Using Electrical Nerve Stimulation to Control Atrial Fibrillation

National Clinical Trial (NCT) Identified Number: NCT04529941

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.2	• **We are removing history of latex allergy as an exclusion criteria for our study. "People with a history of allergy to ECG electrodes, adhesive tape, or nylon"**	Due to improved technology, the medical devices used in the present study no longer contain natural rubber latex. This was confirmed by Preventice, who provide our MCT monitors and patches, as well as with the neurosurgeons who perform the implant procedure. Therefore, it is not a valid exclusion criteria.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

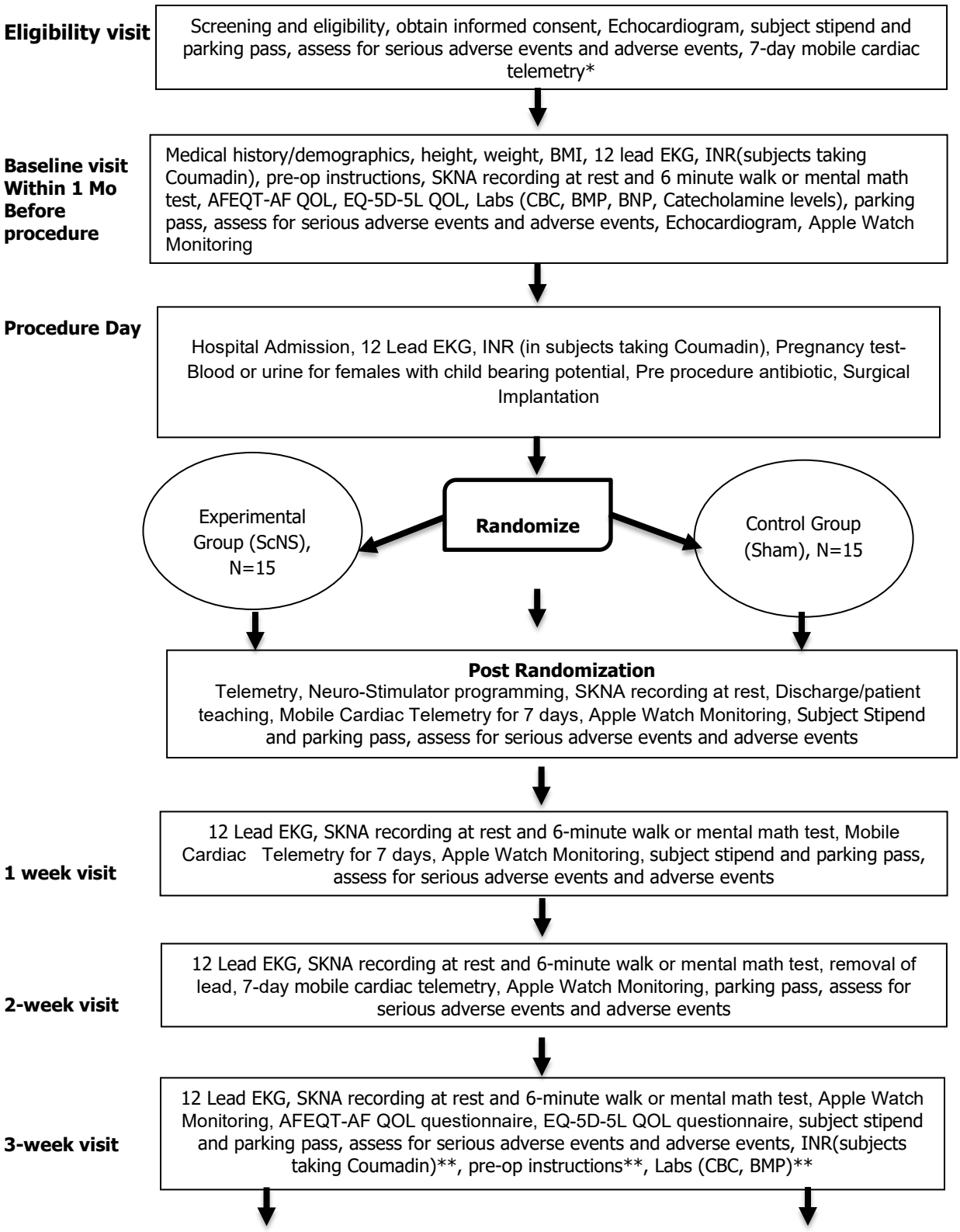
1 PROTOCOL SUMMARY

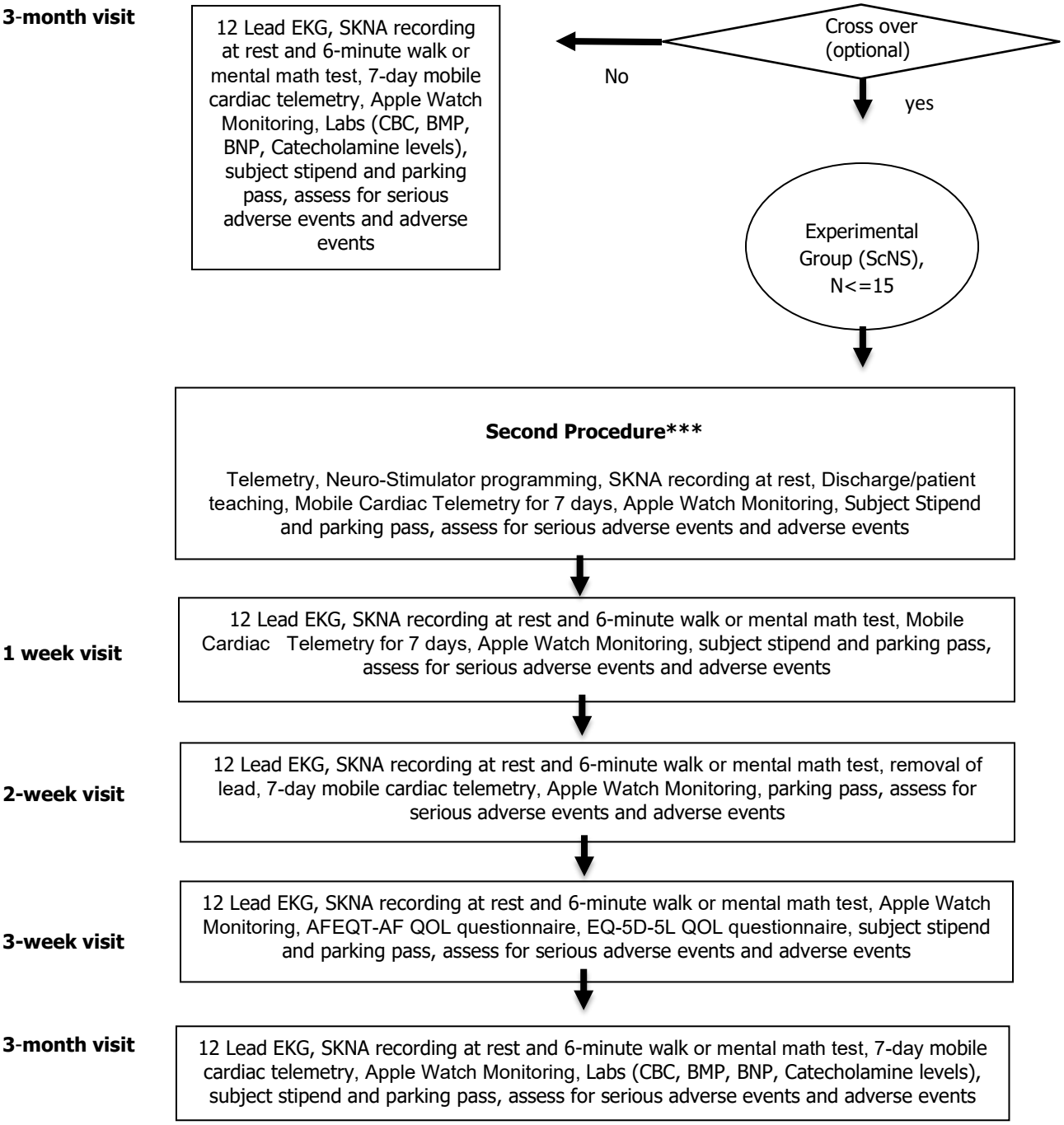
1.1 SYNOPSIS

Title:	Using Electrical Nerve Stimulation to Control Atrial Fibrillation
Study Description:	Patients will have a 1:1 randomization to receive subcutaneous electrical nerve stimulation (ScNS) to observe if the stimulation can reduce atrial fibrillation burden in patients with symptomatic atrial fibrillation (AF). All subjects will undergo the implant of a neurostimulator lead. The experimental group will receive stimulation and the control group will not receive stimulation. All subjects will complete the same follow up visits to compare the 2 groups. The control group will have an option to cross over to the experimental group 3 weeks post-randomization to receive the stimulation. They will repeat the baseline visit, procedure visit and all follow-up visits post-procedure.
Objectives:	**Primary Objective:** To test the hypothesis that chronic subcutaneous nerve stimulation can reduce AF burden in patients with severe symptomatic AF unresponsive to conventional therapies **The secondary objective:** To test the hypotheses that the effect of ScNS on the following endpoints is different between the two randomization groups: 1) Time-dependent reduction of AF burden

	2) Effects of ScNS on ventricular rate control during AF 3) Reduction of SKNA 4) Improvement of quality of life 5) Reduction of AF burden after cross over from control to experimental group
Endpoints:	• The primary Efficacy Endpoint: The average AF burden. • The secondary Efficacy Endpoint(s): 1) Time-dependent reduction of AF burden 2) Ventricular rate during AF 3) average SKNA 4) Quality of life
Study Population:	The study will enroll patients with symptomatic atrial fibrillation unresponsive to conventional therapy defined by not responding to at least 1 antiarrhythmic drug. The study will enroll 30 patients, including 15 men and 15 women between the 18 and 75 years old. There will be no sex/gender/racial/ethnic based exclusion. Patients will be enrolled from the Cedars Sinai Medical Center.
Phase:	Not applicable
Description of Sites/Facilities Enrolling Participants:	The study will enroll patients treated at the Cedars-Sinai Medical Center. This is a single site study.
Description of Study Intervention:	The patients will undergo surgical implantation of an externalized lead under the skin on the chest wall. The wire is then connected to a neurostimulator. The experimental group (Group A) will receive ScNS (3.5 mA) for two weeks. The sham group (Group B) will receive sham (0 mA) stimulation for two weeks. The AF burden will be assessed by a 7-day mobile cardiac telemetry device provided by Preventice. An additional mobile cardiac telemetry device, Bittium Faros, will also be worn at similar time points to monitor skin sympathetic nerve activity. An Apple watch will be used to collect additional information on the frequencies of AF between the Baseline Visit until the 3 Month Visit 7 Day Mobile Cardiac Telemetry is complete. After completion of the week 3 visit,, the sham group (Group B) will be able to receive ScNS (3.5 mA) for two weeks. The AF burden will be assessed post-procedure by mobile cardiac telemetry by Preventice and Bittium Faros.
Study Duration:	36 months
Participant Duration:	Up to 5 months.

1.2 SCHEMA


Eligibility visit
Screening and eligibility, obtain informed consent, Echocardiogram, subject stipend and parking pass, assess for serious adverse events and adverse events, 7-day mobile cardiac telemetry*
Baseline visit Within 1 Mo Before procedure
Medical history/demographics, height, weight, BMI, 12 lead EKG, INR(subjects taking Coumadin), pre-op instructions, SKNA recording at rest and 6 minute walk or mental math test, AFEQT-AF QOL, EQ-5D-5L QOL, Labs (CBC, BMP, BNP, Catecholamine levels), parking pass, assess for serious adverse events and adverse events, Echocardiogram, Apple Watch Monitoring
Procedure Day
Hospital Admission, 12 Lead EKG, INR (in subjects taking Coumadin), Pregnancy test-Blood or urine for females with child bearing potential, Pre procedure antibiotic, Surgical Implantation
Experimental Group (ScNS), N=15
Randomize
Control Group (Sham), N=15
Post Randomization
Telemetry, Neuro-Stimulator programming, SKNA recording at rest, Discharge/patient teaching, Mobile Cardiac Telemetry for 7 days, Apple Watch Monitoring, Subject Stipend and parking pass, assess for serious adverse events and adverse events
1 week visit
12 Lead EKG, SKNA recording at rest and 6-minute walk or mental math test, Mobile Cardiac Telemetry for 7 days, Apple Watch Monitoring, subject stipend and parking pass, assess for serious adverse events and adverse events
2-week visit
12 Lead EKG, SKNA recording at rest and 6-minute walk or mental math test, removal of lead, 7-day mobile cardiac telemetry, Apple Watch Monitoring, parking pass, assess for serious adverse events and adverse events
3-week visit
12 Lead EKG, SKNA recording at rest and 6-minute walk or mental math test, Apple Watch Monitoring, AFEQT-AF QOL questionnaire, EQ-5D-5L QOL questionnaire, subject stipend and parking pass, assess for serious adverse events and adverse events, INR(subjects taking Coumadin)**, pre-op instructions**, Labs (CBC, BMP)**



* Eligibility monitoring with mobile cardiac telemetry provided by Preventice will only serve as an option for potential patients that do not have any clinical ePatch monitoring completed in the past 6 months. Potential patients that have ePatch monitoring results with no change in medication since then, do not have to undergo mobile cardiac telemetry during Eligibility visit. ** Activities are to be repeated for control subjects only who choose to crossover to experimental group prior the second procedure. ***Second procedure is to be done within two weeks of the Week 3 Visit for crossover patients, if not, patient must complete another pre-op visit two weeks before the procedure. Pre-op visit will entail Labs (CBC, BMP), INR if patient is taking Coumadin, 12 Lead EKG and pre-op instructions.

All patients will have baseline cardiac rhythm monitoring using standard ECG patch electrodes. Cardiac rhythm monitoring will be done with clinically available 7-day non-invasive Mobile Cardiac Telemetry.

Among them, the 7-day non-invasive Mobile Cardiac Telemetry provided by Preventice will be performed during the two weeks of ScNS to ensure patient safety. The Bittium Faros monitor, a non-invasive patch electrode, will be applied at similar time points as Preventice Mobile Cardiac Telemetry device to monitor skin sympathetic nerve activity. Mobile cardiac telemetry will also be performed for a week after the end of stimulation and for a week at 3 months after surgery. An Apple watch will be used to detect AF episodes[1], if any, until the completion of the 3 Month Visit 7-day Mobile Cardiac Telemetry.

The patients will be admitted to the hospital and undergo surgical procedure for implantation of externalized subcutaneous neurostimulation lead for ScNS. The patients will be monitored while the stimulation protocol is started. The stimulation in the experimental group will continue for two weeks while all the patients are continuously monitored by the Mobile Cardiac Telemetry system. The lead will be removed at the 2 weeks visit. 7-day mobile cardiac telemetry will be performed at the 2 week and 3-month visits. The study ends after the final week of outpatient cardiac monitoring is performed. The control group will have an option to cross over to the experimental group 3 weeks post-procedure. They will undergo a second procedure and receive stimulation for two weeks. The lead will be removed after stimulation is complete. 7-day mobile cardiac telemetry will be performed for three weeks and at the post 3-month visit.

Surgical procedure:

- Preoperative
    - The patient will complete a standard hibiclens wash the night before the procedure and the morning of the procedure.
    - The patient will be NPO after midnight
    - Instructed to have a driver the day of the procedure

- Procedure Day
    - Antibiotics orders will be written for the procedure based on the patient's known drug allergies
    - Standard institutional procedural consent will be obtained by the investigator performing the procedure. All risks will be explained to the patient.
    - 12 lead EKG performed
    - INR if patient is taking Warfarin (Coumadin)
    - Pregnancy test on females with child bearing potential
    - Mild sedation for the procedure may be used, such as versed or a drug chosen by the investigator performing the procedure

- Implantation

  The patients will be placed in a supine position. The left subclavian area is prepped and draped in the usual sterile manner as in pacemaker surgeries. The skin is anesthetized with lidocaine or a combination of lidocaine and bupivacaine hydrochloride. A Medtronic 977D260 trial screening lead kit is opened and the content placed on the sterile field. A Tuohy needle from that kit will be inserted into the subcutaneous space approximately 3 cm below the clavicle. The stylet inside the needle is removed and the spinal cord trial screening lead is inserted via the lumen of the Tuohy needle. The

externalized portion of the wire is sutured to the skin using a silk suture. The wire is then connected to a Medtronic 97725 neurostimulator, which has an adhesive tape for fixation to the skin. The operating field and the externalized hardware are then covered with sterile dressing. Lead impedance will be checked at this time because swelling or hematoma could increase the impedance.

For the optional second procedure offered to the control group, the implantation protocol will remain the same, however, the Tuohy needle from that kit will be inserted into the subcutaneous space at least 1 cm below or above from the initial implantation site. Lead impedance will be checked after the procedure because swelling or hematoma could possibly increase impedance.

- Post-Operative
  - Programming of the device is completed
  - Discharge patient teaching
  - Apply Mobile Cardiac Monitoring system
  - Patients continue wearing Apple watch for secondary monitoring system

- Removal
  - The patient is placed in a supine position. The sterile dressing is removed. The silk suture is cut and removed. The stimulating lead is then pulled out of skin. The skin is cleaned with alcohol. The puncture site is left open to air.

- Risks of the procedure
  - *Pain at the time of insertion:* This will be minimized by local anesthesia.
  - *Swelling and/or mild hematoma*

Note: The surgical procedure will remain the same for both first and second procedure. However, the second procedure will be done 1cm below or above the initial implantation site on the left chest area.

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Eligibility visit	Baseline	Procedure Day (lead implant) and post-operative observation****	1-week visit****	2-week visit****	3-week visit****	3-month visit*****
Screening and eligibility	x						
Obtain Informed consent	x						
Medical history/demographics		x					
Height/Wt/BMI		x					
Hospital Admission			x				
12 Lead EKG		x	x	x	x	x	x
INR (in subjects taking Coumadin)		x	x				
Pre-op instructions		x				X[b]	
Pregnancy test-Blood or urine for females with childbearing potential			x				
Pre procedure antibiotic			x				
Surgical Implantation			x				
Randomization (after surgery)			x				
Apple Watch Monitoring		x	x	x	x	x	x
Telemetry			x				
NeuroStimulator programming			x				
SKNA recording at rest		x	x	x	x	x	x
SKNA recording during 6-min walk*		x		x	x	x	x
Mental Math Test **		x		x	x	x	x
Discharge/patient teaching***			x				
Removal of Lead					x		

Echocardiogram	x					x	x
Mobile Cardiac Telemetry	X[a]		x	x	x		x
AFEQT-AF QOL questionnaire		x				x	x
EQ-5D-5L QOL questionnaire		x				x	x
CBC		x				X[b]	x
BMP		x				X[b]	x
BNP		x					x
Catecholamine levels		x					x
Subject Stipend	x	x	x	x	x	x	x
Subject Parking fee	x	x	x	x	x	x	x
Assess for Serious Adverse events and Adverse Events	x	x	x	x	x	x	x

The materials and the times of collection for Aim 1A. Labs=laboratory tests; CBC=complete blood count; BMP=basic metabolic panel; BNP=B type natriuretic protein; INR=international normalized ratio. *if subject is able to complete, **will complete only if unable to complete 6 min walk, ***discharge day is based on PI decision. **** will only be repeated for control subjects that crossover to experimental group *****will only be done on experimental group and control subjects that do not cross over a. Eligibility 7-Day Mobile Cardiac Telemetry is available for potential subjects who may not have had an ePatch monitor completed b. will only be repeated by the crossover group before second procedure

2 INTRODUCTION

2.1 STUDY RATIONALE

Atrial fibrillation (AF) is the most common arrhythmia in the United States, affecting approximately 2.7-6.1 million adults that results in $26 billion in healthcare costs. AF prevalence is expected to double over the next 25 years, further contributing to an already high economic burden. AF is associated with significant morbidity and mortality, including a four to five-fold increase in stroke risk, a doubling of dementia risk, a tripling of heart failure risk, and a 40-90% increase in risk for overall mortality. The significant impact that AF has upon healthcare costs, morbidity and health quality has spurred numerous investigations to develop more effective treatments. Despite the aggressive management of hypertension, heart failure and other risk factors for AF, numerous patients in the United States are suffering from this arrhythmia. Current drug treatment and catheter ablation techniques are effective, but a significant number of patients continue to suffer from this arrhythmia in spite of the recent advancements in therapies. In addition, both drug treatment and catheter ablation may be associated with significant complications. There is room for improvement in managing patients with AF.

2.2 BACKGROUND

The autonomic nervous system plays an important role in the initiation and maintenance of AF.[2, 3] Neuromodulation procedures include cryoablation of the stellate ganglion that suppress AF and ablation of ganglionated plexi that modulate extrinsic cardiac autonomic inputs.[4] These findings support the importance of the autonomic nervous system in the etiology of AF, but it is not clear how this system can be leveraged utilizing less invasive and resource intensive methods for assessment and treatment of AF. In ambulatory dogs, sympathetic nerve activation as measured by the stellate ganglion nerve activity (SGNA) is a trigger of paroxysmal AF. SGNA can also accelerate the atrioventricular (AV) node conduction, resulting in increased ventricular rate response to AF. Because it is difficult to record nerve activities from humans, we devoted significant amount of time to develop such method. First, we[5]

discovered that subcutaneous nerve activity (ScNA) and superficial skin sympathetic nerve activity (SKNA) correlate positively with SGNA. Further, ScNA is more accurate in estimating cardiac sympathetic tone in ambulatory dogs with myocardial infarction than the heart rate variability parameters.[6] We[7] next discovered that it is possible to record skin sympathetic nerve activity (SKNA) using conventional ECG patch electrodes. We call this method the "neuECG" because we can use different filter settings on the same signal to display both ECG and SKNA. Using this new method, we[8] showed a positive correlation between SKNA and intrinsic cardiac nerve activity recorded from fat pads of humans in the postoperative period. Subsequent studies show that SKNA precedes both onset and termination of paroxysmal atrial tachycardia and paroxysmal AF episodes.[2, 3] These data suggest that sympathetic nerve activity is a major trigger of paroxysmal cardiac arrhythmias, including AF. A second implication is that the nerves in the thoracic skin connects directly to the stellate ganglion. If there is a connection between these two nerve structures, then stimulating the skin sympathetic nerve may rapidly active the stellate ganglion to cause excessive calcium accumulation and stellate ganglion remodeling.

We[9-12] tested the latter hypothesis in canine models and discovered that subcutaneous nerve stimulation (ScNS) can remodel the stellate ganglion and control AF. Because ScNS involves stimulating the skin without directly accessing the internal organs, it may be more clinically feasible than many other neuromodulation methods. The purpose of the present study is to translate these findings to humans. We will implant externalized electrodes under the skin on the chest wall to perform ScNS in patients with symptomatic paroxysmal AF. The results will be used to test the hypothesis that ScNS can be used to reduce the AF burden in patients with paroxysmal AF.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The Immediate risks include the risks associated with surgery such as pain, allergic reaction to the drugs used during surgery, bleeding and death. The possibility of a second surgery increases the previous risks.

The long-range risks include the following:

Because ScNS remodels the stellate ganglion and reduces sympathetic outflow, it is possible to slow down the sinus rate or atrioventricular (AV) conduction. If the following serious side effects are observed, the ScNS will be terminated:

- Third-degree AV block at any anatomic level associated with any one of the following conditions:
  - Bradycardia with symptoms presumed to be due to AV block.
  - Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia.
  - Documented periods of asystole ≥3.0 seconds or any escape rate <40 beats per minute (bpm) in awake, symptom-free patients.

- Second-degree AV block regardless of type or site of block, with associated symptomatic bradycardia

- Infection of the implanted devices
- Persistent pain at the lead site not responsive to drug therapy.
- Allergic response to the implanted lead or materials used
- Lead, extension or migration that results in loss of ability to perform ScNS

The following adverse events will be managed medically

- Skin irritation related to prolonged placement of 7-day Mobile Cardiac Telemetry patch.
- Pain, goosebumps, hot flashes, and other uncomfortable feelings related to electrical stimulation of the subcutaneous nerves.

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Alternative methods of treating drug resistant symptomatic AF include catheter ablation procedures and open-heart surgery, both carry significant risks of morbidity and mortality.

2.3.2 KNOWN POTENTIAL BENEFITS

- *Immediate potential benefits.* Based on the results of canine experiments, ScNS immediately reduces the sympathetic outflow from the stellate ganglion. This could be confirmed both by the direct measurements of nerve activity and by measuring plasma norepinephrine levels.[9] The reduced sympathetic outflow may then lead to reduced AF burden (primary outcome). The benefit may be time-dependent, i.e., the AF is better controlled in the second week of ScNS than in the first week of ScNS. In addition, the reduced sympathetic outflow may also reduce the ventricular rate, leading to better rate control if AF occurs. The improve rhythm and rate control of AF may lead to better quality of life (secondary outcomes).

- *Long-range potential benefits.* The stellate ganglion remodeling may persist after the stimulation, resulting in persistent reduction of sympathetic outflow and AF control. We will reassess the AF burden 3 months after the ScNS to test that hypothesis.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential benefits

Drug resistant paroxysmal AF is a common and serious clinical condition that happens to a small subset of patients with AF. The risk and benefit of the current management option versus the experimental procedure are as follows:

- Continue the current treatment. The risk is the continued suffering from the symptoms and side effects of drug-resistant paroxysmal AF.

- Catheter ablation of AF,[14] which is a standard treatment for symptomatic AF. Multiple non-randomized and randomized controlled trials have shown that radiofrequency catheter ablation of AF is associated with a > 50% success rate at one year. Roughly 27% of patients have to undergo a second ablation. Even then, the success is not assured. A third or fourth ablation procedures are sometimes performed in the same patient. In addition to the risk of AF

recurrences, the patients may also suffer from complications related to the ablation procedures. A worldwide survey showed that the rate of major complications were 4.5%- 6%, including a procedural death rate of 0.05%-0.15%.[15, 16]

- Surgical ablation of AF.[14] Stand-alone AF surgery should be considered for symptomatic AF patients who prefer a surgical approach, have failed one or more attempts at catheter ablation, or are not candidates for catheter ablation. The success rate for single procedure (without re-intervention) was 49%.[14] The referral of patients for surgery with symptomatic, medically refractory AF in lieu of catheter ablation remains controversial.

Comparing with the catheter or surgical ablation of AF, the proposed experimental procedure (ScNS) requires only the insertion of an electrode under the skin. The electrode and neurostimulator are FDA-approved for spinal cord stimulation. Compared with the risk of catheter or surgical ablation of AF, the proposed procedure is much less invasive and may be associated with lower complication rate. If ScNS can achieve AF control, then the patients do not need to undergo catheter or surgical AF ablation. That is the potential benefit of participating in the study. Because the risk is low and the potential benefit is high, we propose that the benefit to risk ratio of participating in the study is favorable.

Potential risks

- *Redness/Infection:* The overall infection rate is expected to be 1.2%. All infection will be promptly treated with antibiotics and assess if lead removal is necessary. It is expected to the patient will experience skin irritation/edema 3-7 days post procedure. If an infection is mild can be treated with an oral antibiotic and watched closely.
- *Lead extension or migration:* This will be managed by repositioning or removing the lead. The lead cannot be advanced.
- *Persistent pain at the lead site not relieved with OTC medication:* Persistent pain or discomfort will result in lead removal.
- *Allergic reaction:* The patients may be allergic to the local anesthetic agent, the dressing material or the device itself. These allergic reactions will be treated medically and by the device removal.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Primary Objective: The primary objective is to test the hypothesis that ScNS may significantly reduce the AF burden in patients with symptomatic paroxysmal AF.	Total AF burden (the % of time in AF).	AF burden is an objective measure of the severity of AF. It is commonly used in clinical trials. The FDA suggested that we use AF burden as the end point for this IDE study.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To test the hypotheses that the following findings are statistically significant: 1) Time-dependent reduction of AF burden 2) Effects of ScNS on ventricular rate control during AF 3) Reduction of SKNA 4) Improvement of quality of life 5) Reduction of AF burden after cross over from control to experimental group	1) Time-dependent reduction of AF burden 2) Ventricular rate during AF 3) average SKNA 4) Quality of life	We hypothesize that ScNS causes stellate ganglion remodeling, leading to time-dependent changes of AF burden the ventricular rate. We also hypothesize the ScNS will reduce aSKNA and improve quality of life.

4 STUDY DESIGN

4.1 OVERALL DESIGN

- *A statement of the hypothesis.*
  - To test the hypothesis that ScNS can be used to reduce the AF burden in patients with paroxysmal AF

- *Phase of the trial.*
  - Not applicable.

- *A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design).*
  - This is a prospective randomized IDE study. The patients are randomized into Experimental and Control groups. There is an option for the Control group to crossover into the Experimental group after completion of obtaining the primary endpoint.

- *A description of methods to be used to minimize bias.*
  - The investigators are responsible for programming the device and cannot be blinded to the study. However, we will not tell the patients whether they are randomized into the experimental or the control group until the primary endpoint is complete. Technicians and physicians responsible for echocardiogram and ECG monitoring will be blinded.

- *The number of study groups/arms and study intervention duration.*
  - We will randomize the patients into:
    - Group A: Experimental group will undergo 3.5 mA ScNA for two weeks.
    - Group B: Sham control group will receive 0 mA stimulation for two weeks.

- *Indicate if single site or multi-site.*
  - This is a single site study.

- *Name of study intervention(s).*
  - Subcutaneous nerve stimulation (ScNS).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Medical device is known to have strong placebo effects.[17] Therefore, we chose to perform a prospective randomized study with a sham control group. The only difference between experimental and sham control groups is the strength of neurostimulator output (3.5 mA versus 0 mA).

4.3 JUSTIFICATION FOR DEVICE SETTING

Our recent studies in canine models showed that ScNS may be either proarrhythmic or antiarrhythmic depending on the stimulus strength.[9] Very low strength (0.5 mA) ScNS causes nerve sprouting and increases plasma norepinephrine concentration, leading to increased cardiac arrhythmia in ambulatory dogs. On the other hand, high output (3.5 mA) ScNS is antiarrhythmic. Because of these findings, we will only use 3.5 mA output in the Experimental group. No patients will receive low output stimulation.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- 18 to 75 years of age
- Symptomatic paroxysmal AF unresponsive to conventional therapy.
  - Symptomatic paroxysmal AF is defined by paroxysmal AF with patient-reported perception of one or more of the following symptoms: palpitations, dizziness/presyncope, syncope, dyspnea, chest pain, malaise, and fatigue and activity intolerance.
  - There is at least one ECG-documented AF episode.
  - Unresponsive to conventional therapy is defined by not responding to at least 1 antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker).

- The left atrial size <50 mm by transthoracic echocardiography documented by eligibility visit
- Documented atrial fibrillation as defined as atrial fibrillation >30 seconds in duration with an atrial fibrillation burden determined by a minimum of 7 days of continuous ePatch monitoring within 6 months before surgery.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Patients without AF episodes during monitoring period will be excluded from the study and count as screen failure
- Left ventricular ejection fraction <40%
- Heart failure with functional classes III or IV
- Recurrent vasovagal syncope
- Valvular AF (severe mitral regurgitation, mitral stenosis)
- Congenital heart diseases
- Wolff Parkinson-White Syndrome
- Stroke within the past 6 months
- Any history of myocardial infarction
- Malignancies with a life expectancy of < 1 year
- A history of ablation procedures to treat left atrial tachyarrhythmias or other serious comorbidity
- Any history of sustained ventricular tachycardia (VT) defined by (1) > 30 s in duration or (2) < 30 s in duration, but is associated with hemodynamic consequences such as hypotension and syncope.
- Patients with a vagal nerve stimulator
- Active thyrotoxicosis
- Sick sinus syndrome with symptomatic bradycardia
- Heart rate < 50 beats per minute in sinus rhythm on 12-lead ECG
- Systolic blood pressure < 90 mm Hg
- Any experimental medication concomitantly or within 4 weeks of participation in the study
- Subjects with cardiac implantable electronic device (CIED) such as pacemakers and implantable cardioverter-defibrillators (ICDs)
- Pre-existing neuromodulation devices, such as vagal nerve stimulators, spinal cord stimulators and sacral nerve stimulators
- People with a history of allergy to ECG electrodes, adhesive tape, or nylon
- Pregnant women

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- **Day before the implant:**
  - Plan to use the wash 2 times. Once the night before procedure, and again the morning of your procedure.
  - Use about 2 oz. or ¼ cup with each wash

- Take a complete bath or shower with regular soap. Then get a clean wash cloth.
- Do not use Hibiclens soap on your face, ears, or hair
- Use Hibiclens soap on the neck, chest, as far as they can reach over the shoulder and down to the waist, your arms down to the elbows and under the arms
- A gentle wash is good, rubbing and scrubbing is not necessary. Leave on the skin for 1 minute, then rinse off
- Use clean fresh towels and washcloths each time
- The night before the procedure, dress in fresh clean pajamas and sleep on fresh clean sheets
- Dress in fresh, clean clothes after the morning bath/shower to come to the hospital
- Please do not put on lotion, cream, powder, or deodorant after the bath or shower
- Nothing to eat or drink starting at midnight the night before surgery
- Required driver for all patients the day of surgery

- **After implant:**
  - Sponge bath only until the device is removed
  - Do not get the dressing wet. Remember electricity and water do not mix
  - No ointments, powders, lotions, creams, or antibiotic medications on the implant site
  - Abstain from driving during the time the lead is implanted
  - No bending, lifting, or twisting
  - No elbows above your ears, and no reaching up, over, across, or down
  - Your lifting limit is 5 lbs, which is approximately a half gallon of milk
  - No strenuous activities like yard work, vacuuming, lifting laundry baskets or grocery sacks
  - If you smoke, stop. Smoking is not health and can make pain worse, and prolongs healing time
  - No driving or operating machinery, making legal decisions, work, or drinking alcohol until the study is completed
  - May use ice packs on the implant site dressing, but no heat. Heat will affect the way the stimulator works

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. Patients without AF episodes during monitoring period and have an ejection fraction (EF) less than 40% will be excluded from the study and count as screen failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- Sample size: Total of 30 subjects-15 males and 15 females between 18 and 75 years old.
- Anticipated accrual rate: 30 subjects over 36 months
- All subjects will be enrolled at one US site
- Vulnerable subjects will not be recruited
- All sex, racial and ethnic group members will be recruited to participate in the study

Investigators and co-investigators will approach eligible subjects about the study in person at clinical visits. The patients will be consented by investigator or one of the co-investigators utilizing the informed consent form as a guide. After the questions about the research have been answered the patient will be asked to sign the form. We plan to distribute the study brochure to physicians' offices to help patient recruitment. We will include the study information in the Smidt Heart Institute Current Research website. We do not plan to use any other advertising material.
Subjects will receive payment in the form of a reloadable card for study visits completed. They will not receive more than $600.00 total or $900.00 total for study participation depending if they are randomized in the experimental group or control group, respectively. In addition to stipend, the patient will also receive parking passes.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Device Information:

- Medtronic spinal cord stimulation 60-cm trial Lead, model No. 977D260.
- Medtronic wireless external neurostimulator (WENS, model 97725).
- Medtronic Neuromodulation Clinician Programmer (App A710)
    - Description of each component
        - Medtronic spinal cord 60 cm trial lead and wireless external neurostimulator are designed to deliver electrical stimulation for the subcutaneous nerve stimulation (ScNS)
        - Medtronic Neuromodulation Clinician programmer will allow the programming of the lead to be set at 3.5mA to deliver the protocol required electrical stimulation
    - Device settings and programming- The programming of the lead will set at 3.5mA in the experimental group
    - Duration of implant Subjects will have the Medtronic neurostimulator lead implanted subcutaneously for 2 weeks
    - Device has not been approved or cleared for the indications the protocol is designed to investigate. Investigator has obtained an IDE for this protocol. See FDA IDE approval letter

The following device will be donated by Medtronic Inc. for implantation: Medtronic spinal cord stimulation 60-cm trial Lead, model No. 977D260 and Medtronic wireless external neurostimulator

(WENS, model 97725). These devices are currently FDA approved for pain control through spinal cord stimulation.

This IDE study is funded by NIH. Medtronic Inc. will donate the device. The final labeling of the device may change according to the results of the study.

6.1.2 DEVICE ENERGY AND ADMINISTRATION

The experimental group will receive stimulation ScNS at 3.5mA output, while the control group will receive no stimulation for 2 weeks.

The control group will have an option to crossover to the experimental group after three weeks from the first procedure and receive stimulation ScNS at 3.5 mA output.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Medtronic Inc will donate the following devices for this trial:
Medtronic spinal cord stimulation 60-cm trial Lead, model No. 977D260.
Medtronic wireless external neurostimulator (WENS, model 97725).

These devices are approved by FDA for human use, but an investigator-initiated IDE will be required. This allows the trial to be conducted using the devices for symptomatic atrial fibrillation unresponsive to conventional therapies.

Indications for Use: Symptomatic atrial fibrillation unresponsive to conventional drug therapies.

The unused devices will be returned to Medtronic, Inc.

Accountability of the device will be tracked by the study team using a device accountability log. The log will track the inventory of the device including device type, serial number, and expiration date. All devices used on subjects will be also tracked in Red Cap.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Medtronic Inc has committed to donate FDA approved neurostimulator units and nerve stimulation lead for the study. These devices are designed to deliver electrical stimulation of internal organs such as spinal cord and bladder. All devices are FDA approved for human implantation with specific clinical indications. However, because ScNS is not an approved indication, we have obtained Investigator-initiated IDE approval. All devices will be recorded in the redcap database. After the study, the unused devices will be returned to the manufacturer.

6.2.3 PRODUCT STORAGE AND STABILITY

Devices will be sent to CSMC – Smidt Heart Institute and received by clinical research coordinator. These will be stored on a safety cabinet located at the Cath lab after accountability log completed.

6.2.4 PREPARATION

The device comes in a sterile package. It is opened in a sterile manner at the time of procedure. The Medtronic 60cm lead is connected to the Medtronic wireless external neurostimulator (WENS, model 97725). The device is programmed by using the Medtronic Neuromodulation Clinician programmer App A710.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The patient will be consented to undergo surgery. After the device implantation, the patients will be randomized to experimental and control groups using Redcap. We will attempt to blind the patients, although the tingling or pain associated with the stimulation may make blinding difficult. All data analyses performed by the co-investigatorsand the rhythm analyses performed by the Mobile Cardiac Telemetry system technicians will be blinded. The experimental group will receive stimulation at 3.5 mA output, while the control group will receive no stimulation. Data will be obtained during this time to determine atrial arrhythmia frequencies in both groups. The device will then be removed at the end of the second week. After the third week, we will give the option to the control group to crossover to the experimental group. This group of patients will undergo a second procedure to receive stimulation at 3.5 mA and we will follow up for another 3 weeks and 3 months post second procedure.

We will tell the patients that they will be randomized into experimental group or control group during surgery. We will attempt to blind the patients, although the tingling or pain associated with the stimulation may make blinding difficult. We will explain to all patients they may or may not feel tingling and/or pain during the 2-week stimulation time but will not tell them which group they are assigned to. All data analyses performed by the co-investigators and the rhythm analyses performed by the 7-day non-invasive monitoring system technicians will be blinded. After 3 weeks post-procedure, we will unblind the control group to give them the option of crossing over to the experimental group to receive the treatment. If they agree, these group of patients will forego the 3-month follow-up visit and will proceed with a second procedure along with follow up visits post-second procedure. Data will be obtained during this time to determine AF burden in all groups.

6.4 STUDY INTERVENTION COMPLIANCE

The study team will assess compliance with the study intervention by:

- Maintaining accurate study records and documentation of all required visit tests and procedures
- All research staff will be trained in all study activities
- All research staff will be trained in using the HIPAA compliant Redcap electronic data capture system
- Continuous inpatient telemetry. The patient will be continuously monitored in the hospital based on the Principal Investigator’s discretion. Additional ECG electrodes will be used for telemetry recordings. The ECG signals will be transmitted to the heart station staffed by experienced technicians for heart rhythm monitoring.

- Outpatient rhythm monitoring. The patient will undergo continuous outpatient near real time telemetry using a Mobile Cardiac Telemetry system. Significant arrhythmia episodes will be reported to the PI or one of the co-investigators for management.
- An Apple watch will be used to monitor AF between Baseline visit and at the end of the study.
- All tests, labs and procedures will be reviewed by a designated research team member
    - Any abnormal result will be reported to the PI immediately

6.5 CONCOMITANT THERAPY

- Current medications will be recorded at the baseline visit
- Documentation that patient has been treated with at least 1 antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker)
- In patients treated with warfarin, the investigators will review the data to determine if the INR was > 2.0 for at least a month prior to procedure. In addition, the surgery will not be performed if the INR is > 3.0. For patients on DOAC, we will interview the patient to ensure compliance.

We plan to perform the implant procedures with uninterrupted anticoagulation to reduce the possibility of stroke. We estimate that the small bleeding risk does not justify interruption of anticoagulation in most patients.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The study intervention is the subcutaneous nerve stimulation with an externalized neurostimulation lead. The electrical stimulation may be terminated when there are serious adverse events or when patient declines to continue with the stimulation. Discontinuation from electrical stimulation does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reasons for discontinuing the subcutaneous nerve stimulation
- The removal of the subcutaneous electrodes
- Any adverse events

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive subcutaneous nerve stimulation after the electrode is implanted for any reason.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) using the Redcap database. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Based on the results of the canine study, reduced sympathetic nerve discharges may be associated with reduced heart rate. Therefore, we will terminate the study if the patients are found to have the following symptoms/signs which require cardiac pacemaker implantation according to the current ACC/AHA guidelines:

1. Third-degree AV block at any anatomic level associated with any one of the following conditions:
   a. Bradycardia with symptoms presumed to be due to AV block.
   b. Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia.
   c. Documented periods of asystole ≥3.0 seconds or any escape rate <40 beats per minute (bpm) in awake, symptom-free patients.

2. Second-degree AV block regardless of type or site of block, with associated symptomatic bradycardia.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for any scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Procedures/tests/evaluations

- Medical history/demographics will be performed by the investigator
- Height, weight, BMI will be collected by the research team
- 12 lead EKG will be collected to assess rhythm and intervals-will be read by a core lab following a standardized interpretation form
- In patients treated with warfarin, the investigators will review the data to determine if the INR was > 2.0 for at least a month prior to procedure. In addition, the surgery will not be performed if the INR is > 3.0. The study subjects may be anticoagulated for stroke prevention. We will manage the peri-operative anticoagulation according to the standard protocol[18] to minimize bleeding and the risk of stroke.
- Pre-op instructions-all patients will be required to complete a standard hibiclens wash the night before the procedure and the morning of the procedure
- Pregnancy test will be performed on females with child-bearing potential

- Surgical implantation- The study design is inspired by spinal cord stimulation, which is a procedure used for pain control.[19, 20] It is standard for spinal cord stimulation to include a trial period that last 4-29 days during which the patient carries an externalized lead connected to a neuromodulator.[20] All devices are removed at the completion of the trial period.[19, 20] The overall infection rate of the trial period was 1.2% (one out of 84 patients).[20] The low infection rate was attributed to strict asepsis, double layer hydrocolloid dressing during the trial, prophylactic antibiotics, operator experience, and patient education. With these techniques, two-stage procedures with extended trials do not seem to increase the incidence of infections for spinal cord stimulation.[20] The PI and several co-investigators are cardiac electrophysiologists with experience in pacemaker/ICD implantations. Dr. Tiffany Perry or Dr Alexander Tuchman, experienced neurosurgeons who are familiar with spinal cord stimulator implantations, will serve as a co-investigator. They will train the PI and other co-investigators in performing the procedure using externalized lead. Both of them have agreed to perform the implant procedures. The implantation procedures will be performed in full aseptic conditions. Antibiotics will be administered at the beginning of the procedure. Because this is a subcutaneous implantation, no fluoroscopy is needed. In our initial canine studies, we used Cyberonics wrap VNS electrodes to wrap around a small subcutaneous nerve and delivered electrical current only to that nerve.[10] While effective, that approach requires a large incision to identify the subcutaneous nerves. A large incision is highly undesirable and may increase the complications. Therefore, in most recent NIH-funded canine studies, we have inserted subcutaneous electrodes without specifically identifying subcutaneous nerves. Because the skin is extremely well innervated, we posit that a blindly inserted lead will come in contact of subcutaneous nerves. The results showed that within a week of the stimulation, the average ventricular rate of persistent AF had dropped significantly. Therefore, we will insert electrode lead in the subcutaneous tissues blindly through a Tuohy needle. Figure 1 shows the site of insertion is in the left upper thorax, which is convenient to the patient. In canine studies, multiple other stimulation sites in the thorax had the same antiarrhythmic effects.[10, 12] The exact site of insertion will be determined by patient and/or operator preference. The leads will be secured to the skin by a skin suture similar to that is done with spinal cord stimulation. The remaining lead is externalized and connected to a neurostimulator. Double layer hydrocolloid dressing will be used to cover the externalized lead and the neurostimulator. Lead impedance will be checked at this time because swelling or hematoma could increase the impedance. This surgical procedure will be repeated for the control group crossing over to the experimental group. The second procedure will take place no more than 2 weeks from the Week 3 Visit. If the

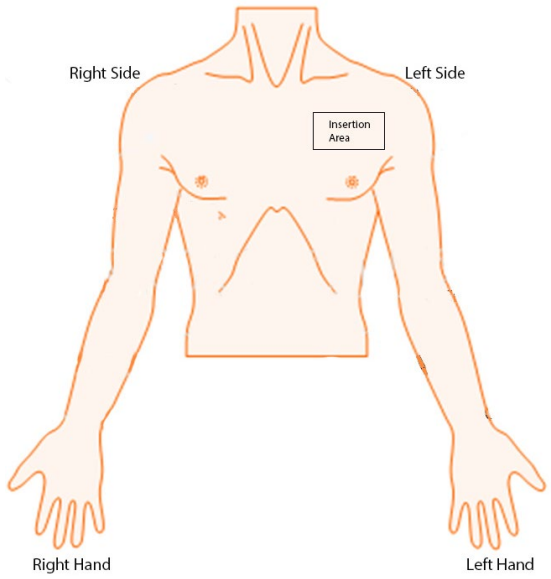

Figure 1. Site for lead insertion. We will insert the lead in the upper thorax 3 cm beneath the clavicle where the skin is innervated by nerves from the stellate ganglion.

second procedure has to take place more than two weeks, the subject will have to undergo a separate pre-op visit which will include a 12-lead EKG, Labs (CBC, BMP), INR if the patient is taking coumadin and pre-op instructions. The procedure will be exactly the same but for the second time, the implant site will be 1-2 cm above or below the original implant site and the stimulation will be turned on. Lead impedance will be checked again once the lead is placed into the chest.

- Randomization-will occur after the implant of the first lead implantation. Randomization will be done electronically within Red Cap.
- Telemetry- The patient will be continuously monitored in the hospital per PI's discretion.. Additional ECG electrodes will be used for telemetry recordings. The ECG signals will be transmitted to the heart station staffed by experienced technicians for heart rhythm monitoring.
- NeuroStimulator programming-program the output to 3.5mA
- SKNA Recording-Skin Nerve Activity recording will be done to compare interactions. The methods of recording are summarized in Figure 2 below.

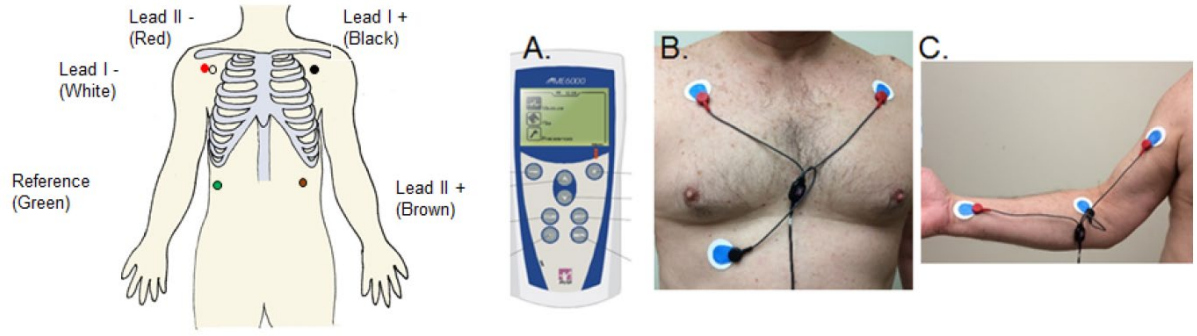

Figure 2. SKNA recording during 6-min walk. The colored dots show electrode location. A shows the ME6000 device. B shows the location of ECG patch electrodes (red buttons) and reference electrode (black button). C shows a second bipolar recording on the right arm. From Supplement Figure 1 of Doytchinova et al.[7]

- A 6-min walk will be conducted to estimate the functional status at baseline (prior to implantation) and during follow up visits (Figure 2). The test will be performed according to the protocol used by Bittner et al.[21] Briefly, we will measure a 30-meter (roughly 100 ft) course in the clinical and recovery area. The patients will be instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the allotted period of 6 minutes. A research coordinator will time the walk test, called out the time every 2 minutes, and encourage the patient every 30 seconds in a standardized fashion (while facing the patient and using one of the two phrases "You're doing well" or " Keep up the good work"). Patients will be allowed to stop and rest during the test, but are instructed to resume walking as soon as they felt they are able to do so.
    - After 6 minutes had elapsed, patients will be instructed to stop walking and the total distance walked will be measured to the nearest meter. Symptoms experienced by patients during the walk (angina, dyspnea, fatigue, dizziness, and syncope) will be recorded. The primary purpose of the 6-min walk is not to measure its distance and predict the prognosis through the measurement of heart rate changes, as it is known that the heart rate alone does not predict the prognosis in

patients in the rate-control arm of the AFFIRM trials. Furthermore, 6-min walk is not effective in measuring the functional status of the healthy volunteers. However, with this standard exercise protocol, we expect to increase both the average SKNA (aSKNA) and the heart rate in these patients. The correlation between aSKNA and heart rate will be calculated and compared with the total AF burden documented by the event monitor. The results will be used to test the hypothesis that the r values between aSKNA and ventricular rate is predicative of the AF burden.[2] Furthermore, the 6-min walk will give us the ability to compare the aSKNA before and after stimulation under conditions of sympathetic activation.

- Mental Math test-In patients who cannot complete 6-min walk, they will be asked to do mental math which will provoke sympathetic nerve activities. The test will have the patient start counting at 100 and subtract by 3 for two minutes.
- Apple Watch Monitoring – An Apple Watch Series 7 and Apple iPhone 6s or later model will be given to the patient during Baseline visit and serve as a secondary monitoring system from Baseline to the completion of the 3 month visit 7-day Mobile Cardiac Telemetry. AF monitoring via Apple iPhone and Apple Watch will not be for safety monitoring. Previous studies have shown that the Apple Watch is able to detect episodes of Atrial Fibrillation in patients with high AF burden.[1] The patients will wear the watch starting Baseline visit and will continue to wear it until the completion of the 3 Month Visit 7-day Mobile Cardiac Telemetry. The patient is to wear the watch as much as possible throughout the day and night. We will encourage subjects to use the Apple Watch's ECG App to record ECGs when the subject suspects they are in Atrial Fibrillation or receive a notification generated by the Apple Watch that a Low Heart Rate, High Heart Rate, or Irregular Rhythm was detected. This is a single-lead ECG that is able to provide information about heart rate, heart rhythm, and has ability to classify Atrial Fibrillation. ECG tracings can also be determined as inconclusive, meaning that the recording cannot be classified. iPhone 6s and later models are the only Apple devices that have the WatchApp, which is required for any data collected on the Watch to be transmitted to the HealthApp on the iPhone.
- If the patient has their own personal Apple Watch Series 7 and Apple iPhone 6s or later model and would like to use their device for secondary monitoring during the Apple Watch Monitoring periods, we will ask patients to share their Heart Rhythm Data from their Apple devices with the Principal Investigator or study-dedicated iPhone from Baseline to the end of the 3 Month Follow up procedures. They are to disclose their subject identifying information including their cellular number and Apple ID in order to share their Apple health app data with the Principal Investigator and research staff. The subject identifiable information disclosed to the research team will remain confidential from any other parties beside the Principal Investigator and research coordinators. Any Apple Health data received from the patient will be de-identified prior to data entry and storage. The study settings for the Apple devices described below will remain the same including abnormal arrythmia notifications and timeline of sharing data with the Principal Investigator or study-dedicated iPhone until the 3 Month Follow Up procedures are complete. After the sharing of health data is complete, we will remove all study data off of the Principal Investigator and/or study-dedicated iPhone. We will set up the research Apple Watch and Apple iPhone on site.

To access the HealthApp, our research team will work with Cedars-Sinai IT Support (EIS). Cedars-Sinai EIS will create an Apple ID that will be assigned to the subject's iPhone and Apple Watch. This Apple ID will not be associated with the subject's identifiable information such as name or email address. EIS and our research team will input the EIS-created Apple ID into the subject's Apple Watch and iPhone and connect the Watch to the iPhone's HealthApp. The HealthApp of the subject(s) will then be shared to a study-dedicated iPhone utilized only by the research team. This study-dedicated iPhone will be associated with an Apple ID created by Cedars-Sinai's IT Support (EIS). Since our team is using an Apple ID created by Cedars-Sinai IT Support (EIS), no subject identifiable information will be stored on the subject's Apple Watch, subject's iPhone, or study-dedicated iPhone.If the patient decides to use their personal Apple devices, the data on the subject's personal Apple devices will not be removed. The patients will provide subject identifiable information in order to share their Health App data that will only be accessible to the Principal Investigator and research staff.Our study team will configure the research and/or personal Apple Watches to enable notifications to appear on the subject's Watch and the on-site iPhones. We will set the Low Heart Rate parameter to 40 beats per minute. We will allow the Principal Investigator to set the High Heart Rate parameter at their discretion for each subject. We will also turn on the Irregular Rhythm parameter. Our study team will encourage subjects to use the Apple Watch's ECG App when they suspect they are in Atrial Fibrillation or receive notifications of Low Heart Rate, High Heart Rate, and Irregular Rhythm, however, this is optional and will not be mandatory for the subjects. ECG results include Normal Sinus Rhythm, Atrial Fibrillation or Inconclusive. ECG tracings determined as Inconclusive will be given to our study investigators, who will provide their interpretations of the tracings. If their interpretations include any tracings that indicate Atrial Fibrillation, we will incorporate this data into our Atrial Fibrillation logs to determine AF occurrences.

- To share the subject's HealthApp with our study-dedicated or PI's iPhone, our study team will press "Share with someone" on the subject's HealthApp. The HealthApp vitals will be shared with the research team including: Cardio fitness, Electrocardiogram (ECG), Heart Rate, Heart Rate Variability, Resting Heart Rate, and Walking Heart Rate Average. By enabling these features, our study team will be able to monitor our subject's Apple Watch recordings via our study-dedicated iPhone or Principal Investigator's phone. The subject's iPhone and Apple Watch will be shared with an onsite iPhone Baseline visit until the completion of the 3 Month Visit 7-day Mobile Cardiac Telemetry. Once the 3 Month Visit 7-day Mobile Cardiac Telemetry is complete, our study team will contact the subject and direct the subject to turn off the sharing feature by pressing "Stop Sharing Health Data" with the research staff.On our on-site iPhone we will select "Stop sharing health data" and "Stop receiving health data". We will reach out to the patient to confirm they are no longer able to send health data. We will instruct Cedars-Sinai IT Support (EIS) to remove the Apple ID that is associated with both the subject's iPhone and Apple Watch and carry out any procedure that will wipe data pertaining to the research study from the subject's research iPhone and Watch. Once Cedars-Sinai IT Support (EIS) confirms the subject's devices are removed from Cedars-Sinai control, the subject can enter their own personal Apple ID for their own

personal use of the devices. At this point, the subject is permitted to keep the research iPhone and Watch. If the Apple Watch and/or the Apple iPhone are lost, damaged and/or stolen, the subjects will not be financially responsible, and the site may provide replacements. This will only cover the Apple devices that are provided to patients for the study excluding personal Apple devices. If a subject withdraws or discontinues with the study after Randomization, they will be able to keep the research Apple Watch and Apple iPhone.

- Mobile Cardiac Telemetry – The patient will be continuously monitored during the following time points: Eligibility (optional), Procedure, Week 1, Week 2 and the 3 Month Visit.
    - Preventice – The BodyGuardian Mini Plus monitors are a non-invasive, light weight, waterproof and highly portable device. This monitor is connected to an electrode patch that may be worn up to 7 days or 21 days. The BodyGuardian Mini Plus monitor will monitor hearth rhythm and are used for safety monitoring. The ECG signals will be transmitted to Preventice staffed by experienced technicians for heart rhythm monitoring. If the subject developed serious heart rhythm disorder, Preventice technicians will notify the Principal Investigator at the time of the event. The Principal Investigator will then make a clinical judgement based on the status of the patient.
    - Bittium Faros—The Bittium Faros monitors are a non-invasive, light weight, waterproof, and highly portable device. The Bittium Faros monitor is connected to an electrode patch that may be worn for up to 7 days. We will use the Bittium Faros monitor to monitor skin sympathetic nerve activity at the specified time points. This device will not be used for safety monitoring.
- Discharge/patient teaching-subject teaching for restrictions and dressing care
- Removal of lead- The patient is placed in a supine position. The sterile dressing is removed. The silk suture is cut and removed. The stimulating lead is then pulled out of skin. The skin is cleaned with alcohol. The puncture site is left open to air
- Echocardiogram-We will obtain an echocardiogram for research purpose at baseline, after the device removal and again during the 3-month follow up visit. The data will be analyzed by Dr. Robert Siegel to determine if ScNS changes the ventricular function
- AFEQT-AF QOL-the symptoms of AF will be assessed by standard questionnaires
- EQ-5D-5L QOL—the symptoms of AF will be assessed by standard questionnaires
- Labs-CBC, BMP, BNP, Catecholamine levels- Blood will be submitted at baseline and again at final follow up visit for laboratory tests that include CBC, metabolic panel, BNP, and serum catecholamine concentration. The BNP will be used as a measure of heart failure, which may improve after better rhythm or rate control. Catecholamine concentration will used to estimate the sympathetic tone.

8.2 SAFETY AND OTHER ASSESSMENTS

Each patient will receive mobile telemetry monitoring during the subcutaneous nerve stimulation (2 weeks). Their heart rhythm is recorded and transmitted to the central monitoring station of the patch manufacturer. The technician will inform the PI or one of the co-investigators for any significant

arrhythmic events. The PI or co-investigator will review the tracings, make the diagnosis and take steps to ensure patient safety.

After surgery, the patients will be examined at one week, two-weeks, three-weeks and three-month time points. The wound will be examined for signs of infection. If the patient had any symptoms related to the experimental procedure, he/she can report the symptoms to the investigators. Additional clinical visits may be arranged to manage those symptoms.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic reactions to the drug or devices, symptomatic bradycardia, dizziness, syncope and death.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF) in Redcap. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Principal investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events (AEs) and, Serious adverse events (SAEs) will be reported to IRB following its guidelines. Adverse events will be reported to the DSMB. The PI will follow the DSMB charter guidelines. The sign off on the adverse event will be done following the DSMB charter and IRB guidelines.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but no later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The patients are continuously monitored by a mobile cardiac telemetry system. The insertion site will be examined to determine if there are signs of infection or electrode migration. The PI will inform the patients of the AEs and SAES when they occur and again during the routinely scheduled follow up. The PI will coordinate with the patient's physician in managing these AEs and SAEs to ensure patient safety.

8.3.8 EVENTS OF SPECIAL INTEREST

We do not expect to observe events of special interest in this study.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor as soon as possible, but no later than 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) as soon as possible, but no later than 10 business days of the IRB's receipt of the report of the problem from the investigator.

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The PI will inform the patients of unanticipated problems when they occur and again during the routinely scheduled follow up. The PI will coordinate with the patient's physician in managing these unanticipated problems to ensure patient safety.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

- Primary Efficacy Endpoint(s):

The average AF burden.

- Secondary Efficacy Endpoint(s):

1) Time-dependent reduction of AF burden
2) Ventricular rate during AF
3) Average SKNA
4) Quality of life
5) Reduction of AF burden after cross over from control to experimental group

Our primary research hypothesis is that chronic subcutaneous nerve stimulation can control AF in patients with severe symptomatic AF unresponsive to conventional therapies.

The primary endpoint is the average of AF burden at the end of the first week. Patients who do not experience AF during the first week will have a value of 0 as AF burden. The average of AF burden at the end of the first week will be calculated per patient as the proportion of time spent in AF during the first week divided by the number of days a patient is under observation during the first week.

We will test the null hypothesis of no difference in the average AF burden between the treatment groups versus the alternative hypothesis that the average AF burden is lower in the intervention group than the sham group.

The following pairs of secondary null and alternative hypotheses will be tested:
1) that the trajectories of reduction of AF burden by time between treatment and control groups are the same versus that the trajectories are different;
2) that reduction of AF burden in treatment group does not depend on time versus that the reduction of AF burden is dependent on time;
3) that effects of ScNS and sham stimulations on ventricular rate control during AF are the same for the treatment and the control groups versus that the effects are different between the two groups;
4) that reduction of SKNA is the same between the treatment and the control groups versus that the reduction of SKNA is different between the two groups;
5) that improvement of quality of life is the same between the treatment and the control groups versus that the improvements of QoL is different between the two groups.
6) There is a reduction of AF burden after crossing over from control to experimental group

9.2 SAMPLE SIZE DETERMINATION

The AF burden is determined by the amount of time spent in AF detected by Mobile Cardiac Telemetry patch. A recent study[22] analyzed the results of ambulatory single-lead ECG patch sensor monitoring for 11.4 days on average in 7934 men and 5359 women with paroxysmal AF. During the monitoring period, there were a total of 1,041,504 paroxysmal AF episodes. The median daily rate of paroxysmal AF was 1.21 episodes per day (interquartile range [IQR] 0.31-4.99), and the median maximum duration per individual was 7.5 hours (IQR 2.4-18.6 hours). The median burden of AF (% of time in AF relative to entire period of monitoring) was 8.9% (IQR 3.4%–25.2%). Assuming that we implant the lead and randomize patients into experimental group (stimulation) and control group (no-stimulation), we expect to see the same average AF burden among our patients. In our previous study in canine models,[9] subcutaneous nerve stimulation reduced atrial arrhythmia burden per 48 hours from 211.0 ± 204.8 s to 134.8 ± 165.2 s (delta=-76.3 ± 44.8 s) versus a reduction of -5 ± 9.5 seconds in the sham group. Assuming the same standard deviation of the change of AF burden from baseline in the two randomized groups as 44.8 and accounting for the patient retention rate of 70%, we need 15 per arm (total 30 patients) for 80% power at 2-sided alpha 0.025 to detect an effect size of 1.59at the end of one week between Group A (experimental) and Group B (control) using the Wilcoxon rank sum test. If the treatment suppresses AF by 75% while the sham does not suppress AF at the end of one week, we have 86% power to detect this difference at 2-sided alpha 0.025 using Fisher's exact test. We have budgeted for 32 patients to ensure that we have sufficient funds to complete the study.

9.3 POPULATIONS FOR ANALYSES

1. Safety set: the set of patients who have undergone surgery to insert the subcutaneous lead

2. modified intention-to-treat set: the set of patients who have either the subcutaneous nerve stimulation or the sham stimulation performed AND have baseline average AF burden AND at least the first week's post-stimulation average AF burden.

Our sensitivity analysis on the modified intention-to-treat set will be using the safety set: we will assume 0 reduction in AF burden for patients missing either the baseline or the first week post-baseline AF burden.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Patient characteristics will be summarized per randomized group using percentages if categorical, or means with standard deviations if continuous. These characteristics will be compared using the Wilcoxon rank sum test if continuous, or Fisher's exact test if categorical. Nominal two-tailed p values will be reported. Repeated measures will be analyzed either by linear mixed effects models or by GEE. Standard model diagnostics will be performed.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the average of AF burden at the end of the first week.

We will use Mobile Cardiac Telemetry to determine AF burden before surgery (eligibility visit), for two weeks during ScNS, 3 weeks following surgery and 3 months following surgery.

The average of AF burden at the end of the first week will be calculated per patient as the time spent in AF during the first week divided by the total time a patient is under observation during the first week. Change of the average AF burden from the baseline will be computed for each patient. The change in the average AF burden will be compared between group A (experimental) and group B (control) using the Wilcoxon rank sum test at a two-sided significance level of 0.025.

The following secondary analyses of the primary endpoint will be performed:

1) We will compare the baseline AF burden and the baseline number of Apple watch-detected AF episodes between groups. The number of Apple watch-detected AF will be standardized by the number of days that a subject is under observation in the respective time period. Further we will compare reduction in AF burden from baseline at weeks 1, 2, 3 and 12 in both Group A and Group B to test the null hypothesis that there is no reduction of AF burden in the two groups and between the two groups. We will also compare the reduction in the number of Apple watch-detected AF episodes from the baseline in the period between week-3 and the end of study in both Group A and Group B to test the null hypothesis that there is no difference in detected AF episodes in the two groups and between the two groups. Linear mixed effect models will be used for the comparisons, with Group, Week and Group by Week interaction as fixed effects, and a random intercept per subject. Week will be coded first as a categorical variable, and appropriate contrasts will be set up for the temporal comparisons. If outcome variables appear to be linear in time, we may model Week as a continuous fixed effect.

2) We may also compute the difference-in-difference statistics for the treatment for the 4 time intervals of the treatment, baseline and t weeks 1, 2, 3 and 12.

We may also use generalized estimating equations (GEE) instead of linear mixed effect models if the validity of the latter is suspect. If there is differential drop-out between the randomized groups, we will adjust the group-comparisons using baseline covariates, such as age, sex and heart failure status. Standard approaches for both model checking and selection based QIC will be applied.[23]

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The analyses of the secondary endpoints will be performed on the modified ITT data set. Unless otherwise stated, two-tailed nominal p values will be reported.

Analysis of mean VR at the end of week 1

In dogs, ScNS reduces ventricular rate during AF. The mean VR was 149±36 bpm after the induction of AF. The VR significantly decreased to 84±16 bpm (p=0.011) at the final week of ScNS.[11] The same device that produces AF burden will also generate VR. First, we will summarize the proportion of patients who are AF-free at the end of week 1. Fisher's exact test will be performed to test if the proportions of AF-free patients are the same between the two treatment arms at a two-sided significance level of

0.025. Second, we will summarize the mean VRs using mean and standard deviation by time and by randomization group among the patients who experience AF.

We will classify patients into 3 groups based on the week 1 average VR: patients who do not experience AF as category 1, patients who experience AF with VR <= 110 bpm as category 2,[24] and patients who experience AF with VR > 110 bpm as category 3. Fisher's exact test will be performed to test if the distribution of the three categories are the same between the two treatment arms and the nominal p-value will be reported.

We will categorize average VR at other time points into three groups as described above, and analyze repeated average VR using ordinal repeated measure analysis with patient as the blocking variable, week and group as well as their interaction as independent variables. Proportional odds assumption will be checked.

Analysis of SKNA and QOL

Subcutaneous nerve stimulation achieves its effects through neuromodulation, resulting in reduced sympathetic nerve activity. A non-invasive method to measure sympathetic nerve activity is through the skin sympathetic nerve activity (SKNA) recording. We will record SKNA using two different equipment. The first is ME6000 which makes high fidelity SKNA recordings with 10,000 Hz sampling rate. However, ME6000 is not sufficiently portable for ambulatory recordings. Therefore, we added Bittium Faros recorder for ambulatory recording at 1,000 Hz sampling rate.

The quality of life (QOL) is measured using the standard questionnaire to assess the overall effects of treatment on the study subjects.

SKNA recorded with ME6000 at rest and during 6-minute walk will be summarized at each time point using mean and standard deviation.

SKNA recorded with Bittium Faros when patients were ambulatory will be summarized at each time point using mean and standard deviation.

Quality of life (AFEQT-AF, EQ-5Q-5L) will be summarized by item and by overall score at the following time points, baseline, 3 week and 3-month visits using mean and standard deviation.

Change in the average values of SKNA (aSKNA) recording at rest on the procedure day from the baseline will be compared between the randomization groups using the Wilcoxon Rank Sum test. Values of aSKNA recording in ambulatory subjects and during 6-minute walk at baseline, 1 week, 2-week, 3 week and 3-month visits will be compared between randomization groups using linear mixed models, with Group, Week and Group-Week interaction as fixed effects, and a random intercept per subject. Week will be coded first as a categorical variable. If aSKNA appear to be linear in time, we may model Week as a continuous fixed effect. Missing at random will be assumed in the above stated linear mixed models. Additionally, the strategy of last-value-carried-forward (LVCF) will be employed to fill in missing data values as an alternative to the missing-at-random assumption and the linear mixed models will be re-

run. The LVCF analysis serves as a sensitivity analysis. Similar analyses will be performed for SKNA during 6-minute walk.

We will compare the number of Apple watch-detected AF episodes between week-3 and the end of study between Group A and Group B to test the null hypothesis that there are no differences in detected AF episodes between the two groups. For each patient, we will record the number of days that the patient is under observation, and the number of days that AF episodes are detected. Assuming that each patient's data follows a binomial distribution and the probability of AF daily detection is the same within group. Since patients' data are independent from each other and the sum of independent binomials are still a binomial, we can compare the two groups as two binomials with potentially different rates of AF detections. Fisher's exact test will be performed for this comparison at a two-sided significance level of 0.05.

The overall scores of Quality of life (AFEQT-AF, EQ-5Q-5L) questionnaires will be compared at the following time points, baseline, 3 week and 3 month visits by the same linear mixed effect models as described for aSKNA. The same missing data treatment as stated above will be employed in the linear mixed model analyses of these two outcomes. Item and total scores may be transformed if deemed necessary to fulfil model assumptions.

Analysis of AF burden in patients crossed over from sham control to experimental group

At the end of week three, patients in the sham control group will be given the option to receive the active treatment and treated the same way as patients on the treatment arm for weeks 1-3. Patient characteristics will be summarized for the subset of patients who accept this option to cross over to active treatment. The averages and SDs of AF burden will be computed for each week from baseline to week 6 for this group, and displayed graphically. Linear mixed models may be employed to explore the temporal changes in this subset of patients.

9.4.4 SAFETY ANALYSES

- Safety Endpoints
    - Safety shall be evaluated throughout participation in the study:
    - Freedom of major implant adverse events related to the procedure
    - Infection
    - Lead, extension or migration
    - Persistent pain at the lead site
    - Freedom of Third Degree AV Block at any anatomic level associated with any one of the following conditions
    - Bradycardia with symptoms presumed to be due to AV Block
    - Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia
    - Documented periods of asystole > 3.0 seconds or any escape rate <40 beats per minute in awake, symptom-free patients

- Freedom of Second-degree AV block regardless of type or site of block, with associated symptomatic bradycardia
- Freedom of skin irritation related to the ECG patches, Mobile Cardiac Telemetry patch
- Freedom of allergic response to the implanted lead or materials used

The number as well as percent of patients experiencing a safety outcome listed above will be summarized overall and by randomized group in the safety set.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Patient characteristics will be summarized per randomized group using percentages if categorical, or means with standard deviations if continuous. These characteristics will be compared using the Wilcoxon rank sum test if continuous, or Fisher's exact test if categorical. Nominal p values will be reported.

9.4.6 PLANNED INTERIM ANALYSES

No interim analysis is planned.

9.4.7 SUB-GROUP ANALYSES

We will not perform subgroup analyses based on age, sex, race/ethnicity or other demographic characteristics because:

1) there is no biological basis for those factors to affect the primary outcome,
2) the sample size is small that we will not consider those subgroup analyses.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

9.4.9 EXPLORATORY ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the

protocol and the written informed consent form(s) and any other written information to be provided to the participants.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study intervention. The following consent materials are submitted with this protocol; Informed consent and HIPAA form. Additional information will be given to the patient at baseline visit; pre-operative instructions and after the implant; post-procedures instructions and a study Participant ID card.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. A copy of the signed informed consent will be uploaded on patient medical record. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Indiana CTSI in Indianapolis, IN. The identifiable information is included in the database but will be made visible only with specific authorization from the PI. Each participant and their research data will be identified by a unique study identification number. This de-identified information will be provided to investigators for analyses.
The study data entry and study management systems used by clinical sites and by Indiana CTSI in Indianapolis, IN research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Indiana CTSI in Indianapolis, IN.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants,

Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.]

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed by Xiaochun Li, PhD and stored in the Redcap database at the Indiana CTSI in Indianapolis, IN. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Data and Resource Center (DRC) of NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, for use by other researchers including those outside of the study. Permission to transmit data to the NIH SPARC DRC will be included in the informed consent.

When the study is completed, access to study data will be provided through the Data and Resource Center (DRC) of NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) program.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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The study is funded by NIH SPARC program. The PI and the co-investigators will form a steering committee to manage the trial. There is a regularly scheduled monthly teleconference for the steering committee to report the progress to NIH, with the participation of Medtronic Inc.

10.1.6 SAFETY OVERSIGHT

A Data Safety Monitoring Board [DSMB] will provide ongoing independent review of the data, further ensuring the continued safety of subjects, as well as the validity and scientific merit of the trials. The DSMB consists of at least three voting members and one non-voting member that is a biostatistician, with relevant expertise.

The DSMB members include an experienced clinical trialist (chair), a clinical cardiac electrophysiologist, a clinical cardiologist and a biostatistician. None of the DSMB voting members are not related to the study or employed by the Cedars-Sinai Medical Center. The DSMB together with the PI will be charged with determining if the study should be stopped based on interim data reports that they will receive from the data coordinating center. IU will evaluate safety information that is reported in the time frame specified in the protocol. It is the responsibility of the PI to oversee the safety of the study. All SAEs will be processed for review to the DSMB within 7- 10 days of receipt.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by Cedars Sinai Medical Center IRB:

- The Clinical Research Monitor will work with the Site PI and Site Contact(s) to schedule monitoring visits. The monitor will contact the study team at least 30 days prior to the visit to schedule a designated date/time to review subject charts and regulatory data.
- Prior to the visit, the PI and other pertinent site personnel will receive a monitoring visit confirmation letter and a list of subjects to be monitored. The monitor will ensure that this information is communicated to the site personnel at least 14 days prior to the mutually agreed upon visit date to allow sufficient time for record acquisition and preparation.
- Monitoring visit findings, resulting action items and suggestions for quality improvement will be documented in the Monitoring Visit Follow-Up Report. The Clinical Research Monitor will send a completed report to the study team within 30 days of the last day of the monitoring visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

There is only one site for recruitment. The investigators will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements and Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Redcap database, a 21 CFR Part 11-compliant data capture system provided by the Indiana CTSI. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

All records produced or collected in connection with the research project, including primary (e.g., laboratory, medical, interview), financial, statistical, supporting, administrative, and regulatory documentation, shall be retained for a minimum of three (3) years from the date of submission of the final expenditure report to the funding agency or the date of study closure with the IRB, whichever is longer.

Records may need to be retained beyond this date, specifically:

- For studies subject to HIPAA, signed HIPAA authorization forms must be retained for a minimum of six (6) years from the date it was obtained.

- For studies conducted under an IDE or HDE, records must be retained during the investigation and for a period of two (2) years after the latest of either: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification.
- If the research involves intellectual property, data must be kept for as long as may be necessary to protect any intellectual property claims resulting from the work.
- If any charges regarding the research arise, such as allegations of misconduct in research or financial conflict of interest, data must be retained until such charges are fully resolved.
- If the research is conducted pursuant to a contract or agreement, data must be retained in accordance with the contract or agreement.

After the specified period of time has elapsed, research personnel may dispose of the documentation relating to a research study in an appropriate manner, including encrypting, shredding, incinerating,

mutilating, erasing, and otherwise rendering the information illegible or unusable. Source documentation must be retained in its original form until this time.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations as soon as possible but not later than 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, uploaded to the Redcap database at Indiana University and reported to NIH SPARC program staff. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The PI and co-investigators will generate manuscripts for publication and will present the data in national scientific meetings. All data will be shared with SPARC investigators and public according to the SPARC program rules. In addition, this study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers one year after the completion of the primary endpoint by contacting NIH SPARC program.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH SPARC program has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

ACC/AHA	American College of Cardiology/American Heart Association
AE	Adverse Event
AF	Atrial fibrillation
AV	Atrioventricular
AFEQT-AF-QOL	Atrial Fibrillation Effect on Quality of Life
aSKNA	Average skin sympathetic nerve activity
BMI	Body Mass Index
BMP	Basic Metabolic Panel
BNP	B-type natriuretic peptide
bpm	Beats per minute
CBC	Complete blood count
CIED	Cardiac implantable electronic device
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
CSMC	Cedars Sinai Medical Center
CTSI	Clinical and Translational Sciences Institute
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DOAC	Direct oral anticoagulants
DSMB	Data Safety Monitoring Board
DRC	Data and Resource Center
DRE	Disease-Related Event
EC	Ethics Committee
ECG or EKG	Electrocardiogram
EF	Ejection fraction
EQ-5D-5L QOL	5-level EQ-5D version (EQ-5D-5L) quality of life
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GEE	Generalized estimating equations
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICDs	Implantable cardioverter-defibrillators
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ISM	Independent Safety Monitor

ISO	International Organization for Standardization
ITT	Intention-To-Treat
LVCF	Last Value Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NPO	Nothing through the mouth
OHRP	Office for Human Research Protections
OTC	Over the counter
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QIC	Quasilikelihood under the Independence model Criterion
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ScNS	Subcutaneous nerve activity
SKNA	Skin sympathetic nerve activity
SMC	Safety Monitoring Committee
SPARC	Stimulant Peripheral Activity to Relieve Conditions
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
VNS	Vagal nerve stimulation
VR	Ventricular rate
VT	Ventricular tachycardia
WENS	Wireless external neurostimulator
Wt	Weight

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
7	1-25-2022	1. Specification of Mobile Cardiac Telemetry devices 2. Apple Watch Monitoring	The Bittium Faros was approved as a device by the IRB on 3/10/21 (MOD00003064). This monitors the change in skin sympathetic nerve activity throughout the study at the desired time points, however, this specific device is not used for safety monitoring. The Preventice mobile cardiac telemetry device was added to the IRB study application approved by the IRB on 3/29/2021 (MOD00003361). This mobile cardiac telemetry device will be used for safety monitoring. Indication that the Apple Watch will act as secondary monitoring system to the Mobile Cardiac Telemetry devices. There are recent studies that provide significant evidence that Apple watches can accurately detect Atrial Fibrillation episodes. However, AF monitoring via Apple Watch will not be used for safety monitoring. In October 2021, Apple obtained FDA regulatory clearance for a new ImF Photoplethysmograph analysis that assists with irregular heart rhythm detection on Apple Watches. Since then, there is greatly increased interest in using Apple watch to detect atrial fibrillation. We wish to incorporate this new technology into our study. This new method is highly portable, accurate and

			non-invasive. It will help us bridge the gap between 3-wk and 3-month visits to determine the frequencies of AF in study participants.
8	6-22-2022	1. Addition of Adverse Events 2. Addressing Inconclusive ECGs from Apple Watch 3. Apple Watch Monitoring and Timeline	Based on patient reported adverse events and past literature, goosebumps and hot flashes are known to have association with spinal cord stimulation. We are adding them as potential adverse events. In the event that the subject does not want to wear the research Apple devices for Apple Watch Monitoring, we want to provide an option of allowing them to continue the monitoring between Week 3 and Month 3 procedures. Apple Watch Monitoring will allow the Principal Investigator and research staff to know when the patient is having AF determined by the Apple Watch detection. To account for Apple watch ECG readings that result as Inconclusive. We found that Apple Watch is effective in detecting AF after randomization. However, because we do not have data before randomization, there are no baseline AF data to compare with. Therefore, we request the permission to give the patient an Apple Watch and iPhone during baseline visit. The patient will wear the watch before randomization to collect baseline information. We also revised the statistical analysis. These changes do not affect the primary outcomes of the study.
9	9-28-2022	1. Inclusion criteria – expand to use of clinical ePatch recordings for AF burden	Most of the patients with atrial fibrillation (AF) had AF burden determined clinically by ePatch recordings. If the ePatch

		2. Optional Crossover study after Week 3 3. Addition of Secondary Endpoint regarding the optional crossover study	recordings were done within 6 months prior to enrollment and there are no changes in antiarrhythmic medications after the recording, then the AF burden recorded by the ePatch will be used as baseline AF burden. This change will eliminate the need of repeating the ePatch recording for eligibility determination and thus improve recruitment. Based on our DSMB recommendations from 9/22/22, we are doing a crossover after week 3 to improve recruitment because all participants are guaranteed an opportunity to receive subcutaneous stimulation. In our original protocol, after the first 3 weeks, additional data collection will be performed with Apple Watch and with a final one-week ePatch monitoring. However, since the latter data are used for secondary exploratory analysis only, we do not need those data to determine the primary endpoint of the study.
10	12-30-2022	1. Removed Catecholamines and BNP for Week 3 Visit. The labs required for a second procedure are only to ensure that the subject is ready for surgery.	Per PI, we do not need catecholamines nor BNP to undergo the second surgery.
11	01-18-2023	1. We are removing the verbiage that states postdocs will be blinded during SKNA data analysis.	In the first 4 patients who underwent stimulation, large stimulation artifacts were noted in the recording. Therefore, the postdoc can immediately recognize who's been stimulated and who's not just by looking at the data. It is not possible to blind the postdoc during data analyses

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