

REnal SympathetiC denervation to sUpprEss Tachyarrhythmias in ICD Recipients
(RESCUE)

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NYC

Table of Contents:

1. CONTACT INFORMATION
- 1.1. STUDY SITES & INVESTIGATORS
2. STUDY OBJECTIVE
3. INTRODUCTION, RATIONALE
 - 3.1. INITIAL PILOT DATA
4. SCHEDULE OF TREATMENTS AND TESTS
5. ENDPOINTS
 - 5.1. PRIMARY CLINICAL ENDPOINT
 - 5.2. SECONDARY CLINICAL ENDPOINTS
6. STUDY SUBJECTS
 - 6.1. INCLUSION CRITERIA
 - 6.2. EXCLUSION CRITERIA
7. STUDY PHASES
 - 7.1 CLINICAL CENTERS
 - 7.1.1. INVESTIGATOR PROFILE
 - 7.1.2. QUALIFICATIONS AND TRAINING
 - 7.1.3. CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE AGREEMENT
 - 7.1.4. SITE APPROVAL
8. PATIENT ENROLLMENT AND WITHDRAWAL
 - 8.1. ROLL-IN PHASE
9. STUDY PROCEDURES
 - 9.1. PRE- AND ABLATION PROCEDURE
 - 9.1.1. PRE-PROCEDURE
 - 9.1.2. PRE-PROCEDURE MEDICATION MANAGEMENT
 - 9.1.3. ABLATION PROCEDURAL DETAILS
 - 9.2. POST-PROCEDURE
 - 9.2.1. POST-PROCEDURE FOLLOW-UP
 - 9.2.2. POST-PROCEDURE MEDICATION MANAGEMENT
 - 9.2.3. ICD PROGRAMMING
 - 9.3. SAFETY
 - 9.3.1. INITIAL INTERIM AND FUTILITY ANALYSES
 - 9.3.2. CLINICAL EVENTS COMMITTEE
 - 9.3.3. DATA SAFETY MONITORING BOARD
 - 9.4. RISKS
 - 9.4.1. SERIOUS ADVERSE EVENTS
 - 9.4.2. UNANTICIPATED SERIOUS ADVERSE EVENTS
 - 9.4.3. UNANTICIPATED ADVERSE DEVICE EFFECTS
 - 9.4.4. UNANTICIPATED PROBLEMS
 - 9.4.5. EVENT RECORDING
 - 9.4.6. CAUSALITY

- 9.4.7. REPORTING OF SERIOUS ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS
- 9.4.8. REPORTING OF UNANTICIPATED PROBLEMS
- 9.4.9. DCC REPORTING TO FDA

- 10. STATISTICAL ANALYSIS PLAN
 - 10.1. STUDY DESIGN
 - 10.2. PRIMARY OBJECTIVES
 - 10.3. PRIMARY EFFECTIVENESS ENDPOINT
 - 10.4. PRIMARY SAFETY OBJECTIVE
 - 10.5. SECONDARY ENDPOINTS
 - 10.6. POWER AND SAMPLE SIZE
 - 10.7. INTERIM MONITORING GUIDELINES
 - 10.8. STATISTICAL ANALYSIS
 - 10.9. PRIMARY SAFETY ANALYSIS
- 11. ETHICAL AND REGULATORY CONSIDERATIONS
 - 11.1. STUDY DATA COLLECTION PROCESSING
 - 11.2. CONFIDENTIALITY
 - 11.3. DEVIATIONS FROM PROTOCOL
 - 11.4. WITHDRAWAL OF SUBJECTS
 - 11.5. ECONOMIC IMPACT ON SUBJECTS
- 12. STUDY MANAGEMENT
 - 12.1. RISK TO SUBJECTS
 - 12.2. POTENTIAL BENEFITS TO SUBJECTS
 - 12.3. ROLE OF DATA COORDINATING CENTER
 - 12.4. ONSITE MONITORING
 - 12.5. MAINTAINING RECORDS
 - 12.6. SITE RECORD RETENTION POLICY
 - 12.7. INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE INFORMATION
- 13. DATA HANDLING

REFERENCES

PROTOCOL SUMMARY

Title:	<u>REnal Sympathetic denervation to sUpprEss Ventricular Tachyarrhythmias in ICD Recipients (RESCUE)</u>
Objective:	The objective of this trial is to determine the efficacy and safety of adjunctive catheter-based renal sympathetic denervation (RSDN) in the primary prevention of ICD therapy in patients with ischemic or non-ischemic ventricular dysfunction, who are to receive an ICD for either i) secondary prevention, or ii) primary prevention + inducible VT by programmed ventricular stimulation at the time of ICD implantation. These patients will be randomized to ICD alone or ICD + RSDN.
Design:	This study is a prospective, multicenter, single-blinded, randomized (1:1) control trial evaluating the effectiveness of RSDN in the primary prevention of ICD therapy in patients with ischemic or non-ischemic ventricular dysfunction who are to receive an ICD for either i) secondary prevention, or ii) primary prevention + inducible VT by programmed ventricular stimulation at the time of ICD implantation. These patients will be randomized to ICD alone or ICD + RSDN. Subjects will only be eligible for this study if they are \geq 18 years of age and have a history of structural heart disease (post-MI, dilated cardiomyopathy, sarcoid myopathy, hypertrophic cardiomyopathy, etc.), and are planned for ICD implantation for: i. Secondary prevention (e.g.: VT/VF arrest, sustained VT, syncope/inducible VT) ii. Primary prevention + inducible MMVT during induction via ICD lead testing. In addition, eligible patients will have accessible renal vasculature (as determined by renal angiography).
	The patient will be blinded to the results of randomization. Once randomized, study group subjects will undergo a strategy of catheter-based renal sympathetic denervation + ICD implantation (if not already present). Control patients will receive standard ICD implantation alone (if not already present). Follow-up will be conducted in regular intervals over a 12-month period.
Enrollment:	Total: 462 subjects (231 control group, 231 study group)
	An interim safety analysis will be performed after the first 50 subjects (25 control group, 25 study group) have completed their 6-month follow-up visit.
Clinical Sites:	<ul style="list-style-type: none">• Icahn School of Medicine at Mount Sinai• Homolka Hospital, Prague, Czech Republic• Heart Center U SV. Anny Hospital, Brno, Czech Republic• Massachusetts General Hospital• Regional Cardiology, Sacramento, California• Medical University of South Carolina• Florida Hospital, Orlando, Florida

	<ul style="list-style-type: none"> • Other Sites TBD
Time Course:	Enrollment: Over 4 years
Subject Description:	Eligible subjects include those \geq 18 years of age with a history of structural heart disease (post-MI, dilated cardiomyopathy, sarcoid myopathy, hypertrophic cardiomyopathy, etc.), who are planned for ICD implantation for: i. Secondary prevention (e.g.: VT/VF arrest, sustained VT, syncope/inducible VT) ii. Primary prevention + inducible MMVT during induction via ICD lead testing. iii. Primary prevention + fragmented QRS complex on 12-lead ECG. In addition, eligible patients will have accessible renal vasculature (determined by renal angiography).
Study Group:	In addition to ICD implantation, the subjects in this group will undergo catheter-based renal sympathetic denervation.
Control Group:	Subjects in the control group will undergo standard ICD implantation alone (if not already present).
Primary Endpoint:	Time to first event requiring any ICD therapy (appropriate or inappropriate) or Incessant VT (VT occurring below the ICD rate cut-off); this will be assessed in the on-treatment patient cohort.
Secondary Endpoints:	<ol style="list-style-type: none"> 1. Appropriate ICD therapy assessed in the full intention-to-treat patient cohort 2. Inappropriate ICD therapy 3. Number of Hospitalizations for Cardiovascular Causes. 4. Total VT burden (Number of episodes). 5. All-Cause Mortality. 6. The occurrence of ICD storm, defined as \geq3 appropriate shock therapies within 24 hours. 7. Differences in BUN/creatinine measurements. 8. Procedure related adverse events including, but not limited to hematomas, pseudoaneurysms and renal artery stenosis. 9. Development of orthostatic hypotension 10. 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer);
Primary Analytical Analysis:	Intent to treat analysis
Secondary Analytical Analysis:	Per protocol analysis

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1 CONTACT INFORMATION

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1.1 STUDY SITES & INVESTIGATORS

Site	Principal Investigator
1. Icahn School of Medicine at Mount Sinai	Vivek Y. Reddy, MD
2. Homolka Hospital, Prague, Czech Republic	Petr Neuzil, MD
3. Texas Cardiac	Andrea Natale, MD
4. State Research Institute of Circulation Pathology, Novosibirsk, Russia	Evgeny Pokushalov, MD
5. OhioHealth Research Institute	Gregory Kidwell, MD
6. Medical University of South Carolina	Frank Cuoco, MD
7. Florida Hospital, Orlando, Florida	Usman Siddiqui, MD
8. TBD	

2 STUDY OBJECTIVE

The goal of this trial is to determine the efficacy and safety of adjunctive catheter-based renal sympathetic denervation (RSDN) in the primary prevention of ICD therapy in patients with ischemic or non-ischemic ventricular dysfunction, who are to receive an ICD for either i) secondary prevention, or ii) primary prevention + inducible VT by programmed ventricular stimulation at the time of ICD implantation. These patients will be randomized to ICD alone or ICD + RSDN. The proposed study is a prospective, multicenter, single-blind, randomized control trial.

3 INTRODUCTION, RATIONALE

Sudden cardiac death (SCD), defined as an unexpected death from a cardiac cause occurring within \leq 1 hour of the onset of symptoms, accounts for 300,000 to 400,000 deaths in the United States annually, or 5.6% of annual mortality.¹⁻³ SCD is most commonly caused by ventricular tachyarrhythmias, including ventricular tachycardia (VT). Several therapies exist for the prevention of VT, including implantable cardioverter-defibrillator therapy (ICD), anti-arrhythmic drug therapy (AAD), and the use of catheter based ablation.

Current guidelines recommend the use of implantable cardioverter-defibrillator (ICD) as therapy to prevent SCD in patients who have survived a prior cardiac arrest due to unstable VT or who have had a previous episode of spontaneous sustained VT.⁴ Several trials have demonstrated the efficacy of ICD therapy in preventing SCD.^{5,6} The MADIT II trial, a randomized trial of patients with prior myocardial infarction and left ventricular ejection fraction \leq 30%, demonstrated a 31%

reduction in the relative risk of death in the defibrillator group.⁶ However, ICD therapy does not prevent VT, and a significant proportion of patients may still experience appropriate shocks. In the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial, 60% of patients had ≥ 1 appropriate ICD therapy for VT/VF during follow-up (31±13 months), and the first arrhythmia resulting in a shock during follow up was frequently identified as VT (63%). Unfortunately, these ICD shocks are associated with both a significant reduction in quality of life and increased mortality. In a study examining quality of life in patients who had received ICD shocks, at 5.5 years post ICD implantation 19% of patients demonstrated signs of post-traumatic stress disorder.⁷ In the MADIT II trial, patients who experienced VT/VF had an increased risk of death, with a hazard ratio of 2.5.⁶ Thus, while ICDs have a clear overall mortality benefit in patients with a reduced ejection fraction, the ICD shocks themselves clearly reduce the quality-of-life of these patients and may have a negative impact on their longevity.

Antiarrhythmic drugs (AADs) are another therapy available for the prevention of VT, but unfortunately they have little effect on ventricular arrhythmia recurrence, and may increase mortality when used in high-risk patients. In the OPTIC trial, 412 patients who had an ICD implanted within 21 days for inducible or spontaneously occurring VT/VF were randomized to either amiodarone plus beta-blocker, sotalol alone, or beta-blocker alone. Although patients in the amiodarone plus beta blocker group were less likely to receive shocks (HR, 0.27; 95% CI, 0.14-0.52; $P<.001$), shocks still occurred in 10.3% of these patients. In addition, serious adverse effects associated with amiodarone resulted in study drug discontinuation in 18.2% of patients at 1 year.⁸

More recently, catheter ablation has emerged as a new option for the primary prevention of ICD shocks. Current guidelines recommend catheter ablation for symptomatic sustained monomorphic VT, including VT terminated by an ICD, that recurs despite AAD therapy or when AADs are not tolerated. In addition, ablation is indicated for control of VT storm refractory to drug therapy when there is a suspected trigger than can be targeted for ablation.⁹ The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia Study (SMASH-VT) randomized patients with a history of myocardial infarction who underwent defibrillator implantation for spontaneous VT or VF, to either defibrillator implantation alone or defibrillator implantation plus substrate-based catheter ablation. In patients who underwent defibrillator implantation alone 33% received ICD therapies (anti-tachycardia pacing or shocks), compared to 12% in patients who received defibrillator implantation plus substrate-based catheter ablation (Hazard ratio in the ablation group, 0.35; 95% confidence interval, 0.15 to 0.78, $P=0.007$).¹⁰ Similar results were seen in another multicenter randomized trial of similar design, VTACH. Despite the efficacy of VT ablation in these trials, this therapy is limited by: i) the complexity of the procedure requiring significant operator experience, ii) the duration of the procedure in these patients with ventricular dysfunction, iii) the potential risk of the procedure (despite the fact that no significant complications were seen in SMASH-VT and VTACH), and iv) SMASH-VT and VTACH only included the post-MI patient population since the substrate ablation approach is less applicable to patients with non-ischemic cardiomyopathy.

Thus, anti-arrhythmic drugs and catheter ablation each have limitations as adjunctive therapy in patients at risk for ICD shocks; new strategies are needed. One strategy under investigation is renal sympathetic denervation (RSDN). Recently, RSDN has been developed as a therapy to treat hypertension in patients resistant to anti-hypertensive drug therapy. In the Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension (Symplicity HTN-1) Trial: a multicenter safety and proof-of-principle cohort study, 45 patients with a mean office blood pressure of 177/101 mm Hg (SD 20/15), (mean 4.7 antihypertensive medications) underwent renal sympathetic denervation with radiofrequency based catheter ablation. After the procedure, these patients experienced a mean decrease in office blood pressure of -27/-17 mm Hg at 12 months, as

well as a 47% reduction in renal noradrenaline spillover.¹¹ In the Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension (Symplicity HTN-2) Trial, a multi-center prospective trial that randomized 106 patients to RSDN or medical management, at 6 months, 84% of patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 35% of controls ($p<0.0001$).

RSDN is thought to decrease blood pressure by a number of mechanisms including its ability to favorably affect whole body norepinephrine spillover and decrease central sympathetic tone. Indeed, RSDN has been shown to reduce whole body norepinephrine spillover by 42%, and efferent muscle sympathetic nerve activity by 66%.¹² Interestingly, increased catecholamine and sympathetic activity are both important factors in the development of ventricular arrhythmias.¹³⁻¹⁸ In addition, chronic hypertension is believed to mediate pathogenesis and progression of cardiac arrhythmias via its remodeling effects on cardiac anatomy through the renin-angiotensin-aldosterone system.¹⁹

Logically, RSDN may be an effective therapy in the prevention of SCD from VT. Interestingly, there are now several case reports examining the impact of RSDN for the treatment of recurrent appropriate ICD shocks; two patients with ICDs for scar-related VT and CHF underwent RSDN for therapy resistant electrical storm.²⁰ One patient with hypertrophic cardiomyopathy had recurrent monomorphic VT despite multiple endocardial and epicardial ablations, while the second patient with dilated non-ischemic cardiomyopathy suffered from recurrent polymorphic VT, and had declined catheter ablation therapy. After undergoing RSDN, both patients experienced significantly less episodes of VT requiring ATP or shocks. Importantly, despite normal to low blood pressure at baseline, both patients maintained a stable blood pressure at 6 months of follow up post procedure.

Rationale for RESCUE:

Despite significant advances in the management of ventricular arrhythmias through the use of ICD therapy, AADs, and catheter-based ablation strategies, considerable challenges remain. The optimal method for the prevention of ICD shocks remains unclear. RSDN may be an effective tool for preventing ventricular arrhythmias, and associated ICD therapies, by reducing central sympathetic tone, catecholamine levels, and the renin-angiotensin-aldosterone system. Although RSDN has been shown to reduce the recurrence of VT in a case report of 2 patients suffering from electrical storm, to date no large prospective randomized study has evaluated the impact of RSDN in the primary prevention of ICD therapy in patients with ischemic or non-ischemic ventricular dysfunction. Also of note, there is data suggesting that RSDN may even decrease the rate of supraventricular arrhythmias such as atrial fibrillation. Thus, RESCUE will specifically evaluate the safety and efficacy of RSDN in the prevention of ICD therapy in patients with ventricular dysfunction who are to receive an ICD for either secondary prevention, or primary prevention if they have inducible VT by programmed ventricular stimulation at the time of ICD implantation. As an alternative to inducible VT, we will also utilize a non-invasive predictor of sudden cardiac death - fragmented QRS complex by 12-lead ECG - as a criterion to identify candidates for RSDN. Fragmented QRS, which is defined by the presence of notching in the R or S wave or the presence of a second R wave in two contiguous leads, has been recognized as a risk predictor for all-cause mortality with relative risk of 1.71 (95% CI 1.02-2.85) and for sudden cardiac death with relative risk 2.20 (95% CI 1.05-4.62) in a recent meta-analysis of studies involving patients with coronary disease or non-ischemic cardiomyopathy.²⁸

3.1 INITIAL PILOT DATA:

In an initial pilot study, an irrigated radiofrequency catheter (Celsius Thermocool F-Curve RF catheter, Biosense-Webster, Inc., Diamond Bar, California) was used in 20 patients with ischemic or non-ischemic ventricular dysfunction, who were scheduled to receive an ICD for either i) secondary prevention, or ii) primary prevention + inducible VT by programmed ventricular stimulation at the time of ICD implantation (V. Reddy, unpublished observation). Although we have favorable single-operator, single-center safety data in another RSDN trial, preliminary review of the six-month renal ultrasound data provided a higher than expected event rate of renal artery stenosis. As such, the protocol has been amended to allow for the use of a dedicated renal sympathetic denervation catheter system: the Vessix™ Renal Denervation System (Boston Scientific, Quincy, Massachusetts).

4. SCHEDULE OF TREATMENT AND TESTS:

TABLE 1:

	Baseline	Procedure*	Discharge	1, 6,12,18,24,36 months**
Type of visit	Office	Hospital		Office
Informed Consent	X			
Brief History & Physical	X			X
Blood Laboratory Testing: CBC, Electrolytes, BUN/ Creatinine, BNP	X			X (6, 12, 24, 36m)
Blood for Renal Hormones (OPTIONAL*)	X			X (12m)
TTE	X			X (12 m)
Renal Angiography		X		
Ultrasound or MR/ CT Angiography				X (6 m)
Randomization		X		
Renal Sympathetic Denervation		X		
ICD Interrogation	X			X
EKG	X			X (12m)
Office BP Measurements (including orthostatic BPs)	X			X
Medications	X		X	X
Adverse Events		X	X	X

* Hormonal measurements are optional in cases where the cost would be prohibitively burdensome to patients or hospital/clinic facilities are not available to allow for their measurement.

** - Visit windows – 1 Month (\pm 14 days); 6, 12, 18, 24, 36 Months (\pm 30 days)

5. ENDPOINTS:

5.1 PRIMARY ENDPOINT:

The following primary endpoint will be assessed: Time to first event requiring any ICD therapy (appropriate or inappropriate) or Incessant VT (VT occurring below the ICD rate cut-off); this will be assessed in the on-treatment patient cohort. An event requiring ICD therapy is defined as an anti-tachycardia pacing (ATP) or shock therapy. The null hypothesis of principal interest is that there will be no difference between the two treatment arms in the time to first event requiring any ICD therapy (appropriate or inappropriate) or Incessant VT in patients randomized to ICD implantation with a single renal sympathetic denervation procedure compared to patients randomized to ICD implantation alone.

5.2 SECONDARY ENDPOINTS:

The following secondary endpoints will be assessed:

1. Appropriate ICD therapy assessed in the full intention-to-treat patient cohort
2. Inappropriate ICD therapy
3. Number of Hospitalizations for Cardiovascular Causes.
4. Total VT burden (Number of episodes).
5. All-Cause Mortality.
6. The occurrence of ICD storm, defined as ≥ 3 appropriate shock therapies within 24 hours.
7. Differences in BUN/creatinine measurements.
8. Procedure related adverse events including, but not limited to hematomas, pseudoaneurysms and renal artery stenosis.
9. Development of orthostatic hypotension
10. 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer)

6. STUDY SUBJECTS

6.1 INCLUSION CRITERIA

1. ≥ 18 years of age
2. Structural heart disease (post-MI, dilated cardiomyopathy, sarcoid myopathy, hypertrophic cardiomyopathy, etc.)
3. Planned for ICD implantation for:
 - i. Secondary prevention (e.g.: VT/VF arrest, sustained VT, syncope/inducible VT)
 - ii. Primary prevention + inducible MMVT during induction via ICD lead testing
 - iii. Primary prevention + fragmented QRS complex on 12-lead ECG
4. Accessibility of renal vasculature (determined by renal angiography)
5. Ability to understand the requirements of the study
6. Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements

6.2 EXCLUSION CRITERIA

1. Patient taking a Class I or III antiarrhythmic drug, unless required for an atrial arrhythmia

2. Planned to undergo a cardiac VT ablation procedure
3. NYHA Class IV Congestive Heart Failure
4. MI within 30 days
5. Known renovascular abnormalities that would preclude RSDN (e.g., renal artery stenosis, previous renal artery stenting or angioplasty)
6. Baseline orthostatic hypotension
7. End stage renal failure on hemodialysis
8. Life expectancy <1 year for any medical condition
9. Known pregnancy or positive β -HCG within 7 days of procedure.
10. Coronary Artery Bypass Graft (CABG) within 30 days of the procedure.

7. STUDY PHASES:

This study is divided into two phases: the initial phase (to include 50 patients) followed by the remaining 412 patients, for a total of 462 patients. The initial 50 subjects will be conducted at up to 10 sites (please see Section 1.1 for a listing of sites). An interim safety analysis for the primary endpoint will be conducted when the initial 50 subjects have completed the 6-month follow up visit.

7.1 CLINICAL CENTERS

The study will be conducted in up to 20 sites (with a maximum of 10 sites during the initial phase) in the United States and Europe. Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the DCC with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

7.1.1 INVESTIGATOR PROFILE

All cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The cardiologist and coordinator must email or fax their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

7.1.2 QUALIFICATIONS AND TRAINING

Clinical investigators will be electrophysiologists with expertise in atrial fibrillation ablation. The certified operator will either perform the ablation and renal denervation on their own patient, or participate in the ablation and renal denervation of an enrolled patient. Sites will be limited to two operators per site. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating investigator at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. Each site will have technical support provided by Boston Scientific for each of its first five patients. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

7.1.3 CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE AGREEMENT

This statement verifies that all investigators have no conflict of interest with any institution that may influence their participation in this study. All investigators need to complete this statement. Investigators will also submit a financial disclosure agreement.

7.1.4 SITE APPROVAL

The following documents must be collected prior to site approval:

- Clinical Study Agreement
- Clinical site IRB roster
- Clinical site IRB approval, version and date for protocol and consent
- Clinical Center Laboratory Certification

A signed agreement between the clinical site and the DCC (Icahn School of Medicine at Mount Sinai) is required prior to site initiation. Prior to enrolling a patient, representatives from the DCC will conduct a site initiation for all investigators, coordinators, and any other health care professionals who may be involved in the study (e.g. engineers, social workers).

8. PATIENT ENROLLMENT AND WITHDRAWAL:

This will be a multicenter trial. Patients meeting the study inclusion criteria will be identified in the outpatient or inpatient setting by one of the study sites' primary or co-investigators. In essence, patients will be followed by one of the study site primary or co-investigators. Sites will be limited to enrollment of no more than 90 patients at their clinical site.

The study will typically be described (including the risks and benefits) during the initial clinic or hospital visit. Consent will typically be obtained at the time of the initial assessment if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be allowed to take a copy of the consent form home to contemplate whether they would like to be enrolled in the study. A sample consent form can be found in Appendix 1. Only patients who voluntarily provide consent will be included in this study. Patients will be considered enrolled once they have signed informed consent. Consent will be obtained prior to undergoing the ablation procedure. Patients will be able to withdraw from the study at any point without compromising their medical care.

Consent must be obtained either before, or within 24 hours of ICD placement. The patient may undergo ICD placement up to 1 month (30 days) before randomization. The patient must undergo either ICD placement and Renal Angiography (Control Group) or ICD placement and RSDN (Study/Experimental Group) within 1 month (30 days).

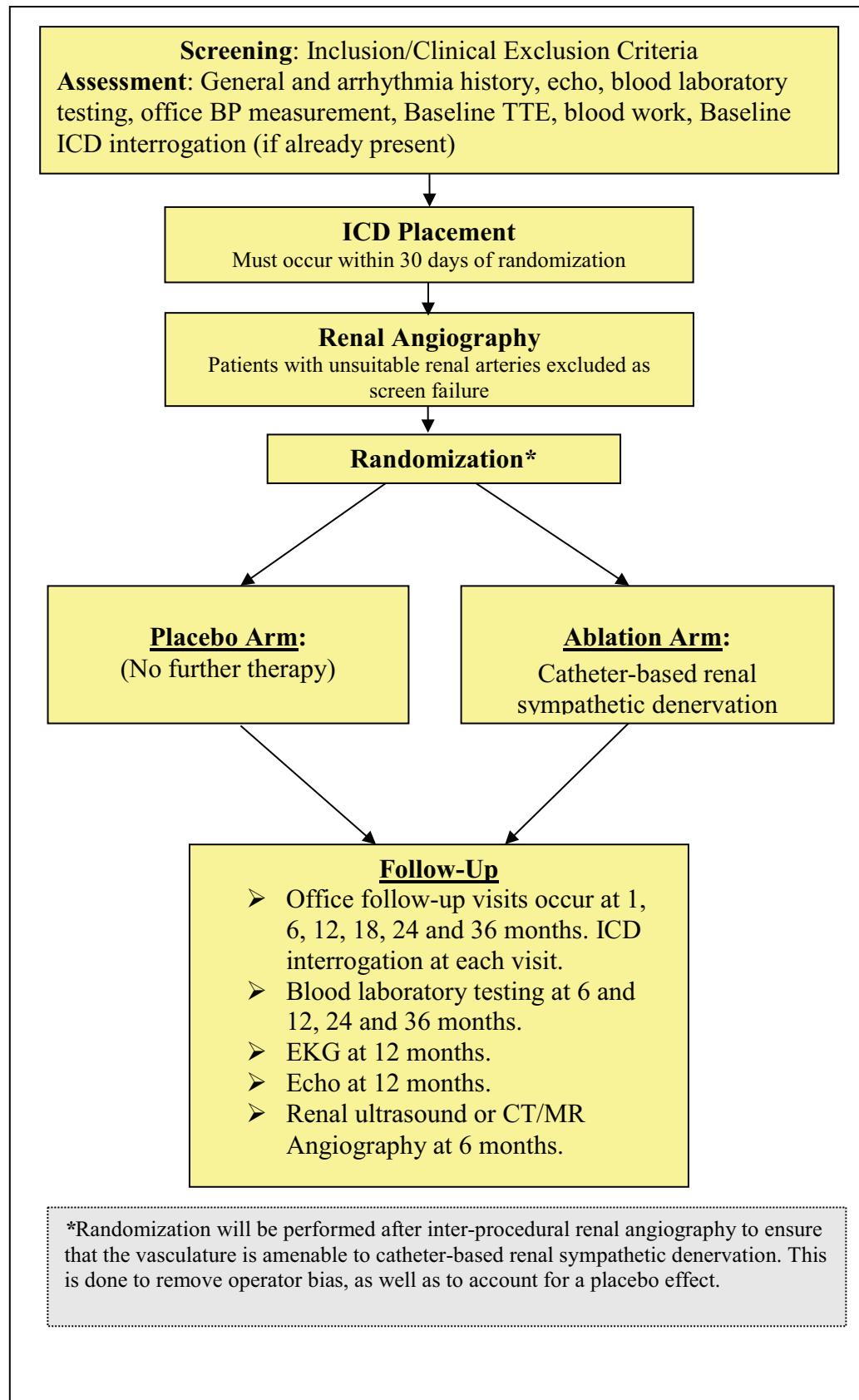
8.1 ROLL-IN PHASE

Each site has the option of enrolling one patient as part of a roll-in phase. Each roll-in patient will have renal angiography and renal sympathetic denervation performed. Patient data on these roll-in patients will not be used for the final analysis.

- Roll-in patients will be required to sign the study ICF, but will not be randomized.

- Although the data will not be used for the primary analysis, patients will be asked to adhere to the same follow up schedule of visits as randomized patients.
- As per FDA, roll-in patients will count toward the enrollment ceiling.
- The CRF must be adjusted to clearly reflect roll-in patients from randomized patients.

9. Pre-Procedure and Ablation Study Design Flow-Chart



9.1 PRE- AND ABLATION PROCEDURE

9.1.1 PRE-PROCEDURE

The following tests and procedures will occur before the ablation (within 30 days prior to randomization unless stated below):

- Recording of patient medical history (including details of VT both clinical/ICD)
- Recording medication history (including all AAD ever used, duration of use)
- Obtain β -HCG in females of child bearing age the morning of the procedure as per usual clinical practice
- Baseline assessment of arrhythmia burden and type: Office/inpatient records, ICD interrogation report
- If performed for any reason, collect any pre-procedural imaging: MRI/CT and Renal Ultrasounds within 6 months of procedure
- Baseline laboratory, including complete blood count, standard electrolyte panel, renal function, and brain natriuretic peptide levels.
- Baseline Transthoracic Echocardiogram within 3 months of procedure
- Baseline Office blood pressure. Proper blood pressure measurement technique is essential: i) patient should sit quietly in a chair with his/her back supported for 5 minutes before taking the measurement; ii) use of the correct cuff size with the air bladder encircling at least 80% of the arm (the adult large cuff for the majority of patients); iii) support the arm at heart level during the cuff measurement; iv) a minimum of 2 readings should be taken at intervals of at least 1 minute and the average of those readings should be taken to represent the patient's blood pressure; v) the blood pressure should be measured
- Consent must be obtained either before, or within 24 hours of ICD placement. The patient may undergo ICD placement up to 1 month (30 days) before randomization. The patient must undergo ICD placement and Renal Angiography (Control Group) or ICD placement and RSDN (Study/Experimental Group) within 1 month (30 days). All ICDs must be devices from Boston Scientific (either single-, dual-, subcutaneous, or biventricular devices).
- Randomization into one of two groups will be performed by opening the Randomization envelope after Renal Angiography.

Study/Experimental Group: These subjects will undergo catheter-based sympathetic renal denervation.

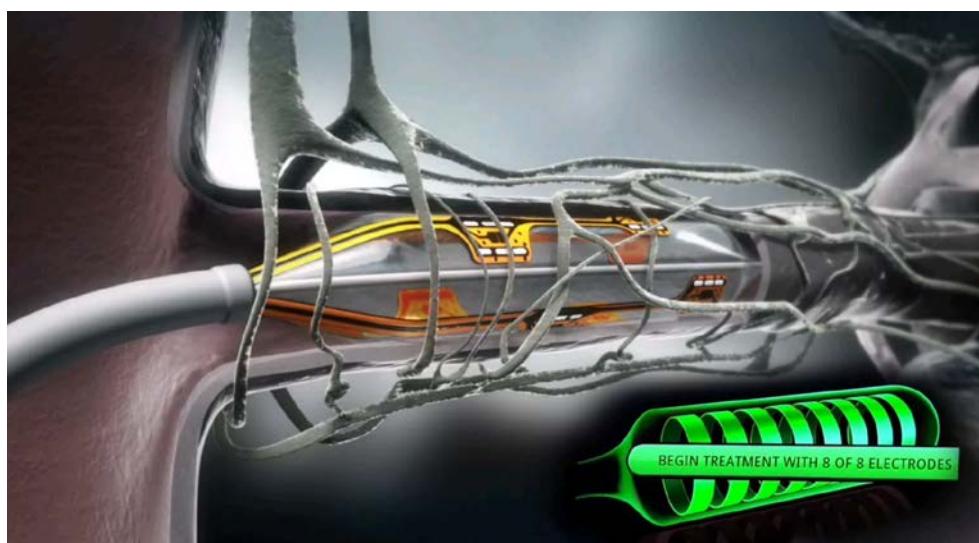
Placebo Control Group: These subjects will receive no further intervention.

9.1.2 PRE-PROCEDURE MEDICATION MANAGEMENT

Patients should not be taking any Class I or III anti-arrhythmic agents during this study unless required for atrial arrhythmia. After the ablation procedure, patients should receive either an antiplatelet agent (aspirin, clopidogrel, etc.) or anticoagulant (warfarin, dabigatran, etc.) for at least 1 week. Further decisions regarding the peri-procedural management of other cardiovascular (including anti-coagulant and anti-thrombotic agents) and non-cardiovascular medications should be as per clinical practice – but every effort should be made to maximize beta-blocker therapy, ACEI/ARB, and spironolactone therapy as per the guidelines.

9.1.3 RENAL SYMPATHETIC ABLATION PROCEDURAL DETAILS

- Patients will be brought to the electrophysiology laboratory in a fasting state
- Patient sedation or anesthesia will be administered according to standard EP lab protocol.
- Vascular access will be achieved in standard fashion.
- IV heparinization will be instituted. Full systemic anticoagulation will be instituted as per standard hospital procedures to a target ACT of 250 seconds or greater (or equivalent level depending on testing system performed).
- Abdominal aortography will be performed to assess the renal arteries for the suitability of catheter-based renal denervation in all patients. For those patients in whom the angiogram demonstrates that the renal anatomy is inappropriate for the RSDN procedure (small renal arteries, extensive atherosclerosis, renal stenosis, etc.), the patient will be excluded from the study as a screen failure. The patient's baseline information will be collected but no further follow-up required (beyond assessing for any adverse events related to the procedure). If the renal arteries are deemed suitable for RSDN, the patient will then undergo randomization.
- Randomization will be done by permuted-block randomization centrally and will be stratified by site. Allocation concealment shall be maintained at all sites by the use of a web-based central randomization scheme. The operating physician controlling the delivery of ablative energy will be aware of the outcome. This approach has been selected to minimize (1) study bias and (2) placebo effect. The randomization schema will be blocked by size for each site.
- Catheter-based sympathetic renal denervation will be performed using the Vessix balloon ablation catheter for denervation (see image below). The operating physician will manipulate the ablation catheter into the renal arteries as per standard operating procedures.



- The Vessix catheter is available in various sizes, and can be used to treat arteries between 3 mm and 7 mm in diameter and more than 20 mm in length. Radiofrequency energy is delivered via 8 electrodes to four distinct sites within the artery in a bipolar fashion. As with other renal denervation procedures, this catheter delivers four lesions in the artery which are separated along the length of the artery and are also separated orthogonally in different planes (anterior, inferior, posterior, and superior).
- The Vessix generator is pre-programmed with a temperature-controlled treatment algorithm. Energy is delivered to achieve a temperature of 68°C. Treatment time is 30 seconds. Average power is approximately 1 watt per electrode and is displayed on the generator screen during treatment. The system is designed to automatically deliver the proper amount of energy to achieve the appropriate temperature. The user does not need to (nor can he/she) adjust or set any of the biophysical parameters when using this system. The generator uses a proprietary algorithm (including impedance measurement) to determine appropriate apposition with the vessel wall. Electrodes which do not have appropriate apposition (such as those extending into the aorta) are automatically disabled by the generator.
- Only one catheter placement is required in most renal arteries. If the operator determines that the initial placement is unsatisfactory to treat the full length of the artery, a second activation will be permitted in a different location. No more than two catheter activations will be allowed in each renal artery.
- After delivery of a complete lesion (30 seconds), no further testing is required to ensure renal denervation. Physiologic endpoints for renal denervation have not been standardized.

9.2 POST-PROCEDURE

9.2.1 POST-PROCEDURE FOLLOW UP

- All patients will be monitored to verify vascular hemostasis prior to discharge from the hospital.
- All patients will receive either oral aspirin (81-325 mg QD) or clopidogrel (75 mg QD) or warfarin or one of the NOACs (dabigatran, rivaroxaban, Apixaban) for at least 1 week upon discharge.
- Medication and adverse event review will be performed prior to discharge.
- Complications including vascular, stroke, heart failure etc., and presence of ventricular arrhythmias will be documented.
- ICD programming: (see below section 9.2.3)
- The total number of episodes of VT, ATP, and Shocks will be documented at all visits.
- The follow-up includes:
 - 1 Month (\pm 14 days):
 - History and Physical
 - ICD interrogation
 - Office BP measurements (x2) including orthostatics
 - Review of Medications and Adverse events
 - 6 Months (\pm 30 days):
 - History and Physical
 - ICD interrogation
 - Office BP measurements (x2) including orthostatics
 - Lab tests (CBC, Electrolytes, BUN/Cr)
 - BNP Level

- Review of Medications and Adverse Events
 - Repeat Renal Ultrasound or MR/CT Angiography
- 12 Months (\pm 30 days):
 - History and Physical
 - ICD interrogation
 - EKG
 - Office BP measurements (x2) including orthostatics
 - Lab tests (CBC, Electrolytes, BUN/Cr)
 - Blood for Renal Hormones (OPTIONAL)
 - BNP Level
 - Review of Medications and Adverse Events
 - Repeat TTE
- 18 Months (\pm 30 days):
 - History and Physical
 - ICD interrogation
 - Office BP measurements (x2) including orthostatics
 - Review of Medications and Adverse Events
- 24 Months (\pm 30 days):
 - History and Physical
 - ICD interrogation
 - Office BP measurements (x2) including orthostatics
 - Lab tests (CBC, Electrolytes, BUN/Cr)
 - BNP Level
 - Review of Medications and Adverse Events
- 36 Months (\pm 30 days):
 - History and Physical
 - ICD interrogation
 - Office BP measurements (x2) including orthostatics
 - Lab tests (CBC, Electrolytes, BUN/Cr)
 - BNP Level
 - Review of Medications and Adverse Events

Patients will be followed for a maximum of 36 months until the final patient reaches the 18 month follow-up time point. Once the final patient reaches the 18 month follow-up time point, all follow-ups will cease.

9.2.2 POST-PROCEDURE MEDICATION MANAGEMENT

- Standard cardiovascular medications are left up to the discretion of the investigator – but BBLs, ACEI, ARBs and aldosterone antagonist use is recommended as per standard guidelines.
- Class I and III antiarrhythmic drug use is not permitted in this study, unless required for atrial arrhythmias.
- Therapeutic anticoagulation (example Warfarin or equivalent agent) beyond the requisite 1 week post-procedure time point is at the discretion of the patient's physician.

9.2.3 ICD PROGRAMMING

The following programmed detection and therapy parameters should be used to optimize therapy delivered to the subject during the course of the study for both the Catheter Ablation Group (Treatment) and Control Group:

ICD Programming Requirements

Arrhythmia	Programming Strategy
VT Zone	175-195 bpm
VF Zone	200 bpm. ATP to 250 bpm
Monitor Zone	130-170 bpm
VT Therapy	ATP – recommended. Programmed at investigators discretion
SVT Discriminators	Should be “ON” in VT zone. Programmed at investigators discretion.

Device Specific Detection Parameters

Arrhythmia	Boston-Scientific
VF	5s (1-25s std, but would be approx.3-10 beats)
VT	5s
Monitor	
Comments	

9.3 SAFETY

We anticipate no significant increase in adverse events as compared to the standard ICD implantation or renal angiography procedure. The local site primary investigator will oversee the safety of the study at his/her site. All adverse events will be reported to the Data Coordinating Center (Icahn School of Medicine at Mount Sinai). Adverse events will be monitored and tallied for each 50 patients enrolled in the study and presented to the Data Safety Monitoring Board. The PI will also be present at the meetings to relate any pertinent trial information. However, recommendations are solely up to the discretion of the DSMB.

9.3.1 INTERIM ANALYSES

An interim safety analysis will be performed after enrollment of the first 50 subjects (25 controls, 25 study group). This analysis will be presented to the DSMB, which has the authority to terminate the study prematurely if an increase in adverse events is encountered. The trial will be terminated early if severe procedure-related adverse events occur in more than 15% of patients in the treatment arm. If the DSMB determines the trial should be stopped early either because of safety concerns, or otherwise modified, the DSMB will prepare formal written recommendations to the PI to consider final action. Moreover, any pressing safety concerns that the DSMB identifies will be verbally communicated to the PI as soon as possible, prior to written documentation.

9.3.2 CLINICAL EVENTS COMMITTEE

A separate Clinical Events Committee (CEC) composed of 2 independent cardiologists/ electrophysiologists will adjudicate all ICD events in this study.

9.3.3 DATA SAFETY MONITORING BOARD

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The DSMB will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Clinical Events Committee every 6 months or as needed. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. The FDA will be provided a copy of any written communication from the DSMB to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The DSMB will be provided a copy of any letter from the FDA to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The clinical centers will have no contact with the members of DSMB regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DSMB members will not be allowed during DSMB closed meetings. However, the PI will only be present at the open session of the meetings to clarify questions concerning the protocol and to provide updates to the DSMB regarding pertinent new trial information. However, recommendations and decisions regarding the study are solely up to the discretion of the DSMB. The DSMB will be composed of 2 cardiologists, 1 electrophysiologist, 1 nephrologist and 1 biostatistician.

9.4 RISKS

ICD implantation will occur according to standard procedure, and therefore the risk includes that of a standard ICD implantation. In addition, the risks of the renal sympathetic ablation and renal angiography procedure include:

Common:

- Discomfort at the site of vascular access
- Groin hematoma

Uncommon:

- Bleeding
- Vascular injury
- Renal artery dissection
- Renal artery stenosis or occlusion
- Thromboembolism, including renal infarction and peripheral atheroembolism. This risk is minimized considerably by the short duration of the procedure, as well as the use of a saline-irrigated ablation catheter.
- Risks associated with sedatives/anesthesia.
- Injury to adjacent structures (phrenic nerve, cardiac valves)
- Renal dysfunction potentially needing hemodialysis
- Vascular complications (including pseudoaneurysm, AV fistula requiring surgical intervention)
- Radiation burns
- Pneumonia and/or sepsis
- Death

An adverse event is any undesirable clinical occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is *not* an AE unless there is a change in the nature, severity or degree of the condition.

9.4.1 SERIOUS ADVERSE EVENTS

Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

9.4.2 UNANTICIPATED SERIOUS ADVERSE EVENTS

An unanticipated (unexpected) serious adverse event is any serious adverse event that is not protocol-defined or documented in the patient consent form. Expedited reporting is required for serious adverse events that are unexpected.

9.4.3 UNANTICIPATED ADVERSE DEVICE EFFECTS

An unanticipated adverse device effects (UADE) is any serious adverse effect on health or safety or any life-threatening problem 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 any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

9.4.4 UNANTICIPATED PROBLEMS

According to the Office for Human Research Protections (*OHRP*), an Unanticipated Problem (UP) generally includes any incident, experience, or outcome that meets **all** of the following criteria: (1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; *and* (2) Related or possibly related to participation in the research (in this guidance document, *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* (3) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Based on the definitions above and as illustrated below (per OHRP guidance), many adverse events are not unanticipated problems, and many unanticipated problems are not adverse events. However, some adverse events are also unanticipated problems. For example, a serious adverse event that is unexpected and at least possibly related to study participation is also by definition an unanticipated problem. As stated above, an unanticipated problem may not necessarily be an adverse event, which is the case when the problem does not cause actual physical harm to participants. For example, if a laptop computer with sensitive, identifiable study data is stolen,

this theft places the participants at greater *risk* of psychological or social harm; this is an unanticipated problem that is not an adverse event. Another example of an unanticipated problem that is not an adverse event is if the FDA announces that one of the study drugs is tainted (e.g., with paint chips), yet no participant experiences any adverse effects.

9.4.5 EVENT RECORDING

The following adverse events will be captured throughout the period of trial participation:

- Protocol-defined (as described above)
- Serious unanticipated events (serious “*Other*” adverse events)

9.4.6 CAUSALITY

The investigator will assess the relationship of an adverse event to the intervention. The investigator should distinguish the relationship between the event and (a) ablation procedure (i.e. AF ablation procedure or other concomitant procedures), and (b) renal sympathetic denervation. Causality will be defined as follows:

Probable

Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the intervention (AF ablation ± renal sympathetic denervation). The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the intervention, and
- The event is a known reaction to the intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

Possible

Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after intervention, and
- The event is not a known reaction to intervention, but cannot be explained by a commonly occurring alternative etiology

Unlikely

Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to the intervention and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the intervention, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the intervention.

9.4.7 REPORTING OF SERIOUS ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

All investigators must report both expected (protocol-defined) and unexpected SAEs. All protocol defined SAEs must be reported directly to the clinical center's IRB and the DCC within 10 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths, UADEs, and unexpected SAEs that are possibly or probably related to the renal sympathetic denervation must be reported to the DCC and the clinical center's IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All *unexpected SAEs* that are *unlikely related to the study intervention* must be reported to the DCC and the clinical center's IRB within 5 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

The DCC will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

9.4.8 REPORTING OF UNANTICIPATED PROBLEMS

All *UPs* that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All UPs that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

9.4.9 DCC REPORTING TO FDA

The DCC will report unexpected SAEs that are possibly or probably related to the investigational device or UADEs to FDA as appropriate. The DCC will send an initial IDE safety report communication to the FDA within 2 business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of a UADE for this IDE trial.

10. STATISTICAL ANALYSIS PLAN

10.1 STUDY DESIGN

This is a prospective, multi-center, parallel groups, single-blinded, randomized clinical trial. Patients with ischemic or non-ischemic ventricular dysfunction who are to receive an ICD for either 1) secondary prevention, or 2) primary prevention + inducible VT by programmed ventricular stimulation at the time of ICD implantation will be randomly assigned using a 1:1 allocation to treatment to ICD alone or ICD + RSDN. Randomization will be stratified by center.

Our study will include U.S. as well as European sites. We do not anticipate that the two populations will be different. We expect the U.S. population to include 85% Caucasian and the EU population to be 100% Caucasian.

Before conducting the primary analysis we will compare the two populations with respect to baseline characteristics. If a difference is found, the region will be included in all our models as a covariate. We do not anticipate that the treatment effect will be differential in EU and the U.S. This hypothesis will be formally tested using an interaction term in our models.

10.2 PRIMARY OBJECTIVES:

The primary objective is to evaluate the effectiveness of RSDN in the primary prevention of ICD therapy in patients with ischemic or non-ischemic ventricular dysfunction who are to receive an

ICD for either i) secondary prevention, or ii) primary prevention + inducible VT by programmed ventricular stimulation at the time of ICD implantation.

10.3 PRIMARY EFFECTIVENESS ENDPOINT:

The primary effectiveness endpoint is time to first event requiring any ICD therapy (appropriate or inappropriate) or Incessant VT (VT occurring below the ICD rate cut-off); this will be assessed in the on-treatment patient cohort. An event requiring ICD therapy is defined as an anti-tachycardia pacing (ATP) or shock therapy. The null hypothesis of interest is that there will be no difference between the two treatment arms in the time to first event requiring any ICD therapy (appropriate or inappropriate) or Incessant VT in patients randomized to ICD implantation with a single renal sympathetic denervation procedure compared to patients randomized to ICD implantation alone.

10.4 PRIMARY SAFETY OBJECTIVE:

The primary safety objective is to demonstrate that the incidence of serious adverse events (events that cause clinically relevant changes in patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay) is not increased with the use of the ICD + RSDN compared to ICD alone.

10.5 SECONDARY ENDPOINTS:

The following secondary endpoints will be assessed:

- Appropriate ICD therapy assessed in the full intention-to-treat patient cohort
- Inappropriate ICD therapy
- Number of Hospitalizations for Cardiovascular Causes.
- Total VT burden (Number of episodes).
- All-Cause Mortality.
- The occurrence of ICD storm, defined as ≥ 3 appropriate shock therapies within 24 hours.
- Differences in BUN/creatinine measurements.
- Procedure related adverse events including, but not limited to hematomas, pseudoaneurysms and renal artery stenosis.
- Development of orthostatic hypotension
- 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer).

10.6 POWER AND SAMPLE SIZE

Power for this study was determined based on the following operating characteristics: (a) two sided type I error fixed at 0.0492, assuming one interim analysis, (b) 85% power, (c) minimum follow-up of 18 months, (d) 18-months event rate in the ICD alone group of 19% (e) expected 18-month relative rate reduction in the ICD + RSDN group of $\geq 40\%$, accrual period of 48 months and non-uniform accrual.

Under the above assumptions it is estimated that 70 events (or 462 patients) will be required to detect a relative decrease in the relative event rate reduction requiring any ICD therapy $\geq 40\%$ in the ICD + RSDN compared to the ICD alone group (19% vs. 11.4%) (Lachin, 1981).

Lost to Follow Up: The term "lost to follow-up" is used to define an individual who has withdrawn consent to be in the study or who can no longer be located or assessed. Such individuals represent those for whom primary outcome assessment is no longer possible. Since the primary outcome will be assessed by interrogating the ICD and since patients come back to

the hospital for regular check we do not anticipate a high rate of lost to follow-up. The estimated sample size accounts for 5% attrition due to withdrawal of consent.

10.7 INTERIM MONITORING GUIDELINES

The objectives of interim monitoring are to (1) monitor for safety, (2) track participant accrual rates, and (3) monitor the primary and secondary outcomes for early evidence of efficacy, harm or futility. To accomplish this, summaries of data quality, accrual, adherence, distribution of baseline factors, toxicity, study endpoints and other analyses as requested will be prepared for review by the Data Safety Monitoring Committee (DSMB).

The primary outcome of the trial, rate of first event requiring any ICD therapy, is the basis for formal interim analysis plan that follows. One interim analysis and one final analysis are planned for this trial, for a total of 2 analyses. These analyses will be performed when 0.5 and 1.0 fraction of the total number of events will have been observed. Since this study will have a target number of events of 70, we will have approximately 35 events observed between each analysis time.

We will use an alpha-spending O'Brien-Fleming sequential procedure as a guideline for decision making. At the interim analysis the value of the test statistic will be compared with the alpha spending function critical values. The two alpha values will be set at 0.0054 at the interim analysis and 0.0492 at the final analysis, which equate to critical values of 2.782 and 1.967 respectively. This monitoring plan maintains the overall type I error at 0.05, given one interim analysis.

10.8 STATISTICAL ANALYSIS

The primary analysis will be an intent-to-treat analysis that will include all randomized participants regardless of treatment actually received or follow-up schedule.

Point Estimation and Interval Estimation: We will report maximum likelihood estimates for point estimation. For routine reporting, two-sided 95% confidence intervals for all parameters will be prepared.

Disposition of Participants and Baseline Comparisons: Summaries of all participants randomized and the number who complete visits at 30-days, and every 6 months after the day of randomization will be provided for each treatment group. The treatment groups will be compared at baseline with respect to demographics, baseline measurements related to efficacy and baseline measurements related to safety.

Univariate Analysis: All outcome measures will be described in a univariate analysis. For continuous variables means and standard deviations will be calculated. For discrete and dichotomous variables we will use contingency tables.

Analysis of Primary Endpoint: The primary endpoint of this study is defined time to first event requiring any ICD therapy (appropriate or inappropriate) or Incessant VT (VT occurring below the ICD rate cut-off); this will be assessed in the on-treatment patient cohort. An event requiring ICD therapy is defined as an anti-tachycardia pacing (ATP) or shock therapy. Time to event will be estimated using Kaplan-Meier curves. Survival time will be defined as the time (in months) between randomization and the occurrence of first ICD therapy. To compare the ICD+ RSDN arm with the ICD alone arm we will use a stratified log-rank statistic (using the stratification variables from the randomization procedure). A Cox proportional hazards model with treatment and other important prognostic factors as covariates will be used for the multivariate analysis of the times to first ICD therapy. Risk ratios and their 95% confidence intervals will be computed. Patients will be included in the analysis as censored if they are alive and free of ICD events at the end of the 18-month follow-up period. Although we do not anticipate interactions between treatment and stratification factors, formal tests for interactions will be assessed using proportional hazards models. A formal test of proportional hazards will assess the significance of

the interaction between the indicator for treatment group and log (t) in a Cox proportional hazards regression model that also includes the main effect for the randomization group. The final analysis will be based on a two tailed 0.0492 level test.

Analysis of Secondary End-points: All continuous variables will be analyzed using mixed effects models (Bagiella et al. 2000; Diggle et al. 1994; Laird and Ware 1982). Log-transformations will be used, if necessary to normalize the variables or stabilize the variance. For binary and discrete outcomes we will use generalized estimating equations (GEE) (Liang and Zeger 1986; Miller et al. 1993; Zeger and Liang 1986) to fit logistic or log-linear models that account for the dependency of the repeated measures.

Missing Data: For participants who withdraw consent to participate we will use all the information available up to the time of withdrawal. For the purpose of the primary analysis these patients will be censored at the time of withdrawal if they have not experienced the primary event. For all other variables, if the data are missing at random (MAR), that is, the probability of being missing depends only on observed values (Little and Rubin 1987), then likelihood-based methods such as mixed-effects models will be used for analysis without bias. If the fraction of missing data is small we expect that even non-ignorability can have only little effect on the final estimates. If the extent of missingness is large compared to the effect size, we will use the multiple imputation procedure proposed by Rubin (1997) and Little (1996).

10.9 PRIMARY SAFETY ANALYSIS

The primary assessment of safety will be based on the incidence of all serious adverse events over the total duration of study follow-up. The between group comparisons of incidence of serious adverse events will be estimated using the incidence rate ratio and corresponding 95% confidence intervals based on Poisson regression.

11.0 STUDY MANAGEMENT

11.1 STUDY DATA COLLECTION AND PROCESSING

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Patients will be identified by a 5 digit number and their initials. The investigator must keep a separate log of patient names and medical record numbers (or other personal identifiers) for their own reference. All study-related documents (CRFs, source medical records, regulatory binder) must be kept in a secure, locked environment with access limited to study personnel only.

The PI is responsible for ensuring the following at his/her site: 1) adherence to the protocol; 2) verifying adherence to local regulations on the conduct of clinical research; and 3) ensuring completeness, accuracy, and consistency of the data entered in the CRF.

Final CRFs in human readable format must be reviewed and verified for accuracy by the study site Principal Investigator and signed-off. A copy of the final CRF will remain at the investigator's site at the completion of the study.

The CRF numbering convention is as follows:

01 - 2 3 4 A -B -A
01 : Site # must be 2 digits (use leading zero) --- (sites 01-10)

2 3 4 : patient screening/enrollment # (001 – 500) — must be 3 digits

A-B-A: Patient initials (if no middle initial, use dash)
Total 5 digits and initials for enrolled patients.

11.2 CONFIDENTIALITY

Patient information will be kept confidential and managed according to the 1996 HIPAA guidelines. All patient information will be de-identified and stored in a secure, locked environment. Each patient will be given a unique subject number and will be identified by this number and their initials. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the patient's privacy is protected.

11.3 DEVIATIONS FROM PROTOCOL

The investigator will not deviate from the protocol except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the IRB/EC must be notified within five days of the incident.

11.4 WITHDRAWAL OF SUBJECTS

A subject may withdraw from the study at any time should they choose to do so. Additionally, subjects may be withdrawn by the investigator if deemed appropriate due to safety or compliance issues.

11.5 ECONOMIC IMPACT ON SUBJECTS

The catheter-based renal sympathetic denervation procedure is part of a research study and is investigational. The cost of the renal sympathetic denervation procedure and follow-up will be the responsibility of the subject or the subject's insurance carrier. No payment will be made to the subject for taking part in this study.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 RISK TO SUBJECTS:

Although it is unlikely, it is possible there may be loss of confidentiality. This is a typical risk of any research study. Stenosis, dissection, and groin complications are possible clinical risks however they are not anticipated risks in this trial.

12.2 POTENTIAL BENEFITS TO SUBJECTS:

After undergoing RSDN, patients may experience less episodes of VT requiring ATP or shocks a result of the expected reduction in whole body norepinephrine spillover and sympathetic nerve activity.

12.3 ROLE OF THE DATA COORDINATING CENTER

As principal investigator and study sponsor of this clinical study, Vivek Y. Reddy, MD assumes the overall responsibility for the conduct of the study, including assurance that the study meets

national and institutional guidelines for study conduct. In this study, Vivek Y. Reddy, MD will have certain direct responsibilities and will delegate other responsibilities to his staff at the Data Coordinating Center at Icahn School of Medicine at Mount Sinai. Together, the Data Coordinating Center will: 1) ensure adherence to the national and institutional regulations; 2) develop and distribute protocols and case report forms; 3) coordinate data organization; 4) perform statistical analyses.

12.4 ONSITE MONITORING

The primary objectives of the DCC in monitoring clinical sites are to educate, support, identify and resolve issues related to the clinical trial. The monitors will discuss the protocol in detail, and clarify any areas of uncertainty. At initiation of the study, the monitors will conduct a tutorial on the EDC system. The coordinators will practice entering data so that the monitors can confirm that the coordinators are proficient in all aspects of data entry, query response, and communication with the data management team.

The DCC will employ a risk-based approach to monitoring for this study. This will be accomplished via centralized or remote monitoring of data via the EDC with a focus on safety, study endpoints, data completion and data outliers. The DCC will also centrally monitor study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event Log periodically to ensure that the sites are adhering to the study protocol and procedures. The DCC will generate performance metrics to analyze site characteristics such as recruitment rates and timeliness of data entry. This will allow the DCC to identify trends across sites and to address low-performing sites appropriately.

The DCC will also conduct one on-site monitoring visit each year for every clinical site for the duration of the study. In addition, interim monitoring will be conducted on an ongoing basis using the EDC system. During the annual on-site monitoring visits, the monitor will collect copies of any source documents (de-identified) for all deaths and AEs. Prior to each EAC meeting copies of any source documents (de-identified) requested by the DCC must be sent via FedEx or secure fax line to the DCC.

The monitors will review the source documents to determine whether the data reported in the EDC system are complete and accurate. They will also verify that all serious and protocol-defined adverse events exist on the source documents, are consistent with the protocol and are documented in the appropriate format. Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission reports, consult notes, radiology reports, lab reports, clinic records, and other study-related notes. The study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

The monitors will also confirm that the regulatory (administrative) binder is complete and that all associated documents are up to date. The regulatory binder should include all revisions of the protocol and informed consent, IRB roster, IRB approvals for all of the above documents, IRB correspondence, investigator's agreements, CVs of all study personnel, institutional HIPAA certificates, monitor site visit log, telephone contact log, a study device log and correspondence with the DCC.

If a problem is identified during the visit (i.e., poor communication with the DCC, inadequate or insufficient staff to conduct the study, missing study documents, etc.), then the monitor will assist the site in resolving the issue. Some issues may require input from the Steering Committee or the Principal Investigator, as well as the sponsor.

The combination of yearly on-site monitoring and ongoing monitoring using the EDC system that includes instantaneous electronic validation, and visual cross-validation to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The monitor will verify a minimum of the following variables for all patients: initials, date of birth, sex, signed informed consent, eligibility criteria, date of randomization, anticoagulation, serious and protocol-defined adverse events, and mortality. These data will be 100% source data verified. All other data collection will be monitored as indicated by the data completeness and accuracy at each clinical site.

12.5 MAINTAINING RECORDS (21 CFR 812. 140 (B))

The Data Coordinating Center will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial.

12.6 SITE RECORD RETENTION POLICY

All clinical sites will maintain study records for two years after research termination.

12.7 INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC) INFORMATION

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by the IRB/EC before the change is made.

The study site Principal Investigator(s) is responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

13.0 DATA HANDLING

Information about patients will be kept confidential and managed according to the requirements of the United States of American Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

1. What protected health information (PHI) will be collected from patients.
2. Who will have access to that information and why.
3. Who will use or disclose that information.
4. The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled registry period.

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