Phase I/II Study of EP-guided Noninvasive Cardiac Radioablation (ENCORE) for Treatment of Ventricular Tachycardia

Protocol #: 5.0
Version Date: 09/26/2018

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Table of Contents

PROTOCOL REVISION HISTORY

Description	Version Date	IRB Submission Date
Initial Approval Version	**06/23/2016**	**06/23/2016**
Amendment 1	**01/16/2018**	**01/16/2018**

Summary of Changes	
Protocol Version Date 06/23/2016	**Protocol Version Date 01/16/2018**
Page 1 **Sub-Investigators** **Modality** Original: Rojano Kashani, PhD Radiation Oncology-Physics	**Page 1** **Sub-Investigators** **Modality** Removal of Sub-Investigator: ~~Rojano Kashani, PhD Radiation Oncology-Physics~~
Page 32 **6.0 Correlative Studies** Original: Not previously included.	**Page 32** **6.0 Correlative Studies** Addition: In patients who die or undergo a heart transplant, clinical reports will be reviewed and abstracted of any pathologic, histologic, or autopsy analysis. Additionally, clinically processed tissue submitted to the Department of Pathology may be requested for additional analysis for research purposes, including, but not limited to, assessment of the location and degree of baseline injury outside the radiotherapy target and evidence of on and off-target injury from radiotherapy.

Amendment 2	**09/26/2018**	**09/26/2018**

Summary of Changes	
Protocol Version Date 01/16/2018	**Protocol Version Date 09/26/2018**
Page 1 **Sub-Investigators** **Modality** Original: Todd Dewees, PhD Radiation Oncology-Biostatistics	**Page 1** **Sub-Investigators** **Modality** Removal of Sub-Investigator: ~~Todd Dewees, PhD Radiation Oncology - Biostatistics~~ Addition of Sub-Investigator: Pamela Samson, MD, MPHS Radiation Oncology - Biostatistics
Page 4 **Protocol Revision History** Original: Not previously included.	**Page 4** **Protocol Revision History** Addition: Addition of protocol amendments, version dates, and summary of changes for all protocol amendments.
Page 31 **5.2 Serious Adverse Events (SAEs)** Original: Not previously included.	**Page 31** **5.2 Serious Adverse Events (SAEs)** Addition: **Definition**: An adverse event that is any undesirable experience associated with the use of a medical product in a patient that results in death, hospitalization (new or prolonged), disability or permanent damage, or is life-threatening. Specific to this protocol, SAEs are defined as AEs with CTCAE v4.0 grade 3 or higher resulting in hospitalization or grade 4-5 AE. Treatment-related SAEs were SAEs that are possibly, probably, or definitely related to protocol treatment.
Page 32 **5.8 Timeframe for Reporting Required Events** Original: Not previously included.	**Page 32** **5.8 Timeframe for Reporting Required Events** Clarification: Adverse events captured in the CRFs will be tracked for 12 months following SBRT. For the purposes of this protocol, reportable adverse events are grade 3, 4, or 5 toxicities that did not predate SBRT and are possibly, probably or definitely attributable to treatment. Patients will be assessed using the CTCAE v4.0.
Page 33 **7.0 Study Calendar** Original: Included up to 12 months of follow up.	**Page 33** **7.0 Study Calendar** Administrative Change: The calendar was updated to match the previously approved Informed Consent Document. Extended follow up time point added to collect medical history, device interrogations, and adverse event assessment. The extended follow up time frame will last up to 5 years post-completion of study treatment.
Page 34 **8.0 Data Submission Schedule** Original: Follow-Form included up to 12 months post-SBRT for the submission schedule.	**Page 34** **8.0 Data Submission Schedule** Addition: Addition of 2 years post-SBRT, 3 years post-SBRT, 4 years post-SBRT, and 5 years post-SBRT for the submission schedule for the follow-up form.

1.0 BACKGROUND AND RATIONALE

1.1 Ventricular tachycardia (VT) and sudden cardiac arrest (SCA)

Sudden cardiac arrest (SCA) is the single largest cause of death in the developed world. In the United States, over 325,000 deaths are due to SCA; more than lung cancer, breast cancer and AIDS combined [1]. A majority of SCA is due to cardiac arrhythmias, namely ventricular tachycardia (VT). Underlying cardiomyopathies and scarring most often cause ventricular arrhythmias. The scar from the cardiomyopathy (i.e., previous heart attack) forms the substrate for abnormal electrical circuits within the heart, which causes VT. Survival from an out-of-hospital SCA is only 10%. Patients who survive SCA have an estimated 40-60% chance of developing another ventricular arrhythmia in the subsequent year. [2, 3]

1.2 Current management of VT

For patients who have survived SCA from VT, the current clinical management strategy consists of two goals: 1) prevent the arrhythmia from happening again and 2) protect the patient from dying if the arrhythmia does happen again.

The second goal (protection) consists of installation of an implantable cardiac defibrillator (ICD) into the body. This device is used to deliver a burst of energy (shock) to restore regular rhythm if VT were to recur. While life-saving, shocks from an ICD are painful to patients and repeated shocks lead to a poor quality of life, largely driven by anxiety and depression [4-6]. Some evidence has also linked ICD shocks to increased risk of death [7].

To prevent VT and subsequent ICD therapies, patients can opt to take oral antiarrhythmic medications. Long-term medication use usually consists of administration of amiodarone, which has a significant cumulative adverse effect profile, including toxicities to hepatic, pulmonary, thyroid, skin, ophthalmologic and neurologic systems. An invasive catheter ablation procedure is often viewed as second-line, adjunctive therapy for the management of VT after failure of medication. This procedure generally takes 4-8 hours, often uses general anesthesia, and requires access to the inside of the heart through the veins or arteries of the leg or access to the outside of the heart through the skin underneath the breastbone. Long flexible catheters are inserted and maneuvered to identify critical components of the abnormal electrical circuit that causes VT. Once identified, radiofrequency energy is applied to the tip of the catheter (usually 3.5mm tip) to heat up the critical tissue to the point of cellular destruction (ablation), thus rendering it electrically inert. These critical components of the circuit are often located within abnormal cardiac tissue, most commonly from previous myocardial infarctions.

Despite important advances in invasive cardiac mapping and catheter ablation technologies, the success rates of catheter ablation to prevent VT in patients with

structural heart disease remain modest. Five randomized clinical trials of VT ablation procedures have been performed [8-12] and are summarized in a recent meta-analysis [13]. Other large multi-center studies have been published which did not randomize catheter ablation against medical therapy but are nonetheless important when assessing the overall success rates of this therapy [14-17]. In the meta-analysis that included 457 participants with largely ischemic cardiomyopathy and mean left ventricular ejection fraction of 30-35%, the recurrence rate of VT was 35% (range 12-50%) with catheter ablation (n=266) during a follow up of 6-22 months. This compared favorably to a recurrence rate of 55% (range 33-75%) in the medical-only control group (n=191). In other large prospective observational studies, risk of VT recurrence at one year after extensive catheter ablation approaches 50% [14-17].

VT ablation procedures can "fail" for many reasons. Commonly cited limitations include: 1) inability to map hemodynamically unstable VT; 2) difficult mapping due to multiple different VT circuits; 3) inability to create necessary radiofrequency ablation due to depth of myocardial scar; 4) inability to reach the critical component of the VT circuit with a catheter; 5) protective structures (i.e., epicardial fat) around the critical component of the VT circuit; and 6) late development of new abnormal circuits through myocardial scar after the original ablation. Methods to improve the success of VT ablation procedures need to address these key limitations. Examples of alternative methods in development for enhanced tissue destruction include: 1) injection of alcohol into smaller blood vessels to induce larger myocardial infarction; 2) development of catheters with extendable needles to impale ventricular myocardium to allow deeper radiofrequency ablation; and 3) using two ablation catheters to encircle the critical component of the scar in hopes of deeper penetration of thermal energy.

Because of its invasive nature, there are risks to a catheter ablation procedure. Risks of serious complications include death (3%), stroke/transient ischemic attack (1-2%), cardiac perforation (1-2%), third-degree heart block (1.6%), pericardial effusion/tamponade (1%), worsening heart failure and cardiogenic shock (1-2%), uncontrollable VT (1%), and sepsis (<1%). Anecdotally, several centers report higher rates of adverse events in patients with more advanced and global cardiomyopathies. Future improvements in VT ablation technologies will need to address these significant adverse event rates, particularly among the sickest patients, and for those who have already failed traditional catheter ablation. A noninvasive approach to cardiac ablation has the potential to significantly improve safety and provide a viable option for VT refractory to ablation and medication. An attractive alternative to thermal ablation with radiofrequency energy may be noninvasive stereotactic radiotherapy.

1.3 Stereotactic body radiotherapy (SBRT)

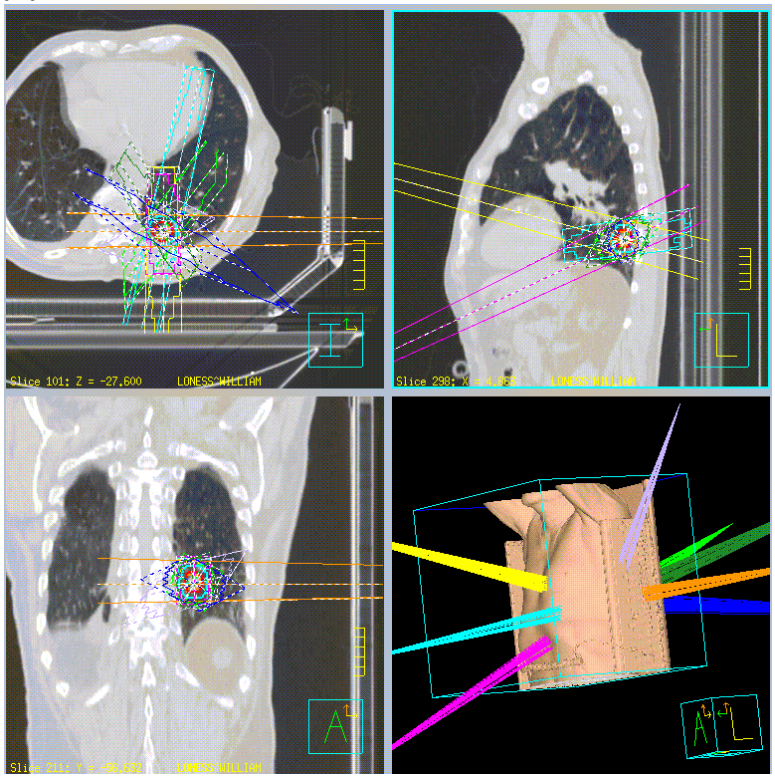
Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR) or stereotactic radiosurgery (SRS), is a culmination of several decades worth of progress in radiation oncology, allowing for the precise delivery of high doses of radiation

to targets in the body over few (typically, < 5) fractions with minimal exposure of normal adjacent tissue. [18]

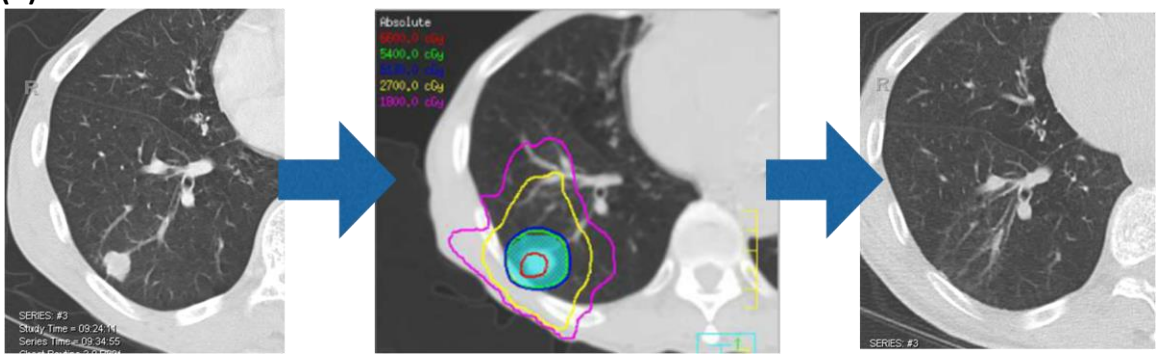
Such treatments have been successfully used to treat malignant and benign tumors in all body sites, most commonly in the brain, lung, liver, and spine. Advances in image guidance (orthogonal kV:kV imaging, conebeam CT (CBCT), etc.) and motion management (4D-CT, internal and external fiducials, etc.) have been central to the success of SBRT, particularly for tumors that are mobile. For example, it is now well established by multiple prospective clinical trials that SBRT delivered over 3-5 fractions results in local control rates > 90% for inoperable early stage lung cancer, with remarkably low rates of toxicity (<5-10% risk of grade 2+ pneumonitis, 15% risk of grade 1+ chest wall pain).[19, 20]) An example of a typical lung cancer SBRT plan and follow-up is provided in Figure 1.

Figure 1. (A) SBRT treatment plan. (B) Pre-treatment, planning volume, and post-treatment images.

(A)



(B)



All manufacturers of modern radiotherapy delivery systems have SBRT options or capabilities, with a variety of different methods for delivery. None of these delivery methods has been shown to be any more successful at delivering SBRT treatments than another when performed in the context of a carefully commissioned machine and workflow including standardization of immobilization, imaging, planning techniques and tissue constraints, and plan and machine QA. To this end, SBRT has now become a commonly used and mainstream method for tumor treatments with rapidly expanding indications.

1.4 SBRT for arrhythmia

Preclinical dose finding studies in porcine models have demonstrated that large (25 to 35 Gy), single fraction doses of SBRT can be accurately delivered to discrete targets in the heart, resulting in fibrosis that correlates to electrical isolation, similar to that found in catheter ablation. [21-26] In the earliest of these publications, Maguire *et al* reported on single fraction Cyber Knife radiosurgery (25 Gy (N=1), 35 Gy (N=1)) delivery to the right superior and left superior pulmonary veins in two Hanford mini-swine. [21] Animals were followed for six months and underwent electrophysiology (EP) testing, transesophageal echocardiography, and subsequently pathologic analysis. At the last time point, the EP study documented intended pulmonary vein isolation (electrical block) using a decapolar Lasso catheter, and echocardiographic monitoring of atrial and ventricular function six months post radiosurgery demonstrated normal cardiac function. Histologic analysis showed transmural fibrosis and contiguity of the ablation scar within the target. No adverse events were noted.

In a follow-up study from the same group, Sharma *et al* reported results from a dose (25 to 50 Gy) and location response experiment using single fraction Cyber Knife radiosurgery in 16 Hanford-Sinclair mini swine. [23] Targets included the cavotricuspid isthmus, AV node, pulmonary vein–left atrial junction, or left atrial appendage. Ranging from 25 to 196 days after treatment, animals were investigated with repeat electroanatomic voltage mapping and transesophageal echocardiography, when possible. The animals then were sacrificed and pathology specimens taken. Dose finding suggested that 25 Gy was the

minimum dose needed to produce an electrophysiologic effect, and this was consistently observed by 90 days. The method was deemed feasible for producing bidirectional cavotricuspid isthmus block and AV nodal conduction block. In addition, the pulmonary vein–left atrial junction and left atrial appendage showed marked voltage reduction to less than 0.05 mV. Histologic analysis demonstrated effects consistent with radiotherapy effect confined to the targeted areas with no evidence of damage outside the heart.

In a more recent publication from Blanck *et al*, a dose response experiment was performed on 9 mini-pigs (0 Gy and 17.5-35 Gy in 2.5-Gy steps) delivered to the right superior pulmonary vein. [7] Baseline MRI and electrophysiology were performed at baseline and 6 months after treatment. In contrast to the CyberHeart group, transmural scarring of cardiac muscle tissue was noted with doses ≥ 32.5 Gy. Likewise, complete circumferential scarring of the RSPV was not achieved at any dose level. Heart function was not affected, as verified by MRI and electrocardiogram evaluation. Adjacent critical structures were not damaged, as verified by pathology.

While the reasons for discrepancy in the required single fraction dose for effect are somewhat unclear, part of the difference may stem purely from subtleties in differences in dose planning and delivery for a given prescription dose. In the studies from the CyberHeart group, for a prescription dose of 25 Gy, maximum doses in the target volume may have exceeded 120-130% of prescription dose (Max doses > 30-39 Gy). In contrast, in the study from Blanck *et al*, for a suggested dose of 32.5 Gy, the maximum dose to the target with their delivery system would generally not exceed 107% of prescription dose by convention (Max dose 35 Gy). As such, both studies may in fact be suggesting the same dose range for effect, despite the differences in prescription dose.

The published literature on the use of SBRT for treatment of arrhythmia in humans is limited and appears restricted to only 5 patients to date (*November 2015*). The first-in-man report was presented in poster form at the Heart Rhythm On Demand meeting in 2013 [27] and has since been published [28]. In this first reported experience by Loo *et al*, a case of a 71 year old male with medically refractory VT was presented. [28] The patient had known coronary artery disease treated with bypass in 2000, a baseline ejection fraction of 24%, and placement of an ICD in 2009 when VT began. The patient also had a history of atrial fibrillation and COPD. He became refractory to escalating doses of sotalol and mexiletine. Catheter ablation was deemed medically contraindicated, and he was therefore treated with single fraction CyberKnife radiosurgery to 25 Gy prescribed to the 70% isodose line (Max dose 33 Gy) delivered in a single fraction to an area of the left ventricular scar as defined by pre-treatment PET and 12-lead ECG, encompassing the infero-septal, inferior, and infero-lateral walls from base to apex. A temporary pacing wire (Oscor, Inc., Miami Lakes, FL) was fluoroscopically placed in the RV apex as an imaging fiducial marker that could be dynamically tracked to compensate for respiratory motion. Total beam-on time was 90 minutes. All dose constraints to nearby organs at risk were met.

There were no immediate complications following treatment. Follow-up ICD interrogations revealed a decrease in total VT episodes from an average of 562 episodes per month in the 2 months pre-SBRT to an average of 52 episodes per month in months 2 to 9 post-STAR. At 3 months post-STAR, frequent nonsustained and pace-terminated VT occurred, associated with reduction of the sotalol dose to 40 mg bid and mexiletine dose to 150 mg bid. Intracardiac electrograms from the patient's ICD during VT were similar to those from pretreatment VT; however, the cycle length of the VT slowed from 380–411ms to 470 ms pre versus post STAR. Titration of mexiletine and sotalol dosing back to 150 mg tid and 80 mg bid, respectively, resulted in no further episodes of VT. Repeat PET/CT at 2.5 months post SBRT demonstrated mild extension of the inferior scar, with a more complete perfusion defect within the inferior scar. Nine months after treatment, the patient was admitted with COPD exacerbation and recurrent VT, and expired from respiratory failure.

In 2014, Cvek *et al* reported their experience in a 72 year old female with VT refractory to medication and both endocardial and epicardial catheter ablations. [29] The patient had been treated for more than a decade for cardiomyopathy, had a baseline ejection fraction of 25%, and grade III/IV mitral regurgitation. ICD was placed in 2013 following an episode of syncope. The patient was maximally treated with beta-blockers as amiodarone was contraindicated due to prolonged QT-interval. Because of repetitive arrhythmic storms, other treatment options were evaluated. She was not a candidate for cardiac surgery due to severe comorbidity, including systemic hypertension, paroxysmal atrial fibrillation, diabetes mellitus, chronic pulmonary obstruction disease, and chronic renal dysfunction. As all standard treatment options were exhausted, she became a candidate for stereotactic radiosurgery. A total dose of 25 Gy was prescribed to the 82% isodose line (Max dose 30.5 Gy) to the base of the lateral wall of the left ventricle based on CARTO mapping and prior EP studies. The LV electrode of the stimulation system in the lateral branch of coronary sinus was used as fiducial marker for respiratory tracking. Ten days after the radiosurgery session, the number of PVCs decreased from 9-10% to 1-3%, and non-sustained ventricle tachycardias (nsVT) diminished as documented in ECG monitoring during hospitalization and during repetitive ambulatory ECG Holter monitoring. Ten days post-treatment, only minimal elevation of troponin T serum level was detected (0.024-0.033). After six weeks, no complications or side effects were found. There were no signs of radiation pneumonitis nor pericardial effusion.

Lastly, in a recently reported abstract at EHRA Europace – Cardiostim 2015, Zei *et al* with the CyberHeart group reported on 4 patients (3 refractory VT, 1 refractory atrial fibrillation) treated with cardiac SBRT, one of which was already reported in the first-in-man report above. [30] A total dose of 25 Gy was delivered in a single fraction for all patients (2- inferior wall of left ventricle; 1 - ventricular septum; 1- atrial myocardium). Average ablation volume was 2.1 cc. There were no post treatment ICD firings. Reduction in arrhythmia burden was seen in all patients. Quality of life was stable or improved.

As such, there is now solid preclinical porcine data suggesting feasibility and safety of

delivering single fraction SBRT to discrete areas in the heart for purposes of creating scar and reducing arrhythmia burden. Similarly, though the literature base is quite small and median follow-up short, there are now at least 5 documented cases in the literature of successfully delivering SBRT to 25 Gy in a single fraction for refractory arrhythmia (4 VT, 1 atrial fibrillation). Thus, the early safety and promising efficacy results, particularly in the at risk VT population who often have limited options (continued medical management, heart transplant, or hospice, etc.), justifies exploring this noninvasive strategy further.

1.5 Electrocardiographic Imaging (ECGI): Noninvasive Electrical Mapping

The scattered previous reports of noninvasive cardiac ablation have been performed in the absence of detailed electrical mapping. Washington University has been at the forefront of developing a noninvasive cardiac mapping system, called Electrocardiographic Imaging (ECGI), which is an important development toward improving four-dimensional precision of imaging cardiac electrophysiology. This is a noninvasive imaging approach, similar to CT or MRI, except that it is designed to image cardiac electrical function. In brief, ECGI measures body surface electrical potentials at over 200 sites on the torso. It incorporates the patient-specific anatomy of the heart with the recording leads on the body surface to noninvasively reconstruct the electrical activity on a three-dimensional model of the patient's heart surface.

This modality has been validated extensively in animal and tank-torso models. It has been used to image cardiac electrophysiology in a number of normal and disease states in humans as well. [32-41]

ECGI represents an important link in the development of an entirely noninvasive mapping & ablation system, as it adds noninvasive electrophysiologic mapping to the other noninvasive myocardial scar imaging (from standard modalities such as echo, SPECT, MRI) to provide the most accurate plan for noninvasive ablation.

1.6 ENCORE for VT at Washington University

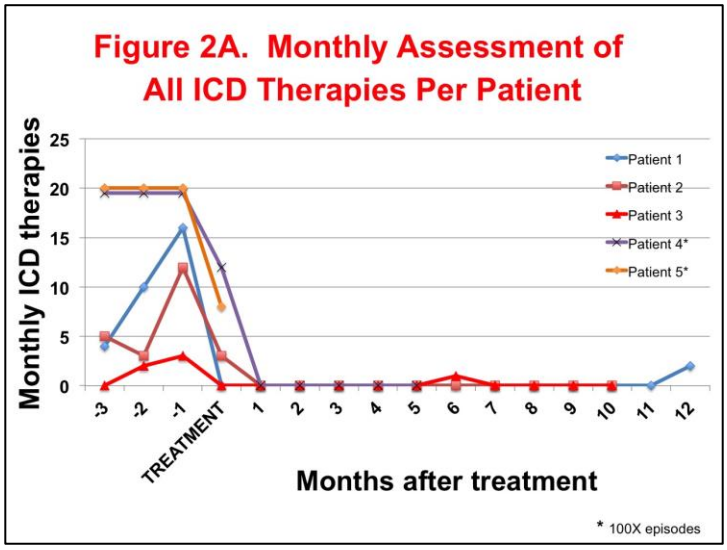
Combining the noninvasive electrical map (ECGI) with noninvasive anatomic/scar images allows for greatest precision to target noninvasive stereotactic beam radiation for cardiac arrhythmias. We call this process **E**P-guided **N**oninvasive **C**ardiac **R**adioablation (ENCORE). In April 2015, the first patient was treated with ENCORE at Washington University for refractory VT. As of May 2016, we have treated a total of 5 patients with refractory VT. Three of the patients had one or more prior catheter ablations with subsequent progression of VT. One patient had recent mitral valve replacement, and catheter ablation was contraindicated. The most recent patient treated was 83 years old, with multiple medical comorbidities, previous intolerance to anesthesia necessitating ICU admission, and subsequently declined catheter ablation. Table 1 summarizes our experience to date.

Table 1. Summary of Wash U ENCORE clinical experience to date.

Pt	Age (years)	Sex	Prior catheter ablations	Target	Target volume (ITV, cc's)	Dose (Gy) in 1 fx	Follow-up as of 5/23/2016	Delivery	Number of VT episodes in 3 months before ENCORE	Number of VT episodes after ENCORE
1	61	M	1	Anteroseptal to anterolateral LV base	51.3	25	13 mo	2 arc VMAT	>30	1 at 12 months, now off meds
2	60	M	0 (contraindicated due to recent heart surgery)	Focal anterolateral LV base	17.3	25	10 mo	Non-coplanar IMRT	>17	3 in first week, now off meds
3	65	M	2	Inferior LV	44.5	25	10 mo	2 arc VMAT	5	1 at 6 months, now off meds
4	62	M	6	Septal RVOT, LV summit, LV basal septum	53.0	25	7 mo	2 arc VMAT	>1000	Invasively mapped 4 weeks post treatment. 0 since, off meds
5	83	F	0 (contraindicated due to severe comorbidities)	Mid inferior, inferolateral LV	81.1	25	2 weeks (censored)	3 arc VMAT	>1000	233 VT episodes over 13 days after treatment

Of the first 3 patients, all had a dramatic reduction in the number and frequency of VT episodes after ENCORE, and all eventually had termination of VT. The 2 most recent patients had substantially more VT (both over 1000 episodes in the month before), and one of the two patients was demonstrating a reduction in VT pattern as of censored follow up. Only one of the five patients who received ENCORE protocol did not have an improvement in VT burden. At 3 weeks post-ENCORE treatment, a repeat catheter ablation was performed. Analysis of the invasive study will help answer questions regarding efficacy. While there have not been any acute toxicities to date with ENCORE protocol, and all patients who received ENCORE protocol were discharged from the hospital, Patient #5 did suffer from an embolic stroke 13 days after ENCORE protocol. She was known to have dilated cardiomyopathy with an EF of 18%, had a history of atrial fibrillation. She was deemed to be a poor candidate for oral anticoagulation. As such, she was at risk of such a complication independent of therapy. However, given the temporal nature of treatment to the stroke, we are assuming that this is possibly related to therapy.

The overall pattern of efficacy for all five patients in the ENCORE-VT Pilot study is shown below in Figure 2A, 2B, 2C. Importantly, all patients who underwent ENCORE had a reduction in ICD therapies and VT burden. This effect is seen in the absence of antiarrhythmic medications, which were aggressively weaned off in the first 6 weeks after treatment. The longitudinal heart function, as measured by cardiac echocardiography, is shown in figure 2D. None of the 5 patients had a reduction in LVEF after treatment (mean +5% in LVEF, range 0 to +15%). Serial CT scans were also performed, showing mild peri-ablation lung fibrosis at 3 months that largely resolved by 12 months (Figure 2E).



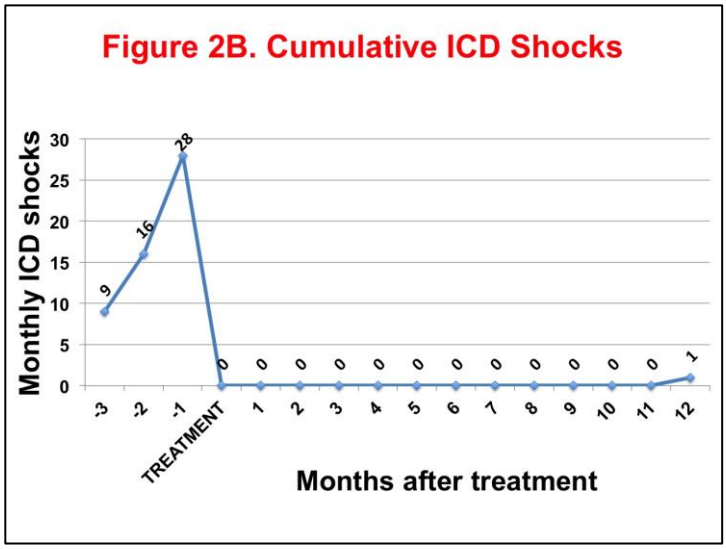


Figure 2B. Cumulative ICD Shocks
Monthly ICD shocks
30
25
20
15
10
5
0
9
16
28
0
0
0
0
0
0
0
0
0
0
0
0
1
-3
-2
-1
TREATMENT
1
2
3
4
5
6
7
8
9
10
11
12
Months after treatment

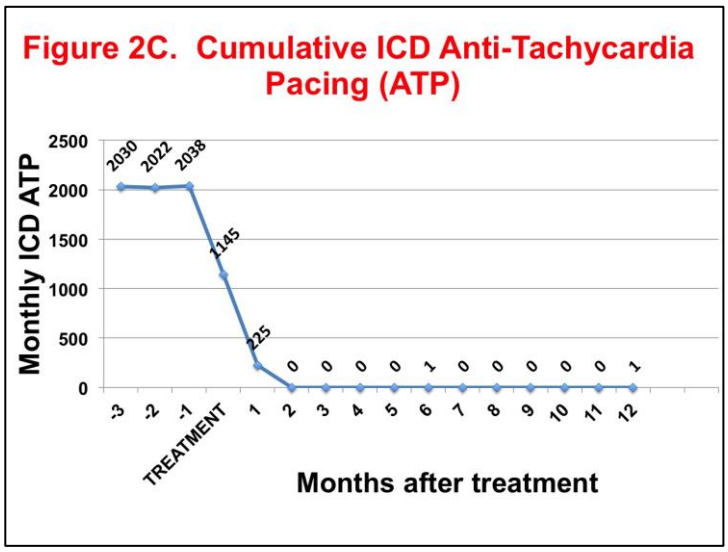


Figure 2C. Cumulative ICD Anti-Tachycardia Pacing (ATP)
Monthly ICD ATP
2500
2000
1500
1000
500
0
2030
2022
2038
1145
225
0
0
0
0
1
0
0
0
0
0
1
-3
-2
-1
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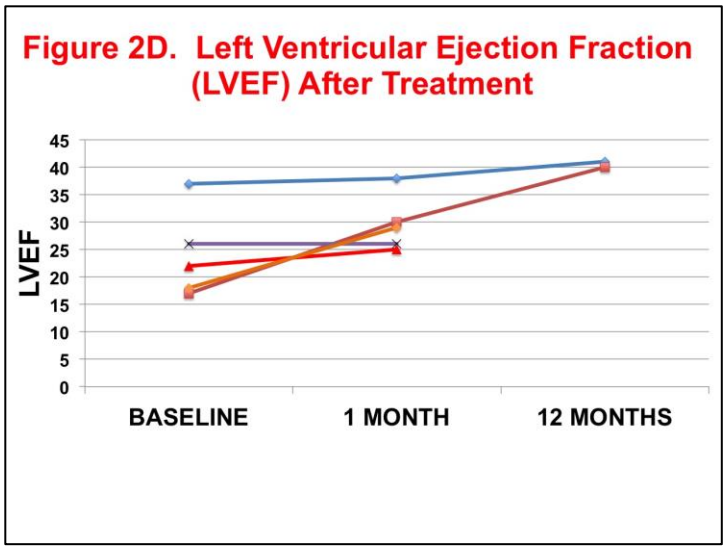
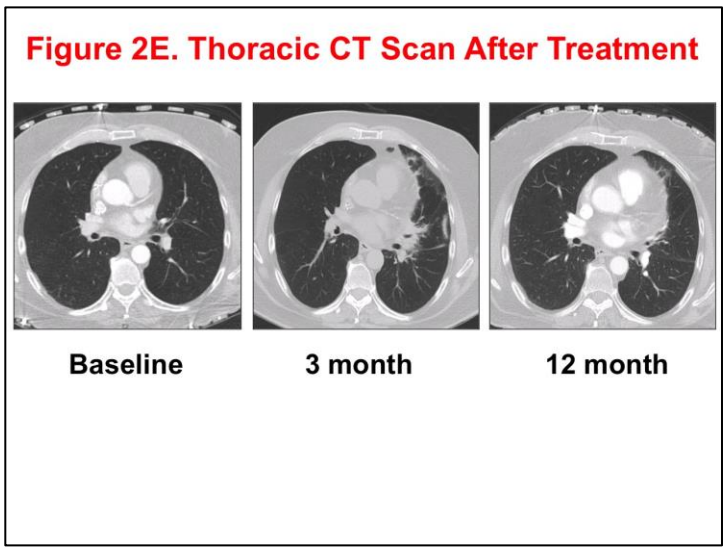
1
2
3
4
5
6
7
8
9
10
11
12
Months after treatment





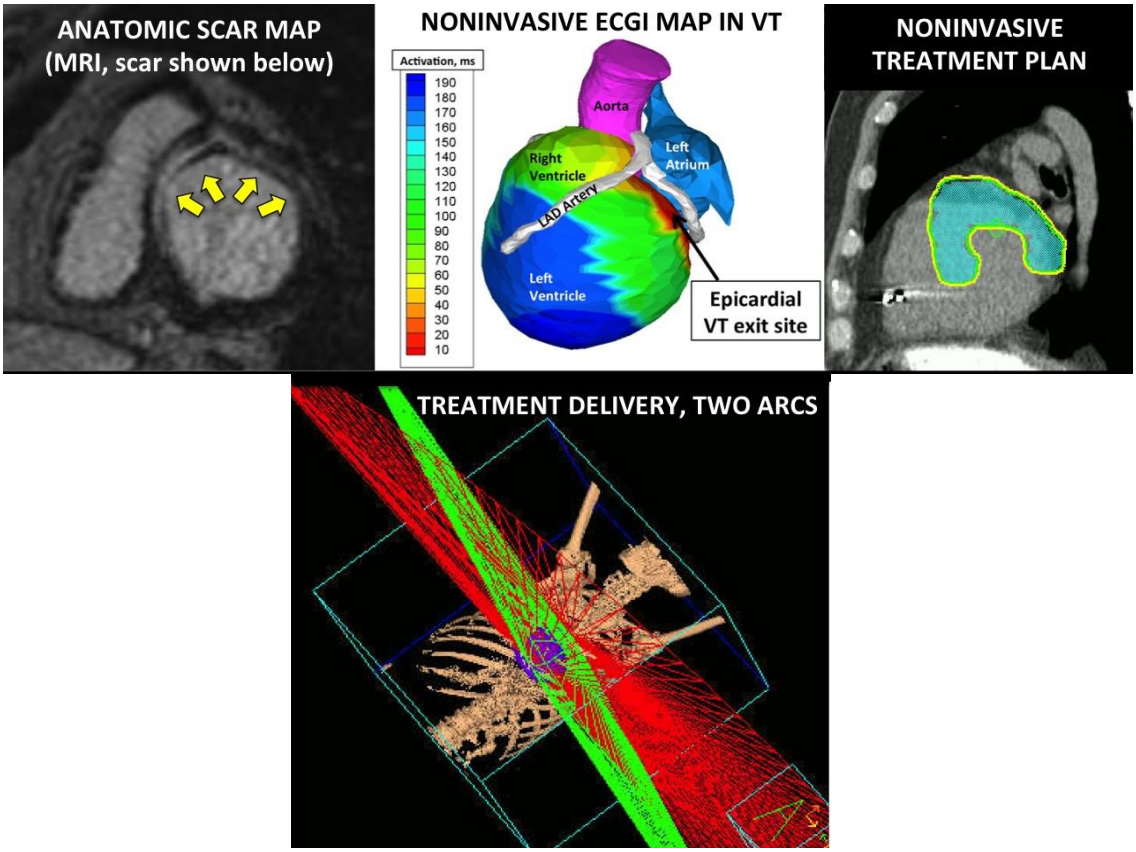
In all of the clinical cases reported in the literature to date, treatment was delivered using the CyberKnife, a robot linac with orthogonal kV:kV image guidance. Such a delivery system allows for diverse treatment to all sites of the body, but does require placement of a fiducial for x-ray image guidance, and due to the nature of the step-and-shoot delivery of the robot linac, treatment times average 1.5 hours.

At Washington University, all treatments delivered to date have been on an image-guided radiotherapy (IGRT)-equipped linear accelerator per our typical lung SBRT workflow. These units are equipped with an onboard cone beam CT (CBCT) which allows for acquisition of high fidelity volumetric images of the thorax which can be directly registered to the planning CT, allowing for accurate, near real time alignment of the heart and target volume. This precludes the need for invasive placement of a fiducial marker. In comparison, VMAT treatment times for our patients have averaged approximately 10

minutes. Figure 3 is an example of a ENCORE treatment plan for patient #1. In all cases, overall treatment time is substantially faster than the previously reported cases in the literature, which results in improved patient comfort and may also improve overall delivery accuracy, as increased time on the treatment machine has been correlated with "drift" away from the isocenter over time. [31]

Unlike other centers, treatments at Washington University have been delivered to regions that combine anatomic and electrical abnormalities. Anatomic abnormalities are defined as regions of ventricular scar, determined from clinical cardiac imaging modalities such as delayed-enhancing cardiac MRI (DE cMRI), nuclear computed tomography (SPECT) and/or previous intracardiac mapping. Electrical abnormalities are identified by 12-lead ECG during a clinical VT or 12-lead ECG during an induced VT from a noninvasive programmed stimulation procedure (NIPS). Figure 3 is an example of a ENCORE treatment plan developed for patient #1, targeting an area of anatomic scar that was identified with DE cMRI which overlapped with the area of electrical abnormalities based on 12-lead ECGs of VT obtained during NIPS. The results for each patient are depicted in the bar graph.

Figure 3. ENCORE procedure. TOP LEFT—Cardiac MRI demonstrating the extensive mid-myocardial scar (yellow arrows); TOP MIDDLE—Noninvasive electrical mapping (ECGI) performed during VT; TOP RIGHT—Noninvasive ablation treatment plan (light green is target volume) combining electrical and anatomic information; BOTTOM—Stereotactic radiotherapy delivered with 2 VMAT noncoplanar arcs to 25 Gy/single fraction.



As such, the delivery methods within this protocol are novel inasmuch as they are 1) rapid; 2) entirely non-invasive; 3) guided by noninvasive imaging of the electrical and structural abnormalities.

1.7 Study Rationale

Patients with VT either refractory to catheter ablation or deemed medically too frail or challenging to treat with catheter ablation have limited options, with one-year survival below 20%. Preclinical data described above demonstrate that single fraction SBRT to discrete portions of the heart is feasible and may result in a reduction or elimination of VT. Overall safety and early efficacy of SBRT have not been rigorously studied in a prospective trial to date. The ENCORE therapy described herein provides for a potentially rapid and totally non-invasive method for delivering such therapy.

The purpose of this phase I/II study is to demonstrate the short-term safety and preliminary efficacy of ENCORE for patients with VT refractory to standard treatments.

2.0 OBJECTIVES

2.1 Primary Objectives

1. Phase I - Demonstrate acute (≤ 90 days) safety of noninvasive stereotactic cardiac ablation radiotherapy (ENCORE). The **primary safety endpoint** is defined by a ≤ 20% rate of serious adverse events (SAEs) using CTCAE v4.0 criteria that are possibly/probably/definitely related to study treatment, based on previously published data for expected invasive catheter-based VT-ablation procedures.

2. Phase II - Demonstrate preliminary efficacy of ENCORE. The **primary efficacy endpoint** is defined by the number of subjects with a reduction in ICD therapies (ATP and ICD shocks) comparing the period six months before ENCORE treatment to the six months after ENCORE treatment as adjudicated by continuous ICD monitoring. There will be a six-week "blanking period" after therapy to allow for ablation effect. For patients with PVC-induced cardiomyopathy, the primary efficacy will be any reduction in PVC burden based on ambulatory heart monitors.

2.2 Secondary Objectives

1. Determine six-month and twelve-month survival **(overall mortality endpoint)** after treatment with ENCORE.

2. Determine **late toxicity endpoint** (>90 days to 12 months), as tracked prospectively after treatment using CTCAE v4.0 criteria.

3. Determine patient-reported health related **quality of life endpoint** (HRQOL) as measured by changes between pre-treatment and 6-week, 6-month, and 12-month post treatment scores on the standardized SF-36 questionnaire.

4. Evaluate **stricter efficacy endpoint** of ENCORE treatment, as defined by number of patients who have had 50% reduction in any VT therapies (ATP or ICD shocks) after ENCORE treatment (6 months before vs. 6 months after treatment, with a 6 week blanking period immediately after treatment). For patients with PVC-induced cardiomyopathy, the stricter efficacy will be >50% reduction in PVC burden based on ambulatory heart monitors.

5. Evaluate **strictest efficacy endpoint** of ENCORE treatment, as defined by number of patients who have had 95% reduction in any VT (ATP or ICD shocks) after ENCORE treatment (6 months before vs. 6 months after treatment, with a 6 week blanking period immediately after treatment). For patients with PVC-induced cardiomyopathy, the strictest efficacy will be abolition of PVC burden (<1%) based on ambulatory heart monitors.

6. Evaluate the **most clinically useful efficacy endpoint** of ENCORE treatment, namely, number of patients with reduction specifically in ICD shocks (6 months before vs. 6 months after treatment, with a 6 week blanking period immediately after treatment). For patients with PVC-induced cardiomyopathy, the most clinically useful efficacy will be improvement in cardiac function in the setting of any improvement in PVC burden.

7. Evaluate **longer-term durability endpoint** of ENCORE treatment, as defined by number of patients with reduction in VT therapies (ATP or ICD shock and ICD shock alone) during the early phase (treatment to 6 months, with 6 week blanking period) vs. the late phase (6 months to 1 year). For patients with PVC-induced cardiomyopathy, the longer-term durability efficacy will be persistence of any reduction in PVC burden based on ambulatory heart monitors during early phase vs. late phase.

2.3 Exploratory Objectives

1. To better understand the **mechanisms and timing of radiotherapy injury**, we will obtain serum blood markers of myocardial injury (troponin), endothelial injury (E-selectin), fibrosis (galectin-3) and prothrombotic markers (von Willibrand factor) at baseline, 3 days and 3 months after ENCORE treatment.

2. Evolution of **electrical remodeling** as obtained with noninvasive ECGI from baseline to 3 months and 12 months after ENCORE treatment

3. To better understand the effect of radiotherapy on **edema, fibrosis, cardiac inflammation, cardiac metabolism and localized cardiac function,** we plan to use serial cardiac imaging (DE-cMRI when possible, FDG-PET in all) at baseline, 3 days and 3 months after ENCORE treatment

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. DOCUMENTED VT:
    a. Patient must have documented sustained monomorphic ventricular tachycardia as documented on either a 12-lead ECG or intracardiac ICD interrogation

    — OR—

    b. Monomorphic PVCs documented on a 12-lead ECG.

2. ANTIARRHYTHMIC MEDICATION: Patient must have failed or become intolerant to at least one antiarrhythmic medication (amiodarone, sotalol, or mexiletine).

    –AND—

3. CATHETER ABLATION: Patient must have failed at least one invasive catheter ablation procedure, or have a contraindication to a catheter ablation procedure (e.g., LV thrombus, severe pulmonary disease), or have VT thought to arise from a protected location (e.g., epicardial VT with history of previous cardiac surgery).

4. MINIMUM VT BURDEN: Patient must have either:
    a. At least 3 VT episodes (sustained VT, ICD ATP or ICD shock) over previous 6 months prior to enrollment

    –OR—

    b. >20% PVC burden with a cardiomyopathy (LVEF<50%)

5. Patient must be deemed medically fit for stereotactic body radiation therapy by the treating physician.

6. Patient must be $\geq$ 18 years old.

7. Patient must be able to understand and be willing to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Patient must not have past history of radiotherapy within the projected treatment field.

2. Advanced symptomatic heart failure as defined as NYHA Class IV heart failure (inotrope dependent and/or current left-ventricular assist device (LVAD))

3. Polymorphic VT or ventricular fibrillation (VF) as a clinical heart rhythm (as determined by 12-lead ECG and/or ICD interrogation).

4. More than 3 distinct clinical VT morphologies observed (ECG or ICD interrogation or invasive EP study) OR more than 5 distinct induced VT morphologies during ECGI testing.

5. Advanced myocardial scar substrate that would require stereotactic delivery to a target volume deemed unsafe by the treating physician.

6. Unlikely to live 12 months, in the absence of VT, as best based on clinical judgment by the treating and enrolling physicians.

7. Patient must not be pregnant and/or breastfeeding and must have a negative pregnancy test within 14 days of study entry.

4.0 TREATMENT PLAN

4.1 Noninvasive Imaging for Scar/Fibrosis, Edema, Inflammation

To maximize the potential benefit and minimize the risks of noninvasive radioablation, we will perform extensive imaging of cardiac ventricular scar or inflammation harboring the VT circuit using clinically available imaging tests, including magnetic resonance imaging (MRI), positron emission testing (PET), and myocardial perfusion imaging (MPI/SPECT) when available. If these studies have been performed previously within one year, additional testing is not needed. Refer to Section 7.0 Study Calendar for anticipated timing of clinical cardiac imaging modalities. The role of each test and potential risk to each is described briefly below.

4.1.1 Magnetic Resonance Imaging (MRI)

When coupled with administration of IV contrast agent (gadolinium), cardiac MRI is the gold-standard imaging study for detailed evaluation of the distribution of fibrosis and scar. In this study, MRI will be performed prior to the procedure (baseline study) to help determine the target volume for radioablation using the best-practices to safely acquire the data and the latest sequences for artifact-reduction, called Wideband sequences (55, 56).

Immediately after treatment (day 3), MRI will be used to evaluate for the presence of local edema at the treated site (T2-weighted imaging) and to screen for acute injury, such as pericardial effusion.

MRI will be performed again 3 months after the treatment to evaluate for any changes in cardiac fibrosis and scar from the baseline study. It will also screen for

potential toxicities, including changes in myocardial function, valvular performance or pericardial effusion.

This type of serial MRI has never been performed after administration of cardiac radiotherapy, and the results are expected to provide important insight into the mechanisms and timing of the radiobiological effect of this treatment. We perceive this knowledge to be of utmost importance in determining the projected time course of the safety and clinical effect for future patients receiving this type of therapy.

We anticipate that most or all of the patients who are enrolled into this study will have cardiac defibrillators (ICDs) to treat ventricular arrhythmias. Historically, the presence of an ICD has been a contraindication to performing MRI for various theoretical and observed concerns. Over the course of the past decade, great strides have been made to safely allow patients with ICDs to undergo MRI scans. These are reviewed in several recent publications (42-53). The most prominent of these is the completion of a large registry to characterize the risks of undergoing MRI with a cardiac device (MAGNASAFE.org). This registry and other publications (50) have defined the substantial safety margin of MRI use in patients with cardiac devices, and these studies form the basis for an upcoming professional guideline statement regarding the expanded and safe use of MRI in patients with cardiac devices (anticipated 2016 release). In short, the MAGNASAFE registry was a multicenter trial of 1,500 patients with cardiac devices who underwent MRI scanning on a 1.5 T scanner. Of the 1500 MRI scans, only 1 patient developed a clinical event (generator failure due to inappropriate sensing) which was deemed to be caused by inappropriate ICD programming. The overall positive results of the MAGNASAFE study have resulted in the national CMS National Coverage Determination (NCD) allowing for coverage of MRIs in patients with cardiac devices if they are performed in a research study that meets CED (coverage with evidence development) criteria." (Medicare website: CAG-00399R2). Since the release of MAGNASAFE, a number of trials including patients who are specific to our population (patients with VT, with implanted ICD, undergoing cardiac MRI) have been published (42-53). In these studies, there were no adverse effects of cardiac MRI with appropriate pre-scan ICD programming, further supporting the overall safety of this scan in the appropriately selected patients.

A second major advance is the development of MRI-conditional cardiac devices, which are now commercially available from several manufacturers (Medtronic, Biotronik). Whenever possible, we plan to use these devices for new implants at our hospital. However, we expect most patients who enroll into this study will have older legacy devices, which do not have specific MRI-conditional labeling.

In this study, we recognize the potential risks involved with MRI in patients with ICDs, and these risks will be shared with patients in full disclosure, using language

and images from a recently published "Cardiology Patient Page" article (54). MRI remains the gold standard for assessment of fibrosis and edema, and we believe the large benefits of precision guidance of radiotherapy outweigh the small potential risks of ICD system changes. Patients who are unwilling to accept these risks, or patients in whom we believe the risks to be excessive will not undergo MRI. We will then use clinically available imaging, such as nuclear MPI/SPECT, which is less specific and sensitive than MRI.

Patients in whom we will NOT offer an MRI include:

a) Newly implanted ICD system (any component added < 6 weeks)
b) Dependence on ICD system for pacing (complete heart block or severe sinus node dysfunction without ventricular escape)
c) Presence of abandoned, fractured or epicardial cardiac leads
d) Active noncardiac implanted device (other than cardiac device)
e) Abdominal position of cardiac device
f) Battery voltage of ICD at elective replacement interval
g) Increased risk to administration of IV gadolinium such as renal impairment (estimated glomerular filtration rate (eGFR) < 40) or previous adverse reaction to IV gadolinium.
h) Patient preference

For patients who undergo MRI, several safeguards have been developed as "best practices" and will be used for this study. These include:

a) Supervision of appropriately trained personnel for the duration of the MRI scan
b) Pre-treatment and post-treatment ICD device checks
c) Pre-treatment ICD programming per standardized protocol (MAGNASAFE registry) to minimize chances of untoward ICD effects, including asynchronous or inhibited pacing mode (VOO/DOO or VVI/DDI setting), disabling magnet response, disabling episode memory, and disabling therapies for tachyarrhythmia. A full risk-mitigation protocol has been developed and is available as a supplement to this protocol.

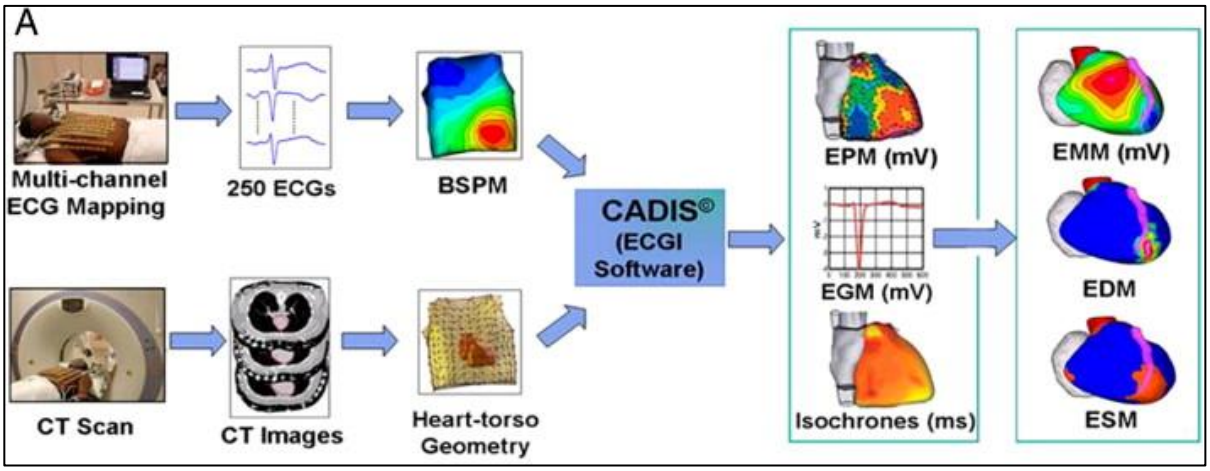
4.1.2 Positron Emissions Testing (PET)

PET uses a special camera to measure specific signal in heart cells emitted from injected radioisotopes (called tracers). The amount of radiation received from PET is small, and the risk of procedural complication is exceedingly low. In this study, the radioisotope will be Fludeoxyglucose (FDG). This isotope tests for areas of inflammation and ischemia, which may be particularly important in patients with nonischemic reasons for cardiomyopathy. The FDG-PET imaging will be done in all patients, unless contraindicated due to previous adverse reaction. The

information gained from FDG-PET cardiac metabolism will be combined with the scar imaging from MRI to help guide radioablation.

4.2 Noninvasive Electrical Imaging

The method of electrocardiographic imaging (ECGI) is described in Section 1.5 above. Graphically, it is illustrated below:



In brief, the patient undergoes a CT scan while wearing a "vest" of electrodes that record heart beats. The electrical information from the surface of the body can then be computed onto the patient-specific heart model to noninvasively display the characteristics of the imaged heartbeat. Useful information includes: where the beat begins, how it depolarizes the heart, which parts of the heart have abnormal signals from previous heart attacks or scar. Fitting the vest of electrodes on the patient, obtaining electrical signals, and performing the CT scan is generally completed in under 30 minutes.

In this study, prior to treatment, patients will undergo ECGI during a noninvasive-programmed stimulation (called NIPS) procedure. A NIPS procedure is a commonly performed procedure in the cardiac electrophysiology lab. The patient receives light IV sedation for the procedure, and vital signs are monitored closely. Communication with the patient's ICD is established, and the ICD is used to intentionally induce ventricular tachycardia through basic pacing maneuvers. Once the VT is induced, a 12-lead ECG and 256-lead ECGI are obtained (less than 10 seconds). The ICD is then again used to pace-terminate the VT (less than 10 seconds).

In this study, the NIPS will be performed in a standardized fashion. In the fasting state, single, double, and then triple extrastimuli will be delivered to refractoriness at drive trains of 600 and 400 ms, via the right ventricular ICD lead. Results from

the NIPS will yield electrical information (ECG and ECGI) that guides targeting of the noninvasive ablation to the areas of origin of the ventricular arrhythmias.

Despite the perceived risk of intentionally inducing a potentially life-threatening arrhythmia, NIPS is considered a rather low-risk procedure in the EP lab. Common risks include:

- Hypotension or adverse reaction to IV sedation (usually propofol);
- Induction of an arrhythmia that cannot be terminated by pacing, requiring external cardioversion/defibrillation or use of the ICD is necessary to restore regular rhythm

Contraindications for NIPS include:

- Because of the possibility for cardioversion/defibrillation, the most common contraindication for NIPS is the presence of atrial fibrillation in a patient that cannot receive anticoagulation
- Hemodynamic or medical instability prior to procedure
- ICD at elective replacement interval (ERI) or end of service (EOS)

During follow-up after treatment, ECGI will be performed as a standalone procedure, without the need to perform NIPS.

4.3 Targeting the Area for Noninvasive Ablation

The clinical cardiac electrophysiologist will determine the region of the heart to be targeted for noninvasive ablation on an individual patient basis. The decision combines: A) scar architecture from cardiac MRI; B) inflammation location from PET; C) 12-lead ECG interpretation; D) 3-dimensional ECGI interpretation, using previously published criteria for origin of VT; E) anatomic considerations from CT scan; F) reduced cardiac motion or myocardial thinning, suggestive of previous cardiac injury or scar. As a general rule, efforts will be made to target all areas of VT origin and adjacent scar or inflammatory regions that harbor related circuits. In almost all cases, the targeted area will avoid areas of healthy tissue and focus on areas that demonstrate severely reduced cardiac motion.

4.4 Radiation Therapy Guidelines

4.4.1 Dose, Fractionation

Radiotherapy will consist of stereotactic body therapy to be given over one fraction. Patients will be planned for a dose of 25 Gy in a single fraction to the PTV.

4.4.2 Simulation Procedures/Patient Positioning

Patients will be immobilized using a system (such as BodyFIX) that is known to keep immobilization setup uncertainty to ≤ 3 mm. All patients will undergo free breathing CT simulation using thin (≤ 3 mm) slice thickness CT. An additional respiratory correlated 4D-CT will be acquired and co-registered to the planning CT for purposes of assessing respiratory motion. IV contrast will be used to facilitate definition of cardiac structures when not otherwise contraindicated. Esophageal contrast will be used to facilitate definition of the esophagus and upper stomach when not otherwise contraindicated. Additional clinical images may be co-registered to the planning CT based on availability and at the discretion of the clinician.

4.4.3 Target Volumes

The treatment target will be defined using radiation oncology principles of target definition. The gross target volume (GTV) will be segmented through corroboration of all previously acquired imaging (MRI, CT, SPECT, etc.) and EP data (12-lead EKG, prior catheter mapping, ECGI, etc.). An internal target volume (ITV) will be created based on the 4D-CT to account for any impact on the summative effect of respiratory and averaged-out cardiac motion. No clinical target volume (CTV) expansions will be utilized. The PTV will be generated at the discretion of the treating physician based on immobilization, machine uncertainties, and setup uncertainty, but should generally range between 0.3 cm and 0.7 cm.

4.4.4 Treatment Planning

All patients will be planned to a target dose of 25 Gy in a single fraction to the PTV, subject to organ at risk (OAR) dose constraints. Coverage goal of the PTV will be for $\geq$ 95% of the PTV to be covered by $\geq$ 95% of the prescription dose, although in situations where a critical OAR structure is violated, coverage of PTV will be compromised in order to meet dose constraints.

Dose limits are being employed as means to minimize the likelihood of toxicity, but true tolerance to OARs are not well described for single fraction schemes to the central thorax, and therefore prioritization will be employed for planning purposes taking into account the balance between PTV coverage and relative consequences of toxicity to specific OARs.

Priority	Definition
1	Obey spinal cord constraints. No deviations allowed.
2	Respect PTV coverage requirements.
3	Respect OAR constraints. If the PTV is next to or involving an OAR (not the spinal cord), then likely the guideline constraints cannot be met. In such cases, dose to OAR should not exceed 105% of

	prescription dose and effort should be made to avoid treating the entire circumference of the structure (particularly trachea, bronchus, esophagus).

4.4.5 OAR Contouring

In order to verify dose limits to OARs, OARs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as listed in the table below. An OAR may be omitted from contouring and subsequent evaluation in the DVH if it is > 10 cm from the PTV, or at the discretion of the treating radiation oncologist if it is determined that no clinically meaningful dose will be received by the OAR.

Serial Tissue	Contouring	Volume	Volume Max (Gy)	Max Point Dose (Gy)**
Spinal Cord and medulla	Entire bony canal	<0.35 cc <1.2 cc	10 Gy 8 Gy	14 Gy
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)		<10% of subvolume	10 Gy	14 Gy
Esophagus*	Include the mucosal, submucosa, and all muscular layers out to the fatty adventitia	<5 cc	11.9 Gy	15.4 Gy
Heart/Pericardium	Contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.	<15 cc	16 Gy	22 Gy
Great vessels	The wall and lumen of the named vessel	<10 cc	31 Gy	37 Gy
Trachea and Large Bronchus*	Contour the trachea and cartilage rings starting 10 cm superior to the PTV extending inferiorly to the bronchi ending at the first bifurcation of the named lobar bronchus.	<4 cc	17.4 Gy	20.2 Gy
Rib		<5 cc	28 Gy	33 Gy
Skin	The outer 0.5 cm of the body surface anywhere within the whole body contour.	<10 cc	25.5 Gy	27.5 Gy

Stomach	The entire stomach wall and the gastric contents included from the GE junction to the proximal duodenum at the pyloris.	<5 cc	17.4 Gy	22 Gy
Parallel Tissue		**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	Contour right and left lung as one structure including all parenchymal lung tissue but exluding the GTV and major airways (trachea and main/lobar bronchi)	1500 cc	7 Gy	
Lung (Right & Left)		1000 cc	7.6 Gy	V-8Gy <37%
Liver	Contour right and left lobes as one structure including all parenchymal liver tissue but excluding the GTV and major draining ducts, extrahepatic portal vein, and gall bladder.	700 cc	11 Gy	

4.5 Evaluability Guidelines

Patients who complete the full intended dose of single fraction SBRT are evaluable for both the primary and secondary objectives.

4.6 General Concomitant Medication and Supportive Care Guidelines

In the rare event that a patient is taking an anti-neoplastic therapy (chemotherapy, targeted therapy) for any reason (immune disease, malignancy), said medication must be withheld at least 7 days prior to and 7 days after delivery of SBRT.

All other standard concomitant medications deemed necessary for management of the patient's arrhythmia and overall health should be continued, and need not be altered for purposes of SBRT delivery.

Though not yet seen in our preliminary experience, given the proximity of the esophagus and stomach to the heart, it is possible that patients may develop esophagitis or gastritis. Treatment of esophagitis/gastritis varies with the severity of the patient's symptoms; for example, diet adjustment and narcotic management may be sufficient for grade 2 complications. Nutritional support via gastric tube or jejunostomy tube may be initiated upon development of grade 3-4 complications, per mutual preference of the treating physician and patient.

4.7 Women of Childbearing Potential

Women of childbearing potential (women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the start of SBRT.

If a patient is suspected to be pregnant, SBRT should not be administered. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume therapy.

4.8 Duration of Therapy

Because this study involves administration of a single fraction of SBRT over the course of approximately 10 minutes, there is no option for discontinuation of treatment once initiated.

4.9 Duration of Follow up

Patients will be followed per protocol for 12 months following the completion of SBRT or until death, whichever occurs first. Follow-up is per the treatment calendar (see Section 8.0) and consists of routine clinical visits, 12-lead EKG and implanted device interrogations to evaluate toxicity and treatment response, and evaluation of QOL. Patients will be followed by office visits, phone calls, and review of medical record. Any additional follow-up and imaging will be obtained off-study as per routine clinical policies of the treating physician. After 12 months, patients will be followed at the discretion of the treating physicians. Patients will be tracked for clinical outcomes up to 5 years after completion of radiation via review of the medical record.

4.10 Management of ICD Programming and Antiarrhythmic Medications During Follow up

ICD programming parameters and antiarrhythmic medication dosing should be patient-specific decisions, left to the treating physician taking into account risks and benefits of the various strategies. Ideal settings are suggested below:

- ICD programming should include a zone for detection at least 20ms slower than the slowest clinical or induced VT. ICD therapy may or may not be programmed to deliver therapy in this zone, subject to decisions about patient symptoms and tolerances during VT.
- Antiarrhythmic medications should be maintained at pre-treatment doses for at least the first 6 weeks, barring any development of adverse medication effect.
- With each subsequent visit after the first 6 weeks, doses of at least one antiarrhythmic medication should be reduced if no VT has been observed on ICD device check.

- If not contraindicated, oral anticoagulation is preferred during the first month after treatment (warfarin, dabigatran, rivaroxaban, apixaban or edoxaban) to minimize risks of stroke.

5.0 REGULATORY AND REPORTING REQUIREMENTS

5.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Advancing heart failure symptoms will be monitored closely, and represent a difficult endpoint to assess objectively. It is acknowledged that heart failure progression is an expected natural history irrespective of cardiac ablation. Inotrope or mechanical support may become necessary, and if used, specific scoring criteria will be used to adjudicate treatment-related HF progression vs. natural history of HF. For the purposes of this study, which studies the short-term toxicities of the therapy, treatment-related adverse heart failure event will be defined as either:

1) Acute worsening of heart failure symptoms requiring initiation of new IV vasoactive medications (inotropes or vasopressors) within the first six weeks of treatment;
2) Acute reduction in left ventricular ejection fraction (>10% reduction) within the first six weeks of treatment

We recognize that because of the relatively slow-acting nature of radiotherapy, potential treatment-related heart failure progression fall outside the six-week window defined above. Long-term clinical care and observation will be important, but are outside the scope of this project. For best patient care, decisions regarding heart transplant status and candidacy for inotrope or mechanical support will not be affected by enrollment in this study.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

5.2 Serious Adverse Events (SAEs)

Definition: An adverse event that is any undesirable experience associated with the use of a medical product in a patient that results in death, hospitalization (new or prolonged), disability or permanent damage, or is life-threatening.

Specific to this protocol, SAEs are defined as AEs with CTCAE v4.0 grade 3 or higher resulting in hospitalization or grade 4-5 AE. Treatment-related SAEs were SAEs that are possibly, probably, or definitely related to protocol treatment.

5.3 Unanticipated Problems

Definition:

- 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;
- 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

5.4 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB

5.5 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm

5.6 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

5.7 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event

5.8 Timeframe for Reporting Required Events

Adverse events captured in the CRFs will be tracked for 12 months following SBRT. For the purposes of this protocol, reportable adverse events are grade 3, 4, or 5 toxicities that did not predate SBRT and are possibly, probably or definitely attributable to treatment. Patients will be assessed using the CTCAE v4.0.

6.0 CORRELATIVE STUDIES

Quality of life (QOL) will be measured at baseline, 6 weeks, 6 months, and 12 months post completion of ENCORE, using the SF-36 questionnaire. Changes between baseline and each time point, as well as changes between time points, will be measured.

ECGI will be obtained at baseline, 3 and 12 months after ENCORE treatment. Comparisons will be made of the putative purely ECGI-derived target volume vs. clinically-derived target volume on protocol, as well as comparison of post-ENCORE month ECGI with baseline ECGI with correlation of changes on ECGI with ENCORE dose distribution

Delayed contrast enhanced cardiac MRI (DE cMRI) will be obtained at baseline, 1-3 days and 3 months after ENCORE treatment. While initial MRI will help identify anatomic scar to target therapy, follow up DE cMRI will be used to identify tissue edema and myocardial ablation, as well as assess for cardiac and extracardiac complications.

Blood work will be drawn at baseline, 3 days and 3 months after ENCORE treatment. Specific markers will be used to assess for biochemical evidence of myocyte injury (troponin), endothelial

injury/activation (E-selectin), fibrosis (galectin-3), and prothrombotic effects (von Willibrand factor).

In patients who die or undergo a heart transplant, clinical reports will be reviewed and abstracted of any pathologic, histologic, or autopsy analysis. Additionally, clinically processed tissue submitted to the Department of Pathology may be requested for additional analysis for research purposes, including, but not limited to, assessment of the location and degree of baseline injury outside the radiotherapy target and evidence of on and off-target injury from radiotherapy.

7.0 STUDY CALENDAR

	Screening	**Baseline**	**ENCORE tx**	**Day 3**	**2 wk**	**4 wk**	**6 wk**	**3 mo**	**6 mo**	**12 mo**	**Extended F/U****
Informed consent	X										
Medical history	X										X
Pregnancy test	X										
Device interrogation (Standard of care)	X		X	X	X	X	X	X	X	X	X
24 Hour heart monitor* (Standard of care)	X						X	X	X	X	
SF-36 QoL		X					X		X	X	
12-lead EKG		X		X			X	X	X	X	
NIPS		X									
Cardiac CT + ECGI		X						X		X	
Cardiac MRI + PET		X		X				X			
Adverse events assessment		X	X	X	X	X	X	X	X	X	X
Blood work		X		X			X	X			

*** For patients with PVC-induced cardiomyopathy-indications only**

**** Patients will be followed as per routine clinical practice, with data being collected from the medical record on outcomes for up to 5 years post-completion of study treatment. Device interrogation, 24 hour heart monitors, and imaging will be performed as clinically indicated but are not mandated by the protocol. Capture of AEs will be performed as described in Section 5.1.**

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
ENCORE Form	Completion of last fraction of SBRT
Toxicity Form	6 weeks post-SBRT 3 months post-SBRT 6 months post-SBRT
QOL Form	Baseline 6 weeks post-SBRT 6 months post-SBRT 12 months post-SBRT
Follow-Up Form	6 weeks post-SBRT 3 months post-SBRT 6 months post-SBRT 12 months post-SBRT 2 years post-SBRT 3 years post-SBRT 4 years post-SBRT 5 years post-SBRT

9.0 MEASUREMENT OF EFFECT

1. Acute (≤ 90 days) safety of ENCORE will be defined as a ≤ 20% rate of protocol-specific serious of serious adverse events (SAEs) using CTCAE v4.0 criteria that are possibly/probably/definitely related to study treatment, based on previously published data for expected invasive catheter-based VT-ablation procedures. Early stopping rules have been created such that if 5 or more patients develop ENCORE related SAEs out of the first 10 patients, this would be deemed significantly greater than 20% (alpha < 0.05), and the trial will be halted.

2. Preliminary efficacy of ENCORE will defined by the number of subjects with a reduction in ICD therapies (six month period before ENCORE treatment compared to six month period after ENCORE treatment) as adjudicated by continuous ICD monitoring.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will meet to review data semi-annually beginning six months after accrual has begun. The report will be prepared by the study statistician with assistance from the study team and will be reviewed by the DSMC, which will consist at minimum of a radiation oncologist, a cardiologist, and a statistician. The report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician.
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, study status, and phase of study.
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason.
- Study-wide target accrual and study-wide actual accrual.
- Protocol activation date.
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective.
- Measures of efficacy.
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules.
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 Early Stopping Criteria

Through a one sample test for proportions, assuming a maximal clinically acceptable SAE rate of 20%, 5 or more SAEs out of the first 10 patients would be significantly greater than 20% (alpha < 0.05). As such, the protocol will be halted if 5 or more of the first 10 patients develop a SAE.

11.2 Sample Size Justification

A total of 19 patients will be enrolled, which provides an optimal balance between assuring a high likelihood of safety (Phase I) with a preliminary assessment of efficacy (Phase II).

For the phase I component, the baseline rate of SAEs for catheter ablation is assumed to be 10-15%. Given the population being studied and a reasonable expectation that patients may be at a higher than typical risk of toxicity from any salvage therapy, we assume that SAE rates up to 20% would be clinically acceptable. Having said that, given that this is a totally noninvasive technique, it may well be that rates of toxicity are lower than that expected with catheter ablation. After exploring patient ranges from 15-25 patients, it was determined that 19 patients would provide a 75.4% power to detect an SAE rate about 20% (range, 5%-20%, alpha = 0.0829).

For the phase II component, while some single institution series report much higher success rates, the baseline efficacy rate of catheter ablation in prospective trials ranges from 50-65%. As this is a salvage therapy in a high risk population, we assume that efficacy rates as low as 40% would be clinically acceptable. Using the 19 patient sample determined above, it was determined that 19 patients would provide 81.5% power to determine that ENCORE is not worse than 40% effective for the treatment of VT (range, 40-65%, alpha = 0.0885).

11.3 Analytic Plan for Primary Objectives

SAEs defined by CTCAE v4.0 criteria within 90 days of ENCORE that are possibly/probably/definitely related to study treatment will be recorded. ENCORE therapy will be deemed safe if the rate of SAEs is ≤ 20%. An additional early stopping rule dictates that if 5 or more out of the first 10 patients develop ENCORE related SAEs, the trial will be halted.

The number of ICD therapies delivered in the 6 month periods preceding and following ENCORE therapy will be recorded for each patient by interrogation of the ICD. ENCORE therapy will be deemed efficacious if there is a reduction in ICD therapies before and after treatment. The proportion of patients with efficacious ENCORE therapy will be calculated, with the intent of demonstrating at least 40% efficacy.

11.4 Analytic Plan for Secondary and Exploratory Objectives

Adverse events will be tabulated by type and grade.

Descriptive statistics will be used to describe efficacy and strict efficacy, changes in SF-36 scores, changes in ECGI, differences in purely ECGI derived vs. clinically-derived target volumes.

Dose-volume parameters to the ENCORE target as defined by ECGI and the clinical target volume will be correlated with the reduction in VT through descriptive statistics and Cox regression.

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