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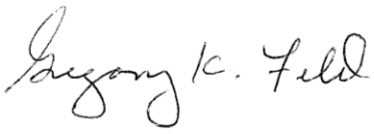
Date: 5/29/2021

RE: Circa/EGD Study Initial Protocol

To whom it may concern:

This protocol (attached below) was initially submitted to our IRB on 12/2014, and subsequently approved on 3/19/2015 (approval letter on file).

Sincerely,



Gregory Feld, MD

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Version date: 9/30/2013

1. PROJECT TITLE

Project Title: A Prospective, Non-Randomized Study to Evaluate the CIRCA Esophageal Temperature Monitoring System in Prevention of Esophageal Lesions Following Atrial Fibrillation Radiofrequency Catheter Ablation

2. PRINCIPAL INVESTIGATOR

Gregory Feld, M.D

3. FACILITIES

UCSD Medical Center – Sulpizio Cardiovascular Center

4. ESTIMATED DURATION OF THE STUDY

12 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

One rare but potentially fatal complication of radiofrequency catheter ablation (RFCA) with the use of the Circa™ monitoring system is the development of atrio-esophageal fistula due to thermal injury of the esophageal tissues. The Circa™ temperature monitoring probe (S-Cath) and temperature monitoring system are currently used in RFCA procedures here at UCSD to monitor thermal output in an effort to reduce the risk of complications due to thermal injury. This study is being conducted to determine the short-term effects of radiofrequency AF ablation with the use of the Circa™ monitoring system on the esophageal (swallowing tube) lining immediately following AF ablation. Patients who choose to participate will receive an esophagoscopy at the end of the ablation procedure to identify the presence or absence of esophageal lesions (number and size) reflecting damage to the lining of the esophagus.

6. SPECIFIC AIMS

To evaluate the effects of left atrial endocardial radiofrequency catheter ablation for AF, guided by the Circa ™ esophageal temperature monitoring system, on formation of esophageal thermal lesions with post-ablation esophagoscopy.

7. BACKGROUND AND SIGNIFICANCE

Radiofrequency catheter ablation (RFCA) for treatment of AF has been performed for nearly 15 years, but is associated with a small percentage of complications, including the rare but potentially fatal atrio-esophageal fistula. In patients where the esophagus traverses the left atrium near posterior left atrial endocardial ablation sites, it is thought that thermal injury to the atrial and esophageal wall may lead in rare cases to the formation of an atrio-esophageal fistula, which can lead to fatal gastrointestinal hemorrhage, or fatal systemic embolization causing stroke and/or cardiac arrest. The diagnosis of atrio-esophageal fistula after ablation has unfortunately most commonly been after one of these fatal events, but earlier recognition of this rare complication based on symptoms, fever, transient bleeding or embolic events, has led to use of esophageal stenting, or emergency thoracic surgery, which can be life-saving in some cases.

Due to the rarity of this complication, systematic study of its cause(s) is impossible, but in order to avoid it, it has been recommended in guidelines that ablation power and duration on the posterior left atrial wall be empirically limited, and in some cases esophageal position is marked by a barium swallow, or esophageal temperature and position can be monitored by a naso-gastric tube with an embedded temperature sensor (typically a single sensor in the past).

Recently a multi-senor (12 sensors) temperature monitoring probe (Circa™) has been developed and FDA approved, that can be placed in the esophagus (while the patient in under general anesthesia) and positioned

under fluoroscopy directly posterior to the left atrium during RFCA for AF or left atrial flutter (LAAFL). This multi-sensor probe has the theoretical advantage of monitoring temperature at multiple locations in the esophagus (cranial to caudal temperatures spanning the left atrium are simultaneously displayed on monitor) during ablation, warning the operator of impending temperature rises during ablation and allowing ample time to terminate ablation and prevent esophageal heating above a target temperature of typically 38-39˚C. Limiting esophageal heating to this maximum level of temperature may prevent potentially serious thermal injury to the esophagus that could lead to potentially fatal atrio-esophageal fistula.

In the electrophysiology laboratories at UCSD, where we have performed RFCA for AF and LAAFL for nearly 15 years, in several thousand cases, and to our knowledge have had possibly 1 or 2 atrio-esophageal fistulas (presumed but not confirmed) develop in our patients, over a decade ago. These patients were treated at outside hospitals for associated comorbidities however, which were fatal, and the diagnosis was thus only suspected and not confirmed. Since that time we have always monitored esophageal position and temperature, and then for the last several years since its FDA approval, we have used the Circa™ temperature probe in all our patients and have had no reported cases of atrio-esophageal fistula.

Previous studies have suggested that even when one reduces power during ablation at the posterior left atrium and monitors temperature, approximately 27% of patients will develop some evidence of esophageal thermal lesions (including endothelial esophageal ulcers or mediastinal changes). In addition, one center reports an even greater number of lesions observed when using the Circa™ probe during RFCA (although in this study power delivery and temperature were not modulated based on the temperature monitoring during ablation).

In contrast, we believe that due to its sensitivity and ability to monitor esophageal temperature at multiple locations spanning the atrium, use of the Circa™ probe should result in fewer or no esophageal thermal lesions, if esophageal temperature measured by the Circa™ probe is used to guide power delivery and duration of ablation on the posterior left atrial wall.

8. PROGRESS REPORT

There is a paucity of data in patients on the value of temperature monitoring during RFCA for AF to reduce thermal esophageal injury. However, during the routine clinical use of the device in hundreds of cases over the past few years we have clinically observed a marked reduction in ablation time and power delivery in the posterior left atrial wall as compared to prior years before FDA approval of the Circa™ device.

In addition, in some patients we have been unable to ablate critical areas in the left atrium due to such temperature rises observed on the Circa™ probe, and have resorted to having the GI service attending move the esophagus with an endoscope to the right or left away from the critical ablation sites, thus allowing normal power delivery to achieve transmural atrial ablation and cure AF.

Thus, we believe that by using the Circa™ probe, to guide and limit power delivery and duration of ablation on the posterior left atrial wall, to avoid excessive esophageal temperature rises, and yet successfully complete the ablation, we will limit the potential for any esophageal thermal injury that might lead to an atrio-esophageal fistula.

9. RESEARCH DESIGN AND METHODS

Study Design:

This will be a non-randomized, prospective, single-centered clinical trial. Twenty consecutive patients who agree to enroll in the study will undergo esophagoscopy immediately following their AF ablation (during which all patients will have been monitored using the Circa™ esophageal temperature probe. Patients will receive esophagoscopy while still under general anesthesia before leaving the electrophysiology laboratory, in order to determine if there is any evidence of esophageal lesions that might be due to thermal injury.

The gastroenterologist performing esophagoscopy will be blinded to any intra-procedural data during the atrial fibrillation ablation, specifically any data relating to esophageal position during the ablation procedure, any observed temperature rises, and the power and duration of radiofrequency energy delivery during the ablation.

Following endoscopy, all patients will then be returned to the PTU when criteria are met, as is standard of care after AF ablation. All patients will be discharged from the hospital the day following ablation, as is standard of care, and followed up in the outpatient arrhythmia clinic in the same manner as all other patients undergoing AF ablation at UCSD. This routine follow-up process will have been described to the patient prior to ablation as part of his/her clinical consent for the procedure, and does not involve any research procedures related to this study.

Methods:

The only research component of this study is the post-ablation esophagoscopy which is not standard of care for patients receiving RFCA for atrial fibrillation. Immediately following the patient's AF ablation, provided there have been no complications and vital signs are stable, he/she will undergo esophagoscopy while still under general anesthesia. During this procedure all vital signs will be monitored in a standard manner as they had been during the AF ablation, and the esophagus inspected in a standard manner for any evidence of lesions that might be thought to be due to thermal injury. Photographic evidence will be obtained and stored on disk of any lesions observed. Written description will also be provided by the gastroenterologist in his report of the procedure. Following the procedure the patient will be monitored for the appropriate time to ensure stability of vital signs, and the patient will then be discharged home when appropriate criteria are met.

The patient will be provided written instructions, as to allowed and disallowed activities following ablation and endoscopy, as they would normally be provided for any clinically indicated procedure.

There will be no other research related procedures or follow-up required for this study.

10. HUMAN SUBJECTS

A total of 20 patients will be recruited from the Cardiology Electrophysiology clinics and PTU. 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. Patients will be approached and consented for the post-ablation esophagoscopy prior to AF ablation. 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. It is the patient's prerogative to withdraw from this study at any time before the esophagoscopy, or prior to ablation, without effect on his/her usual clinical care.

Inclusion Criteria: (all must be met)

1. Must have atrial fibrillation and be schedule for AF ablation, during which the Circa™ esophageal temperature probe will be used to guide ablation.
2. Must give 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. Any known esophageal disease or prior injury that would preclude esophagoscopy.
3. Any complications occurring during or after AF ablation that would result in esophagoscopy being an added significant risk to the patient beyond the known potential risks from the esophagoscopy itself.
4. Prior AF ablation

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Patients seen in the UCSD cardiac arrhythmia clinic or hospital inpatients, who are referred for consideration of AF ablation, 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 group 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 AF ablation. Standard of care for RFCA ablation for atrial fibrillation would not include post-ablation esophagoscopy.

14. POTENTIAL RISKS

The published literature indicates that there are known risks during routine esophageal endoscopic procedures including:

Minor irritation leading to a sore throat, and major complications including esophageal perforation leading to potential mediastinal infection and death, the potential need for surgery to repair a perforation, and major traumatic injury leading to bleeding.

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

After AF ablation and endoscopy, patients will be monitored in the PTU, including vital signs, until all criteria are met for patient discharge. The PTU is a fully staffed, licensed facility where all recovery from AF ablation is currently routinely clinically performed during a patient's overnight stay, and where all trans-esophageal echocardiograms (similar procedure to esohphagoscopy) and cardioversions are also currently performed safely and effectively.

The cardiac arrhythmia clinic is staffed by two nurse practitioners, four attendings and four fellows, for procedural related issues. 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 cardiac 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, who are available 24 hours daily for urgent issues. Or the patients can call the page operator to reach a fellow or attending with questions at (619) 543-6737.

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 in the cardiac electrophysiology division who can 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 research team at 858-657-5323 or the HRPP.

17. POTENTIAL BENEFITS

The patient may or may not benefit directly from participation in this study. If significant thermal lesions are observed in the esophagus as determined by the gastroenterologist performing the esophagoscopy, the patient

will receive the directed to appropriate clinical treatment or follow-up care. It is possible that observation of few or no esophageal lesions will confirm the utility and benefit of the routine use of the Circa™ temperature monitoring probe, and that publication of this data would results in it being disseminated worldwide to benefit other patients undergoing atrial fibrillation, and further reduce the risk of atrio-esophageal fistula formation, a rare, but known and potentially fatal complication of AF ablation.

18. RISK/BENEFIT RATIO

It is possible that identification of few or no esophageal thermal lesions will lead to more widespread use of the Circa ™ temperature monitoring probe, and thus reduce the risk of atrio-esophageal fistula, as we believe it has in our laboratory. Furthermore, early identification of any thermal lesions in an individual patient would lead to directed treatment in such an individual subject's case, in this study, possibly preventing progression to a more serious condition. However, the current subjects may derive no direct benefit from this study. The risk of esophagoscopy is low, although there are finite risks, including those noted above in section 14. However, the assessment of the principal investigator, the benefits outweigh the small risks to the subjects in this study.

19. EXPENSE TO PARTICIPANT

There will be no additional expense to patient for participation in this research study. The cost associated with the esophagoscopy procedure will be paid for by the sponsor, Circa Scientific, LLC. 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 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 physicians and the clinical research coordinator will be involved in performing this study. All procedures will take place at UCSD Medical Center PTU.

1. Dr. Gregory Feld, M.D., Dr. Jonathan Hsu, Dr. David Krummen: Faculty, Division of Cardioloy, 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. Dr. Thomas Savides, MD or his delegated attending physicians
3. Faculty, Division of Gastroenterology, licensed in California with full Attending privileges at UCSDwill be performing the esophagoscopy component of the protocol.
4. 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

22. BIBLIOGRAPHY

1. Martinek M, Bencsik G, Aichinger J, Hassanein S, Schoefl R, Kuchinka P, Nesser HJ, Purerfellner H. Esophageal damage during radiofrequency ablation of atrial fibrillation: impact of energy settings, lesion sets, and esophageal visualization.J Cardiovasc Electrophysiol. 2009;20:726-33.
2. Dagres N, Anastasiou-Nana M. Prevention of atrial-esophageal fistula after catheter ablation of atrial fibrillation. Curr Opin Cardiol. 2011;26:1-5.
3. Halm U(1), Gaspar T, Zachäus M, Sack S, Arya A, Piorkowski C, Knigge I, Hindricks G, Husser D. Thermal esophageal lesions after radiofrequency catheter ablation of left atrial arrhythmias. Am J Gastroenterol. 2010;105:551-6.

4. Sause A, Tutdibi O, Pomsel K, Dinh W, Füth R, Lankisch M, Glosemeyer-Allhoff T, Janssen J, Müller M. Limiting esophageal temperature in radiofrequency ablation of left atrial tachyarrhythmias results in low incidence of thermal esophageal lesions. BMC Cardiovasc Disord. 2010;10:52.
5. Zellerhoff S, Ullerich H, Lenze F, Meister T, Wasmer K, Mönnig G, Köbe J, Milberg P, Bittner A, Domschke W, Breithardt G, Eckardt L. Damage to the esophagus after atrial fibrillation ablation: Just the tip of the iceberg? High prevalence of mediastinal changes diagnosed by endosonography. Circ
6. Carroll BJ, Contreras-Valdes FM, Heist EK, Barrett CD, Danik SB, Ruskin JN, Mansour M. Multi-sensor esophageal temperature probe used during radiofrequency ablation for atrial fibrillation is associated with increased intraluminal temperature detection and increased risk of esophageal injury compared to single-sensor probe. J Cardiovasc Electrophysiol. 201;24:958-64.
7. Feld GK, Tate C, Hsu J. Esophageal temperature monitoring during AF ablation: multi-sensor or single-sensor probe? J Cardiovasc Electrophysiol. 2013;24(12):E24.
8. Ben-Menachem T, et.al. for the ASGE Standards of Practice Committee. Gastrointestinal Endoscopy 2012:76;707-718

23. FUNDING SUPPORT FOR THIS STUDY

This is a single-centered, PI initiated study, however the necessary research procedures, including esophagoscopy, are to be funded by the sponsor of this study, Circa Systems, LLC 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

Most of the research-related procedures will be performed by the research team (PI, Sub-I's, or study coordinators). However, the Gastroenterology department will be required for the research post-ablation esophagoscopy.

27. CONFLICT OF INTEREST

There is no conflict of interest between the sponsor of this study and the investigators. The Circa™ esophageal temperature probe is already routinely used in all cases during atrial fibrillation at UCSD Medical Center, and the investigators have no ownership interest in the company sponsoring this study, nor have they received in the past or will receive in the future any payments, honoraria, or equivalent from the sponsor.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not needed at this time.

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

Not applicable.