UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

DIVISION OF CARDIOVASCULAR MEDICINE
TELEPHONE: (858) 657-8530
NIGHTS & WEEKENDS: (619) 543-6737
FAX: (858) 657- 5054

OFFICE OF:
GREGORY K. FELD, M.D
PROFESSOR OF MEDICINE
DIRECTOR EP PROGRAM
9452 MEDICAL CENTER DR MC 7411
LA JOLLA, CALIFORNIA 92037
gfeld@ucsd.edu

Date: June 7, 2019

To: PRS Reviewers

Re: NCT# 02467179
Evaluation of the Amigo Robotic System for Ablation of the Cavo-Tricuspid Isthmus (Amigo-AFL)

Dear Committee,

Please note that the date on the uploaded protocol (10/29/2010) is the date of the approved template from our IRB onto which we typed our protocol. Not the date of the protocol.

Please see our uploaded protocol attached. We originally received approval for the study from our IRB on 3/19/2015, so I edited that date as well on the site.

Sincerely,

Gregory K. Feld

Gregory Feld, MD
Professor of Medicine
Director Cardiac Electrophysiology Program
University of California, San Diego

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Version date: 10/29/2010

1. PROJECT TITLE

Project Title: Evaluation of the Amigo Robotic System for Ablation of the Cavo-Tricuspid Isthmus.

IRB Project #: 150318

2. PRINCIPAL INVESTIGATOR

Gregory Feld, M.D

3. FACILITIES

UCSD Medical Center Cardiac Electrophysiology Laboratories

4. ESTIMATED DURATION OF THE STUDY

12 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS

A randomized comparison of manual (ablation) catheter manipulation to robotic (ablation) catheter manipulation with the Amigo Robotic System™, measuring catheter stability and catheter-tissue contact (force in grams) with the Carto mapping system (Biosense Webster, Inc), and duration of ablation and fluoroscopy time, in patients undergoing cavo-tricuspid isthmus ablation (CTI) as part of their clinically indicated ablation procedure.

6. SPECIFIC AIMS

To determine if robotic catheter manipulation will improve catheter stability and contact force, and reduce ablation and fluoroscopy time compared to manual catheter manipulation, during ablation of the CTI.

7. BACKGROUND AND SIGNIFICANCE

Radiofrequency catheter ablation (RFCA) has been shown to be an effective treatment for most cardiac arrhythmias. It is particularly effective for Wolff-Parkinson-White syndrome, AV nodal reentrant tachycardia, and typical atrial flutter (efficacy in excess of 95% has been reported in most studies). RFCA has also been used to treat atrial fibrillation, although with a lesser degree of success compared to the aforementioned arrhythmias (60-85%). One possible reason for this lesser degree of efficacy, is catheter stability and contact force, a finite level of both being required to create permanent transmural atrial lesions that eliminate potentially arrhythmogenic tissue responsible for atrial fibrillation (AF).

Recently several robotic catheter manipulation systems have become clinically available but there is limited data confirming their effectiveness in assisting RFCA for AF or atrial flutter (AFL). These systems include the Sterotaxis Niobe™ system, the Hansen Sensei™ system, and more recently the Amigo Catheter Robotic™ system. The differences between these systems are significant, including the much simpler and less costly nature of the Amigo Catheter Robotic™ system. We are currently assessing the clinical utility of the Amigo Catheter Robotic™ system for RFCA of AF and AFL in our laboratory and are interested in comparing it to manual catheter manipulation, initially for ablation of the CTI, a standard treatment for AFL, which is also performed adjunctively during all AF ablations.

In addition, the manufacturer of the ablation catheter used in our laboratory (the externally irrigated Thermocool™ catheter) has added a sensor to this catheter and software to their mapping system that allows determination of catheter-tissue contact force in grams and vector of force, at each location the catheter is placed against tissue in the heart. The system also tracks catheter position in the heart within 1-2 mm accuracy.

The software will then allow construction of time-stability and force-time-stability data (which is stored in a database) for each ablation lesion. This data can then be compared to specific parameters (finite limits) believed to be required to achieve an effective ablation lesion at each location. This ablation catheter and mapping system can be used either manually or with the Amigo Catheter Robotic™ system, in order to compare their efficacy in achieving these parameters.

8. PRELIMINARY STUDIES/PROGRESS REPORT

Manual catheter manipulation has been used in our laboratory for several decades, including the past 15 years for ablation of atrial fibrillation and 24 years for ablation of atrial flutter, with relatively high success rates. The procedure duration for AF ablation and long-term efficacy have improved over time (i.e. 304 hour procedure time with up to 85% one-year efficacy), but improvements beyond this level have not been achieved. One possible reason is the limitation of manual catheter manipulation on catheter stability and contact force, using existing technology.

Although we have not studied the benefits of contact force measurements for improving efficacy of RFCA in our laboratory, several studies have confirmed the benefits of contact force measurements in improving acute and chronic efficacy of ablation of AF.

In addition, although studies on the effects of robotic catheter manipulation have shown reductions in fluoroscopy times during AF ablation, studies have not been done to assess improvements in catheter stability compared to manual manipulation during AF ablation.

9. RESEARCH DESIGN AND METHODS

Study Design:

This will be a randomized, prospective, clinical trial, to be performed in 50 patients. All patients enrolled will undergo ablation of the CTI as part of routine ablation during RFCA for AF. Ablation of the CTI, to be performed prior to left atrial ablation for AF, will be done in a randomized fashion in blocks of 10 patients, the order of which will be determined by computer algorithm. Research personnel will be blinded to randomization assignment.

Methods:

Ablation of the CTI will be performed using the Thermocool™ externally irrigated ablation catheter (Biosense Webster, Inc.) at a power of 40-50 watts, with a maximum temperature of 42ºC for up to 30 seconds at each location as the catheter is gradually withdrawn from the tricuspid valve annulus, through the cavo-tricuspid isthmus, to the Eustachian ridge (in a standard manner). Ablation will be performed in a randomized fashion, with either manual or robotically guided catheter manipulation first, followed by the alternative method. Following ablation, measurement of trans-isthmus conduction time and atrial activation sequence will be done in a standard manner during pacing from the proximal electrodes of the coronary sinus catheter and the distal electrodes of the ablation catheter positioned in the low lateral right atrium, at a cycle length of 600 or 700 msec (whichever is faster than the intrinsic sinus cycle length).

Group A: Twenty-five patients will undergo RFCA of the CTI using manual manipulation of the Thermocool™ ablation catheter, with catheter position, duration of ablation and contact force documented by the Carto™ mapping system utilizing the VisiTag™ software algorithm. After completion of ablation trans-isthmus conduction time and activation sequence will be performed to determine the success in creating bi-directional isthmus block. All data will be stored in the Carto™ mapping system computer.

Group B: Twenty-five patients will undergo RFCA of the CTI first robotically guided catheter manipulation of the Thermocool™ ablation catheter with the Amigo™ robotic catheter system, with catheter position, duration

of ablation and contact force documented by the Carto™ mapping system utilizing the VisiTag™ software algorithm. After completion of each ablation trans-isthmus conduction time and activation sequence will be performed to determine the success in creating bi-directional isthmus block. All data will be stored in the Carto™ mapping system computer.

10. HUMAN SUBJECTS

A total of 50 patients, of either gender, will be recruited from the Cardiology Electrophysiology clinics and PTU among those scheduled for either AF or typical AFL ablation. There will be no discrimination in enrollment based on gender or ethnic background. We expect the population of enrolled subjects to reflect similar percentages for gender and ethnicity as the overall population of patients receiving CIED procedures at UCSD. If the eligibility of the subject changes between the time the subject is consented and the procedure, the subject will be considered a screen failure and the subject's participation will not be counted towards accrual for the study.

Inclusion Criteria: (all must be met)

1. Must be scheduled to undergo radiofrequency catheter ablation of the cavo-tricuspid isthmus for AF or AFL according to appropriate clinical indications.
2. Must be able and willing to provide written informed consent
3. Must be at least 18 years old

Exclusion Criteria: (presence of any one or more)

1. Patient's refusal to participate in the study
2. Lack of indication for CTI ablation (e.g. prior CTI ablation with persistent bidirectional isthmus block)
3. Any medical condition or complication that would interfere with the patient's ability to complete the protocol or would place the patient in additional risk
4. Pregnancy (ruled out by pregnancy test for all women of child bearing potential prior to procedure according to standard of care procedures)

11. RECRUITMENT

Patients referred to the arrhythmia clinic or hospital inpatients referred for RFCA of AF or AFL, will be evaluated to see if they meet enrollment criteria by Dr. Feld and/or the co-investigators. Medical records of potential patients will be screened prior to enrollment to ensure eligibility. If eligible, they will be asked if they would like to participate in the study. All patients will be under the care of the cardiac electrophysiology service at UCSD medical center.

A partial waiver of HIPAA and waiver of consent will be needed to screen medical records of patients of Sulpizio Cardiovascular Center to determine study eligibility. The partial waiver of HIPAA and waiver of consent for recruitment are necessary to ensure that patients who are approached for the study meet all inclusion and exclusion criteria in addition to reaching the enrollment goal for the study. The medical records of patients in UCSD cardiac arrhythmia clinic will be screened to assess eligibility for the study. Patients who have been determined to be eligible will be recruited in clinic or PTU by Dr.Feld or his research staff. The privacy risk to patients is minimal as all PHI collected for screening purposes will be stored in a password protected document in a limited access drive on the UCSD secured computer system. The waiver of consent and partial waiver of HIPAA will not adversely affect the rights and welfare of the potential subjects as only the

minimal PHI necessary to determine eligibility will be collected for screening. This would include name, age, procedure type, procedure dates, medical record number, and medical information indicting satisfaction of the inclusion and exclusion criteria for the study. This will also benefit patients by reducing the likelihood of ineligible patients being consented to participate in the study or that patients are approached more than once to participate. Only Dr.Feld and his research staff will have access to the PHI and will be involved in the screening process. As soon as recruitment for the study is complete, identifiers for all screened patients who did not enroll in the study will be destroyed or deleted from our system. The only information that will be retained from screened patients will be information necessary for publication, including reason for study exclusion and date the patient was screened. If at any point during the study, there is a change in the risk to benefits ratio affecting a patient' safety or willingness to participate, those enrolled or screened (as applicable) will be notified. There will be no advertising (brochures, flyers, posters, etc.) used in recruitment for this study.

12. INFORMED CONSENT

Patients must sign the most current IRB approved informed consent form prior to any study related procedures. Only the principal investigator, sub-investigators, or research coordinators will obtain informed consent, after complete explanation of the nature and purpose of this study. The consent for this study will be signed by the subject and the individual obtaining informed consent.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternatives to participation in this study are to not participate in the study, and to continue to receive standard care and follow up after RFCA for AF or AFL.

14. POTENTIAL RISKS

The published literature indicates that there are known immediate and delayed risks from RFCA, although those during CTI ablation are low compared to those during AF ablation. These risks or explained to the patient as part of their regular clinical consent for AF or AFL ablation.

The risks include cardiac perforation with pericardial effusion and tamponade requiring pericardiocentesis or surgical repair, systemic arterial embolization with cerebrovascular, cardiac or other solid organ injury, venous thromboembolism, conduction system injury resulting in need for permanent pacemaker implantation, vascular injury requiring surgical repair or percutaneous intervention, blood transfusion due to bleeding from cardiac or vascular injury. These risks are standard risks associated with CTI ablation, and their type or frequency will not be altered by participation in this research.

Radiation Exposure:
Fluoroscopy is used as standard of care throughout the ablation and is not affected by the research study. Each patient will only undergo the RFCA procedure once. The RFCA for atrial flutter should take 45-60 minutes, average fluoroscopy time for CTI ablations are 10 minutes and can run up to about 20 minutes. This will be the same regardless of study participating. The estimated radiation exposure for this procedure is 70.4mSv.

Although every effort will be undertaken to maintain confidentiality, there is a risk of possible loss of participant's confidentiality.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

We currently perform over 300 ablations for AF each year, and have performed over 5000 CTI ablation procedures over the past 20 years at UCSD. Immediately following ablation, patients will be monitored for any adverse events in the PTU (patient treatment unit) at the UCSD Sulpizio Family Cardiovascular Center, as per usual clinical routine. The PTU is a fully licensed facility, staffed by nurses trained in management of post-ablation patients. The Cardiac Electrophysiology program fellows and faculty are on-call 24 hours a day for any

questions or complications arising in our ablation patients.

Following discharge, patients will be seen in the arrhythmia clinic by a nurse practitioner 4 weeks after RFCA, and at 6, 12 and 24 months after RFCA for any complications or arrhythmia recurrence, as is our routine clinical practice. This follow-up will not differ from standard clinical care and is not part of the research.

The arrhythmia clinic is staffed by two nurse practitioners and cardiac electrophysiology fellows and attendings. The clinic number (858) 657-8530 is answered daily from 8 AM to 5 PM, and the nurse practitioners are always available during this time period. The nurse practitioners discuss all phone calls with the primary electrophysiologist and make notes into the EPIC electronic medical record. After business hours, the answering machine provides the number for the electrophysiology fellow and attending on call 24 hours a day for urgent issues.

The research staff, also, will be monitoring patients during the study procedure and prior to discharge for adverse events. All adverse events will be reported according to current IRB requirements. The Research Coordinator will assist with the reporting of any adverse events to the Human Studies Committee.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Every effort will be made to protect subject confidentiality. Only the Principal Investigator, the Sub-Investigators, and the research coordinators will have access to the patient's identifying information. All collected participant information will be stored in locked cabinets and maintained in a password protected database in UCSD system. Subjects will be assigned a non-identifiable study number based on order of enrollment. The master-log linking subject PHI with study ID number will be kept separate from other study information, in a password protected document on a limited access drive on UCSD secured computer system, accessible only by Dr. Feld and his research staff. Data reported to Circa Scientific, LLC will not contain any PHI. If the results of this study are published, the subject's identity will remain confidential. Records may be viewed by the Sponsor, or their representatives, the FDA, or the UCSD HRPP. However, no personal information about the study subject will be recorded at these times.

Patients who may have any questions or concerns can contact the principal investigator at 858-657-5311 or the HRPP.

17. POTENTIAL BENEFITS

It is possible that CTI ablation performed by robotic catheter manipulation may result in reduced fluoroscopy time, procedure time, or increased efficacy, but it is possible that the patient may not benefit directly from this study. Other patients may benefit in general by use of robotic catheter manipulation if this study demonstrated positive results with its use.

18. RISK/BENEFIT RATIO

While the risk of CTI ablation is small and during comparison of manual vs. robotic catheter manipulation has not been shown to be different, the benefits of reduced fluoroscopy time, and potentially greater efficacy with robotically guided ablation are expected to outweigh the risks.

19. EXPENSE TO PARTICIPANT

There will be no additional expense to patient for participation in this research study. As the ablation and any expenses related to the procedure are standard of care, those costs will be covered by the patient and/or the patient's insurance.

20. COMPENSATION FOR PARTICIPATION

On completion of research activities, each participant will be provided $25 for the inconvenience associated with the research-related procedures. No other compensation will be provided for participation in this study.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Only licensed physicians and the clinical research coordinator will perform this study. All procedures will take place at UCSD Medical Center.

1. Dr. Gregory Feld, M.D., Dr. Jonathan Hsu, Dr. David Krummen: Faculty, Division of Cardiology, licensed in California with full attending privileges at UCSD will implement the protocol, perform ablations, screen and consent patients, as well as performs data analysis and reviews images.
2. Jessica Hunter, BHS, Maylene Alegre, and Kathryn Lewis: Clinical research coordinators assisting with screening, consenting, data collection, data analysis, adverse event reporting, and serve as the liaison between the PI and the IRB. Kathryn Lewis will be the primary contact and lead coordinator for IRB communications. Jessica Hunter will serve as administrative contact on the study.

22. BIBLIOGRAPHY

1. Wood MA, Orlov M, Ramaswamy K, Haffajee C, Ellenbogen K; Stereotaxis Heart Study Investigators. Remote magnetic versus manual catheter navigation for ablation of supraventricular tachycardias: a randomized, multicenter trial. Pacing Clin Electrophysiol. 2008;31:1313-21.
2. Proietti R, Pecoraro V, Di Biase L, Natale A, Santangeli P, Viecca M, Sagone A, Galli A, Moja L, Tagliabue L. Remote magnetic with open-irrigated catheter vs. manual navigation for ablation of atrial fibrillation: a systematic review and meta-analysis. Europace. 2013;15:1241-8.
3. Hlivák P, Mlčochová H, Peichl P, Cihák R, Wichterle D, Kautzner J. Robotic navigation in catheter ablation for paroxysmal atrial fibrillation: midterm efficacy and predictors of postablation arrhythmia recurrences. J Cardiovasc Electrophysiol. 2011;22:534-40.
4. Feld G, Wharton M, Plumb V, Daoud E, Friehling T, Epstein L; EPT-1000 XP Cardiac Ablation System Investigators. Radiofrequency catheter ablation of type 1 atrial flutter using large-tip 8- or 10-mm electrode catheters and a high-output radiofrequency energy generator: results of a multicenter safety and efficacy study. J Am Coll Cardiol. 2004;43:1466-72.
5. Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK. Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. Am J Cardiol. 2009;104:366-72.
6. Steinberg JS, Palekar R, Sichrovsky T, Arshad A, Preminger M, Musat D, Shaw RE, Mittal S.Very long-term outcome after initially successful catheter ablation of atrial fibrillation. Heart Rhythm. 2014;11:771-6.

23. FUNDING SUPPORT FOR THIS STUDY

This is a single-centered, PI-initiated study, however financial support for research procedures will be provided by Catheter Robotics, Inc., manufacturer of the Amigo Robotic System, through an OCGA contract.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable.

26. IMPACT ON STAFF

All research activities will be done in the cardiac electrophysiology lab by the investigators or the research staff.

27. CONFLICT OF INTEREST

Not applicable.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable.