria defined in this protocol.

The target patient population includes patients at risk of POAF based on the CHA2DS2-VASc and HASBLED scoring.

Patient must meet all inclusion/exclusion criteria (including intra-operative exclusion criteria) before enrollment or randomization.

During the planned structural heart procedure, the intra-operative exclusion criteria will be assessed. If any intra-operative exclusion criteria are met, the subject will be a screen fail and will not be enrolled or randomized.

To execute randomization, at the time of enrollment, subjects will be assigned a sequential identification number at each site and a corresponding sealed envelope which will be opened in the operating room to reveal the treatment group. Subjects will be randomized 2:1 (2 with AtriClip® to 1 with no AtriClip®). Randomization sequences will be generated by the AtriCure Statistician and will be stratified by site. The subject population will be randomized using a blocking scheme for each surgeon to ensure equal and balanced treatment group allocations and to avoid bias with respect to known or unknown subject variables that could affect the outcome of this study.

Post-index procedure, all subjects will be monitored per the hospital standard of care processes for POAF.

Four (4) treatment arms result:
- Surgery with AtriClip (POAF diagnosed / Institution SoC anticoagulation therapy)
- Surgery with AtriClip (No POAF)
- Surgery with no AtriClip (POAF diagnosed / Institution SoC anticoagulation therapy)
- Surgery with no AtriClip (No POAF)

Subjects will be assessed for AEs related to the placement of the AtriClip and will be instructed to notify the PI of any AEs that occur during the study. All subjects that develop POAF during the hospital stay will be followed for approximately 1 year (365 days) post index procedure. In addition, all the subjects in the AtriClip group that do not develop POAF will also be followed for 365-days post index procedure.

4.2 Selection of Study Population

4.2.1 Recruitment

All patients who meet the inclusion criteria will be tracked on a Screening Log. Patients will be provided the IRB approved ICF and will have the opportunity to read, understand, and have their questions answered prior to signing the ICF. If the patient agrees to participate in the study and signs consent, the ICF will be completed. The subject must sign and date the ICF prior to any study-specific procedures being performed. The person reviewing the ICF with the subject will also sign and date the ICF. The subject will be given a copy of the signed ICF to keep.

All subjects who sign the ICF will be documented on a paper Screening and Enrollment Log. Only subjects enrolled into the study will be entered into the EDC.

4.2.2 Enrollment

Patients are considered **enrolled** in the study once they have met Inclusion/Exclusion (including intra-operative exclusion) criteria and are **randomized**.

4.2.3 Inclusion Criteria

Patients satisfying the following criteria will be considered the screening population and will be eligible for participation:

1. Age > 18 years male or female.
2. Scheduled for any non-mechanical valve and/or CABG (structural heart) procedure where direct access to the LAA is expected.
3. No documented preoperative AF.
4. CHA2DS2-VASc score of $\geq$ 2
5. HASBLED score of $\geq$ 2
6. Acceptable surgical candidate, including use of general anesthesia.
7. Willing and able to provide written informed consent.
8. Female patients must be of non-child bearing potential, or have a negative pregnancy test within 7 days prior to index procedure
9. Willing and able to return for scheduled follow-up visits.

4.2.4 Exclusion Criteria

Patients satisfying the following criteria will not be eligible for participation:

1. Redo cardiac surgery.
2. Mechanical heart valve or other anticipated or current requirement for anticoagulation therapy during the post-operative (30 day) period.
3. Hypercoagulability conditions that may confound the study.
4. Ejection Fraction < 30.
5. Left Atrium > 6 cm.
6. Severe Diastolic Dysfunction.
7. Requires anticoagulation therapy.
8. Any known reason that the patient would be unable to tolerate post-surgical anticoagulation therapy.
9. Patient had a stroke/cerebrovascular accident (CVA) within previous 30 days prior to signing informed consent.
10. Any medical condition or finding for which the Investigator used medical discretion to determine the subject should be excluded.

11. Patient is currently or has participated in a clinical study in the last 30 days prior to signing informed consent. Participation in survey clinical studies with no treatment is not an exclusion criterion.
12. Patient has a condition that, in the opinion of the investigator, may jeopardize the patient's well-being, the soundness of this clinical study, or could interfere with provision of informed consent, completion of tests, therapy, or follow-up.

4.2.5 Intra-Operative Exclusion Criteria

Prior to randomization subjects must also meet the following intra-operative criteria. (If criteria are not met, the subject will be a screen fail and will not be eligible to be randomized into the study.)

1. Presence of thrombus in the left atrium or LAA.
2. LAA tissue is deemed friable or has significant adhesions (as evaluated by the surgeon) near or on the LAA making AtriClip placement overly risky.
3. Left atrial appendage is outside the range of manufacturer's recommendations - width < 29mm or > 50mm.
4. Direct visualization access is not available for AtriClip placement.
5. Any medical condition or finding for which the Investigator used medical discretion to determine the subject should be excluded. Any medical condition or finding for which the Investigator used medical discretion to determine the subject should be excluded.

4.2.6 Removal of Subjects from Study

In accordance with the Declaration of Helsinki and the Code of Federal Regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw; all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. Subjects who withdraw from the study will not be replaced.

The primary reason for early termination and the date of termination will be recorded in the electronic case report form. Reasons may include:

Investigator Decision

If the subject experiences an adverse event and the Principal Investigator or Medical Monitor believes it is in their best interest to discontinue participation in the study, they will be withdrawn from the study.

Lost to Follow-up

When contact with the subject has been lost without completing the final visit assessment, and every attempt to contact has failed, the subject will be considered lost to follow-up. Final documentation regarding all attempts to contact the subject requesting their return for the final visit should be documented.

Withdrawal of Consent

The subject withdraws consent for participation in the study. Any method of contact with the subject in which they state they no longer want to participate in the study specific activities

constitutes withdrawal of consent. When possible the reason for withdrawal will be documented.

Site Termination or Study Termination

A site or study may be terminated. When this occurs all subjects at the site will be withdrawn and documented as early termination. Reasons for site or study termination may include, but are not limited to the following:

- Administrative Concerns (e.g., inadequate subject enrollment, Investigator/institution non-compliance, change of business strategy, etc.);
- Safety Issues, including those due to non-compliance, which substantially affect the risk to benefit ratio of the study subjects at a site or for the study as a whole;
- Regulatory Body Mandate(s)

Other (which may include):

- Protocol deviation, noncompliance or violation
- Sponsor recommendation
- Device/index procedure failure
- Death

4.2.7 Follow-up for Early Terminated Subjects

In the event that a subject is eligible, enrolled, and randomized into the study but must early terminate either prior to the index procedure (AtriClip placement) or even after the index procedure; the subject will be followed for 30 days for safety purposes.

5.0 PROCEDURE

5.1 General Description

Individual centers and investigators will be selected based upon their expertise in the targeted structural heart disease procedures (non-mechanical Mitral Valve Repair/Replacement, Aortic Valve Repair/Replacement, and Coronary Artery By-Pass procedures) as well as proficiency in AtriClip placement.

The term index procedure refers only to the placement/non-placement of the AtriClip (dependent on randomization). All procedures leading up to and after the placement of the AtriClip are considered part of the structural heart procedure and are to be conducted under the discretion of the surgeon in accordance to the hospital's standard of care.

Transesophageal Echocardiography (TEE) with Doppler

Transesophageal echocardiography (TEE) with Doppler must be performed prior to any epicardial surgical intervention. The purpose of the TEE with Doppler is to assess for presence of thrombus. ***If a thrombus is present in the left atrium or LAA, the subject will not be enrolled or randomized into the study and no AtriClip will be placed.***

The AtriClip LAA Exclusion System must be used only by properly trained and qualified medical personnel in accordance with the Instructions for Use (IFU). Failure to properly follow instructions may result in improper functioning of the device.

If the subject continues to meet all study eligibility criteria (including intra-operative exclusion criteria), they will be enrolled and randomized. If the subject is randomized to the group to receive the AtriClip LAA Exclusion System placement, the following steps are performed:

Note: A recommended surgical technique is presented below. It is recognized that individual patient anatomic variation, surgical conditions, or surgeon preference may necessitate modifications to the outlined procedures. Regardless, surgeons must adhere to the AtriClip LAA Exclusion System sizing criteria, device selection, and device use instructions as outlined in the IFU.

5.2 Left Atrial Appendage (LAA) Exclusion (Index Procedure)

5.2.1 No AtriClip arm

If the subject is randomized to the no AtriClip arm, the left atrial appendage should be left intact with no management.

5.2.2 AtriClip arm

If the subject is randomized to the AtriClip arm, the left atrial appendage should be managed using the AtriClip LAA Exclusion System. The left atrial appendage is typically accessible and exclusion of the Left Appendage by the AtriClip is believed to introduce little time or risk to the primary operation. In the event that, the surgeon deems that the AtriClip device is not able to be utilized for left atrial appendage after randomization, because of anatomical limitations or that it is not feasible or safe to address the LAA, the appendage may be left intact. In the event that a subject is randomized but must early terminate before or after the index procedure; the subject will be followed for 30 days for safety purposes.

[redacted]

Post Index Procedure - Subject Assessment

To assess the subject status with regard to potential bleeding, assessments of hemoglobin and hematocrit shall be performed post index procedure per the hospital's standard of care.

5.3 Post-Surgical Follow-up Anticoagulation Therapy

Subjects who are diagnosed with POAF during their postoperative course should be treated per the institution's standard of care and may include anticoagulation therapy.

The decision to administer anticoagulation therapy in the post-operative/follow-up setting is at the discretion of the Investigator/Institution taking into consideration, the subject's ability to safely initiate and sustain anticoagulation therapy.

The anticoagulants that may be used in medical management may include:

- Acenocoumarol
- Acetylsalicylic acid
- Apixaban
- Dabigatran
- Edoxaban
- Heparin
- Nadroparin
- Rivaroxiban
- Warfarin
- Other (to be specified)

These are the anticoagulants that may be utilized in medical management. The decision of which anticoagulant to use (if any) is left to the discretion of the Investigator.

6.0 IDENTITY OF STUDY DEVICES

The devices utilized for the study include:

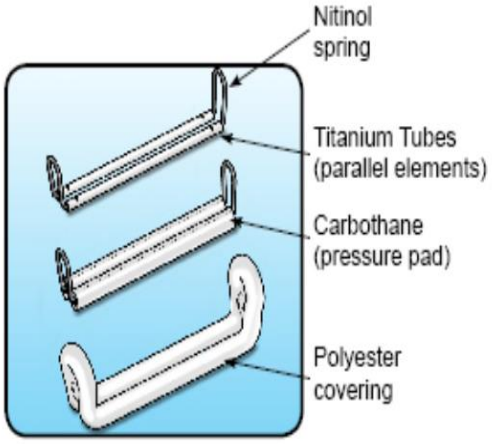
AtriClip Gillinov-Cosgrove LAA Exclusion Systems which are indicated for the occlusion of the left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. Direct visualization, in this context, requires that the surgeon is able to see the heart directly, without assistance from a camera, endoscope, etc., or any other viewing technology. This includes procedures performed by sternotomy (full or partial) as well as thoracotomy (single or multiple).

All medical devices used during this study are cleared for commercial distribution and are to be used in accordance with approved product labeling.

Device Description

When closed, the AtriClip applies uniform pressure over the length of the AtriClip to ensure consistent, reproducible, and secure exclusion of the LAA. The AtriClip is available in the following lengths to accommodate different sizes of LAA: 35 mm, 40 mm, 45 mm, and 50 mm.

The AtriClip was cleared under K093679. The frame assembly of the implantable AtriClip consists of two Nitinol (nickel titanium) springs connecting two opposing titanium tubes (core), which are covered with a Polyurethane elastomer. This assembly is covered with a knit braided polyester fabric, composed entirely of Polyethylene terephthalate (PET). The Nitinol springs are biased toward the closed position allowing the device to close in the absence of opposing forces (Figure 1). When closed, the AtriClip applies uniform pressure over the length of the AtriClip to ensure consistent, reproducible, and secure exclusion of the LAA.



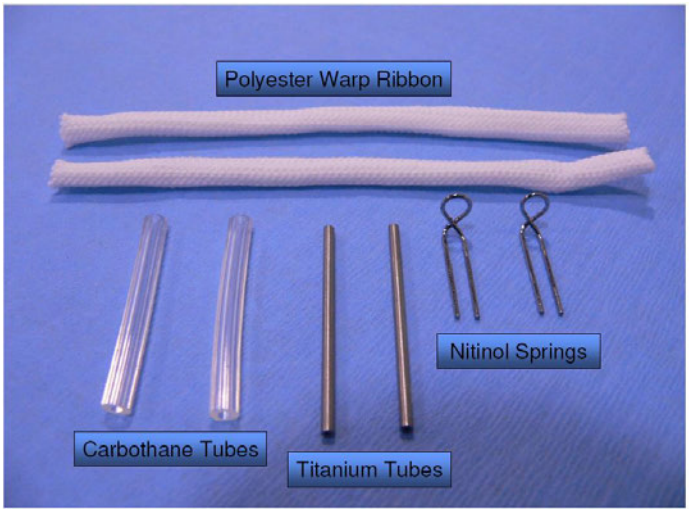
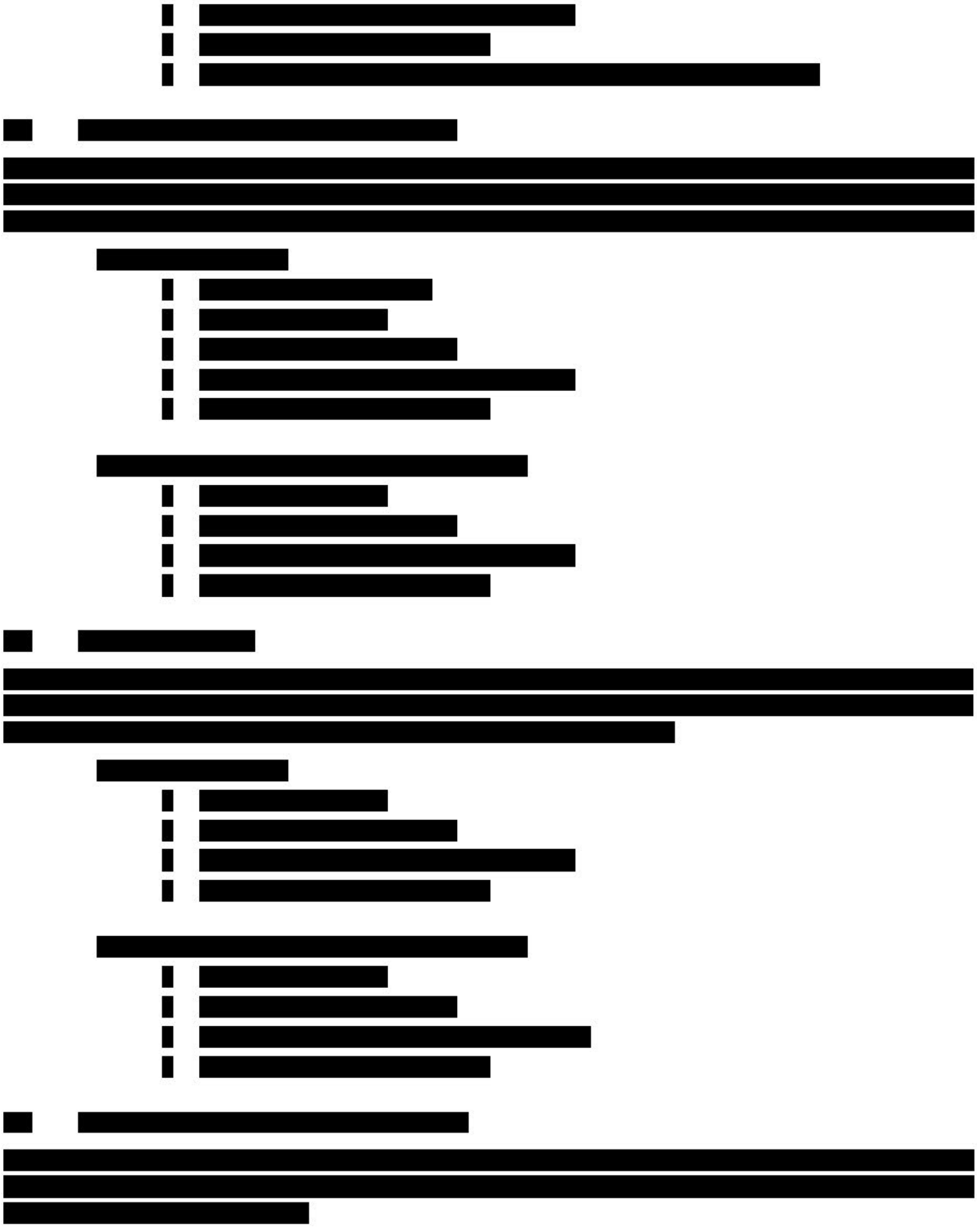


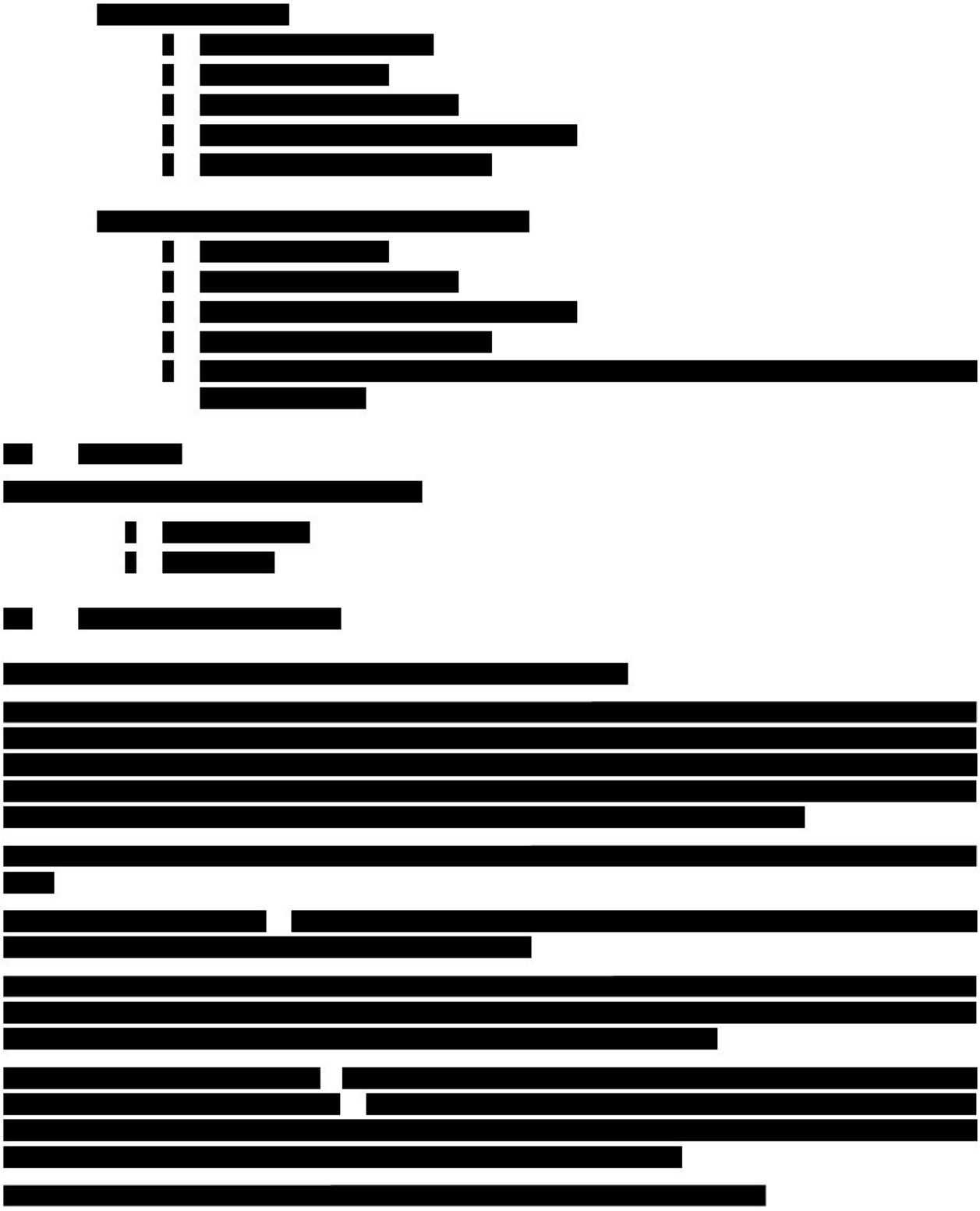
Figure 1

6.1 Product Accountability

The investigator will maintain control over and keep a complete device inventory record for all study devices received from AtriCure. All shipping record receipts received with the study devices will be maintained. All study devices that are used during each procedure will be documented.

[redacted]





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8.0 DATA MANAGEMENT AND INTEGRITY

8.1 Data Completion and Record Keeping

8.1.1 Source Documents

Source documents are documents on which information regarding subjects are first recorded. PI subject files or hospital records generally are the basis of source document information. This may include but is not limited to, original subject files, hospital/clinic records, original recordings/tracing, and digital images from automated instruments, X-ray films, and laboratory results.

Source documents must be retained by the PI as part of the subject's permanent medical record. The information in the source documents is used to complete the eCRFs. All information captured on the eCRFs should be completely and accurately supported in source documentation. Study Monitors will verify data reported on eCRFs with site source documents. Any additional information relevant to the study should be included in the source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents. The PI will retain originals of all source documents, subject consent forms, and study data.

8.1.2 Data Collection

An EDC system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application This system is designed, developed, and maintained in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The platform software has been validated in accordance with 21 CFR Part 11, European Commission's Directive on Data Protection and US Safe Harbor Certification. Prior to being released for data entry, validation of the study level components (i.e. data entry screens, associated edit checks and work flow) will be conducted in accordance with approved user acceptance testing procedures. Access to this system will be controlled so that only authorized users will have the ability to enter into the system. The system is considered a closed system according to 21 CFR Part 11 Electronic Records; Electronic Signatures.

The EDC system will be used to facilitate the collection of all study data at the site. Designated site personnel will be responsible for entering subject data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function.

An EDC digital User Manual will be available under the help menu within the EDC website to assist in the collection and entry of source data into the electronic casebook.

Investigative study sites will be asked to enter subject data into the eCRFs no later than 2 weeks from the time the subject was seen for their scheduled study visit.

Detailed description of the eCRF components are included in the eCRF Completion Instructions. These will be provided to the Investigators prior to initiating subject enrollment. The respective eCRFs must be fully completed for each subject and signed electronically.

Data collected during the clinical investigation for each subject will be maintained as accurately and completely as possible with entries into an electronic data capture system provided by AtriCure. The personal data recorded on all documents, including copy documents, and within the system will be regarded as confidential. The Investigator will be responsible for the timing, completeness and accuracy of the details entered within the electronic data capture system. All data entered in the database must have source documents in the subject's medical records.

Data will be entered into the electronic data capture system by members of the Investigational team who have received training in the use of the system. The system will generate data queries at the point of data entry based on validation checks defined by AtriCure. Such validation checks will primarily be focused on validation of key variables including selected subject demographics, appropriate value ranges and date checks. Resolution of the queries will be the responsibility of the Clinical Investigator and investigation team members. Following completion of all data queries on each eCRF, the Clinical Investigator will be responsible for reviewing and confirming agreement to the data within the system.

The Investigator must record the subject's participation in this clinical investigation in the subject's hospital notes. In addition, the Investigator must keep a separate list of all subjects entered into this clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes). A subject Identification Log will be provided in the Investigator's File for this purpose.

8.1.3 Data Correction

Corrections to eCRFs will be prompted via automated electronic edit checks and queries manually created by reviewers. The corrections and the individual making the correction(s) to the eCRF will be within EDC.

8.1.4 Investigator Regulatory Binder

Each Investigator must maintain an accurate, complete, and current copy of the Investigator Regulatory Binder. Upon receipt of copies of changes or revision updates to the Binder from the Sponsor, the Investigator will add the updated document to the Regulatory Binder. If an Investigator holds multiple copies of the Regulatory Binder, then all copies must be updated with the current revisions.

8.1.5 Study Correspondence

Each Investigator and all personnel from the investigational site will maintain records of all correspondence, electronic, written, and verbal, relating to any aspect of the clinical investigation. The records are maintained in the Investigator Regulatory Binder consisting of, but not limited to correspondence with other participating clinical investigators, the reviewing IRB, and the Sponsor. The CRA will examine the contents of the correspondence.

8.1.6 Data Privacy

Subjects will be made aware that their personal data will be collected and processed in accordance with data protection legislation including the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subjects will be asked to sign an Authorization for Release of Personal Health Information (PHI) for the purpose of this investigation. This authorization may be combined with the ICF depending on local IRB preference. Results from the Clinical Investigation may be published. However, subject confidentiality will be maintained at all times and it will not be possible to identify individual subjects from any data presented.

8.1.7 Record Retention, Inspection, and Custody

The PI must maintain all documentation related to the study until notified by the Sponsor. The PI will allow representatives of the Sponsor, IRB, the FDA, or other government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Subject medical records will be kept confidential. Study reports will not identify subjects by name. These reports may be submitted to the FDA and/or regulatory authorities.

If custody of the records is transferred, notice of such a transfer should be given to the Sponsor no later than ten (10) working days after the transfer occurs.

The Investigator should retain copies of all documents pertaining to this clinical investigation (including source documentation, the informed consent document and any other documents to identify the subjects) for at least 2 years after this clinical investigation is completed. In addition, if the Clinical Investigator moves/retires, etc., he/she should provide AtriCure Inc. the name and address of the person who will look

after and be responsible for the subjects' clinical investigation related records.

8.1.8 Medical Dictionary Coding

Medical dictionary coding will be performed using a coding thesaurus algorithm. The MedDRA will be used upon data entry and query resolution for AEs, SAEs, via automated and manual coding processes.

8.1.9 Data Quality Assurance

Quality control and quality assurance processes implemented during this study to ensure subject safety rights, and welfare are protected and to foster data integrity are characterized below.

8.1.10 Investigator Training - Protocol Specific Training

Protocol training will be scheduled once IRB approval is obtained and the Clinical Study Agreement is executed. AtriCure, Inc. will train the study site on the protocol and that training will be documented. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this study are trained.

The index procedure may only be performed by qualified investigators, familiar with the study procedures and techniques.

8.1.11 Monitoring

This study will be monitored by the sponsor to ensure:

- The rights, safety and well-being of the subjects are protected;
- The reported study data is accurate, complete, and verifiable from source documents; and
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), applicable GCPs, and with applicable local/regional regulatory requirements.

[redacted]

In order to perform the monitoring role effectively, the CRA must verify eCRF entries with source documents. The CRA must be given access to primary subject data which supports the information recorded on the eCRF, i.e. hospital notes, appointment books, original laboratory records, etc. Access to

these documents must also be given should the regulatory authority in the instance of an external inspection. Since a subject has the right to refuse access to these documents on the grounds of confidentiality, consent to access is included in the informed consent document, which the subject signs.

The Principal Investigator will receive reasonable notification prior to each monitoring visit during the course of this clinical investigation. At each visit, the Principal Investigator will be expected to co-operate with the CRA for the review and verification of eCRFs and any additional records that may have been previously arranged between the Principal Investigator and the CRA.

8.2 Changes to Protocol, Protocol Deviations and Protocol Amendments

8.2.1 Changes to Protocol

The Investigator should not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in CRA(s), change of telephone number(s)). In the event of an emergency situation, the Investigator must notify the CRA or AtriCure immediately. A full written report of the situation must be forwarded to the IRB who approved the original protocol and AtriCure within 10 working days of the event.

8.2.2 Protocol Deviations

The Investigator agrees to conduct the study in accordance with this protocol; however, protocol deviations may occur during the course of the study. Protocol deviations are events occurring during the conduct of the study which are not in compliance with the protocol and for which an amendment has not been granted. Protocol deviations can be committed by the Sponsor, the PI, or study subject. A deviation can be identified from a number of sources. Potential sources include, but are not limited to: a member of the PI's staff, the CRA during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. The PI or PI's representative are encouraged to contact the CRA or AtriCure as soon as possible upon observing a protocol deviation. Regardless of the source, it is crucial to document the deviation and record all corrective actions. Protocol deviations will be reported in the final report.

The process for capturing deviations will be detailed in the monitoring plan. The process will require that documentation describe the deviation, appropriate actions taken, and will be included in the study file for the respective PI and subject. The study site representative will be advised to record the deviation and relevant discussion with the Sponsor about the deviation in subject source documents.

Protocol deviations affecting the scientific soundness of the study or the rights, safety, or welfare of the subjects, will be reported by the PI, as required by the IRB.

Protocol deviations will be summarized and grouped into relevant categories for analysis and may include, but not be limited to, subjects who:

- Entered the study although they did not satisfy the eligibility criteria; or
- Developed withdrawal criteria during the study, but not removed.

8.2.3 Protocol Amendments

If it becomes necessary to amend the protocol, then the nature of the amendment will be agreed between the Sponsor and the Principal Investigator(s) and this will be recorded with a justification for the amendment. The appropriate IRBs will be informed of amendments prior to implementation of the change.

9.0 STATISTICAL METHODS

9.1 Clinical Study Objective

The objectives of this study are to:

1. Compare impact of POAF among two randomized treatment arms; patients with POAF and surgical LAA closure (using AtriClip Gillinov-Cosgrove LAA Exclusion Systems) versus patients with POAF and no surgical LAA closure.
2. Evaluate Healthcare resource utilization [i.e. Hospital length of stay (LOS), emergency room and/or hospital re-admissions, and costs associated with specific adverse events that may be related to atrial fibrillation].
3. Evaluate long-term outcomes of LAA closure with AtriClip in patients at risk of developing POAF.

These patients will be enrolled prior to a scheduled existing cardiac procedure and randomized prior to the study index procedure (AtriClip placement). Perioperative event rates and postoperative outcomes including reoperation for bleeding, hospital length of stay, neurologic consults for stroke/TIAs, ED visits, and hospital readmissions through interval follow ups [redacted] will be determined.

9.2 Study Endpoints

The following endpoints will be collected for this hypothesis generating pilot study:

1. Perioperative complications associated with AtriClip placement. [Defined as: stroke, major bleeding that requires re-operation and/or transfusion of > 2 U packed red blood cells (PRBC) within any 24-hour period during the first 2 days' post-index procedure, myocardial infarction (MI), or death.]
2. Intraoperative successful exclusion of LAA. [Defined as no (0 mm) flow between LAA and LA and < 5 mm LAA remnant by intraoperative TEE with Doppler.]
3. Composite event rates between the group of subjects diagnosed with POAF (AtriClip vs no AtriClip) through 365 days' post index procedure and between the group of subjects not diagnosed with POAF (AtriClip vs no AtriClip) through 30 days' post index procedure. Events to be evaluated include: Thromboembolic & Hemorrhagic Events such as cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral ischemia, hemorrhagic stroke, neurologic bleed, gastrointestinal (GI) bleeds, or other major bleeding event.
4. Composite event (listed above) rates through 365-days post index procedure for all AtriClip patients, regardless of whether the patient develops POAF.
5. Healthcare resource utilization variance between groups as related to the composite events above. [Specifically hospital length-of-stay (LOS), reoperation for bleeding, neurologic consults for stroke or TIA, emergency department (ED) visits, and hospital readmissions.]

9.3 Healthcare resource utilization

Healthcare resource utilization will be compared between groups. Major resource use collected at various study visits/follow-up calls will include hospital resources (OR time, LOS, etc.), cardiac related medication use, readmissions, including 30 days readmit, neurological consults, additional procedures during follow-up related to index procedures, and rehabilitation associated with post index procedure strokes. Costs from standard sources (DRGs, CPT codes, RedBook, published studies for SAE and Rehab, etc.) may be assigned to assess economic impact and summed over the 365-day treatment period to obtain total treatment costs.

9.4 Sample Size and Power

This is a prospective, multicenter, randomized (2:1), unblinded study conducted in up to 2000 patients at risk of POAF based on the CHA2DS2-VASc and HASBLED scoring at up to 20 USA sites. All patients who undergo a valve or CABG (structural heart) procedure with direct visual access to the LAA will be eligible to participate based upon the inclusion and exclusion criteria defined in this protocol.

[redacted]

[redacted]

[redacted]

A total of up to 2000 patients (approx. 1333 in AtriClip group, approx. 667 in SOC group) at risk of POAF will be enrolled in this study. It is assumed that 40% of the patients will be diagnosed with POAF. A two treatment group one-sided Z-test with continuity correction and an $\alpha = 0.05$ will have 80% power to detect the difference between a medical management (SOC) safety rate of PS = 12.5% and a mechanical exclusion

(AtriClip) safety rate of PC = 6.25% at 30-days post-op when the sample size (for completers) for patients diagnosed with POAF is 485 in the AtriClip group and 243 in the SOC group (a total sample size of 728). Adjusting for loss to follow-up, 533 patients in the AtriClip group and 267 in the SOC group (a total sample size of 800) are expected to be diagnosed with POAF.

9.5 Randomization

Upon enrollment, subjects will be assigned a sequential identification number at each site and a corresponding sealed envelope which will be opened prior to the index procedure to reveal the treatment group. Subjects will be randomized 2:1 (2 with AtriClip to 1 anticoagulation therapy and without AtriClip). Randomization sequences will be generated by AtriCure Statistician using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and will be stratified by site.

9.6 Analysis Populations

Intent-To-Treat (ITT) Population: The effectiveness, safety, health economic and Qualify of life analyses will be based on the ITT population. The ITT Population is defined as all subjects randomized to either the AtriClip LAA Closure or anticoagulation therapy and without AtriClip LAA Closure group and on whom the surgical index procedure is attempted (even if the index procedure is aborted).

POAF Diagnosis (POAF) Population: This population will include all ITT subjects diagnosed with POAF. This will be the primary analysis population for effectiveness and health economic endpoints.

Per-Protocol (PP) Population: A PP population may be defined for effectiveness, health economic and Quality of Life analyses. This population is defined by POAF population but without any major protocol violations, that is, those that could potentially bias the results.

9.7 Analysis of Study Endpoints

Study endpoints will be summarized by treatment group and overall as appropriate. Continuous variables will be summarized by presenting the number of subjects, mean, standard deviation, median, minimum, maximum by procedure group (AtriClip LAA Closure or anticoagulation therapy and without AtriClip LAA Closure). Tabulation of categorical variables by group will include counts and percentages. 95% confidence intervals will be provided as appropriate.

Since this is an exploratory study, additional analyses, additional analysis populations, covariates and summary tables and/or graphs will be generated as needed.

In all analyses described below, the null hypothesis will be a two-sided test of no treatment group difference. All statistical tests will use a two-sided significance level of α=0.05.

9.7.1 Effectiveness and Health Economic Analysis

A Pearson's Chi-Squared test will be used to compare the incidence of successful LAA exclusion between the two procedure groups. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported.

In addition, LAA exclusion might also be analyzed using multiple logistic regression model with the proportion of the event of successful LAA exclusion as the dependent variable and the following independent variables: sites (or clusters of sites), surgical approach (sternotomy, right mini-thoracotomy or other), age, gender, CHA2DS2- VASc score, HASBLED score and relevant interaction terms.

Healthcare resource use will be assessed by examining either total resource use, treatment costs or formal cost effectiveness/cost utility analysis. Resource use such as hospital length of stay, OR time, and total treatment costs will be compared between the treatment groups using a two-way analysis of variance (ANOVA) model with procedure group (AtriClip LAA Closure or anticoagulation therapy and without AtriClip LAA Closure) and site as fixed effects in the model.

These endpoints will also be compared using the two-sided t-test. A Shapiro-Wilk test of normality will be performed and if the normality assumption is not met, an approximate non-parametric model (e.g. Wilcoxon rank-sum test) may be performed.

A Pearson's Chi-Squared test will be used to compare difference in 30 day readmits, number of neurological consults, additional procedures, and patient medication use between the two procedure groups.

Formal economic models utilizing treatment effectiveness (Quality adjusted life years, costs to reduce stroke, etc.) may be built with collected data and other secondary sources accounting for specific country perspective and discounted appropriately.

9.7.2 Safety Analysis

A Pearson's Chi-Squared test will be used to compare the incidence of complications associates with LAA exclusion between the two procedure groups. Alternatively, a Fisher's Exact test will be used if justified by small cell counts (less than 5) and Clopper-Pearson (Exact) 95% CI will also be reported. Thromboembolic and hemorrhagic events will be similarly analyzed.

In addition, complications associated with LAA exclusion and thromboembolic/hemorrhagic might also be analyzed using multiple logistic regression model similar to the effectiveness endpoint (successful LAA exclusion) described above.

9.8 Detailed Analysis Plan

Prior to looking at the data and database closure, if needed, a detailed statistical analysis plan will be prepared and finalized to completely specify the statistical procedures to be applied to the data by the statistician who will conduct the analysis. The plan will amplify on the methods discussed in this protocol, will address any protocol changes that would affect the analysis, and will provide a rationale for any changes to the analysis.

10.0 Safety Monitoring

Subject safety will be monitored throughout the course of this study by monitoring for Adverse Events and Product Complaints related to the AtriClip device. The AtriClip device used during the index procedure for the clinical study has been cleared for marketing by the FDA and is being used within the current labeling and indications for use. Any event that occurs that may have caused or contributed to a death or serious injury or that indicates the AtriClip device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur will be reported in compliance with 21 CRF Part 803.

In addition to general surgical risks, additional risks specifically associated with the AtriClip implant are as follows:

- Incomplete exclusion of left atrial appendage (LAA)
- Additional surgery if the device is not placed in the correct position.
- Allergic reaction to the implant materials

- Device misplacement or embolization
- Device breakage
- Inability to move or retrieve device

There may also be other risks that are unforeseen at this time.

10.1 Adverse Events

10.1.1 Definition of an Adverse Event

Adverse Event (AE): any undesirable clinical occurrence or change from a patient's baseline (pre-index procedure) condition, whether it is device related or not.

Adverse Event Identification: a condition that is one of the following:

a. A unique symptom or event that is a change from the subject's baseline status
b. A series of symptoms or events that can be categorized as a single entity based on definitions found herein
c. A specific diagnosis responsible for a clinical change
d. A worsening or exacerbation of a pre-existing condition

10.2 Serious Adverse Events

10.2.1 Definition of a Serious Adverse Event

Serious Adverse Event (SAE): any adverse event is considered serious if it results in death, is life threatening, requires hospitalization (initial or prolonged), results in disability or permanent damage, causes congenital anomaly/birth defect, requires intervention to prevent impairment or damage, or other serious (important medical events) which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

Note: "Death" should not be reported as an adverse event. The cause of death should be reported as an adverse event. The only exception is "Sudden Death" when the cause is unknown.

10.2.2 Subject Death

Subject death during the investigation must be reported by the Investigator (or designee) by completing the Study Exit eCRF in the database along with the cause of death. The electronic Adverse Event Form is necessary if the event was related to the AtriClip device or placement of the device. In addition, subject death must be reported to the IRB in accordance with IRB requirements.

10.2.3 Adverse Event Classification

The investigator is required to provide:

- Time interval of the event – The time interval of the occurrence of the adverse event should be assessed in relationship to timing of the index procedure (AtriClip placement)
- Date of event onset and outcome of the event, or date of death
- Severity of the event – (Mild, Moderate, Severe)
- Action taken for medical management of the event
- Relationship of the event – it is the PIs responsibility to assess the relationship of an AE and provide primary cause. Events will be categorized by relationship to the AtriClip device, the applier, ancillary device, and the index procedure or other.

- Adverse events will be assessed to determine if the event meets the definition of a serious adverse event.

10.2.4 Reporting Adverse and Serious Adverse Events

The investigator (or designee) will record all AEs (both serious and non-serious and regardless of relationship) in the source documents. The Investigator at each site participating site is responsible for reporting AEs and SAEs to AtriCure only when they are related to the LAA exclusion index procedure or device. AEs related to the LAA exclusion procedure or device will be reported on the eCRF. The CRFs allow the investigator to indicate whether or not the adverse events are related to the AtriClip device or AtriClip placement (index procedure).

- Use a separate Adverse Event Form to document each event
- The Adverse Event Form must be electronically signed by the Investigator
  Note: It is the responsibility of the Investigator to inform their IRB of SAEs as required by their IRB procedures and in conformance with FDA requirements.

All Serious Adverse Events that are related to the LAA exclusion index procedure or device must be reported by the Investigator by submitting the AE eCRF to AtriCure within 10 days of becoming aware of the AE and recorded on the Serious Adverse Event Source Document Collection Form An event determined by the Investigator to be life threatening or to have led to death should be reported within 24 hours.

The Investigator shall send a written report including a narrative description of the SAE to AtriCure within three (3) working days of the initial report. The Investigator should follow all unresolved SAEs until the events are resolved, or the subject has exited the study or the AE is otherwise explained.

11.0 PRODUCT COMPLAINTS

11.1 Medical Device Reporting and Product Complaints

All reported device observations, malfunctions or failures for AtriClip LAA products will be reported on the **Device Complaint Form** within 10 days of observation of the Product Complaint via email to [redacted]. In the event of a suspected observation or device problem, the device shall be returned to the sponsor for analysis. In addition, the **Investigational Device Observation** eCRF should be completed within 10 days of a suspected observation or device problem.

Whenever an event involving an AtriCure device is subject to reporting under that Medical Device Reporting (MDR) regulation, AtriCure shall submit to the FDA the appropriate reports required by MDR within the time frames as identified in 21 CFR Part 803. Criteria for reporting malfunctions and potentially serious injuries is based on interpretations of medical intervention, potential for serious injury, and impact of a malfunction to a device's essential functionality. AtriCure will follow - reference documents [redacted] medical device in compliance with reporting, 21 CFR Part 803 and 21 CFR Part 820: Code of Federal Regulations, Quality system Regulations.

11.2 Source of Product Complaint Data

Means of obtaining product complaint data include review of the subject's medical records or observation by the PI and/or study staff or the CRA.

12.0 STUDY OVERSIGHT

12.1 Independent Oversight

No independent oversight is anticipated for this study.

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13.0 Appendices

APPENDIX 1 - EQ-5D-5L Questionnaire

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

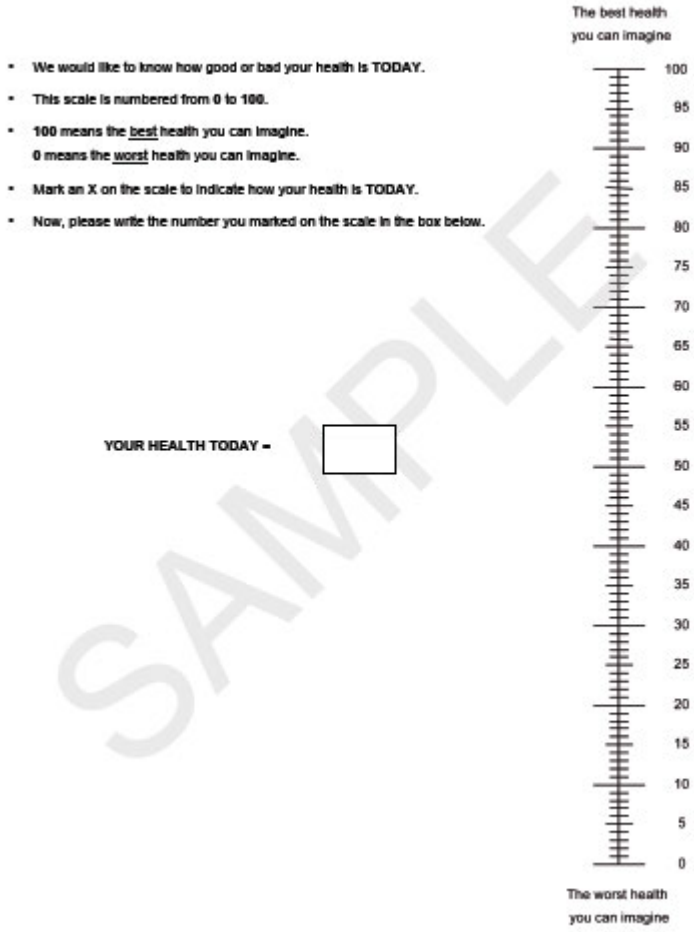
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

SAMPLE

VAS


The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine
We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Mark an X on the scale to indicate how your health is TODAY.
Now, please write the number you marked on the scale in the box below.
YOUR HEALTH TODAY =

SAMPLE

Health Questionnaire / English version for the USA SCRIPT FOR TELEPHONE INTERVIEW

GENERAL INTRODUCTION

It is suggested that the telephone interviewer follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on pages 2 and 3, the exact wording must be followed.

It is recommended that the interviewer has a copy of the EQ-5D in front of him or her as it is administered over the telephone. This enables the respondent's answers to be entered directly on the EQ-5D by the interviewer on behalf of the respondent (i.e. the appropriate boxes on pages 2 and 3 are marked and the scale on page 4 is marked at the point indicating the respondent's 'health today'). If the respondent asks for clarification, the interviewer can help by re-reading the question verbatim. The interviewer should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty regarding which box to mark, the interviewer should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

INTRODUCTION TO EQ-5D

(Note to interviewer: please read the following)

We are trying to find out what you think about your health. I will first ask you some simple questions about your health TODAY. I will then ask you to rate your health on a measuring scale. I will explain what to do as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

EQ-5D DESCRIPTIVE SYSTEM: INTRODUCTION

First I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY. Do not choose more than one answer in each group of questions.

(Note to interviewer: it may be necessary to remind the respondent regularly that the timeframe is TODAY. It may also be necessary to repeat the questions verbatim)

EQ-5D DESCRIPTIVE SYSTEM MOBILITY

First I'd like to ask you about mobility. Would you say that:

1. **You have no problems walking?**
2. **You have slight problems walking?**
3. **You have moderate problems walking?**
4. **You have severe problems walking?**
5. **You are unable to walk?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

SELF-CARE

Next I'd like to ask you about self-care. Would you say that:

1. **You have no problems washing or dressing yourself?**
2. **You have slight problems washing or dressing yourself?**
3. **You have moderate problems washing or dressing yourself?**
4. **You have severe problems washing or dressing yourself?**
5. **You are unable to wash or dress yourself?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

USUAL ACTIVITIES

Next I'd like to ask you about your usual activities, for example work, study, housework, family or leisure activities. Would you say that:

1. **You have no problems doing your usual activities?**
2. **You have slight problems doing your usual activities?**
3. **You have moderate problems doing your usual activities?**
4. **You have severe problems doing your usual activities?**
5. **You are unable to do your usual activities?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

PAIN / DISCOMFORT

Next I'd like to ask you about pain or discomfort. Would you say that:

1. **You have no pain or discomfort?**
2. **You have slight pain or discomfort?**
3. **You have moderate pain or discomfort?**
4. **You have severe pain or discomfort?**
5. **You have extreme pain or discomfort?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

ANXIETY / DEPRESSION

Finally, I'd like to ask you about anxiety or depression. Would you say that:

1. **You are not anxious or depressed?**
2. **You are slightly anxious or depressed?**
3. **You are moderately anxious or depressed?**
4. **You are severely anxious or depressed?**
5. **You are extremely anxious or depressed?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

EQ VAS: INTRODUCTION

(Note for administrator: If possible, it might be useful to send a visual aid (i.e. the EQ VAS) before the telephone call so that the respondent can have this in front of him or her when completing the task)

Now, I would like to ask you to say how good or bad your health is TODAY.

I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.

EQ VAS: TASK

I would now like you to tell me the point on this scale where you would put your health today.

(Note to interviewer: mark the point on the scale at the point indicating the respondent's 'health today')

Thank you for taking the time to answer these questions.

APPENDIX 2 - Risk/Benefit Assessment

Risk Category: Minimal.

Summary: The AtriClip device is commonly used for the exclusion of the left atrial appendage (LAA). The risks to subjects undergoing surgery to place the AtriClip device are listed below.

1.0 POSSIBLE RISKS AND DISCOMFORTS:

Risks associated with having the AtriClip placed (does not address the risks and discomforts associated with cardiac surgery).

Possible risks and discomforts that may be associated with the use of the AtriClip during procedure are identified below.

- Incomplete exclusion of left atrial appendage (LAA)
- Additional surgery if the device is not placed in the correct position.
- Allergic reaction to the implant materials
- Device misplacement or embolization
- Device breakage
- Inability to move or retrieve device
- Injury, perforation or tear of the LAA which may lead to blood loss

POTENTIAL RISKS

Complications may occur at any time during the procedure, post procedure or follow-up period that could specifically occur with the AtriClip® or the placement of the AtriClip® include the following:

- Myocardial infarction
- Blood loss requiring transfusion
- Cerebrovascular accident (CVA)
- Circumflex artery impingement
- Death
- Stroke
- Pericarditis
- Peripheral ischemia
- Transient ischemic attack (TIA)

2.0 POSSIBLE BENEFITS

Benefits may include but are not limited to, the following:

- Prevention of thromboembolic events (blood clots).
- Prevention of ischemic stroke and systemic (non-CNS) embolism.

- Elimination of oral blood thinners resulting in a reduction of bleeding complications associated with long-term anticoagulation.
- Eliminating the need for life-long compliance to oral anticoagulant therapy and the frequent blood tests (depending on oral anticoagulant agent), and lifestyle changes associated with blood thinning medications.
- Advancing the medical and scientific knowledge that may benefit future patients with similar conditions may be gained through this clinical study.
- There may also be other benefits that are unforeseen at this time.

3.0 ALTERNATIVE PROCEDURES/TREATMENTS

There are some alternative ways for closing your left atrial appendage that does not involve using the AtriClip:

- Sewing or closing appendage with sutures or ligatures
- Stapling the appendage closed with a medical stapling device

MINIMIZATION OF RISKS

Measures which will be taken to minimize risks related to the study include:

- The investigators in this study will be selected based on their experience in treating patients with atrial fibrillation and performing surgical procedures
- Investigators will be chosen that are qualified to complete study index procedures and are experienced in the placement of the AtriCure AtriClip device.
- Well defined clinical study protocol, including specific inclusion/ exclusion criteria to enroll appropriate subjects in the trial.
- Close patient monitoring during the surgical procedure and follow-up period.

Alternative to Participation: Patients may decline and would be treated with the same standard of care.

CONCLUSION: This clinical study is justified because the study sponsor and clinical investigators believe the potential benefits outweigh the potential risks.