# Utilizing Novel dipole density Capabilities to Objectively Visualize the Etiology of Rhythms in Atrial Fibrillation (UNCOVER-AF)

**Protocol: CL-AF-002, Revision 01**

**Date: 10 May 2016**

**Sponsor:**

**Acutus Medical, Inc.**

**2210 Faraday Ave, Suite 100**

**Carlsbad, CA 92008**

**NCT02825992**

## CONFIDENTIALITY STATEMENT

## PROTOCOL SIGNATURE PAGE

CL-AF-002 Rev 1

The signature below constitutes the approval of this Clinical Investigational Plan (CIP) and provides assurances that this clinical study will be conducted in accordance with all stipulations of the CIP including all statements regarding patient confidentiality. The CIP will be followed according to all national and local legal and regulatory requirements.

Site Investigator Printed Name

Site Investigator Signature

Date

dd-mmm-yyyy

## Revision History

| *Revision #* | *Date* | *Description* |
|---|---|---|
| 01 | 10 May 2016 | Initial release |

# 1 CLINICAL STUDY SYNOPSIS

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|---|---|
| **STUDY TITLE** | Utilizing Novel dipole density Capabilities to Objectively Visualize the Etiology of Rhythms in Atrial Fibrillation (UNCOVER-AF) |
| **DEVICE NAME** | AcQMap™ High Resolution Imaging and Mapping System |
| **DEVICE SHORT NAME** | AcQMap™ |
| **DEVICE COMPONENTS** | The AcQMap™ System consists of the following components:<br>• The AcQMap™ 3D Imaging and Mapping Catheter (AcQMap™ Catheter)<br>• The AcQGuide™ Steerable Delivery Sheath<br>• The AcQMap™ Console<br>• The AcQMap™ Workstation<br>• The AcQMap™ Patient Electrode Kit |
| **INDICATION FOR USE (INTENDED USE)** | The AcQMap™ Imaging and Mapping System is intended for imaging and mapping of cardiac chambers, which will be utilized in the management of cardiac arrhythmias. |
| **SPONSOR** | Acutus Medical, Inc.<br>2210 Faraday Ave., Suite 100<br>Carlsbad, CA 92008 |
| **STUDY OBJECTIVE** | To evaluate the incidence of device- and procedure-related safety, efficacy, and efficiency (6 and 12 month outcomes) when using the AcQMap™ as an imaging and mapping system for ablation of persistent atrial fibrillation (AF). |
| **STUDY DESIGN** | A prospective, single-arm, multi-center, multi-national, non-randomized, post-market study designed to provide clinical data regarding the use of the AcQMap™ System in the ablation of persistent atrial fibrillation.<br>Subject assessments will occur at screening, procedure, hospital discharge, 1, 3, 6, 9, and 12 months.<br>Data may be published at 6 and 12 months |
| **PRIMARY MEASURABLE OBJECTIVE** | The primary measurable objective is an analysis of the proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs) that occur within the first 24 hours post-procedure. MAEs include any of the following:<br>• Death<br>• Cardiac perforation/pericardial tamponade<br>• Cerebral infarct, transient ischemic attack (TIA), or systemic embolism |

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| | • Major bleeding<br>• Mitral or tricuspid valvular damage<br>• Other serious adverse device effects (SADEs) adjudicated by an independent Clinical Events Committee (CEC) as "probably related" to the AcQMap |
| **SECONDARY MEASURABLE OBJECTIVES** | Secondary measurable objectives include the following:<br><u>Safety Outcomes Measure</u><br>• Recording and analysis of all identified adverse events (AEs) and adverse device effects (ADEs) through 12 months post-procedure. Events will be adjudicated by an independent Clinical Events Committee (CEC) for severity and relationship to the AcQMap<br><u>Procedural Outcome Measures</u><br>• Analysis of the proportion of subjects with acute procedural (ablation) success defined as:<br>– Conversion to sinus rhythm (with or without DC cardioversion) within 12 hours of the ablation procedure<br>– Procedural conversion to atrial flutter, atrial tachycardia or other organized supraventricular rhythm<br><u>Clinical Outcome Measures</u><br>• Analysis at 3, 6, 9, and 12 months post ablation (with a 24 hour continuous ECG monitor) of the proportion of subjects with freedom from documented episodes of AF lasting longer than 30 seconds. Analysis will include:<br>– Freedom from AF/AT/AFL without anti-arrhythmic drugs (AADs)<br>– Freedom from AF/AT/AFL with AADs<br>– Freedom from AF/AT/AFL with a single procedure<br>– Freedom from AF/AT/AFL with multiple procedures |
| **SAMPLE SIZE** | Up to 125 subjects will be enrolled.<br>Up to 15 clinical sites in Europe. |
| **STUDY CENTER AND LOCATION** | TBD |
| **PATIENT POPULATION** | The patient population will consist of men and women between the ages of 18 – 80 years of age scheduled for an endocardial ablation of persistent atrial fibrillation (AF).<br>A potential study patient will be eligible for study enrollment only if all of the following inclusion and none of the exclusion criteria apply:<br><u>Inclusion Criteria</u><br>IC 1 Male or female between the ages of 18 and 80 years<br>IC 2 Currently scheduled for an ablation of <u>persistent atrial fibrillation</u> defined as AF lasting at least 7 days but no more |

than 12 months without electrical cardioversion

IC 3 Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study

IC 4 Willing and able to give informed consent

Exclusion Criteria

EC 1 In the opinion of the Investigator, any known contraindication to an AF ablation, TEE, or anticoagulation

EC 2 Any duration of continuous AF lasting longer than 12 months

EC 3 History of previous left atrial ablation or surgical treatment for AF/AFL/AT

EC 4 Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause

EC 5 Structural heart disease as described below:

a. Left ventricular ejection fraction (LVEF) < 40% based on TTE within 6 months of enrollment
b. Left atrial size > 50 mm based on TTE within 6 months of enrollment
c. An implanted pacemaker or ICD
d. Previous cardiac surgery, ventriculotomy, or atriotomy (excluding atriotomy for CABG (see EC 5, j)),
e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve
f. Interatrial baffle, closure device, patch, or PFO occluder
g. Presence of a left atrial appendage occlusion device
h. Coronary artery bypass graft (CABG) or PTCA procedure within the last 6 months
i. Unstable angina or ongoing myocardial ischemia
j. Myocardial infarction within the previous six (6) months

EC 6 History of blood clotting or bleeding disease

EC 7 ANY prior history of documented cerebral infarct, TIA or systemic embolism

EC 8 Pregnant or lactating (current or anticipated during study follow up)

EC 9 Current enrollment in any other study protocol where testing or results from that study may interfere with the procedure or outcome measurements for this study

EC 10 Any other condition that, in the judgment of the investigator, makes the patient a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable patient population, mental illness, addictive disease, terminal illness with a life expectancy of

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| | less than two years, extensive travel away from the research center) |
| **STUDY DURATION** | Enrollment is anticipated to take approximately six (6) to eight (8) months. Post-procedure follow up will occur at hospital discharge, 1, 3, 6, and 12 months. The total study duration is anticipated to be approximately 18 months. |
| **STATISTICAL METHODS AND ANALYSIS SUMMARY** | The primary outcome measure for the study is the primary safety objective, defined as the proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs) that occur within the first 24 hours post-procedure. Subjects who remain free from such device/procedure related MAEs will be considered a success with respect to the primary safety objective, and subjects who experience at least one such MAE will be considered a primary safety failure.<br><br>The analysis of the primary safety objective will be performed on the treatment population, which will include all enrolled subjects who complete a procedure up to the point the AcQMap catheter is deployed in the left atrium. The number and proportion of subjects in the treatment population who are primary safety successes will be computed, along with a 95% exact binomial (i.e., Clopper-Pearson) confidence interval on the proportion.<br><br>Descriptive statistics will be applied to all other outcome measures. |
| **FOLLOW-UP EVALUATIONS** | See Table Below |

**Table 1: Schedule of Events**

| | **Screening**[1] **& Baseline** | **Procedure** | **Discharge** | **7 Days** (± 3 days) **Phone Contact** | **1-month** (± 7 days) | **3-month** (± 14 days) | **6-month** (± **30 days**) | **9-month** (± **30 days**) | **12-month** (± **30 days**) |
|---|---|---|---|---|---|---|---|---|---|
| **CIP Informed Consent** | **X** | | | | | | | | |
| **Medical History** | **X** | | | | | | | | |
| **History & Physical Exam** | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **Medications** | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **Transthoracic Echo (TTE)** | **X** (within 6 months) | | | | | | | | **X** |
| **Trans Esophageal Echo (TEE)** | | **X** (within 72 hours) | | | | | | | |
| **Adverse Events** | | **X** | **X** | **X** | **X** | **X** | **X** | | **X** |
| **12-lead ECG** | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **Labs** | **X** | | | | | | | | |
| **HCG (female patients)** | **X** | | | | | | | | |
| **Patient Reported Outcome Measures (AFEQT)** | **X** | | | | **X** | **X** | **X** | | **X** |
| **24-hour Continuous ECG Monitor Recording** | | | | | | | **X** | **X** | **X** |

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# 3 CONTACT INFORMATION

## 3.1 Name and Address of Sponsor

Acutus Medical, Inc.

2210 Faraday Ave., Suite 100

Carlsbad, CA 92008

# 4 ABBREVIATIONS

| | |
|---|---|
| 3D | Three Dimensional |
| AAD | Anti-Arrhythmic Drug |
| ACT | Activated Clotting Time |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AF | Atrial Fibrillation |
| AFEQT | Atrial Fibrillation Effect on Quality of Life |
| AFL | Atrial Flutter |
| AT | Atrial Tachycardia |
| CABG | Coronary Artery Bypass Grafting |
| CEC | Clinical Events Committee |
| CIP | Clinical Investigational Plan |
| CMP | Clinical Monitoring Plan |
| CPM | Clinical Project Manager |
| CRA | Clinical (or Contract) Research Associate |
| CRO | Contract Research Organization |
| CRF | Case Report Form |
| CTA | Clinical Trial Agreement |
| DCCV | Direct Current Cardioversion |
| DCF | Data Clarification Form |
| DMP | Data Management Plan |
| EC | Ethics Committee |
| EU | European Union |
| eCRF | Electronic Case Report Form |
| ECG | Electrocardiogram |
| EGM | Electrogram |
| EMR | Electronic Medical Record |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practices |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IA | Investigator Agreement |
| ICD | Implantable Cardioverter Defibrillator |
| IFU | Instructions For Use |
| IM | Investigator Meeting |
| IMV | Interim Monitoring Visit |
| ISF | Investigator Site Files |
| ISO | International Organization for Standardization |

| | |
|---|---|
| LA | Left Atrium |
| LFU | Lost to Follow-Up |
| LVEF | Left Ventricular Ejection Fraction |
| MAE | Major Adverse Event |
| PAF | Paroxysmal Atrial Fibrillation |
| PFO | Patent Foramen Ovale |
| PI | Principal Investigator |
| PROs | Patient Recorded Outcomes |
| PTCA | Percutaneous Transluminal Coronary Angioplasty |
| PV | Pulmonary Vein |
| PVI | Pulmonary Vein Isolation |
| QAP | Quality Assurance Procedure |
| RMV | Routine Monitoring Visit |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SC | Study Coordinator |
| SD | Standard Deviation |
| SIV | Site Initiation Visit |
| SQV | Site Qualification Visit |
| SOP | Standard Operating Procedure |
| SVT | Supraventricular Tachycardia |
| TEE | Transesophageal Echocardiogram |
| TIA | Transient Ischemic Attack |
| TMF | Trial Master File |
| TS | Trans-septal Puncture |
| TTE | Transthoracic Echocardiogram |
| UADE | Unanticipated Adverse Device Effect |
| USFDA | United States Food and Drug Administration |
| WACA | Wide Area Circumferential Ablation |

# 5 INTRODUCTION TO THE CLINICAL INVESTIGATIONAL PLAN

## 5.1 Background

Atrial fibrillation (AF) is among the most prevalent arrhythmias in the world today affecting approximately 1.5-2% of the general population. The age of patients with AF is steadily rising and now averages between 75 and 85 years of age. AF is associated with a five-fold risk of stroke, a three-fold incidence of congestive heart failure, and higher mortality.[1]

Symptoms arise from the rapid, irregular rhythm as well as the loss of cardiac pump function related to uncoordinated atrial contractions. These uncoordinated contractions also allow blood to pool in the atria and may ultimately lead to thromboembolism and stroke.

AF is characterized by a chaotic contraction of the atrium in which an electrocardiogram (ECG) recording is necessary to diagnose the arrhythmia. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm strip, should be considered an AF episode.[2,3]

The diagnosis requires an ECG or rhythm strip demonstrating: (1) Irregular RR intervals (in the absence of complete AV block), (2) no distinct P waves on the surface ECG, and (3) an atrial cycle length (when visible) that is usually variable and less than 200 milliseconds.[3]

AF can be characterized into four classifications:

- Paroxysmal AF (PAF) is defined as recurrent AF (≥two episodes) that terminates spontaneously within seven days.
- Persistent AF is defined as recurrent AF that is sustained for seven days. In addition, patients with continuous AF who undergo cardioversion within seven days should be classified as having paroxysmal AF if the cardioversion is performed within 48 hours of AF onset, and persistent AF if the cardioversion is performed more than 48 hours after AF onset.

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[1] Camm AJ, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*, 2012 Oct; 14(10):1385-413

[2] Calkins H, Brugada J, Packer DL et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. Jun 2007;4(6):816–861

[3] Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* Oct 2010;31(19):2369–2429

- Long-standing persistent AF is defined as continuous AF of greater than one year's duration.
- Permanent AF is defined as AF in which the presence of the AF is accepted by the patient (and physician). Within the context of any rhythm control strategy, including catheter ablation, the term permanent AF is not meaningful. The term permanent AF represents a joint decision by the patient and a physician to cease further attempts to restore and/or maintain sinus rhythm at a particular point in time.[3]

For many years, three major schools of thought competed to explain the mechanism(s) of AF: multiple random propagating wavelets, focal electrical discharges, and localized reentrant activity with fibrillatory conduction.[4,5,6,7,8] Significant progress has been made in defining the mechanisms of initiation and perpetuation of AF. One of the most important breakthroughs was the recognition that, in a subset of patients, AF was triggered by a rapidly firing focus and could be "cured" with a localized catheter ablation procedure.[9,10] This landmark observation caused the EP community to refocus its attention on the pulmonary veins (PVs) and the posterior wall of the left atrium (LA), as well as the autonomic innervation in that region. It also reinforced the concept that the development of AF requires a "trigger" and an anatomic or functional substrate capable of both initiation and perpetuation of AF.

Sustained high rates in the atrium and/or the presence of heart disease are associated with structural and electrophysiological remodeling of the atria and can alter the substrate even further and help to perpetuate AF.[11] Atrial Fibrillation can also be the result of preexisting atrial disease. Although much has been learned about the mechanisms of AF, they are not

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[4] Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res*. May 2002;54(2):204–216.

[5] Nattel S. New ideas about atrial fibrillation 50 years on. *Nature*. Jan 10 2002; 415(6868):219–226.

[6] Dobrev D, Voigt N,Wehrens XH. The ryanodine receptor channel as a molecular motif in atrial fibrillation: pathophysiological and therapeutic implications. *Cardiovasc Res*. Mar 1 2011;89(4):734–743.

[7] Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev*. Jan 2011;91(1):265–325.

[8] Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J Clinical Invest*. Aug 1 2011;121(8):2955–2968

[9] Jais P, Haissaguerre M, Shah DC et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. *Circulation*. Feb 4 1997;95(3):572–576.

[10] Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. Sep 3 1998; 339(10):659–666.

[11] Everett TH 4th, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. Am J Physiol Heart Circ Physiol. Dec 2006;291(6):H2911–2923

completely understood. Because of this, in the great majority of AF patients, it is not yet possible to precisely tailor an ablation strategy to a particular AF mechanism.

*3D Mapping*

Three-dimensional (3D) electroanatomical contact and noncontact mapping systems have been reported to facilitate ablation of AF by identifying anatomical structures and highlighting the location of ablated sites. This can guide the initial ablation and help identify existing gaps in an incomplete lesion set.[12] Additionally, electromagnetic navigation systems have been shown to substantially reduce the fluoroscopy time required for AF ablation.[13,14,15]

*The AcQMap System*

The AcQMap™ High Resolution Imaging and Mapping System (AcQMap System) has been designed to provide information on cardiac dipole densities as a function of time and project that information on an image of a cardiac chamber. In this study, the AcQMap System will collect data from the AcQMap 3D Imaging and Mapping Catheter (AcQMap Catheter) to create anatomical reconstructions of the chamber(s) being mapped and to create Dipole Density maps on those reconstructions. These maps will then be used to identify mechanisms of atrial fibrillation, which can be targeted for ablation.

## 5.2 Clinical Study Design Justification

Previous clinical studies utilizing the AcQMap System in an ablation procedure for SVTs have initially demonstrated an acceptable safety profile when mapping and imaging cardiac chambers. The UNCOVER-AF study is a multi-center, multi-national, non-randomized, post-market study designed to provide clinical data regarding the use of the AcQMap™ System in the ablation of persistent atrial fibrillation. The study objective is to evaluate the safety, efficacy and efficiency of using the AcQMap catheter exclusively in the atrial chambers during the ablation of persistent AF. Recording of all Serious Adverse Events/Device Effects occurring during the first twenty-four (24) hours post-procedure will be used to assess the safety related to the AcQMap Catheter. An independent Clinical Events Committee (CEC)

[12] Hindricks G, Willems S, Kautzner J, De Chillou C, Wiedemann M, Schepel S, Piorkowski C, Risius T, Kottkamp H; EuroFlutter Investigators. Effect of electroanatomically guided versus conventional catheter ablation of typical atrial flutter on the fluoroscopy time and resource use: a prospective randomized. J Cardiovasc Electrophysiol. 2009 Jul;20(7):734-40.

[13] Sporton SC, Earley MJ, Nathan AW, Schilling RJ. Electroanatomic versus fluoroscopic mapping for catheter ablation procedures: a prospective randomized study. J Cardiovasc Electrophysiol. 2004 Mar;15(3):310-5.

[14] Kottkamp H, Hügl B, Krauss B, Wetzel U, Fleck A, Schuler G, Hindricks G. Electromagnetic versus fluoroscopic mapping of the inferior isthmus for ablation of typical atrial flutter: A prospective randomized study. Circulation. 2000 Oct 24;102(17):2082-6.

[15] Smeets JL, Ben-Haim SA, Rodriguez LM, Timmermans C, Wellens HJ. New method for nonfluoroscopic endocardial mapping in humans: accuracy assessment and first clinical results. Circulation. 1998 Jun 23;97(24):2426-32.

will adjudicate all reported events for relationship to the device/procedure. A composite list of anticipated Serious Adverse Device Effects (SADEs) and Unanticipated Serious Adverse Device Effects (USADEs) are considered Major Adverse Events and will be used in a statistical analysis for the primary outcome measure. All safety events reported throughout the follow-up period will also be evaluated for device relationship and utilized in developing a complete risk assessment.

Since it is hypothesized the technology advances of dipole density mapping may better identify and more precisely direct lesion locations during AF ablation, the study is additionally designed to record longer term (six- and twelve-month) data on the effectiveness of the ablation procedure in the treatment of the arrhythmia. An analysis of treatment success (defined as freedom from atrial fibrillation at 6 and 12 months), compared to literature based historical controls, may offer insight regarding the ability of the AcQMap System to effectively and accurately identify appropriate ablation targets. However, since ablation techniques and catheter choices are not controlled during the study, clinical outcomes will not be used to imply the effective creation of lesion sets in the left atrium substrate.

Automatic, instantaneous, and simultaneous 3D display of the left atrial surface with associated charge densities may potentially shorten AF ablation procedure time and provide an intuitive tool to rapidly identify and guide effective treatment. To further assess these potential benefits of the AcQMap System during the study procedures, data will be collected for many other procedural and clinical outcomes.

Data from this study will be combined with a nearly identical pre-market clinical study conducted in Canada and Australia. Data are considered suitable for pooling based on identical patient inclusion and exclusion criteria, procedures, and measurement methods for outcomes data. The patients in the general population of the countries conducting the study have similar demographics. Analysis of primary safety data will be adjudicated by a common, independent CEC. The pooled data will be utilized to statistically assess the safety and performance of the device when used in the ablation treatment of persistent AF.

### 5.2.1 Patient Reported Outcomes (AFEQT)

The clinical study is designed to include reported changes in a patient's quality of life following an ablation for atrial fibrillation. The Atrial Fibrillation Effect on Quality of Life (AFEQT) Questionnaire is a "validated, comprehensive, disease-specific measure to quantify the impact of AF and its treatment on a full spectrum of a patient's health".[16] By evaluating a subject's perception of their symptoms and functional impairment at pre-procedure and all

[16] Spertus, J.,Dorian, P., Bubien, R., et al. Development and validation of the Atrial Fibrillation Effect on Quality of Life (AFEQT) Questionnaire in Patients with Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2011;4:15-25.

follow-up visits, the test will measure the impact of rhythm management on their health and wellbeing.

## 5.3 Indication for Use Statement

The AcQMap™ Imaging and Mapping System is intended for imaging and mapping of cardiac chambers, which will be utilized in the management of cardiac arrhythmias.

## 5.4 Device Description

### 5.4.1 General System Description

The AcQMap™ System is designed to create a 3D image of a heart chamber's endocardial surface in which catheters can be navigated and a chamber-wide electrical activation map can be overlaid for percutaneous procedures. The AcQMap™ System should only be used by physicians thoroughly trained in electrophysiology procedures and trained on the use of the AcQMap™ System

### 5.4.2 AcQMap System Hardware

The AcQMap™ System hardware consists of the AcQMap™ Console, AcQMap™ Workstation and the AcQMap AIU/PIU. The AcQMap Console contains all electronics for interfacing with patient-contacting devices such as the AcQMap™ Catheter and the Patient Electrode Kit.

### 5.4.3 The AcQMap 3D Imaging and Mapping Catheter

The AcQMap 3D Imaging and Mapping Catheter is a diagnostic, sterile, single-use device that has a polymeric catheter torque shaft, an integral handle and a flexible, metallic deployable/retractable array.

### 5.4.4 AcQGuide Steerable Sheath

The AcQGuide Steerable Sheath is a single-use, sterile, delivery sheath consisting of a deflectable shaft with a lumen, integral handle with steering mechanism, hemostasis valve and flush port. The sheath is compatible with other Acutus Medical catheter products. The sheath can be placed within the desired heart chamber thus allowing the AcQMap Catheter to be introduced, deployed and directed within the chamber as needed.

# 6 CLINICAL STUDY

## 6.1 Clinical Study Objective

The objective of the clinical study is to evaluate the incidence of device- and procedure-related safety, efficacy, and efficiency (6- and 12-month outcomes) when using the AcQMap as an imaging and mapping system for ablation of persistent atrial fibrillation (AF).

## 6.2 Clinical Study Design

The clinical study is a prospective, single-arm, multi-center, multi-national, non-randomized, post-market study designed to provide clinical data regarding the use of the AcQMap System during an ablation of persistent atrial fibrillation. In parallel with this clinical study, a second study, identical in design, inclusion/exclusion criteria and reportable outcomes, will be conducted in geographical locations where regulatory approval has not been obtained. The data from these collaborative studies will be pooled for analysis and eventual publication on the use of the AcQMap System for mapping and imaging during ablation of persistent AF.

### 6.2.1 Primary Measurable Objective

The primary measurable objective is an analysis of the proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs) that occur within the first 24 hours post-procedure. MAEs include any of the following:

- Death
- Cardiac perforation/tamponade
- Cerebral infarct, transient ischemic attack (TIA), or systemic embolism
- Major bleeding
- Mitral or tricuspid valvular damage
- Other serious adverse device effects (SADEs) adjudicated by an independent Clinical Events Committee (CEC) as "probably related" to the AcQMap System

### 6.2.2 Secondary Measurable Objectives

Secondary measurable objectives include the following:

Safety Outcome Measure

- Recording and analysis of all identified adverse events (AEs) and adverse device effects (ADEs) through 12 months post-procedure. Events will be adjudicated by an independent Clinical Events Committee (CEC) for severity and relationship to the AcQMap

Procedure Outcome Measure

- Analysis of the proportion of subjects with acute procedural (ablation) success defined as:
  - Conversion to sinus rhythm (with or without DCCV) within 12 hours of the procedure
  - Procedural conversion to atrial flutter, atrial tachycardia or other organized supraventricular rhythm

Clinical Outcome Measures

- Analysis at 3, 6, 9, and 12 months post ablation (with a 24 hour continuous ECG monitor) of the proportion of subjects with freedom from documented episodes of AF lasting longer than 30 seconds. Analysis will include:
  - Freedom from AF/AT/AFL without AADs
  - Freedom from AF/AT/AFL with AADs
  - Freedom from AF/AT/AFL with a single procedure
  - Freedom from AF/AT/AFL with multiple procedures

## 6.3 Clinical Study Duration

Enrollment is anticipated to take approximately six (6) to eight (8) months. Post-procedure follow up will occur at hospital discharge, 1, 3, 6, and 12 months. The total study duration is anticipated to be approximately 18 months.

## 6.4 Clinical Study Sample Size and Clinical Sites

Up to one hundred and twenty-five (125) patients will be enrolled at up to fifteen (15) clinical sites in Europe. No site may enroll more than 25 patients (20% of the study population).

## 6.5 Clinical Study Enrollment Definitions

For the purposes of this clinical study, the following definitions regarding the status of a subject will apply:

Screen Failure Subject – Any subject who has not met all of the inclusion and exclusion criteria. This includes a subject who may be excluded based on the results of the pre-procedure TEE. Screen failure subjects should have the screening eCRF completed and the screening data entered in the database.

Enrolled Subject – Any subject who has signed an informed consent form and is deemed study eligible by meeting all of the inclusion and exclusion criteria.

Pre-treatment Subject – Any enrolled subject who has the venous access portion of the ablation procedure initiated. Pre-treatment patients that do not complete the AcQMap procedure will be followed for adverse events through hospital discharge. In addition to the discharge eCRF, a study completion eCRF will be completed. No follow-up beyond the hospital discharge will be required.

Treatment Subject – Any pre-treatment subject who completes the ablation procedure to the point the AcQMap catheter and AcQGuide sheath has been deployed in the left atrium. Treatment subjects will be followed for all study outcome measures for the full duration of the clinical study. The number of treatment subjects will be used for the study sample.

## 6.6 Clinical Study Population

The patient population will consist of men and women between the ages of 18 – 80 years of age scheduled for an endocardial ablation of persistent atrial fibrillation (AF).

A potential study subject will be eligible for study enrollment only if all of the following inclusion and none of the exclusion criteria apply:

### 6.6.1 Inclusion Criteria

IC 1 Male or female between the ages of 18 and 80 years of age

IC 2 Currently scheduled for an ablation of persistent atrial fibrillation defined as AF lasting at least 7 days but no more than 12 months without electrical or chemical cardioversion

IC 3 Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study

IC 4 Willing and able to give informed consent

### 6.6.2 Exclusion Criteria

EC 1 In the opinion of the Investigator, any known contraindications to an AF ablation, TEE, or anticoagulation

EC 2 Any duration of continuous AF lasting longer than 12 months

EC 3 History of previous left atrial ablation or surgical treatment for AF/AFL/AT

EC 4 Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause

EC 5 Structural heart disease as described below:

a. Left ventricular ejection fraction (LVEF) < 40% based on TTE within 6 months of enrollment

b. Left atrial size > 50 mm based on TTE within 6 months of enrollment

c. An implanted pacemaker or ICD

d. Previous cardiac surgery, ventriculotomy, or atriotomy (excluding atriotomy for CABG (see EC 5, j)),

e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve

f. Interatrial baffle, closure device, patch, or PFO occluder

g. Presence of a left atrial appendage occlusion device

h. Coronary artery bypass graft (CABG) or PTCA procedure within the last 6 months

i. Unstable angina or ongoing myocardial ischemia

j. Myocardial infarction within the previous six (6) months

EC 6 History of blood clotting or bleeding disease

EC 7 ANY prior history of documented cerebral infarct, TIA or systemic embolism

EC 8 Pregnant or lactating (current or anticipated during study follow up)

EC 9 Current enrollment in any other study protocol in which testing or results from that study may interfere with the procedure or outcome measurements for this study

EC 10 Any other condition that, in the judgment of the investigator, makes the patient a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable patient population, mental illness, addictive disease, terminal illness with a life expectancy of less than two years, or extensive travel away from the research center)

## 6.7 Subject Withdrawal

Individual subjects may withdraw their consent to participate in the study at any time. Also, an Investigator may discontinue a subject's participation in the study at any time to protect the safety, rights, or welfare of the subjects.

Subjects missing follow-up visits will not be considered lost to follow-up until adequate attempts to contact the subject has been made by telephone, e-mail, and/or mailed letter.

# 7 CLINICAL STUDY TREATMENTS AND FOLLOW-UP VISITS

## 7.1 Informed Consent

It is the responsibility of the Investigator to give each subject full and adequate verbal and written information regarding all aspects of the study procedure, device, and associated risks. A signed, informed consent must be obtained from the subject before any study procedures not considered standard of care for an AF ablation are undertaken. The informed consent form must be signed by the subject and witnessed by the Investigator (or designee). The original signed consent is filed in the patient's study records with one copy placed in the patient's medical notes and one copy provided to the patient.

## 7.2 Patient Screening and Baseline

The following information must be acquired to verify eligibility in the clinical study:

- Subject demographics
- Medical history review including:
  - All history of AF and other arrhythmias, including onset, duration, previous testing, etc.
  - Prior and current AAD treatments for AF
  - Medication history including AADs, pertinent cardiovascular drugs, and anticoagulation
  - DCCV history
  - Information supportive of determining a $CHADS_2$ and $CHA_2DS_2$-VASc scores
- Review of all inclusion/exclusion criteria to confirm patient eligibility
- Physical exam
- Transthoracic echocardiogram (TTE) within the previous six (6) months to document:
  - Left atrial size
  - Left ventricular ejection fraction
  - Severity of any valvular heart disease
- Pregnancy test (if applicable)
- Routine standard of care laboratory and X-ray tests for pre-ablation work-up
- ECG or continuous ECG monitor tracing/report documenting AF

- Completion of a Patient Reported Outcome (AFQET)

## 7.3 Ablation Procedure

### 7.3.1 Mapping and Ablation

The objective of this clinical study is to evaluate the safety and performance of the AcQMap System when mapping and imaging the left and right atria during persistent AF ablation. Therefore, the utilization of devices for 3D anatomic reconstruction, navigation and electrical mapping should be limited to the AcQMap System. Furthermore, RF ablation catheters utilized during the procedure should be limited to those compatible with the AcQMap System.

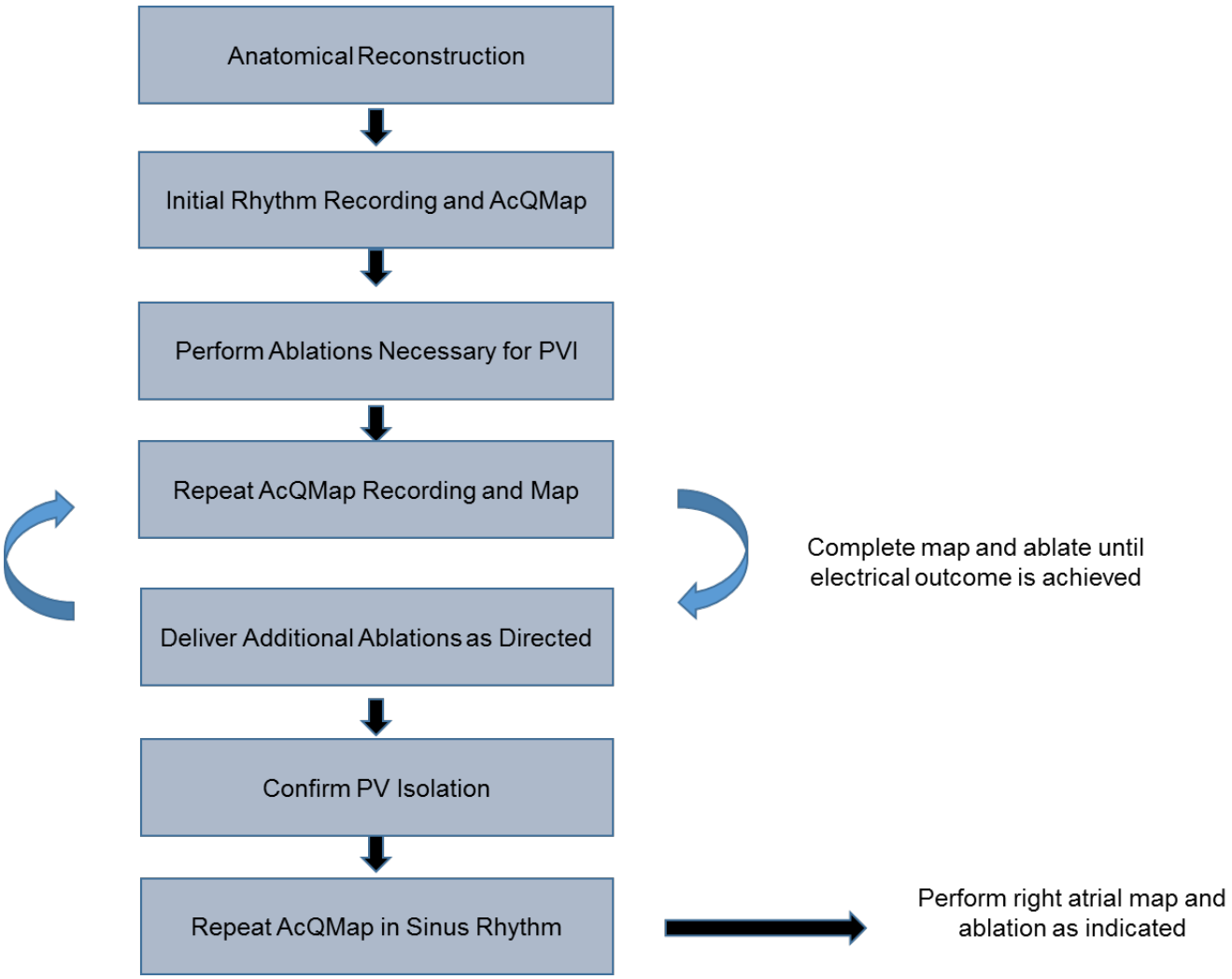



**Figure 1: Ablation Procedure Flow Diagram**

### 7.3.2 Procedure Data Collection

Collection of data generated during the procedure should include:

- Medications and any change in health prior to the ablation
- Recording of 12 lead ECG at procedure start
- Recording of 12 lead ECG at procedure completion
- Total procedure time (from first venous access to study completion)
- Total fluoroscopy time and times to complete segments of the ablation procedure
- Ablation time to complete PVI (delineate RF vs Cryo)
- Ablation time for additional LA lesions (separate AF from AT ablations)
- Ablation times for right atrial ablations
- Recording of all DCCV used during the procedure
- EP recording of all atrial tachyarrhythmias noted during the procedure
- EP recording of conversion to sinus rhythm (either spontaneous or DCCV)
- EP recording demonstrating PV isolation of all treated veins
- Recording of any right atrial arrhythmias mapped and/or treated
- Recording of all AADs infused during the procedure
- Recording of any medications administered for anticoagulation reversal

## 7.4 Follow-Up Procedures

### 7.4.1 Hospital Discharge

The subjects should be monitored with telemetry prior to hospital discharge for the documentation of recurrence of atrial fibrillation or other atrial tachyarrhythmias.

The following evaluations should be completed prior to discharge:

- Physical exam (including neurological assessment)
- Medication history
- Evaluation of Adverse Events
- 12-lead electrocardiogram

Careful attention should be placed in the identification of potential cardiac effusions and post-procedure cardiac tamponade. Unexplained reduction in blood pressure, chest pain or

shortness of breath require a post-procedure TTE and further evaluation and management as indicated.

### 7.4.2 Seven Day Phone Follow-Up

Subjects should be contacted by phone at seven (7 ± 3) days following their discharge from the hospital. Information regarding their groin access sites and sense of any irregular heart rate should be obtained. The Study Coordinator should also review current medications, review the follow-up schedule, and answer any questions the subject might have. If any concerns arise that suggest adverse events, the subject may be asked to return to clinic for a thorough evaluation. Any visits prior to the one-month visit should be captured on the Unscheduled Visit eCRFs.

### 7.4.3 Visits at One, Three, Six, and Twelve Months

The following evaluations will be performed during each clinic follow-up visit. Data will be recorded on the Follow-Up eCRFs.

- History and Physical exam (including neurological assessment)
- Medication history
- Adverse events assessment
- 12-lead electrocardiogram
- Echocardiogram (TTE at 12 months only, for comparison to baseline)
- AFEQT Questionnaire (completed prior to visit)
- 24-hour continuous monitor (3, 6, 9, and 12 months)
    - Since the 24-hour continuous monitor at 9-months does not coincide with a follow-up visit, the subject will be instructed how and when to wear the recording device. Once the recording is completed, the device will be returned to the study site and the results of the recording will be entered into an eCRF.

### 7.4.4 Unscheduled Visits

Any visit outside of the scheduled follow-up visit windows will be considered an unscheduled visit. All pertinent data will be recorded on the Follow-up Visit eCRF.

## 7.5 Recurrence of Atrial Fibrillation/Atrial Flutter/Atrial Tachycardia (AF/AFL/AT)

<u>Arrhythmia Recurrence during the Blanking Period</u>

Occurrences of symptomatic atrial fibrillation or other (tachyarrhythmias) during the first 90 days post-ablation (blanking period) may be transient in nature and not associated with the

long-term effectiveness of the ablation treatment. However, prolonged AF should be treated as soon as possible to maintain sinus rhythm during the remodeling period. Treatment should follow the Investigator's standard of care for AF recurrence, which may include a DCCV and/or AAD administration. Repeat ablations may be considered during the blanking period; however, they are discouraged.

Arrhythmia Recurrence beyond the Blanking Period

Development of AF/AFL/AT beyond the blanking period should first be documented with an ECG or a24-hour continuous ECG monitor. Recurrence of an arrhythmia will be recorded on the eCRF as part of the continued management process of the subject in follow-up. These will be documented at unscheduled or routine (three-, six- and twelve-month) follow up visits.

Treatment should follow the Investigator's standard of care and may include DCCV, AAD administration or repeat ablation (retreatment procedure). Use of a DCCV is recommended prior to an ablation as many of these arrhythmias may be self-limited. One retreatments is allowed and may only occur in the time range from day 91 through day 270 post-ablation.

In a retreatment procedure, the AcQMap System should be used following the same protocol as the index procedure. Documentation of the retreatment will be on the procedure retreatment eCRF form. Follow-up visits will restart using the same schedule as with the index procedure (7-day call, 1, 3, 6 months); however, the study completion date (12 months from the index procedure) will not change.

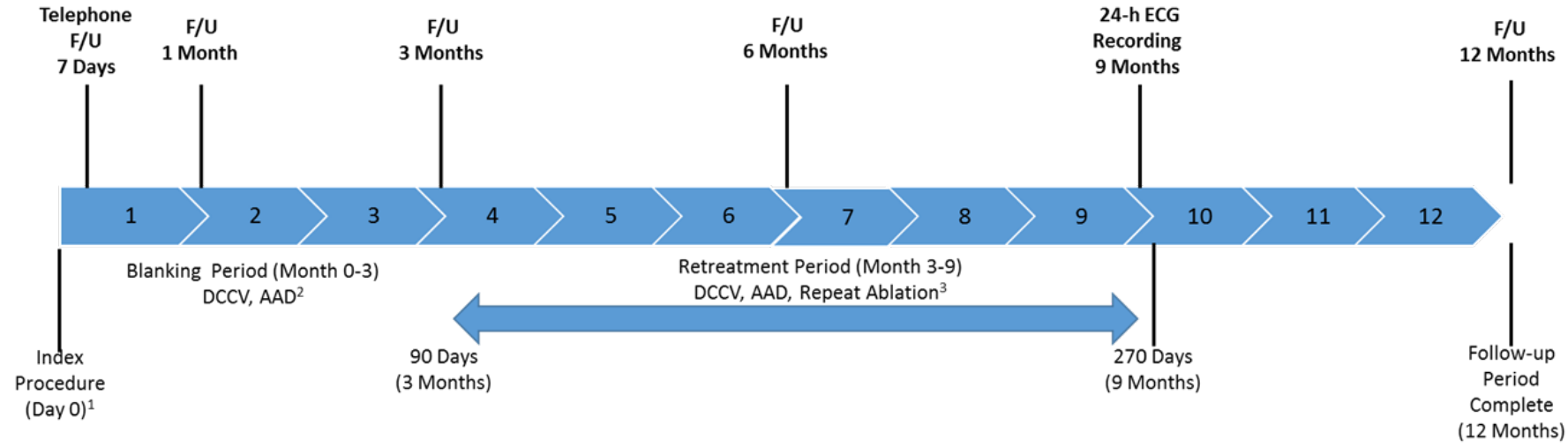
**Hospital admissions and clinic visits to treat these arrhythmias (cardioversion, in-patient medication change and ablation) will not constitute an SAE but will be reported as an additional intervention to the management of the persistent AF**. In the event the subject suffers an untoward or unanticipated complication as a result of the arrhythmia (i.e. thrombotic event, pulmonary edema etc.), an adverse event reporting will occur and be adjudicated by the Clinical Events Committee in accordance with the CEC Charter.

Screening, procedure and follow-up visits are outlined in Table 2 and a flow diagram of visits is pictured in Figure 10.

**Table 2: Schedule of Events**

| | **Screening**[1] **& Baseline** | **Procedure** | **Discharge** | **7 Days** (± 3 days) **Phone Contact** | **1-month** (± 7 days) | **3-month** (± 14 days) | **6-month** (± **30 days**) | **9-month** (± **30 days**) | **12-month** (± **30 days**) |
|---|---|---|---|---|---|---|---|---|---|
| **CIP Informed Consent** | **X** | | | | | | | | |
| **Medical History** | **X** | | | | | | | | |
| **History & Physical Exam** | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **Medications** | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **Transthoracic Echo (TTE)** | **X** (within 6 months) | | | | | | | | **X** |
| **Trans Esophageal Echo (TEE)** | | **X** (within 72 hours) | | | | | | | |
| **Adverse Events** | | **X** | **X** | **X** | **X** | **X** | **X** | | **X** |
| **12-lead ECG** | **X** | **X** | **X** | | **X** | **X** | **X** | | **X** |
| **Labs** | **X** | | | | | | | | |
| **HCG (female patients)** | **X** | | | | | | | | |

| | **Screening**[1] **& Baseline** | **Procedure** | **Discharge** | **7 Days** (± 3 days) **Phone Contact** | **1-month** (± 7 days) | **3-month** (± 14 days) | **6-month** (± **30 days**) | **9-month** (± **30 days**) | **12-month** (± **30 days**) |
|---|---|---|---|---|---|---|---|---|---|
| **Patient Reported Outcome Measures (AFEQT)** | **X** | | | | **X** | **X** | **X** | | **X** |
| **24-hour Continuous ECG Monitor Recording** | | | | | | | **X** | **X** | **X** |




1. Index Ablation and no additional procedures
2. Index Ablation and only DCCV or AAD through Month 3
3. DCCV, AAD, repeat ablation beyond blanking period, through Month 9

**Figure 2: Flow Diagram of Follow-Up and Retreatment Procedures**

# 8 STATISTICAL METHODS

## 8.1 Analysis Population

The following analysis populations will be defined for the study:

**Safety Population** – The safety population will include all enrolled subjects who have the venous access portion of the ablation procedure initiated.

**Treatment Population** – The treatment population will include all enrolled subjects who complete a procedure up to the point the AcQMap catheter is deployed in the left atrium.

## 8.2 Statistical Analysis for Primary Safety Outcome Measure

The primary outcome measure for the study is the primary safety objective, defined as the proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs), as adjudicated by the CEC, that occur within the first twenty-four (24) hours post-procedure. Subjects who remain free from such device/procedure related MAEs will be considered a success with respect to the primary safety objective, and subjects who experience at least one such MAE will be considered a primary safety failure. MAEs that occur during the first 24 hours will be reported and adjudicated by the CEC for any probable relationship to the device and/or procedure.

## 8.3 Statistical Analysis for Secondary Outcome Measures

Descriptive statistics will be applied to the secondary outcome measures

## 8.4 Study Size Justification

The total sample size for the combined studies was selected based on the primary safety objective of the study. In order to estimate the primary safety objective within a margin of error of 3.89% (i.e., this is the 95% confidence interval half-width), assuming the observed proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs) that occur within the first 24 hours post-procedure is 96.0%, a total of 125 subjects is required. These calculations assume the data are from a binomial distribution and that the confidence interval will be computed using the Clopper-Pearson exact approach.

# 9 ADVERSE EVENTS

For the purpose of this protocol, an adverse event is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs in subjects whether or not related to the AcQMap System, and includes events related to the procedures involved

in the clinical investigation plan. Any adverse event (AE) that occurs in a subject once they are considered a "safety" population is considered an AE. Any medical conditions, problems, signs, symptoms, and findings occurring prior to enrollment are to be reported as pre-existing conditions on the Medical History eCRF.

**Serious Adverse Events (SAEs)**

A Serious Adverse Event is any adverse event that:[17]

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

Reports relating to the subject's subsequent medical course following an SAE must be submitted to the Sponsor and the reviewing EC until the event has subsided or, in the case of permanent impairment, until the event has stabilized and the overall clinical outcome has been ascertained.

**A planned, in-patient hospitalization, without a serious deterioration in health, is not considered to be a serious adverse event.**

**Adverse Device Effects (ADEs)**

Adverse device effects (ADE) are a subset of adverse events. The ADEs are only those adverse events caused by, or related to, the device, including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the System components, or any product malfunction, including any event that is a result of a user error or intentional misuse.

With any procedure or treatment, there are known possible risks and complications. A list of known or anticipated adverse events for the AcQMap™ System is found in the IFU.

**Unanticipated Adverse Device Effects (UADEs)**

[17] ISO 14155: 2011 section 3.37

Investigators are required to submit a report to the Sponsor as soon as possible of any suspected Unanticipated Adverse Device Effect (UADE) occurring during an investigation, but in no event later than five (5) business days after the Investigator first learns of the effect.

When an Investigator suspects an event meets the definition for a UADE, then the event, date of onset, seriousness, severity, duration, treatment, outcome and relationship to device will be recorded on the Adverse Event CRF. Additionally, reports must be provided to the reviewing EC per national and local requirements.

The Sponsor/manufacturer must then conduct an evaluation of the suspected UADE and report the results of the findings to the Notified Body and to all reviewing ECs and participating Investigators within five (5) business days after first receiving notice of the effect. Thereafter, the Sponsor shall submit such additional reports concerning the effect as the Notified Body requests.

## 9.1 Adverse Event Reporting

The Investigator is responsible for reporting all adverse events that occur during the study. Initial reporting will be with the Adverse Event eCRF; however, additional information may be required by the Sponsor, the CEC, the Ethics Committee, or any other regulatory authority. The Investigator should report any serious adverse events (SAEs), serious adverse device effects, (SADEs), or unanticipated adverse device effects (UADEs) to the Sponsor as soon as possible after becoming aware of the event, but not later than five (5) business days after receiving knowledge of the event occurrence. All SAEs, SADEs, and UADEs will be documented on the Adverse Event eCRF along with an explanation of any medical treatment administered. Documentation should include the time of onset, complete description of the event, severity, duration, actions taken and outcome.

## 9.2 Event Relationship to the Device

The Investigator should provide information regarding the relationship of the event to the AcQMap™ System and the persistent AF ablation procedure. The device relationships are defined in the table below:

**Table 3: AE Relationships**

| | |
|---|---|
| Not Related | The cause of the AE is known and is not related to any aspect of the mapping and imaging portion of the persistent AF ablation procedure. |
| Possibly Related | There is a reasonable possibility that the event may be related to the mapping and imaging portion of the persistent AF ablation procedure. The AE has a **timely relationship** to the study procedure(s); **however, it follows no known pattern of response** and an alternative cause seems more likely or there is significant uncertainty. |
| Probably Related | It is probable that the event was related to the mapping and imaging portion of the persistent AF ablation procedure. The AE has a **timely relationship** to the study procedure(s) and **follows a known pattern of response**, but a potential alternative cause may be present. |
| Definitely Related | The event was definitely related to the mapping and imaging portion of the persistent AF ablation procedure. A related event has a strong temporal relationship and an alternative cause is unlikely. |

## 9.3 Death Notice

When a site becomes aware of a subject's death, it should be reported to the Sponsor. Notification should be made to the reviewing EC per local requirements.

The materials to be submitted to the Sponsor for a death include the following:

- Death narrative: A short description by the treating physician of record at the time of death regarding the circumstances of death.
- An assessment by the Investigator as to whether the death is related to study interventions.
- A copy of the patient's death certificate.
- When applicable, a copy of an autopsy report.

For reported deaths, the Investigator or designee should supply the Sponsor and the presiding EC with any additional requested information, if available (i.e., hospital records).

### 9.4 Device Complaint and Malfunction

Each clinical procedure will be attended by Acutus Medical personnel responsible for the proper use of the technology. In the event that a malfunction occurs, the Sponsor representative will report the findings to the Clinical and R & D departments. Evaluations of all complaints will follow Acutus Medical QAPs for complaint handling. Any trends information for complaints may be evaluated by the CEC.

### 9.5 Clinical Events Committee (CEC)

Acutus Medical (or designee) will coordinate the convening of meetings of a Clinical Events Committee (CEC) in accordance with the QAP and the CEC Charter specific to this study. The CEC has the responsibility to independently review and comment on all data and safety aspects of the trial. Based on their review, the committee may make recommendations regarding all aspects of the conduct of the study, including the termination of the study. All recorded minutes of the meetings and actions will be kept on file and available for review as requested.

## 10 RISK: BENEFIT ANALYSIS

### 10.1 Risks

The following adverse events are associated with electrophysiology mapping and ablation procedures:

- Adult Respiratory Distress Syndrome
- Air embolism
- Anemia
- Anesthesia reaction
- Arrhythmias
- AV fistula
- Atrial esophageal fistula
- Cardiac perforation/tamponade
- Cardiac thromboembolism
- Cerebral infarct (hemorrhagic or thromboembolic)
- Chest pain/discomfort
- Complete heart block
- Congestive heart failure
- Coronary artery spasm
- Death
- Endocarditis
- Obstruction, perforation or damage to the vascular system
- Pericardial effusion
- Pericarditis
- Phrenic nerve damage
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Radiation injury
- Respiratory depression
- Seizure
- Skin burns
- Temporary complete heart block
- Thrombi

- Expressive aphasia
- Heart failure
- Hemothorax
- Increased phosphokinase level
- Infections
- Laceration
- Leakage of air or blood into the lungs or other organs due to perforation
- Local hematomas/ecchymosis
- Myocardial infarction
- Thromboembolism
- Transient ischemic attack
- Unintended (in)complete AV, sinus node block or other heart block or damage
- Valvular damage/insufficiency
- Vascular bleeding
- Vasovagal reactions
- Ventricular tachycardia
- Worsening chronic obstructive pulmonary disease

### 10.2 Mitigation of Risks

Pre-clinical research and current clinical studies have demonstrated that the system is safe for human use. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels. Acutus Medical believes that the potential benefits of the system outweigh the potential risks.

## 11 DATA QUALITY ASSURANCE

Acutus Medical will oversee a database for this study in accordance with regulatory data integrity requirements, the Data Management Plan (DMP), and corporate QAPs. Data will be collected and entered on the eCRFs in the database. Data will be reviewed for accuracy and completeness by Acutus Medical (or designees) during all onsite and remote monitoring visits, and throughout the data management process. Any discrepancies will be resolved with the Investigator or designees, as appropriate. In order to preserve data integrity and security of the database, access to the database will be controlled by Acutus Medical and shall be limited to appropriately trained personnel with assigned log-on credentials.

### 11.1 Data Management

The standard procedures for handling and processing records will follow Acutus Medical (or designee) QAPs for data management. All data collection will be in compliance with Good Clinical Practice (GCP). A comprehensive Data Management Plan (DMP) will be developed prior to the start of the clinical study.

For the duration of the study, the Investigator and their designees will maintain complete and accurate documentation, including but not limited to, medical records, study progress notes, laboratory reports, signed patient informed consent forms, device accountability logs, correspondence with the reviewing EC, correspondence with

Acutus Medical (or designees) and study monitors, adverse event reports, and information regarding subject discontinuation/withdrawal or completion of the study.

The Investigator/Institution will permit direct access to source data and documents in order to complete study-related monitoring, audits, EC reviews, event adjudication and regulatory inspections that may be performed. The Investigator will obtain, as part of the informed consent process, permission for authorized Sponsor employees, study monitors or regulatory authorities to review, in confidence, any records that identify subjects in this study.

## 11.2 Subject Identification

Subjects will be identified on all eCRFs and source documents by a unique identification reference, which will be issued once the Informed Consent has been signed. An identification reference may not be reused for any reason.

## 11.3 Screen Failure Subjects

Subjects who are screened for the study but are not enrolled for any reason will not be followed and their data will not be used for any outcomes analysis. The screening eCRF should be completed for all screen failure subjects.

## 11.4 Subject Study Completion and Withdrawal

A subject will be considered completed when the twelve- (12) month visit is completed and all data collection is complete. Subjects who withdraw for any reason will have all available data entered into the database. Reasons for withdrawal will be entered on the Study Completion eCRF.

## 11.5 Subjects Lost-to-Follow-Up

A subject will be considered lost-to-follow-up from the last missed clinical evaluation if all reasonable efforts made to contact the subject and request their continued participation in the study have failed. All attempts to contact the subject will be documented.

Whenever possible, subjects who have been withdrawn for reasons other than lost-to-follow-up will be contacted and requested to participate in ongoing safety data assessments, which will be conducted by phone.

## 11.6 Confidentiality of Data

Information regarding study subjects will be kept confidential and managed according to the requirements and regulations of the local and national governing bodies and QAPs of Acutus Medical or participating CROs.

All data and information collected during this study will be considered confidential by Acutus Medical and their delegates. All data used in the analysis and summary of this study will be anonymous, and without reference to specific subject names. Access to subject files will be limited to authorized personnel of Acutus Medical (including core labs), the Investigator, Clinical Site research staff and authorized Regulatory Authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study.

## 11.7 Source Documents

Source data encompasses all information, original records of clinical findings, observations, or other activities, which are required in a clinical trial for the reconstruction and evaluation of the trial. Examples of these original documents, and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, copies of clinic and procedural site coding and billing records, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, and at the laboratories involved in the clinical trial.

Regulations require that the Investigator maintain information in the patient's medical records that corroborate data collected for the study. In order to comply with these regulatory requirements, the following is a list of information that should be maintained, at a minimum:

- Medical history/general physical condition of the subject before involvement in the study, which will be of a sufficient nature to verify the protocol eligibility criteria.
- Study/progress notes, including the date of entry into the study, documenting the following:
  - The general health of the subject.
  - The discussion of the study risks and benefits with the patient.
  - Completion of the informed consent process.
  - A statement that the subject reviewed and signed the patient informed consent form.
- Dated notes from each subject visit to support all data recorded on the eCRFs.

- Adverse Events reported and their continuation or resolution at each visit, including supporting documentation, such as discharge summaries, lab results, non-invasive testing reports, etc.
- Notes regarding protocol-required and prescription medications taken during the study (including start and stop dates, dosage, and routes of administration, if known).
- Subjects general health and medical condition upon completion of, or withdrawal from the study.

## 11.8 Electronic Case Report Forms (eCRFs)

This study will use an electronic Case Report Form (eCRF) as the primary data collection instrument and will record data by electronic capture. All data requested on the eCRF must be entered in a timely manner. All missing data must be explained. If an entry on the eCRF is left blank because the procedure was not done or the question was not asked, a query will be generated for the site data entry staff. If a data entry error has been made, the corrected information will be entered on the eCRF. All such changes are recorded in the audit and queries report.

Specific instructions to complete the eCRFs will be provided to the Investigator and other site personnel, as appropriate. The Investigators (and designees) are responsible for reporting clinical study-requested information in the eCRFs.

## 11.9 Records Retention

The Investigator will retain study essential documents for two (2) years after formal closure or discontinuation of the trial. These documents must be retained for a longer period if required by an agreement with Acutus Medical or defined by local or national regulations. Acutus Medical will inform the Investigator/Institution as to the date of formal closure or discontinuation of the trial and when these documents no longer need to be retained.

## 11.10 Clinical Monitor

A clinical research organization has been designated as the clinical monitor for this study. Their personnel are qualified by training and experience to oversee the conduct of the study. The Clinical Monitor's responsibilities include maintaining regular contact with each investigational site through telephone contact and on-site visits to ensure that: 1) the CIP is followed; 2) complete, timely, and accurate data are submitted; 3) problems with inconsistent and incomplete data are addressed; 4) complications and Unanticipated Adverse Device Effects are reported to the Sponsor; and 5) the site facilities continue to be adequate.

## 11.11 Clinical Data Monitoring Procedures

Acutus Medical Clinical Trial Monitors (or designees) will conduct site visits at the study facilities to monitor the study, which will be in compliance with the CIP, QAPs, and the Clinical Monitoring Plan (CMP). Monitoring visits will occur as defined in the CMP. The Investigational site agrees to allow these monitors and other authorized Acutus Medical personnel access to information and clinical supplies related to the study. The Acutus Medical monitors will verify data entered into the eCRFs against hospital/clinic records or other source documents, in order to ensure accuracy and completeness of the eCRFs for each subject. Clinical Investigators and their staff agree to assist the monitors in their activities. Requests may be made to review patient charts by Acutus Medical personnel and/or designee(s) so that protocol adherence and source documentation can be verified.

Monitoring visits will be performed at regular intervals throughout the course of the study to ensure compliance with the protocol. Monitoring activities may include, but are not limited to:

- Evaluation of subject screening and selection methods
- Verification of signed informed consent for each subject
- Verification of source documentation against completed case report forms for each subject
- Assurance that required study reports, including reports to the applicable EC, are generated in a timely manner
- Monitoring of Safety Events, including device deficiencies that may have led to an SAE
- Monitoring of device deficiencies, irrespective of associated safety events
- Review of device accountability records and device reconciliation
- Review of protocol deviations
- Overall study compliance
- Review of the Investigator Site File

## 11.12 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, the principles of Good

Clinical Practice (GCP), ISO 14155: 2011, applicable regulatory requirements, and institutional procedures.

## 11.13 Deviations from the Clinical Investigational Plan

A protocol deviation is defined as an event in which the Investigator or site personnel deviates from the study protocol or study procedures. It is the Investigator's responsibility to ensure that there are no deviations from the protocol. On a rare occasion, a waiver to a screening test, exclusion criteria, or protocol-specific procedure may be granted in advance by Acutus Medical and must be reported in full compliance with all established procedures and conditions of the reviewing EC.

An Investigator may deviate from the protocol without prior written approval from Acutus Medical in cases of medical emergencies to protect the life or physical well-being of a subject. In the event of an emergent deviation, the Investigator is required to notify Acutus Medical and the applicable EC as soon as possible, but in no event later than 5 business days from the occurrence of the deviation from the protocol.

Except in such an emergency, prior approval by Acutus Medical is required for changes in, or deviations from, the protocol. Additionally, if these changes or deviations affect the scientific soundness of the investigational plan or the rights, safety, or welfare of human subjects, EC notification is required.

Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., the subject was not available for a scheduled follow-up office visit or has moved without providing a forwarding address). These events, although outside the Investigators control, are still required to be reported on the appropriate Protocol Deviation eCRF in order to ensure that all deviations from the standard subject population are adequately documented and reported. The Investigator will inform Acutus Medical and the reviewing EC of all protocol deviations as per the EC requirements established for this study.

If Acutus Medical becomes aware that an Investigator is not complying with the any part of the Clinical Investigation Plan, including the signed Investigator Agreement, the protocol, or any conditions of approval imposed by the reviewing EC, Acutus Medical will immediately secure compliance, and may suspend the Investigator's participation (including enrollment at the site). Acutus Medical may terminate an Investigator's participation in the study at its discretion.

### 11.13.1 Maintaining Records

The Investigator will maintain the following accurate, complete, and current records related to the Investigator's participation:

- Correspondence with another Investigator, an EC, Acutus Medical, a Sponsor monitor or designee, or any regulatory agency.
- Records of each patient's case history and exposure to the device, including:
  - Documents evidencing informed consent and for participation in the clinical study without informed consent,
  - Any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent
  - All relevant observations, including records concerning adverse device effects (whether anticipated or not),
  - Information and data on the condition of each subject upon entering, and during the course of the investigation, including information related to relevant previous medical history and the results of all diagnostic tests,
  - A record of the procedure involving treatment with the AcQMap for each subject, including the date and time of the procedure.
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

### 11.13.2 Submitting Reports

In compliance with local and national laws, each Investigator may be required to prepare and submit complete, accurate, and timely reports to Acutus Medical and/or ECs. These reports may include:

- Any unanticipated adverse device effect occurring during an investigation.
- Any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency.
- A protocol deviation requiring prior written Acutus Medical approval (except in emergency situations). If the deviation affects the scientific soundness of the plan or the rights, safety, or welfare of subject, prior documentation of EC approval may be required.
- Any further information requested by an EC about any aspect of the investigation.

The Investigator will provide, in writing, any withdrawal of EC approval of the study or an Investigator within five (5) business days of such action.

## 11.14 Acutus Medical Responsibilities

### 11.14.1 General Duties

Acutus Medical has the overall responsibility for the conduct of the study, including assurance that the study satisfies the regulatory requirements of the appropriate regulatory agencies, ensuring EC approvals, selecting Investigators, ensuring proper monitoring and that informed consent is obtained. Acutus Medical will provide all information necessary to conduct the study, including the Clinical Study Protocol, and any reports of prior investigations, as appropriate. During the conduct of the clinical study, updates regarding information that may impact the clinical study will be made available to all appropriate national and local regulatory authorities.

### 11.14.2 Selection of Investigators

Acutus Medical will select Investigators (including Sub Investigators performing the procedure) qualified by training and experience. Sites will be selected based on a site assessment, appropriate facilities, clinical experience and the qualifications of the Principal Investigator. Investigators will be evaluated by Acutus Medical based on:

- Curriculum vitae, or other statement of Investigator's relevant training and experience, including type of experience with the intended procedure and clinical research, specifically
- Education and experience in the ablation management of arrhythmias
- Whether the Investigator has an adequate patient population to meet requirements of the study enrollment
- Whether the Investigator has adequate time to be personally involved in the conduct of the study, and adequate research staff and resources to support the study
- Whether the Investigator's Study Center is associated with an EC that satisfies all applicable regulatory requirements
- Whether an Investigator was involved in an investigation or other research that was terminated. This may require an explanation of the circumstances that led to the termination.

Prior to study initiation, each Investigator must also submit a:

- Certificate of human patient's protection training (if required by the reviewing EC),

- Signed Investigator's Agreement, indicating an Investigator's commitment to:
  - Conduct the investigation in accordance with the agreement, the Clinical Investigational Plan/protocol, GCP, and any conditions of approval imposed by the EC;
  - Supervise all testing of the device involving human subjects;
  - Ensure that the requirements for informed consent are met;
  - Conduct the study according to the Clinical Investigational Plan/protocol.

The Sponsor reserves the right to apply additional criteria to site and/or Investigator selection.

## 11.15 Training

Acutus Medical will provide training on the AcQMap™ System **prior** to enrolling any subject. Training may consist of a review of the IFU, hands-on training on the device and procedure, presentations, literature, etc. The training program will be standardized and will be documented. Additional training will include a review of the protocol, the regulations for medical device investigations and general study logistics required to complete the study.

Training of appropriate clinical study personnel will be the responsibility of Acutus Medical. To ensure uniform data collection and protocol compliance, Acutus Medical will review the Clinical Investigational Plan/protocol (including the ICF), techniques for identification of eligible subjects, instructions on data collection, methods for scheduling follow-up visits in the window, etc. Detailed feedback regarding completion of the eCRFs, study requirements, and protocol compliance will be provided by Acutus Medical, its study monitors, and/or designees, functioning in a data management capacity.

### 11.15.1 Changes in the Clinical Investigational Plan

Acutus Medical will obtain appropriate regulatory approval for any change to the Clinical Investigational Plan/protocol that may affect the scientific soundness of the investigation or the rights, safety and/or welfare of the subjects.

Acutus Medical will provide approved protocol amendments to the Investigators prior to implementing the amendment. The Investigator will be responsible for notifying the reviewing ECs of the protocol amendment (administrative changes) or obtaining

EC approval of the protocol amendment (changes in subject care of safety), according to the instructions provided with the protocol amendment. The EC acknowledgement/approval of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must be provided to Acutus Medical and placed in the Trial Master File (TMF).

### 11.15.2 Withdrawal of Regulatory Approval

Acutus Medical will notify all reviewing ECs and participating Investigators of any withdrawal of regulatory approval to conduct the clinical study, and shall do so within five (5) business days after receipt of notice of the withdrawal of approval.

## 12 ETHICS AND REGULATORY COMPLIANCE

### 12.1 Conduct of the Clinical Study

Conduct of the clinical study will follow QAPs from Acutus Medical, as well as the Declaration of Helsinki, Good Clinical Practices, ISO 14155: 2011, and other regional and local laws. Each Investigator must sign and date the Investigator Agreement prior to the start of this study. With the signature, the Investigator agrees to perform all study procedures according to the governing local and national regulations and the Clinical Investigational Plan Protocol.

### 12.2 Ethics Committee Approval

A properly constituted, valid Ethics Committee (EC) must review and approve the Clinical Investigational Plan (CIP), Informed Consent, and related patient information and recruitment materials prior to initiation of the study. It is the responsibility of the Investigator to obtain protocol approval from the institution's EC, and to keep the EC informed of any serious adverse events or serious adverse device effects and amendments to the protocol. Additional requirements imposed by the EC or other regulatory authority shall be followed as appropriate. All correspondence with the EC should be filed by the Investigator and copies sent to Acutus Medical (or designees).

### 12.3 Clinical Study Informed Consent Approval

In accordance with the principles of Informed Consent, the Declaration of Helsinki, Good Clinical Practice (GCP), and ISO 14155: 2011, informed consent will be obtained and documented in writing before a patient is enrolled in the clinical study.

It is the responsibility of the Investigator to ensure that a written informed consent is obtained from the patient (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care. Information obtained during

the conduct of the clinical study that may impact the patient informed consent may require revisions to the informed consent. If so, revisions and approvals of such changes by the appropriate regulatory authority is required. Documentation of the current versions of the informed consent will be documented in the clinical study TMF.

## 12.4 Identification and Confidentiality

Patient identification and confidentiality will be ensured in accordance with all applicable regulatory and Ethics Committee governance. This includes, but is not limited to, the following:

- Subjects will be identified on all eCRFs and source documents by a unique identification reference
- eCRFs are confidential documents and will only be made available to Acutus Medical (and appropriate designees), the Investigator, the biostatistician, the Clinical Events Committee (CEC), and, if requested, to advisory committees and regulatory authorities (including USFDA)
- Data will be stored and analyzed by computer following national regulations for handling of computerized data

Each Study Center will maintain (anonymous to Acutus Medical) a list identifying all patients entered into the trial. The list will be maintained as part of the investigation file and monitored for completeness.

## 12.5 Site Qualification Visits

A site qualification visit will be performed to evaluate site facilities, Investigator qualifications, and site knowledge of Good Clinical Practice (GCP) guidelines. Acutus Medical's QAP for site qualification visits will be followed and a report filed in the Trial Master File (TMF), which will be maintained by Acutus Medical.

## 12.6 Site Initiation Visits

All study personnel will be required to participate in a site initiation visit that follows Acutus Medical's QAP. Components of this initiation visit may include:

- Introduction of the study design including the protocol-specific treatment and follow-up phase
- Informed Consent process
- Product training to all end-users
- eCRF completion training

- Safety reporting instructions
- Training on the regulations governing human research
- Procedure training on the use of the device

## 12.7 Insurance

Acutus Medical shall maintain insurance coverage for this study. Pertinent information regarding the coverage shall be made available to the site upon request.

## 12.8 Site Audit Plan

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices. The Investigator and/or designee must be available to respond to reasonable requests and queries made by authorized regulatory representatives during the audit process. The Investigator must provide Acutus Medical with copies of all correspondence that may affect the review of the current study or their qualifications as an Investigator in this and future clinical studies conducted by Acutus Medical.

### 12.8.1 Site Data Audits by Acutus Medical

In accordance with local and national regulations and Acutus Medical's operating procedures, an internal audit may be requested to access all study records, including source documents, for inspection and duplication. The investigator will ensure the capability for inspections of applicable study-related functions.

Site data quality assurance audits may be conducted at various sites during the clinical study. Selection of sites to undergo auditing will be determined by the Acutus Medical as needed.

### 12.8.2 External Audits

Requests by regulatory agencies to inspect the study sites may be made as well. The Investigator and/or designee is required to report to Acutus Medical as soon as possible after receiving a request from a regulatory authority to perform an audit. The clinical Investigator agrees to allow inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

## 12.9 Investigational Device Traceability

The AcQMap™ System components will be stored at each site. All sites will maintain a device accountability log that will match patients to a particular device by a unique manufacturer number. At the conclusion of the study all unused devices will be returned to Acutus Medical.

### 12.10 Public Domain Access to the Clinical Study

A description of this clinical trial will be available on http//www.Clinicaltrials.gov. Information regarding the public access will be presented in the informed consent.

### 12.11 Required Reports

Acutus Medical will remain in compliance with all required and pre-specified reports during the enrollment and follow-up of the clinical study. EC requirements for reports, including minutes from CEC meetings, will be provided as requested.

## 13 GENERAL CONSIDERATIONS

### 13.1 Discontinuation of the Clinical Study

The Sponsor reserves the right to discontinue the study at any stage, with suitable written notice to the Investigator and the appropriate government regulatory agencies. Such decisions will be based on advice from the Scientific Advisory Board or Clinical Events Committee. Similarly, Investigators may withdraw from the study, subject to providing written notification to the Sponsor within 30 days of their intent to withdraw. However, the Sponsor and Investigators will be bound by their obligation to complete the follow-up of subjects already enrolled into the study.

Acutus Medical, as Sponsor, may terminate Investigator and site participation in the study if there is evidence of an Investigator's failure to maintain adequate clinical standards or evidence of an Investigator's or staff's failure to comply with the Clinical Investigation Plan/protocol.

Notification of suspension or termination will occur no later than five (5) business days after Acutus Medical makes the determination. In the event of study suspension or termination, Acutus Medical or designee will send a report outlining the circumstances to the reviewing EC, the appropriate regulatory agencies, and to all participating Investigators. Any suspension or termination may not be re-initiated without prior approval of the EC and Acutus Medical.

### 13.2 Use of Information and Publications

All information concerning Acutus Medical operations, patent applications, manufacturing processes, and basic scientific data supplied by Acutus Medical to the Investigator and not previously published, are considered confidential and remain the sole property of Acutus Medical This includes all study materials, CRF forms, worksheets and eCRFs.

The information developed in this study may be used by Acutus Medical as support for a regulatory filing and in connection with the continued development of the AcQMap™ System. Any publication or other public presentation of the data resulting from this study will require prior review and written approval of Acutus Medical.

At the conclusion of the study, it is expected that Acutus Medical and the Investigators will promptly prepare and submit a multi-center manuscript for publication in a reputable scientific journal. The publication of the principal results, including abstracts, from any single-site experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior written approval of Acutus Medical.

Further analyses, beyond those presented in the initial multi-center publication may be proposed to Acutus Medical. Many secondary manuscripts are anticipated. For purposes of timely abstract presentation and publication, such secondary publications may be delegated to the appropriate principal authors; however, final analyses and manuscript review for all multi-center data will require the prior written approval of Acutus Medical.

None of the results, in whole or part, of the study carried out under this protocol, nor any of the information provided by Acutus Medical for the purposes of performing the study, will be published or passed on to any third party without the consent of Acutus Medical. Any Investigator involved with this study is obligated to provide Acutus Medical with complete test results and all data derived from the study.

# 14 APPENDIX

## 14.1 Bibliography

A bibliography of pertinent publications identified or supportive of the clinical study will be maintained by Acutus Medical and available upon request.

# Statistical Analysis Plan (SAP)

## Utilizing Novel dipole density Capabilities to Objectively Visualize the Etiology of Rhythms in Atrial Fibrillation (UNCOVER-AF)

**Study Numbers: CL-AF-001 and CL-AF-002**

**Version 2.0**
**May 20, 2019**

**NCT02825992**

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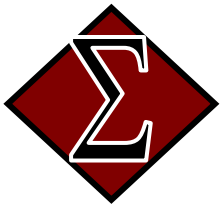

STATKING Clinical Services

# Revision History

**Version 1.1 to 2.0**

1. Listing 6 (AEs): modified to add columns specifying device relationship to AE for each device.
2. Listing 15 (Catheter Data): Part 5 header corrected. Part 4 Sheath Model number and Lot number added.
3. Listing 16 (PVI Data): Column added to identify visit and PVI count.
4. Table 2 and Time-to-event specification: TTE defined as TTE = End-Date – Start-Date rather than End-Date – Start-Date + 1.
5. Tables 7 and 35: Footnote added to state data source as continuous monitor data with 12 lead imputation when continuous monitor data are unavailable.
6. Table 16: Highest Relationship to Device expanded to summarize relationships to System, Catheter, Sheath, and PEK (in accord with added tables 20- 22).
7. Tables 16, 17, 18, 19 (AEs): Table sources modified to use CEC adjudication only, titles changed to reflect this. Text of Section 4.2.2 changed to reflect these changes.
8. Table 19 (AE Relationship to Device) – Changed to Relationship to AcQMap Catheter.
9. Tables 20-22 – Added to summarize additional AE relationship assessments.

**Version 1.0 to Version 1.1**

1. In Appendix B, the shell for Table 6 modified to include Total Procedure Time.

2. In Appendix B, the shell for Table 7 extensively modified to add AF only subtables. It is split into Table 7 (AF, AFl, and AT) and Table 32 (AF only). A complete list of the subtables is given below (*italics* represent current subtables):

   Table 32 (New)
   a. Freedom from AF with a single procedure.
   b. Freedom from AF with a single procedure without AADs.
   c. Freedom from AF with a single procedure with AADs.
   d. Freedom from AF with multiple procedures.
   e. Freedom from AF with multiple procedures without AADs.
   f. Freedom from AF with multiple procedures with AADs.

   Table 7 (Existing)
   *g. Freedom from AF/AT/AFL with a single procedure.*
   *h. Freedom from AF/AT/AFL with a single procedure without AADs.*
   *i. Freedom from AF/AT/AFL with a single procedure with AADs.*
   *j. Freedom from AF/AT/AFL with multiple procedures.*
   k. Freedom from AF/AT/AFL with multiple procedures without AADs.
   l. Freedom from AF/AT/AFL with multiple procedures with AADs.

3. Imputation of 12-Lead ECG rhythm for missing Holter data added to Appendix B. Table 22 divided into three parts to display 12-lead results at baseline, 1, 3, 6, and 12 months, Holter monitor data at 3, 6, 9, and 12 months, and results after imputation.

4. Appendix B. Table 33 added to cover medical history co-morbidities.

5. Treatment Population redefined in terms of atrial mapping rather than sensor deployment.

6. Data Listing 2: Date-of-birth column removed, because it is not present in the data file.

7. AFEQT questionnaire scoring algorithms added to text.

8. Data Listing 15 divided across 5 pages (from 3) to reduce line breaks.

# Table of Contents

# 1.0 Synopsis of Study Design Procedures

This Statistical Analysis Plan (SAP) describes the analysis of data from Acutus Medical Studies CL-AF-001 and CL-AF-002, both referred to by the acronym UNCOVER-AF. The CL-AF-001 study is being conducted in Canada as a pre-market study, and the CL-AF-002 study is being conducted in Europe as a post-market study.

Data from both studies are considered suitable for pooling based on identical patient inclusion and exclusion criteria, procedures, and measurement methods for outcomes data. Moreover, the patients in the general population of the countries conducting the study have similar demographics. For the purposes of the analysis tables planned in this SAP, the data will be treated as data originating from a single study. Data listings will report the study number in order to identify the protocol under which each individual subject was enrolled.

Each study is a prospective, single-arm, multi-center, multi-national, non-randomized study designed to provide clinical data regarding the use of the AcQMap® System in the ablation of persistent atrial fibrillation (AF).

The objective of the statistical analyses is to evaluate the incidence of device- and procedure-related safety, efficacy, and efficiency (six and 12 month outcomes) when using the AcQMap as an imaging and mapping system for ablation of persistent AF.

## 1.1 Design and Treatment

Subjects will be enrolled in the trial for approximately 12 months. All enrolled subjects will undergo an ablation procedure using the AcQMap Imaging and Mapping System as the only advanced 3D navigation system. The AcQMap Imaging and Mapping System is intended for imaging and mapping of cardiac chambers, which will be utilized in the management of cardiac arrhythmias.

## 1.2 Study Procedures

Subject assessments will occur at screening, procedure, hospital discharge, one, three, six, nine, and 12 months. A follow up phone call will also occur seven days post-procedure.

Inclusion and exclusion criteria will be assessed prior to enrollment and during the screening period up through the pre-procedure required transesophageal echocardiogram (TEE). Assessments performed during screening will include subject demographics, medical history, physical exam findings, transthoracic echo (TTE) results (within previous six months), clinical laboratory exams, electrocardiograms (ECGs), the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire and the aforementioned TEE.

Subjects who meet all inclusion and exclusion criteria will be enrolled into the study and will proceed to receive an ablation procedure. Prior to hospital discharge, the following post-procedure evaluations will be completed: physical exam, 12-lead ECG, collection of concomitant medications and reporting of all adverse events. A phone call will occur seven days following hospital discharge to review concomitant medications, adverse events, and scheduled follow up visits.

Follow up clinical visits will occur at one, three, six, and 12 months. The following evaluations will be performed:

- History and physical exam (including neurological assessment)
- Medication history
- Adverse events assessment
- Vital Signs
- 12-lead electrocardiogram
- Echocardiogram (TTE at 12 months only, for comparison to baseline)
- AFEQT Questionnaire (completed prior to the clinic visit)
- 24-hour continuous monitor (three, six, nine, and 12 months post ablation procedure)
    - Since the 24-hour continuous monitor at nine months does not coincide with a follow-up visit, the subject will be instructed how and when to wear the recording device. Once the recording is completed, the device will be returned to a core lab. Results will be compiled and reported to the site and Sponsor. Results of the recording will be entered into an electronic case report form (eCRF).

### 1.3 Sample Size

The total sample size for the combined studies was selected based on the primary safety objective of the study. In order to estimate the primary safety objective within a margin of error of 3.89% (i.e., this is the 95% confidence interval half-width), assuming the observed proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs) that occur within the first 24 hours post index procedure is 96.0%, a total of 125 subjects is required. These calculations assume the data are from a binomial distribution and that the confidence interval will be computed using the Clopper-Pearson exact approach.

## 2.0 Data Analysis Considerations

### 2.1 Types of Analyses

Data analyses will consist of descriptive statistics and confidence intervals. Tests of hypotheses will not be conducted.

## 2.2 Analysis Populations

The following analysis populations will be defined for the study:

**Safety Population** – The safety population will include all enrolled subjects who have the venous access portion of the ablation procedure initiated.

**Treatment Population** – The treatment population will include all enrolled subjects who complete a procedure up to the point the AcQMap catheter has completed mapping the atrial anatomy.

The analysis of the primary safety objective of the study will be based on the safety population. The analysis of the secondary safety and effectiveness outcomes will be based on the safety population or the treatment population as indicated in Sections 4 and 5 below.

### 2.2.1 Subgroup Definitions

There are no subgroup analyses planned for this study.

## 2.3 Missing Data Conventions

With the exceptions noted below, no missing value imputation will be used. That is, all analyses will be based on the observed data (i.e., complete case analysis).

Missing 24-hour Holter rhythm data will be imputed from 12-lead ECG results for the corresponding visit at 3, 6, and 12 months. Statistics will be computed for complete case analysis and with the imputed data present.

In case of missing data for dates, January will be imputed for missing months and the first will be imputed for missing days for purposes of elapsed time computations.

## 2.4 Interim Analyses

No formal interim analysis is planned for this study. However, data collected up through the first 24 hours post procedure may be analyzed prior to all subjects completing this time point. This data may be used for publications and/or marketing purposes, but will not be used to change the study design or procedures. The study will continue as planned until the required sample size has been enrolled.

Additionally, once all subjects have completed the six month follow up visit, the data collected up through that visit may be analyzed. Data from the 12 month follow up visit will not be analyzed until all subjects complete the study.

Separate Interim Data Review Plan (IDRP) documents will be written to describe the procedures for performing the data reviews at 24 hours and six months post procedure.

### 2.5 Study Center Considerations in the Data Analysis

A study center is defined as a treatment administration site or group of treatment administration sites under the control and supervision of the same Principal Investigator (PI). There will be no selective pooling of study centers.

### 2.6 Documentation and Other Considerations

The data analyses will be conducted using SAS© Software, version 9.4 or later.

## 3.0 Analysis of Baseline Patient Characteristics

Baseline and demographic characteristics, including a detailed arrhythmia history, will be summarized for all subjects in the safety population. Continuous variables will be summarized via mean, standard deviation, median, range, and number of non-missing responses. Categorical variables will be summarized via counts and percentages.

Time-to-event (e.g., Time since first documented AF diagnosis) will be computed as

$$TTE = End\text{-}Date - Start\text{-}Date,$$

where TTE represents the time to the event, End-Date the ending date for the event, and Start-Date the starting date for the event.

## 4.0 Analysis of Safety

### 4.1 Description of Safety Objectives

#### 4.1.1 Primary Safety Objective

The primary measurable objective is an analysis of the proportion of subjects who are free from device/procedure related Major Adverse Events (MAEs), as adjudicated by the Clinical Events Committee (CEC), that occur within the first 24 hours post index procedure. MAEs include any of the following:

- Death
- Cardiac perforation/tamponade
- Cerebral infarct, transient ischemic attack (TIA), or systemic embolism
- Major bleeding
- Mitral or tricuspid valvular damage
- Other serious adverse device effects (SADEs) adjudicated by an independent CEC as “probably related” to the AcQMap System

### 4.1.2 Secondary Safety Objectives

The secondary safety analysis measures are defined as follows:

- All adverse events (AEs) reported through 12 months
- 12-lead ECGs and Holter monitor results
- Physical exam findings
- Vital signs

## 4.2 Analysis of Safety Objectives

### 4.2.1 Analysis of Primary Safety Objective

Subjects who remain free from device/procedure related MAEs, as adjudicated by the CEC, that occur within the first twenty-four (24) hours post index procedure will be considered a success with respect to the primary safety objective, and subjects who experience at least one such MAE will be considered a primary safety failure. MAEs that occur during the first 24 hours will be reported and adjudicated by the CEC for any probable relationship to the device and/or procedure.

The analysis of the primary safety objective will be performed on the safety population. The number and proportion of subjects in the safety population who are primary safety successes will be computed, along with a 95% exact binomial (i.e., Clopper-Pearson) confidence interval on the proportion.

### 4.2.2 Analysis of Secondary Safety Objectives

With the exception of treatment emergent adverse events (TEAEs), all analysis of secondary safety objectives will be conducted on the treatment population. TEAE analyses will be conducted on the safety population.

#### Adverse Events

All treatment-emergent AEs (TEAEs) occurring during the study will be recorded and classified on the basis of the Medical Dictionary for Regulatory Activities (MedDRA®) terminology. Treatment-emergent AEs are those AEs with an onset on or after the start time of the ablation procedure (defined as the point the AcQMap catheter is deployed in the left atrium). All TEAEs will be categorized by the number of subjects reporting the TEAE, severity, device relationship as adjudicated by the CEC (not related, possibly related, probably related, and definitely related), procedure relationship as adjudicated by the CEC (not related, possibly related, probably related, and definitely related), and seriousness. A separate relationship table will be provided for each device in the study (AcQMap System, AcQGuide Sheath, AcQMap Catheter, and Patient Electrode Kit).

A separate TEAE summary table will be constructed to display the number of TEAEs, the number of subjects with at least one TEAE, the maximum severity per subject, the maximum device relationship per subject, the maximum procedure relationship per subject, the number of subjects experiencing at least one serious TEAE, the number of withdrawals from the study due to a TEAE, and the number of deaths.

The device and procedure relationships used in the analysis tables will be based on the CEC adjudicated results. However, the relationships assigned by the investigators will be listed. TEAE adjudicated as non-events by the CEC will not be analyzed.

### 12-Lead ECGs

12-Lead ECGs will be performed in screening, prior to procedure (baseline), at the completion of procedure, prior to hospital discharge, and at one, three, six, and 12 months post-procedure. The number and percent of subjects with each ECG rhythm will be reported by time point.

### 24-Hour Holter Monitor

A 24-Hour Holter monitor of heart rhythm will be completed at three, six, nine, and 12 months. The number and percent of subjects with each heart rhythm will be reported by time point. The Holter data will be listed along with the 12-Lead ECG data.

### Physical Exam Findings

Physical exams will be performed at screening (baseline), pre-procedure, discharge, and at the one, three, six, and 12 month follow up visits. A physical exam shift table will be constructed for each post-procedure time point in order to count the frequency of each shift for each body system. Shifts include normal/normal, normal/abnormal, abnormal/normal, and abnormal/abnormal.

### Vital Signs

Vitals signs will include heart rate, blood pressure, and temperature. Vital signs will be taken at screening (baseline), discharge, and at the one, three, six, and 12 month follow up visits. For each vital sign, summary statistics (mean, standard deviation, median, range, n) on the raw as well as their changes from baseline will be presented by timepoint. If repeat vital signs are taken at a given time point, then the last measurement will be used for the analysis tables. All vital signs will be listed.

# 5.0 Analysis of Effectiveness

## 5.1 Description of Effectiveness Objectives

### 5.1.1 Description of Primary Effectiveness Objective

The primary objective of this study is categorized as a safety measure (see Section 4.1.1). All effectiveness objectives are considered to be secondary and are described in Section 5.1.2.

### 5.1.2 Description of Secondary Effectiveness Objectives

Secondary measurable effectiveness objectives include the following, which are divided into procedure outcome measures and clinical outcome measures.

The **procedure outcome measures** are:

- Proportion of subjects with acute procedural (ablation) success defined as:
  - Conversion to sinus rhythm (with or without direct current cardioversion [DCCV]) within 12 hours of the procedure
  - Procedural conversion to atrial flutter, atrial tachycardia or other organized supraventricular rhythm
- Procedure fluoroscopy time
- Ablation time to complete PVI
- Ablation time for non-PVI ablation
- Ablation time for right atrial ablation
- Number of DCCV completed during the procedure

The **clinical outcome measures** are:

- Proportion of subjects with freedom from documented episodes of AF/AT/AFL lasting longer than 30 seconds, based on the 24-hour continuous ECG monitor at three, six, nine, and 12 months post ablation. Analysis will include:
  - Freedom from AF/AT/AFL without AADs
  - Freedom from AF/AT/AFL with AADs
  - Freedom from AF/AT/AFL with a single procedure
  - Freedom from AF/AT/AFL with multiple procedures
- Improvement of left atrial (LA) size at 12 months compared to baseline
- Number of repeat ablation procedures in follow-up period from day 91-270 (i.e., from three months to nine months)
- Number of DCCV in first 90 days post-ablation
- Number of DCCV from day 91-365 (i.e., from three months to 12 months)
- Changes in patient reported outcomes (PROs) in the follow-up period, based on the AFEQT questionnaire

## 5.2 Analysis of Effectiveness Objectives

### 5.2.1 Analysis of Primary Effectiveness Objective

N/A

### 5.2.2 Analysis of Secondary Effectiveness Objectives

All secondary effectiveness analyses will be conducted on the treatment population.

**Procedure Outcome Measures**

The continuous procedure outcome measures, which include procedure fluoroscopy time, ablation time to complete PVI, ablation time for non-PVI ablation, ablation time for right atrial ablation, and the number of DCCV completed during the procedure will be summarized via mean, standard deviation, median, range, and number of non-missing responses. Ninety-five percent (95%) confidence intervals (CIs) on the mean will also be provided.

The categorical procedure outcome measure of acute procedural success will be summarized by the number of successful subjects and the proportion of successful subjects. An exact binomial 95% CI on the proportion will also be provided.

**Clinical Outcome Measures**

The number and proportion of subjects with freedom from documented episodes of AF/AT/AFL lasting longer than 30 seconds, based on the 24-hour continuous ECG monitor at three, six, nine, and 12 months post ablation will be displayed, along with exact binomial 95% CI's for each proportion. Separate proportions and confidence intervals will be calculated for:

- Freedom from AF/AT/AFL with a single procedure
- Freedom from AF/AT/AFL with a single procedure without AADs
- Freedom from AF/AT/AFL with a single procedure with AADs
- Freedom from AF/AT/AFL with multiple procedures
- Freedom from AF/AT/AFL with multiple procedures without AADs
- Freedom from AF/AT/AFL with multiple procedures with AADs.
- Freedom from AF with a single procedure
- Freedom from AF with a single procedure without AADs
- Freedom from AF with a single procedure with AADs
- Freedom from AF with multiple procedures
- Freedom from AF with multiple procedures without AADs
- Freedom from AF with multiple procedures with AADs.

Descriptive statistics (mean, standard deviation, median, range, and number of non-missing responses) on the raw and change from baseline (CFB) LA size will be reported

at 12 months, along with a separate set of descriptive statistics for the raw baseline data. A 95% CI on the mean will also be provided.

The number of repeat ablation procedures in follow-up period from day 91-270 (i.e., from three months to nine months) will be summarized via mean, standard deviation, median, range, and number of non-missing responses. A 95% CI on the mean will also be provided.

The number of DCCV in first 90 days post-ablation and the number of DCCV from day 91-365 (i.e., from three months to 12 months) will be summarized via mean, standard deviation, median, range, and number of non-missing responses. A 95% CI on the mean will also be provided.

Raw and CFB scores for the AFEQT questionnaire will be computed and summarized with descriptive statistics (mean, standard deviation, median, range, and number of non-missing responses) by time point (one, three, six, and 12 months post ablation). The overall AFEAQT score is calculated according the following formula:

$$AFEQT_{\text{Overall}} = 100 \times \left(1 - \frac{\sum A_j - n}{6n}\right),$$

where the summation extends over all items with a response, ***excluding questions 19 and 20***, and *n* represents the number items with responses. Items lacking responses are dropped from the analysis. If all items are missing, then the overall score is also missing.

This analysis will be performed for the overall score and its three subscales (symptoms, daily activities, and treatment concern) and for the separate treatment satisfaction score. The subscale scores are computed similarly on the following subsets of questionnaire items:

| Subscale | Questionnaire items included |
|---|---|
| Symptoms | 1, 2, 3, 4 |
| Daily Activities | 5, 6, 7, 8, 9, 10, 11, 12 |
| Treatment Concerns | 13, 14, 15, 16, 17, 18 |

As in the overall score, missing items are dropped from the analysis. If all items in a subscale are missing, the subscale score is also missing.

As noted above, items 19 and 20 are *not* included in the overall AFEQT score. These items form a separate scale for treatment satisfaction:

$$AFEQT_{\text{Treatment Satisfaction}} = 100 \times \left(1 - \frac{A_{19} + A_{20} - n}{6n}\right),$$

where *n* is the number of items answered.

# 6.0 Other Relevant Data Analyses/Summaries

## 6.1 Subject Completion

A table will be constructed with counts and percentages of subjects who completed the study and subjects who withdrew from the study. Of the subjects who withdrew from the study, the number and percent of subjects with each withdrawal reason will be reported.

## 6.2 Prior and Concomitant Medications

All prior/concomitant medications taken by or administered to a subject will be collected according to the time intervals described in the clinical study protocols. All prior/concomitant medications will be coded the WHO Drug Dictionary prior to analysis.

A table of the WHO-coded medications will be constructed with medications summarized by anatomical therapeutic chemical (ATC) code levels. The number and percent of subjects on each drug will be summarized. A separate table summarizing antiarrhythmic medications (AADs) will also be constructed.

The analysis of concomitant medications and AADs will be performed for the safety population and for the treatment population.

# 7.0 References

N/A

# Appendix A – Tables, Figures and Listing Specifications

## Orientation

Tables and figures will be displayed in landscape.

## Margins

Margins will be 1 inch on all sides. Table and listing boundaries will not extend into the margins.

## Font

Courier New, 8 point.

## Headers

The table number will be on the first line of the title. The title area will contain the Sponsor name, the study number, and the name of the table. The title area will contain the page number (Page x of y) on the far right, one line above the name of the table.

## Footers

- The first line will be a solid line.
- Next will be any footnotes regarding information displayed in the table.
- Below these footnotes will be displayed “STATKING Clinical Services (Date)” on the far left.
- The last line will display the name of the SAS program that generated the table and (if applicable) the source data reference.

## Table Disclaimer

The format of the mock tables shown in the appendix of this Statistical Analysis Plan (SAP) will be the format of the deliverable tables to the extent that Word document constructed tables can match production tables produced by SAS. This formatting includes the content and format of the header and footer areas of the tables. The Sponsor agrees to the format of the tables as shown in the appendix.

Further programming charges will be applicable for changes in the format of tables (including title statements, notes, data dependent footnotes, etc.) made after the approval of the SAP.

## Missing Values

All missing values will be displayed on the output tables/listings as blanks.

## Display of Study Dates

The date format to be used is yyyy-mm-dd. Missing parts of dates are not shown (i.e., for a missing day value, the value displayed is in yyyy-mm format).