

**Prospective Assessment of Premature Ventricular Contractions  
Suppression in Cardiomyopathy (PAPS): A Pilot Study**

**CLINICAL INVESTIGATION PLAN**

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## Protocol Synopsis

<b><u>PROSPECTIVE ASSESSMENT OF PVC SUPPRESSION IN CARDIOMYOPATHY (PAPS): A Pilot Study</u></b>	
<b><u>Part I - PAPS pilot randomized trial</u></b>	
<b>Study / Objectives</b>	Assess the feasibility of enrolling, randomizing treatment strategies and retaining participants with frequent PVCs and associated CM.
<b>Interventions</b>	3-month observation period followed by either radiofrequency ablation (RFA) or antiarrhythmic drugs (AADs). All interventions (RFA and all proposed medications) are FDA approved and are currently standard of care for subjects with frequent PVCs.
<b>Study Design</b>	Multicenter randomized prospective study
<b>Eligible subjects</b>	Subjects with frequent PVCs (equal to or greater than 10% burden) and cardiomyopathy with calculated left ventricular ejection fraction (LVEF) ≤ 45%.
<b>Planned number of subjects</b>	This study will enroll between 36-39 subjects – 3 subjects per center (enrollment completed within 18 months).
<b>Number of participating sites/ countries</b>	At least 12 centers in the United States and one in Canada
<b>Primary Endpoint(s)</b>	<ol style="list-style-type: none"> <li>1. <i>Improvement of LVEF after PVC suppression at 12-month follow-up.</i> This is chosen as the primary-endpoint due to the known prognostic value of LVEF. The lower the LVEF, the higher the risk of sudden cardiac death and heart failure<sup>1-3</sup>. This will compare the overall improvement or change in LVEF between RFA and AAD groups. This end-point will support that either RFA or AADs have an overall better outcome due to significant improvement of LV function with potential impact on morbidity and mortality associated with PVC-CM.</li> <li>2. <i>Responders to PVC suppression strategy at 12-month follow-up.</i> Assessment of the number of responders (delta LVEF ≥ 10%) after PVC suppression strategies (RFA or AADs) will assess the effectiveness of RFA and AADs to reverse or improve cardiomyopathy induced by frequent PVCs. Evidence that either RFA or AADs is superior to improve or even reverse LV dysfunction in subjects with high burden PVCs could have significant impact of morbidity and mortality including future heart failure and ventricular arrhythmias, and also may avoid ICD implantation.</li> </ol>
<b>Additional Endpoint(s)</b>	<ol style="list-style-type: none"> <li>1. <i>Efficacy of RFA vs AADs groups to achieve successful PVC suppression at 12-month follow-up, defined as a reduction of PVC burden ≥80% (regardless of LVEF change). Understanding the success rate of PVC suppression between RFA and AADs will help better determine the best treatment to those subjects with high PVC burden.</i></li> <li>2. <i>Composite end-point of adverse events at 12-month follow-up, including worsening in NYHA functional class (I-IV), number of HF and cardiac-related admissions, RFA complications and AAD adverse effects and cardiovascular death.</i></li> <li>3. <i>Composite end-point of arrhythmia burden at 12-month follow-up, including PVC recurrence, non-sustained (&lt; 30sec) and sustained (&gt; 30sec) ventricular arrhythmias and arrhythmic sudden cardiac death.</i></li> </ol>

<p><b>Follow up Schedule</b></p>	<p>Subjects will be screened via chart review. If the inclusion criteria is met, subject will be asked to participate in the study during Visit 1 (Week 0)  Each enrolled subject will be followed at the following visits:</p> <ul style="list-style-type: none"> <li>- Week 0 –, Enrollment, informed consent and clinical evaluation</li> <li>- Week 9 – ECG and ambulatory ECG recording</li> <li>- Week 12 – Clinical evaluation and echocardiogram</li> <li>- Week 12-15 – Initiation of intervention (RFA or AADs)</li> <li>- Week 21 – Clinical evaluation</li> <li>- Every 3 months after RFA or AADs (week 38, 50 and 64) – Clinical assessment with occasional testing (echocardiogram and ambulatory ECG recording)</li> <li>- Week 64 – Complete protocol.</li> </ul> <p>All visits and testing are clinically indicated and considered standard of care. Most of these subjects receive this follow up regardless of participation in the study.</p>
<p><b>Study Duration</b></p>	<p>Study duration is approximately 36 months.  Each subject will be followed for at least 15 months, which includes a 3-month observation period and 12months after intervention is initiated.</p> <ul style="list-style-type: none"> <li>- Enrollment and subject follow up of all subjects is estimated to be completed within 3 years.</li> </ul>
<p><b>Key Inclusion Criteria</b></p>	<ul style="list-style-type: none"> <li>- LV dysfunction (calculated LVEF <math>\leq</math>45% based on Echo) within 150 days of Enrollment (Day 0)</li> <li>- Average PVC burden <math>\geq</math> 10 % by at least a 24-hr ambulatory ECG monitor (within 150 days of Enrollment (Day 0)</li> </ul>

<b>Key Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>- Age &lt; 18 years old</li> <li>- Current amiodarone use or within last 2 months</li> <li>- Current use of any antiarrhythmic drug class I or III</li> <li>- Contraindication to use amiodarone or any other class III antiarrhythmic</li> <li>- Severely symptomatic PVCs (defined as incapacitating palpitations or pre-syncope) and unable to complete a 3-month observation period</li> <li>- Severe/ significant CAD with planned revascularization in the near future</li> <li>- Complete AV block and pacemaker dependent</li> <li>- Pacemaker or ICD with &gt; 10% of right ventricular pacing</li> <li>- Severe valvular heart disease or planned valvular/cardiac surgery</li> <li>- Uncontrolled or untreated endocrinopathies</li> <li>- Uncontrolled HTN systolic (BP &gt; 180mmHg or diastolic &gt;110 mmHg)</li> <li>- Hypertrophic cardiomyopathy</li> <li>- Systemic infiltrative and immune disorders</li> <li>- Family history of dilated CM in a first degree relative</li> <li>- Alcohol abuse or illicit drug use</li> <li>- Contraindication to short-term acute anticoagulation (due to possible randomization to RFA)</li> <li>- Atrial fibrillation and flutter with Rapid VR with possible tachycardia-induced cardiomyopathy</li> <li>- Pregnant or lactating women</li> <li>- Possible infectious etiology of cardiomyopathy</li> <li>- Previous PVC ablation</li> </ul>
<b>Statistical Methods</b>	
<b>Primary hypothesis</b>	<p>1) A large-scale randomized PAPS clinical study is feasible with minimal barriers of enrollment, treatment crossover and drop out due to a <i>unique design</i> including a short observation period and PVC suppression strategy in all participants.</p> <p>2) The <u>rate of responders (defined as improvement of LVEF <math>\geq</math> 10% points)</u> with HF medical therapy alone during observation period will be less than 15% <i>in subjects with CM associated with frequent PVCs</i>. In contrast to HF medical therapy alone, RFA and AADs will have a responder rate of <i>at least 35% in the same population</i>. <i>Furthermore, RFA will have a greater 1-year response rate when compared to AAD therapy.</i></p> <p>3) <i>RFA will have a lower rate of composite adverse events (worsening NYHA class, HF admission, treatment side effects &amp; complications, and death), arrhythmia burden and a better long-term tolerance than AADs.</i></p>
<b>Sample Size</b>	<p><i>This has been estimated solely on primary end-point of improvement in LV ejection fraction between PVC suppression strategies (RFA vs. AADs groups). Assuming that subjects would have a LVEF level of 25% (SD=5%) in each of the groups at baseline and LVEF levels of 40% and 35% (SD=10%) in the RFA and AAD groups at 12 months, respectively. A within subject correlation of 0.25 was assumed along with an inter-site standard-deviation of 1%. <u>This model was fit assuming that, on average, 10% of the subjects would drop out randomly.</u> Approximately 140 total subjects (70 per group) should be enrolled to reject the null hypothesis that the mean LVEF between RFA and AAD groups are equal with probability (power) 0.8 and Type I error probability of 0.05. <u>As a pilot study we have determined to enroll at least 20% (30 subjects) of preliminary sample size estimation to understand feasibility and key aspects of subject enrollment, randomization and retention to properly power a large-scale randomized PAPS study.</u> Sample size is increased</i></p>

	by 15% (6 additional subjects, between 36-39 subjects total – 19 to 20 subjects in each treatment group) to take into account possible spontaneous improvement of LV dysfunction during 3-month observation period between treatment strategies.
<b><u>Part II</u> - Prevalence of PVC- Cardiomyopathy in the overall ambulatory Holter population</b>	
<b>Study / Objectives</b>	Estimate the prevalence of cardiomyopathy (CM, LVEF $\leq$ 45%) and frequent premature ventricular contractions (PVCs $\geq$ 10%) in the overall population receiving ambulatory ECG Holter monitors.
<b>Primary hypothesis</b>	The prevalence of CM (LVEF $\leq$ 45%) and frequent PVCs ( $\geq$ 10% burden) is largely under recognized in subjects undergoing ambulatory ECG Holters.
<b>Study Design and duration</b>	Multicenter prospective and retrospective population-based database of all subjects undergoing ambulatory ECG monitor during 24-month period.
<b>Eligible subjects</b>	All-comers undergoing at least a 24-hr ambulatory ECG monitor for any clinical indication
<b>Planned number of subjects</b>	A total of 20,000 ambulatory ECG monitors – 1,500 subjects per center (to be completed within 24 months).
<b>Planned number of participating sites/ countries</b>	At least 12 centers in the United States and one in Canada

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## List of Abbreviations

AADs	Antiarrhythmic Drugs
AE	Adverse Events
AV	Atrio-ventricular
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CCB	Calcium Channel Blockers
CCTR	Clinical Center for Translational Research
CM	Cardiomyopathy
CMR	Cardiac Magnetic Resonance
CRF	Case Report Form
CRP	C-reactive Protein
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECV	Extracellular volume fraction
EPS	Electrophysiologic study
ESR	Erythrocyte sedimentation rate
FS	Fractional Shortening
HF	Heart Failure
HTN	Hypertension
ICD	Implantable cardioverter defibrillator
LA	Left atrium
LFTs	Liver Function Tests
LV	Left Ventricle
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic dimension
LVESD	Left ventricular end-systolic dimension
MR	Magnetic resonance
MV	Mitral Valve
NYHA	New York Heart Association
Obs	Observation
OMT	Optimal Medical Therapy
PAPS	Prospective Assessment of PVCs Suppression
PI	Principal Investigator
Pro-BNP	Pro-brain Natriuretic Peptide
PVC	Premature Ventricular Contractions
PVC-CM	PVC-Cardiomyopathy
QOL	Quality of Life
R	Randomization
REDCap	Research Electronic Data Capture
RFA	Radiofrequency Ablation
SAE	Severe Adverse Events
SCD	Sudden Cardiac Death
SD	Standard Deviation
TSH	Thyroid Stimulating Hormone
VCU	Virginia Commonwealth University
VR	Ventricular response
Zio	Ziopatch (IRhythm) ambulatory ECG Holter monitor

# **PROSPECTIVE ASSESSMENT OF PVC SUPPRESSION IN CARDIOMYOPATHY (PAPS):**

## **A Pilot Study**

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### **PROJECT SUMMARY / ABSTRACT**

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Premature ventricular contractions (PVCs) coexist in subjects with heart failure (HF) and LV dysfunction. Frequent PVCs have been shown to induce a reversible cardiomyopathy (PVC-CM). Yet, it is unclear why some subjects develop PVC-CM, while others do not. Retrospective and observational studies have shown improvement of LV function after PVC suppression via radiofrequency ablation (RFA). Thus, appropriate diagnosis and treatment of subjects with PVC-CM is believed to carry significant benefits, improving quality of life (QOL), HF symptoms / admissions and life expectancy. Currently, these subjects are offered RFA, antiarrhythmic drugs (AADs) or no treatment depending on physician's experience and resources. Thus, there is clear need for a large clinical trial comparing these treatment strategies. Yet, we need to better understand the prevalence of PVC-CM, feasibility and limitations of such a trial.

**Research Design and Methods.** We propose a clinical pilot study, enrolling between 36-39 subjects with frequent PVCs (burden  $\geq 10\%$ ) and CM (LVEF  $\leq 45\%$ ) and randomize them to either: 1) RFA or 2) AADs. Prior to treatment, a baseline cardiac MR will be requested if clinically indicated followed by a 3-month observation period. We plan to follow changes in LV function/scar, PVC burden/arrhythmias and clinical/functional status (QOL, HF symptoms and admissions, NYHA class) and adverse events throughout the observation period and compare with PVC suppression strategies (RFA or AAD). Similar comparison will be made between RFA and AAD treatment groups during a 12-month follow up using a Prospective Randomized Open, Blinded End-point (PROBE) study design. The treatment regimens will be compared in an intention-to-treat analysis.

In addition, we plan to screen 20,000 consecutive ambulatory ECG Holter monitors of all participating centers (1,500 per participating center) to identify all subjects with probable diagnosis of PVC-CM (PVC burden  $> 10\%$  and LVEF  $< 45\%$ ).

This pilot study is intended to estimate the prevalence of this clinical entity and pave the way for a large full scale randomized trial to identify the best treatment strategy for subjects with PVC-CM. Treating and reversing this underestimated PVC-CM may improve subject's health and subsequently decrease HF healthcare spending.

# **PROSPECTIVE ASSESSMENT OF PVC SUPPRESSION IN CARDIOMYOPATHY (PAPS):**

## **A Pilot Study**

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### **SPECIFIC AIMS**

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**Rationale.** Premature ventricular contractions (PVCs) are commonly associated with heart failure (HF) and cardiomyopathy (CM). Frequent PVCs have been shown to induce a reversible cardiomyopathy (PVC-CM)<sup>4-7</sup>. Yet, it is unclear why some subjects develop PVC-CM, while others do not. *Recent publications*<sup>8,9</sup> *have demonstrated an incidence of systolic HF of 62.8 (95% CI 61.2 to 64.4) per 1,000 subject years among those with PVCs during a 5-year period and an overall age- and sex-adjusted incidence of PVC-CM of 2.6 per 100,000 (95% CI 1.6-3.5).* Appropriate diagnosis and treatment of subjects with PVC-CM is believed to carry significant benefits, improving quality of life (QOL), HF symptoms / admissions and life expectancy. *Currently, these subjects are offered radiofrequency ablation (RFA), antiarrhythmic drugs (AADs) or no treatment depending on physician's experience and resources.*<sup>4-6,10</sup>. Nevertheless, no randomized-prospective study exists to support the benefit of RFA. *Thus, there is clear need for a large-scale multicenter randomized clinical trial comparing these treatment strategies, which we plan to launch entitled "Prospective Assessment of PVC Suppression in Cardiomyopathy (PAPS) Study". However, we need to better understand the prevalence of PVC-CM, feasibility and limitations of such a trial.*

Thus, we propose a PAPS pilot study using a multidisciplinary team approach to better estimate the potential affected subject population, limitations of enrollment, rate of clinical outcomes, potential crossover and drop out. This pilot study is key to better design and power the large-scale multicenter PAPS trial.

**Aim 1 (Part I).** PAPS pilot randomized trial: to assess the feasibility of enrolling, randomizing treatment strategies and retaining participants with frequent PVCs and associated CM.

**Aim 2 (Part II).** Estimate the prevalence of CM (LVEF  $\leq$  45%) and frequent PVCs ( $\geq$ 10%) in the overall population receiving ambulatory ECG Holter monitors.

**Hypotheses.** Our main hypotheses of the PAPS pilot study are:

- 1) A large-scale randomized PAPS clinical study is feasible with minimal barriers of enrollment, treatment crossover and drop out due to a *unique design* including a short observation period and PVC suppression strategy in all participants.
- 2) The rate of responders (defined as improvement of LVEF  $\geq$  10% points) with HF medical therapy alone during observation period will be less than 15% *in subjects with CM associated with frequent PVCs*. In contrast to HF medical therapy alone, RFA and AADs will have a responder rate of *at least 35% in the same population*. *Furthermore, RFA will have a greater 1-year response rate when compared to AAD therapy.*
- 3) *RFA will have a lower rate of composite adverse events (worsening NYHA class, HF admission, treatment side effects & complications, and death), arrhythmia burden and a better long-term tolerance than AADs.*
- 4) The prevalence of CM (LVEF  $\leq$  45%) and frequent PVCs ( $\geq$ 10% burden) is largely under recognized in subjects undergoing ambulatory ECG Holters (Part II).

**Methods.** To test our hypotheses, we propose: 1) a clinical pilot study to prove the feasibility of a large-scale multicenter clinical trial (PAPS study) of subjects with probable PVC-CM, and 2) screen near 20,000 consecutive ambulatory ECG Holter monitors of all participating centers to identify all subjects with probable diagnosis of PVC-CM (PVC burden  $\geq$ 10% and LVEF  $\leq$ 45%). The clinical pilot study will enroll between 36-39 subjects with frequent PVCs (burden  $\geq$ 10%) and CM (LVEF  $\leq$ 45%) and randomize them to either: 1) RFA or 2) AADs. Prior to treatment, a baseline cardiac MR will be performed if clinically indicated and be allowed a 3-month observation period. To assess the effects of PVC suppression, we plan to compare changes in LV function, rate of responders (defined above), PVC burden/arrhythmias and clinical/functional status (QOL, HF symptoms and admissions, NYHA class) and adverse events between observation period both PVC suppression strategies (RFA or AAD).

To identify the best PVC suppression strategy, we will perform similar comparisons between RFA and AAD treatment groups during a 12-month follow up using a Prospective Randomized Open, Blinded End-point (PROBE) study design. The treatment regimens will be compared in an intention-to-treat analysis.

Our study is *unique due to its multidisciplinary approach and design* including: 1) observation/control period that allows us to assess for spontaneous improvement of PVCs and/or CM, and 2) active treatment to all subjects, which will allow for easier subject enrollment and retention with minimal drop out.

*In summary, the multicenter PAPS pilot study is intended to better estimate the prevalence of PVC-CM, prove feasibility and rates of clinical outcomes. This pilot study with a multidisciplinary approach will pave the way for a large-scale randomized PAPS trial to identify the best treatment strategy for subjects with PVC-CM. Treating and reversing PVC-CM with its associated HF morbidity and mortality will impact not only healthcare spending, but most importantly it will improve patient's health, quality of life and long-term prognosis.*

# PROSPECTIVE ASSESSMENT OF PVC SUPPRESSION IN CARDIOMYOPATHY (PAPS):

## A Pilot Study

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### INTRODUCTION

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Premature ventricular contractions (PVCs) are commonly associated with heart failure (HF), cardiomyopathy (CM), ventricular arrhythmias and sudden cardiac death (SCD)<sup>4-7,11,12</sup>. Several studies have shown that the frequency of PVCs correlate at least modestly with the extent of LV dysfunction and ventricular dilation at the time of initial clinical presentation<sup>4,5,13-15</sup>. Moreover, case reports<sup>16,17</sup> and retrospective studies<sup>4,5,7,10,15,18-21</sup> have found a reversal of CM after elimination of PVCs; leading to the description of a reversible CM referred to as “PVC-induced CM” (PVC-CM). Some of these studies have also noted independent predictors for PVC-CM such as high PVC frequency (PVC burden greater than 10%), male gender and epicardial location<sup>7,22</sup>. Yet, some subjects do not develop a CM even with similar features. Thus, it is likely that other subject’s characteristics and/or PVC features play a role in the pathophysiology of PVC-CM. A challenge is to identify when PVCs are the etiology of a CM or just “innocent bystanders” in subjects with CM. Even if PVCs are the result of CM, PVCs may contribute and further worsen CM and HF symptoms<sup>10,23</sup>.

PVCs in a 60-second 12-lead ECG are found in 1% to 4% of subjects without heart disease. However, the prevalence of PVCs is significantly higher in ambulatory ECG recordings, (40% and 75% of participants on 24- to 48-hour ambulatory Holter monitoring)<sup>6</sup>. This can be explained due to a significant variability of PVC frequency with time<sup>24</sup>. It is not surprising that a 2-week ECG ambulatory recording is ideal to determine more accurately the PVC frequency<sup>25</sup>.

A recent retrospective analysis of the Cardiovascular Health study (CHS)<sup>12</sup> in subjects with normal cardiac function demonstrated an adjusted odds ratio of 3.10 and hazard ratio of 1.48 and 1.31 to develop LV dysfunction, CHF and mortality in subjects within the highest PVC quartile (PVC burden 0.123 - 17.7%). This supports frequent PVCs as a significant and modifiable risk factor for HF and increased mortality.

*PVC-CM is probably underestimated. A recent retrospective study<sup>7</sup> of 245 subjects with non-ischemic CM and frequent PVCs (mean PVC burden 20 ± 13%) demonstrated improvement of LV function in 67% of subjects after radiofrequency ablation (RFA). The mean improvement of LV function after RFA in most studies ranges from ≥ 12-15%<sup>7,22,26</sup>. Similarly, a prospective study of 66 subjects with LVEF <35% (ischemic and non-ischemic) with ICD indication and PVC burden >4% demonstrated that 24% of subjects had a complete normalization of LVEF after eliminating PVC via RFA, resulting in subsequent absence of an indication for ICD implantation in 38 and 42 subjects (57 and 63%) at 6- and 12-month follow up, respectively.<sup>26</sup>*

Currently, a PVC suppression strategy with RFA or antiarrhythmic drugs (AADs) is a widely accepted intervention to treat a CM that might be secondary to frequent PVCs. Nevertheless, no randomized-prospective study has compared the effectiveness and benefit of different PVC suppression strategies. Furthermore, the clinical outcomes associated with PVC suppression strategies in PVC-CM and the PVC features (e.g. coupling interval, location, QRS duration) prone to induce CM are unknown. Current literature speculates that elimination of PVCs may be a modifiable risk factor for heart failure and cardiovascular events including death.<sup>12</sup>

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## SIGNIFICANCE

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Approximately, 6.6 million patients in the U.S. had heart failure (HF) in 2010 and more than one million hospital admissions were associated with HF in 2009. HF incidence in age group >45 years of age increases yearly with an estimated 650,000 new cases each year, approaching 10 cases per 1000 population after 65 years of age<sup>2</sup>. PVCs are highly prevalent in subjects with CM and HF, and they have been recently identified as a potential cause of a reversible CM<sup>6</sup>. Most recent *publications*<sup>8,9</sup> of large population-based cohorts have estimated an incidence of systolic HF of 62.8 (95% CI 61.2 to 64.4) per 1,000 subject years among those with PVCs during a 5-year period and an overall age- and sex-adjusted incidence of PVC-CM of 2.6 per 100,000 (95% CI 1.6-3.5) with a similar age-adjusted incidence by gender (2.4 and 2.7 per 100,000 in females and males respectively). The true prevalence of CM and HF induced by PVCs is unknown, but it has been long suspected to be underestimated since the prevalence of PVCs increases with age and PVC-CM appears to develop in a time-dependent manner<sup>6</sup>. At 40 years of age, the lifetime risk of developing HF for both men and women is 1 in 5<sup>2</sup>, and PVCs could well contribute to the development of some instances of CM and HF<sup>6</sup>.

This project will address these two common chronic cardiac conditions, CM and ventricular ectopy (PVCs). Only retrospective/observational studies have supported that LV dysfunction or CM can be restored after elimination of frequent PVCs, so called PVC-CM<sup>5,10</sup>. However, there is no prospective randomized study that demonstrates PVC suppression using radiofrequency ablation (RFA) to be superior to standard medical therapy, yet most practitioners offer RFA to patients with high PVC burden.

Since 1998, several case reports and retrospective and observational studies have shown that radiofrequency ablation (RFA) of frequent PVCs in patients with LV dysfunction can improve LV function. However, it is unclear who is susceptible to develop PVC-CM, but most importantly who will respond to PVC suppression. Furthermore, the best PVC suppression strategy (RFA vs. AADs) to improve LVEF and outcomes has not yet been elucidated. For that reason, clear guidelines of treatment of frequent PVCs with associated CM are not available and treatment can be quite variable between EP physicians.

To better understand the difference of treatment in patients with CM and frequent PVCs, we conducted a 12-question survey with different clinical scenarios. A total of 155 cardiac electrophysiologists (EP) within the United States answered this survey. It was quite clear that the management of a single patient is quite different between electrophysiologists. For instance, a patient with LV dysfunction (LVEF 45%) with frequent asymptomatic PVCs (25% burden) would receive conservative management (HF therapy only) by 50% of physicians, whereas the remaining 18.8% and 29.9% of doctors would treat this patient with antiarrhythmic drugs or RFA, respectively. Yet if the same patient (20% PVC burden) had a lower LVEF of 35%, 23% of EP physicians would continue to treat conservatively, while 64% and 12% of EP doctors would recommend RFA and AADs, respectively. Furthermore, if this patient had stable CAD, more physicians (35%, 12% absolute increase) would recommend conservative management, while 50% and 17% of doctors would recommend RFA or AADs, respectively.

Over the past few years it has become clear that comparative effectiveness trials to understand how to best treat subjects with frequent PVCs and CM are needed<sup>12,26</sup>. *Thus, we propose a multicenter study to better understand the prevalence of frequent PVCs and CM, as well as conduct a clinical pilot study to: 1) prove feasibility of a large-scale randomized clinical trial, 2) determine rate of improvement of LV function (responders), cardiovascular and adverse events in both RFA and AADs treatments and 3) determine the rate of spontaneous improvement of LV function (during observation period). Understanding the prevalence of PVC-CM will give us a better perspective of the magnitude of this clinical entity, while the prospective pilot study will allow us to properly design and power a large multicenter prospective randomized study, the Prospective Assessment of PVC Suppression (PAPS) study.*

PVC-CM, as any CM, leads to HF admissions and implant of internal cardiac defibrillators and cardiac resynchronization devices<sup>6,27</sup>, which likely translates into increased healthcare costs. Therefore, appropriate diagnosis and treatment of PVC-CM will not only reverse LV dysfunction with its associated HF morbidity, mortality and healthcare spending, but most importantly improve subject's health, quality of

life and long-term prognosis. A better understanding of the PVC features required to induced CM and the clinical impact of RFA and AADs could help us prevent and better target therapy in those subjects with PVC-CM<sup>6</sup>.

### **Impact of proposed PAPS pilot study**

This study will not only generate data to demonstrate the need of a clinical trial, but also to better design our large-scale multicenter randomized clinical trial, the PAPS study.

This grant application with a multidisciplinary approach intends to:

- 1) *Identify the prevalence of subjects with potential PVC-CM ( $\geq 10\%$  PVC burden and LVEF  $\leq 45\%$ ) in the overall population receiving Holters in participating tertiary high-volume centers.*
- 2) *Identify demographics, rate and limitations of enrollment, rate of responders (defined as improvement of LVEF  $\geq 10\%$ ; rationale found in Section: Approach – Study Design: Aim 2) during observation period and active PVC suppression, and potential crossover between PVC suppression arms (RFA and AADs).*
- 3) *Understand the feasibility and better design and power a large multicenter trial (PAPS Study).*

Thus, the proposed pilot study will pave the way for a large-scale multicenter randomized PAPS study to identify the best treatment strategy for subjects with PVC-CM.

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## INNOVATION

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Both RFA and AADs are current therapies used to suppress frequent PVCs. While other studies registered in clinicaltrials.gov compare RFA versus optimal HF medical therapy in a similar population, our study includes 3 types of innovations:

- 1) **Clinical innovation** by a) identifying the prevalence of PVC-CM in a specific population and identify the safest and effective therapy to improve clinical outcomes, and b) comparing PVC strategies of RFA to AADs and include secondary end-points such as adverse events, arrhythmia burden and clinical outcomes (New York Heart Association class, quality of life, HF admissions, and need for ICD implants).
- 2) **Trial design innovation** by incorporating a 3-month observational period, which allows: a) each subject to serve as his/her own control when we compare to PVC suppression strategy, whether RFA or AADs, and b) assess natural history and the rate of spontaneous resolution of PVCs and/or CM.
- 3) **Mechanistic innovation** with cardiac magnetic resonance (CMR) imaging to ascertain baseline myocardial tissue characteristics (indicative of interstitial versus replacement fibrosis) and LV contraction patterns to identify potential mechanisms of lack of response despite PVC suppression.

***PAPS pilot randomized trial: to assess the feasibility of enrolling, randomizing treatment strategies and retaining participants with frequent PVCs and associated CM.***

The lack of treatment guidelines of PVC suppression results in the use of different treatment strategies or no treatment at all of subjects with possible PVC-CM, which is solely based on personal physician's experience and availability rather than outcomes.

**A. Study Population and Eligibility**

This is a prospective randomized pilot study including between 36-39 subjects with cardiomyopathy (CM) and high PVC burden with a likely diagnosis of PVC-CM<sup>6</sup>, where all subjects will be assigned to a 1:1 random allocation to one of two un-blinded PVC suppression groups: 1) PVC radiofrequency ablation (RFA) vs. 2) antiarrhythmic drugs (AADs).

**Definitions:**

The *diagnosis criteria for PVC-CM* is based on LVEF  $\leq$  45% (by echocardiography) and average PVC burden  $\geq$  10% in an ambulatory ECG Holter monitor that meet the inclusion and exclusion criteria (Table 1), regardless of severity and time of onset. LVEF and PVC burden must be within 150 days of Enrollment Visit (Day 0).

*Responders are defined as an LVEF increase greater than 10% points regardless of intervention.*

If screening confirms eligibility (LVEF  $\leq$ 45% and PVC burden  $\geq$  10%), a baseline visit will be scheduled to obtain subject's demographics and medical history, 12-lead ECG, Minnesota living with HF quality of life (QOL) questionnaire, NYHA functional class and cardiac magnetic resonance (CMR) if clinically indicated. Subjects that refuse enrollment, will be asked to participate in a PVC-CM registry to follow their response and crossover to different treatment strategies.

If subjects meet inclusion criteria (Table 1) during screening, informed consent should be obtained. Stratified randomization to either RFA or AADs will be performed at the time of enrollment (baseline visit, week 0). Based on our preliminary data, we expect that around 30% of subjects will have a PVC burden  $>$ 20%<sup>5</sup>. Thus, a *stratified randomization based PVC burden (assessed by Holter) above and below 20% is needed to assure that subjects in both groups (RFA vs. AAD) are equally distributed between PVC burden above and below 20%.* Stratified randomization will be performed using approved software available at the Coordinating Center only.

If a subject is randomized to the RFA arm, a RFA procedure (Visit 1) should be scheduled at the time of randomization due to usual 8-week next available RFA appointment in most participating centers. Yet both, RFA and AAD interventions should only occur or be initiated after completion of a 3-month observation (Table 2 - Visit Tx-V1, week 12-15).

A 3-month observation period will assess spontaneous variation of PVC burden and improvement or deterioration of LV function. During the final 3-month observation visit (Week 12), LVEF and Holter will be repeated to confirm eligibility if PVC burden and LVEF remains  $\geq$ 10% and  $\leq$ 45%, respectively.



## Table 1. Inclusion and Exclusion Criteria.

### Inclusion Criteria

1. LV dysfunction (calculated\*\* LVEF  $\leq$ 45% based on Echo) within 150 days of Enrollment Visit (Day 0)
2. Average PVC burden  $\geq$  10% by ambulatory ECG Holter monitor within 150 days of Enrollment Visit (Day 0)

**\*\*If only the estimated LVEF is available at time of enrollment, request calculated LVEF within five days of enrollment**

### Exclusion Criteria

1. Age < 18 years old
2. Current Amiodarone use or within last 2 months
3. Current use of any antiarrhythmic drugs class I or III
4. Contraindication to use amiodarone or any other class III antiarrhythmic
5. Severely symptomatic PVCs (defined as incapacitating palpitations or pre-syncope) unable to complete a 3-month observation period
6. Severe/significant CAD with planned revascularization in the near future
7. Complete AV block and pacemaker dependent
8. Pacemaker or ICD with > 10% of right ventricular pacing
9. Severe valvular heart disease or planned valvular/cardiac surgery
10. Uncontrolled or untreated endocrinopathies
11. Uncontrolled HTN (systolic >180 mmHg or diastolic > 110 mmHg)
12. Hypertrophic cardiomyopathy
13. Systemic infiltrative and immune disorders
14. Family history of dilated CM in a first-degree relative
15. Alcohol abuse or illicit drug use
16. Contraindication to short-term anticoagulation (due to possible randomization to RFA)
17. Atrial fibrillation and flutter with Rapid VR with possible tachycardia-induced cardiomyopathy
18. Pregnant or lactating women
19. Possible infectious etiology of cardiomyopathy
20. Previous PVC ablation

*If both PVC and/or LVEF criteria are not met after the observation period, the subject will be withdrawn from the study and treatment will be as recommended by primary provider. We will ask the subject to participate in a PVC-CM registry with assessment of PVC burden and LVEF as clinically indicated during the following 12-month study. When allowed by the IRB, informed consent will include an option for participation in this registry as a contingency in case subjects no longer meet criteria or decide to withdraw participation. These subjects will continue treatment as recommended by their local clinical electrophysiologist.*

**Table 2. Table of Study Procedures**

	3-month Observation			12-month Treatment Phase					
	Obs-V1 Baseline	Obs-V2 2-mo	Obs-V3 3-mo	Tx-V1 Baseline	Tx-V2 1-mo	Tx-V3 3-mo	Tx-V4 6mo	Tx-V5 9-mo*	Tx-V6 12-mo
Timeline in Weeks (range of days)	Week 0 (Day 0)	Week 9 (51-63)	Week 12 (84-96)	Week 12-15 (84-105)	Week 21 (141-153)	Week 26 (176-188)	Week 38 (260-272)	Week 50 (344-356)	Week 64 (441-454)
Informed consent	X								
Inclusion/Exclusion Criteria	X								
Collection of demographic data	X								
Medical History	X								
Physical Exam	X		X		X	X	X	X	X
Functional status/NYHA class	X		X		X	X	X	X	X
QOL Minnesota HF Questionnaire	X		X		X	X	X	X	X
Current / change of medications	X		X		X	X	X	X	X
12-lead ECG	X*	X*	X		X*	X*	X*	X*	X*
Ziopatch	X	X <sup>‡</sup>			X <sup>€</sup>	X	X		X
Echo	X <sup>£</sup>		X <sup>‡</sup>			X	X*		X
BNP / ProBNP levels ESR & CRP	X* <sup>£</sup>		X*		X*	X*	X*	X*	X*
Urine pregnancy test (if applicable)	X		X	X	X	X	X	X	X
CMR	X*								
TSH (if assigned to amiodarone)			X				X		X
LFT (AST) (if assigned to amiodarone)			X				X		X
Treatment randomization	X								
Initiation of RFA or ADD				X					

<b>Collection of unsolicited AEs</b>	From Obs-Visit 1 until Tx-Visit 6
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Footnote: \*, visit/intervention if clinically indicated.

‡ LVEF results of 2D-echocardiogram and Ziopatch have to be available at the time of Observation Visit 3 (Obs-V3). € If PVC burden >10%, subject should be considered to either adjust antiarrhythmic therapy (AAD group) or second ablation procedure (RFA group) based on their randomization group. ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein. £ Must be done within 150 days of Enrollment Visit (Day 0)

Crossover between PVC suppression strategies is not encouraged. We request that crossover only be considered after 6 months of initiation of treatment, for which an intention-to-treat analysis will be performed. However, if crossover occurs before 6 months of initiation of treatment, subjects will be withdrawn from the study and included in the PVC-CM registry if the subject provided consent.

Every effort will be made to have females enter this study. Medically accepted birth control is required to enter this study. This may include, but is not limited to, birth control pills, IUD's, condoms, diaphragms, implants, being surgically sterile, or being in a post-menopausal state. However, no birth control method completely eliminates the risk of pregnancy and potential risk of miscarriage, birth defects, other medical complications or unforeseen risks to subject or to the unborn baby (i.e. embryo or fetus) is possible if pregnancy occurs during the study. Any female of childbearing age must have a negative pregnancy test before entering the study.

A pregnancy test will be obtained on females of childbearing age that are assigned to the RFA treatment prior to procedure due to fluoroscopy exposure. In contrast, a pregnancy test will be performed on a monthly basis on those randomized to the antiarrhythmic treatment arm to confirm the lack of pregnancy throughout the 12-month follow up. If a female on the antiarrhythmic arm becomes pregnant during the 12-month follow up we will consider stopping antiarrhythmics and the subject will be withdrawn from the study.

Thus, subjects that no longer meet criteria after the 3-month observation period, those that crossover before 6 months of treatment initiation or become pregnant during the study will be included in the PVC-CM registry if the subject provided consent. Subjects that refuse participation in this portion of the study (Part I) will also be included in the PVC-CM registry if they provide consent.

**A.1. PVC-CM registry.** This registry will consist of patients that: 1) refuse to participate in the randomized treatment protocol, 2) no longer meet criteria after 3-month observation, 3) crossover before 6 months of treatment initiation, or 4) become pregnant during the study. When allowed by the IRB, informed consent will include an option for participation in this registry as a contingency in case subjects no longer meet criteria, become pregnant, crossover treatment arms or decide to withdraw from the study. A separate informed consent to participate in this registry will be provided only for those patients that refuse participation in the randomized treatment study (main study). Data will be collected at Baseline (day subject refuses enrollment in the randomized study), 6 and 12 months for these subjects. Alternately, subjects included in this PVC-CM registry who screen fail or withdraw early for any reason, will have data collected only by chart review at 6 and 12 months after withdrawing from the study. Data to be collected will include demographics, past medical history, treatment interventions including outcomes and related complications, NYHA functional status, 12-lead ECG, ambulatory ECG Holter including heart rate, PVC burden and arrhythmia burden, echocardiographic data including LVEF, medications and cardiac-related hospital admissions. The purpose of this registry is to assess different treatment options offered to patients with this medical condition in the “real world” as well as the clinical response to these treatments.

## **B. Scheduled Visits**

When a subject is first identified during a visit or when reviewing a 24-48 hour or 2-week ambulatory ECG monitor (Zio Patch), we request that sites briefly screen the subject by reviewing the inclusion/exclusion criteria of the protocol. Assessment of calculated LVEF (obtained by transthoracic echocardiogram) and PVC burden is acceptable as long as it has been obtained within the prior 150 days. If the subject meets both, then the subject should be scheduled for a Baseline Visit (Observation – Visit 1).

Subjects enrolled in the study will have visits as outlined in Table 2 and Figure 1. There are some circumstances where the screening and Observation Visit 1 may occur the same day.

*i. Observation – Visit 1.* After inclusion/exclusion criteria is confirmed, the study protocol will be explained to the subject and informed consent should be obtained. If the subject agrees to participate, the following data should be collected using appropriate forms (see Data collection forms), including general info and demographics, current medical therapy, physical exam, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). Physical examination and NYHA functional class can be completed

based on a prior visit (up to 120 days prior). A 12-lead electrocardiogram and cardiac MR should be requested if clinically indicated. Alternatively, we will request that sites provide images of prior ECG or CMR if performed within the prior 120 days. Sites should obtain a copy of the transthoracic echo (during screening Visit) and mail it to the Echo Core laboratory led by Dr. John Gorcsan III, M.D. The Echo report should be uploaded to REDCap. Finally, a 2-week Zio Patch (IRhythm ambulatory ECG device) should be placed on the subject to obtain a long-term PVC burden. The subject will mail the device to IRhythm for analysis. Instructions will be provided to all centers on the placement of this device.

During this 3-month observation period, all subjects are allowed to titrate medical therapy to be optimized or continue on *optimal medical therapy* throughout the study. We define *optimal medical therapy* as maximal tolerated/recommended target doses of beta blockers (carvedilol 25mg twice daily, metoprolol succinate / tartrate 200mg daily or bisoprolol 10mg daily), angiotensin converting enzyme (ACE) inhibitors (lisinopril 20-40mg daily, ramipril 10mg daily, enalapril 10-20mg twice daily or quinapril 40mg twice daily) or angiotensin receptor blockade (ARB, valsartan 160mg twice daily or candesartan 32mg daily), aldosterone antagonists (spironolactone 25mg daily or eplerenone 25mg daily) and loop diuretics if indicated to achieve dry weight<sup>28</sup>. Entresto (sacubitril 49-97mg/valsartan 51-103mg bid) could be used if clinically indicated. Except for non-dihydropyridine calcium-channel blockers (CCB, amlodipine and felodipine), diltiazem, verapamil, and nifedipine (dihydropyridine CCB) are not allowed during the study due to negative inotropic effect. Class Ia AADs will not be allowed during study due to risk of proarrhythmia.

During this visit, randomization to either antiarrhythmic drugs (AADs) or radiofrequency ablation (RFA) will be obtained. If the subject is assigned to the RFA arm, we request that the RFA procedure be scheduled at 3-months from this visit (Treatment – Visit 1). All subjects should be optimized or continue current medical therapy without change. If the subject is randomized to antiarrhythmic therapy (see Section C: Description of the intervention/treatment), this should be withheld until the 3-month observation period is completed.

ii. *Observation – Visit 2.* During this visit, subjects are asked to return to have a repeat Zio Patch (2-week ECG monitor) and ECG (if clinically indicated). Similarly, subjects will be instructed to mail back the Zio Patch to IRhythm, for assessment of PVC burden. At this time, a transthoracic echocardiogram should be scheduled in preparation for Observation – Visit 3.

iii. *Observation – Visit 3.* Similar to Visit 1, appropriate data collection forms should be used to collect current medical therapy, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). 12-lead ECG should be obtained if clinically indicated. Transthoracic echocardiogram should be performed to assess LVEF and a copy mailed to the Echo Core laboratory led by Dr. John Gorcsan III, M.D. The local PI and designated site staff will be able to log in to iRhythm's ZioReports to obtain the Zio Patch report that should include a 2-week PVC burden.

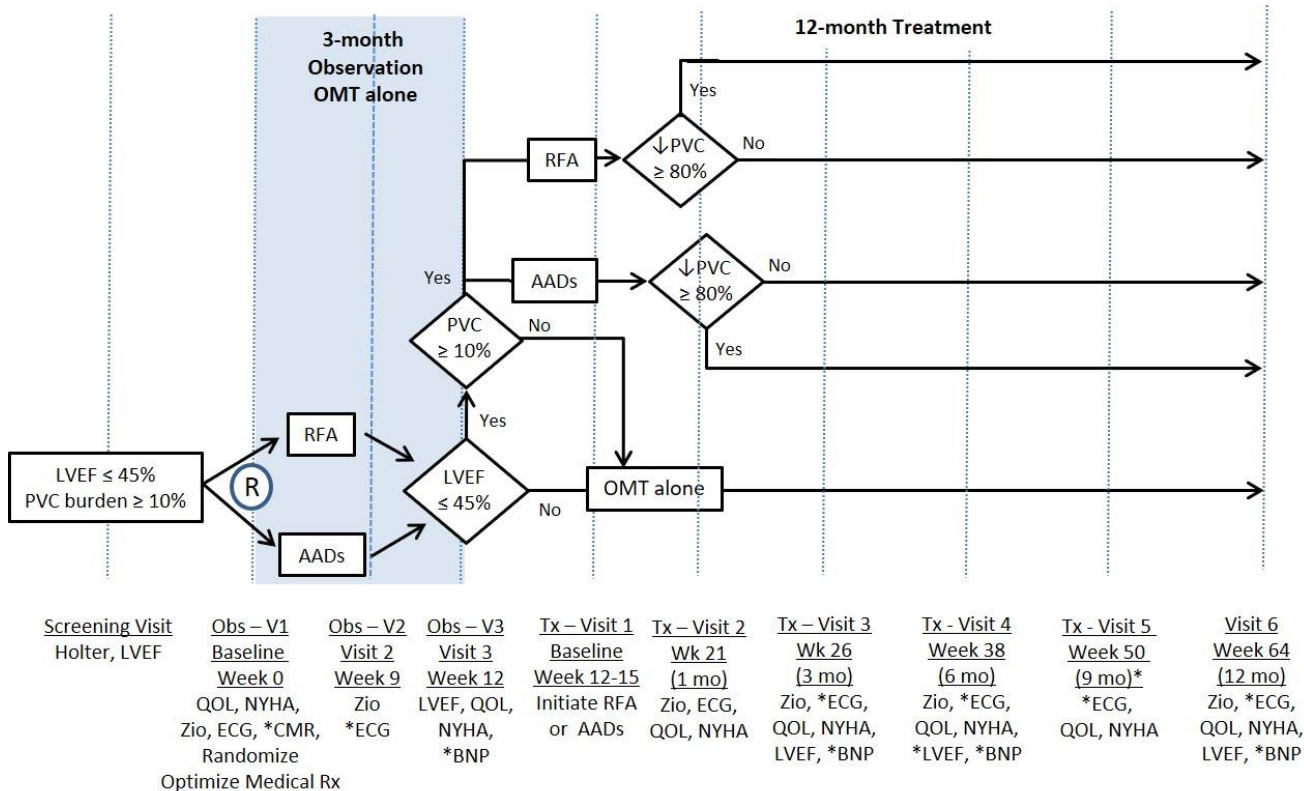
If PVC burden remains  $\geq 10\%$  and LVEF  $\leq 45\%$ , then the subject will either initiate antiarrhythmic drugs or undergo RFA procedure (see Section C: Description of the intervention/treatment) and will continue on protocol as scheduled. However, if these criteria are no longer met, the subject is considered a screen failure and is withdrawn from the study. In such a case, the treatment decision is solely at the discretion of the electrophysiologist caring for subject. Nevertheless, this subject will be included in a PVC-CM registry if consent was provided (described above Section A.1).

i) *Treatment – Visit 1.* This is considered the baseline visit where PVC suppression strategy assignment is initiated (either RFA or AADs). If the subject is randomized to RFA, we will request that sites complete the RFA data collection form which includes information during the RFA procedure as well as recovery, complications and hospital stay. EPS will be performed on their baseline medications, except for antiarrhythmic drugs class II (beta blockers) which will be held at least 5 half-lives prior to procedure. Beta blockers should be resumed after RFA.

iv. However, subjects randomized to AADs can have this visit combined with Observation-Visit 3. In addition, subjects in the antiarrhythmic (AAD group) will require a baseline TSH and LFTs (AST only) if amiodarone is chosen.

v. *Treatment – Visit 2.* Using appropriate data collection forms, we will ask that sites obtain current medical therapy information, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). 12-lead ECG should be obtained if clinically indicated. A repeat Zio Patch should be placed to re-assess adequate PVC suppression after RFA or initiation of AADs. The local PI and designated site staff will be able to log in to iRhythm’s ZioReports) 3 weeks later to obtain a Zio Patch Report with repeat PVC burden after intervention. If PVC burden is suppressed by more than 80%, intervention is considered successful and the subject should continue with treatment visits as scheduled,

However, if PVC burden does not decrease by more than 80%, intervention is considered a failure. In such a case, the subject should be considered for a second RFA procedure or a different antiarrhythmic drug depending on the randomization group that the subject was assigned (see Section C: Description of the Intervention/treatment). We discourage crossover of treatment arms since this will result in automatic withdrawal from the study. Nevertheless, subjects that withdraw from the study will be included in a PVC-CM registry if the subject provided consent. (described above Section A.1).



**Figure 1.** PAPS study design. A 3-month Observation (Obs) period allows each subject to serve as their own control to assess benefits of PVC suppression. All subjects will be randomized (R) to either RFA or AADs. OMT, optimal medical therapy. QOL, quality of life questionnaire; NYHA, New York Heart Association class; LVEF, LV ejection fraction; Zio, ambulatory ECG Ziopatch Holter, CMR, Cardiac MRI (\*, visit/intervention if clinically indicated).

vi. *Treatment – Visit 3.* Appropriate data collection forms should be used to collect current medical therapy information, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). 12-lead ECG should be obtained if clinically indicated. A transthoracic echocardiogram should be performed to assess LVEF and a copy mailed to the Echo Core laboratory led by Dr. John Gorcsan III, M.D. A repeat Zio Patch should be placed to re-assess PVC burden. Local PI and designated site staff will be able to log in to iRhythm’s ZioReports 3 weeks later to obtain a Zio Patch Report if desired for any clinical decision.

vii. *Treatment – Visit 4.* Appropriate data collection forms should be used to collect current medical therapy information, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). 12-lead

ECG should be obtained if clinically indicated. If clinically indicated, a transthoracic echocardiogram should be performed to assess LVEF and a copy mailed to the Echo Core laboratory led by Dr. John Gorcsan III, M.D. A repeat Zio Patch should be placed to re-assess PVC burden. The local PI and designated site staff will be able to log in to iRhythm's ZioReports 3 weeks later to obtain a Zio Patch Report if desired for any clinical decision. In addition, subjects in the antiarrhythmic (AAD group) will require a follow-up TSH and LFTs if amiodarone is part of the current treatment.

viii. *Treatment – Visit 5.* Using appropriate data collection forms, we will ask that sites obtain current medical therapy information, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). 12-lead ECG should be obtained if clinically indicated. If a transthoracic echocardiogram is performed for any reason prior to this visit, we will ask that sites mail a copy to the Echo Core laboratory (Dr. John Gorcsan III, M.D.).

ix. *Treatment – Visit 6.* Using appropriate data collection forms, we will ask that sites obtain current medical therapy information, NYHA functional class and Minnesota HF quality of life questionnaire (QOL). 12-lead ECG should be obtained if clinically indicated. A final, transthoracic echocardiogram should be performed to obtain assessment of LVEF and images should be sent to the Echo Core laboratory (John Gorcsan III, M.D.). A repeat Zio Patch should be placed to re-assess PVC burden. The local PI will be able to log in to iRhythm's ZioReports to obtain a Zio Patch Report if thought to be needed for treatment decisions. In addition, subjects in the antiarrhythmic (AAD group) will require a follow-up TSH and LFTs if amiodarone is part of the current treatment.

### **C. Clinical Assessment and tests**

Regardless of group assignment, all subjects will undergo clinical evaluation and a series of clinically indicated tests and interventions as outlined in Table 2 and Figure 1.

c. 1. 12-lead ECG will be performed at each center and sent to the ECG/Holter core lab (led by Dr. Edward Gerstenfeld, UCSF, San Francisco, CA) where a cardiologist blinded to treatment group will provide a final interpretation. Scheduled ECG is requested as noted in Table 2 if clinically indicated. We will assess QRS duration and QT interval of non-PVC beats and PVC features such as location, QRS duration and coupling interval or prematurity.

c. 2. Ambulatory Holter monitor (Zio Patch, iRhythm, Inc). This Holter monitor will be provided directly by iRhythm, Inc. to participating centers. Subjects will mail the device back directly to iRhythm where it will be analyzed and results will be provided to each center. This monitor will provide automatic assessment of daily PVC burden remaining blinded to the group assignment. Custom software designed by Dr. Gerstenfeld will be used to measure PVC coupling interval, coupling interval variability, and number of PVC morphologies. This will allow us to assess important PVC features during the observation period and treatment arms. Reports will be sent to the ECG/Holter core lab (noted above) for final interpretation. Similar to the ECG, the reader will be blinded to the group assignment. The ambulatory Holter monitor will allow us to assess long-term PVC burden and morphology and compare efficacy to achieve successful PVC suppression (defined as PVC reduction  $\geq 80\%$ ) between RFA and AAD groups. Furthermore, it will provide information such as PVC recurrence, and the presence of non-sustained and/or sustained ventricular tachycardia.

c. 3. Transthoracic Echocardiogram. Scheduled 2D-Echocardiograms should be requested as noted on Table 2 if clinically indicated. Echocardiograms will be performed using a commercial system with a 5MHz standard cardiac probe with at least 70-80 frames per second. Echocardiography will be considered adequate if echocardiographic windows allow assessment of the following parameters, otherwise, echo contrast should be performed. LV function will be assessed by quantifying the calculated LVEF (Simpson's formula), fractional shortening (FS), LV end-systolic and diastolic dimensions (LVESD, LVEDD), LV thickness, left atrial (LA) size, mitral valve (MV) function, LV compliance (E/A ratio and E/E' ratio), and dyssynchrony<sup>29</sup>. Interventricular dyssynchrony will be evaluated by RV and LV electromechanical delay (time from onset of QRS to the onset of pulmonary and aortic systolic flow, respectively). LV mechanics / dyssynchrony will be assessed by 1) septal to posterior wall delay, 2) PW-TDI maximum systolic motion delay between septal, anterior, posterior and lateral wall, and 3) 2D

speckle tracking strain analysis (radial, circumferential and longitudinal strain)<sup>18</sup>. A copy of the echocardiogram images should be sent to the Echo core laboratory (led by Dr. John Gorcsan, III) for final interpretation by a cardiologist blinded to the randomization arm. Assessment of LVEF by echocardiography will be repeated during observation and treatment phases in order to assess changes in LV function during observation period and between PVC suppression strategies.

c.4. Cardiovascular magnetic resonance (CMR). If clinically indicated, a delayed enhancement CMR will be performed at each center following a single protocol (approved by CMR core laboratory Director: Dr. Gregory Hundley, Richmond, VA) and sent to the CMR core lab for final interpretation. Similarly, CMR core lab and participants will remain blinded to group assignment. CMR will be obtained at baseline if clinically indicated to assess LV volumes, mass, ejection fraction, and mid-wall circumferential strain; overall myocardial T1, T2, and extracellular volume fraction (ECV); and scar location and extent using late gadolinium enhanced methods according to previously published techniques<sup>30,31</sup>. Associations between each CMR assessment and improvement in LV function (responders) will be determined after PVC suppression strategy. Interstitial myocardial fibrosis and outcomes between early- vs. late-coupled PVCs in an attempt to support a mechanistic aim in final PAPS study. The CMR will be considered clinically indicated to exclude other types of cardiomyopathy, and all sites have agreed to order CMR on enrolled subjects.

c.5. Minnesota living with heart failure quality of life (QOL) and NYHA functional class questionnaires to be used in the PAPS study will be approved by Dr. Teresa DeMarco (Heart failure core lab). These questionnaires will be provided to each center to be answered by each subject in their local institution. This will allow us to assess heart failure symptoms and change in quality of life and functional status during the observation period and between both treatment groups. Questionnaires will be sent directly to the Heart failure core lab. *All QOL and NYHA questionnaires will be evaluated and graded by an event adjudication committee (independent of the steering committee, see Section G. Ethical / Regulatory Affairs). If clinically indicated, we will request to provide brain natriuretic peptide (BNP) levels as well as CRP and ESR as per schedule on Table 2.* Participants who are evaluated by study staff and suspected to be depressed will be referred to a primary care provider to facilitate the evaluation.

c. 6. Complications, heart failure admissions and adverse events. *All events* including mortality, hospital admissions and heart failure exacerbations and treatment-related complications will be documented on each subject throughout the observation and treatment periods. Each center will report any adverse events to the Coordinating Center (McGuire VA Medical Center, Richmond VA) within 24-48 hours of the occurrence or knowledge of the event. *All SAE/hospital admissions, procedure complications and events will be evaluated and assigned by an event adjudication committee (see Section G. Ethical / Regulatory Affairs and documents: Human subjects and Data Safety Monitoring plan for details).*

*Participating centers will provide all available clinical data to respective core labs (echocardiogram, cardiac MR and Holter) and Coordinating Center (McGuire VA Medical Center) through REDCap with a case number without identifiers and treatment randomization as outlined in the Manual of Operations and Standard Operating Procedures manual.*

Of note, subject participation and results of this study will not change diagnostic testing (e.g. electrophysiologic studies for other indications) and medical management including medical therapy (unless safety drug interactions are clear) and indicated procedures (e.g. left heart catheterization). ICD implantation is not encouraged (but not prohibited) during the study as the CM may improve or even resolve after RFA of PVCs as recently shown by Penela et al.<sup>26</sup>.

#### **D. Description of the intervention(s)/treatment(s).**

Prior to intervention, all subjects should complete a 3-month observation period consisting of a total of 3 visits. Subjects that are not able to wait or be observed for this period of time should not be considered for this study. Subjects will be randomized to intervention at the baseline visit of observation. Crossover between different treatment arms (RFA vs. AADs) is not encouraged and will not be allowed before 6-month follow-up duration of the treatment period, unless considered critical for the subject's well-being.



ii) Treatment or intervention arms will consist of: Antiarrhythmic drug (AAD) therapy. AAD therapy of choice is amiodarone due to its proven safety in subjects with LV dysfunction. Amiodarone loading dose of 10 grams is recommended, followed by maintenance dose of 200-400mg daily to achieve successful PVC suppression. We define successful PVC suppression only if  $\geq 80\%$  absolute reduction in PVC burden is achieved after a drug or intervention<sup>4,24</sup>. Alternatively, sotalol and/or propafenone could be considered at the discretion of the electrophysiologist (sotalol dose of at least 120mg twice daily, propafenone 150-300mg tid) if there is a significant concern of safety profile of amiodarone. Finally, other AADs (class Ic) are acceptable if there is a clear preference by the clinical electrophysiologist while a rationale is requested for such choice. Overall, we suggest avoiding class Ia antiarrhythmic drugs due to the prior documented risk of pro-arrhythmia, however, they could be considered in subjects with an implantable or external defibrillator (Lifetest). Optimal heart failure medical therapy should be continued in combination with AAD throughout the 12-month follow-up. Throughout the 12-month follow up period, subjects will have a total of 5 visits to assess changes in clinical status, arrhythmia burden including PVCs and LVEF as outlined in Table 2 and Figure 1. In addition, subjects receiving amiodarone as antiarrhythmic (AAD group) will require a baseline TSH and LFTs and should be repeated every 6 months.

A 2-week ambulatory ECG Holter (Zio Patch, IRhythm, Inc.) will be obtained 4-6 weeks after initiation of AAD to assess whether PVC suppression was successful (defined above). If successful PVC suppression is not achieved, we will ask sites to consider either an increase in the antiarrhythmic dose or change of antiarrhythmic as noted above. A repeat 2-week ambulatory Holter monitor will be done 4 weeks after adjustment of AAD to re-assess PVC suppression.

Radiofrequency Ablation (RFA) of PVCs. RFA will be performed after completion of 3-month observation period). EPS will be performed on their baseline medications, except for antiarrhythmic drugs class II (beta blockers) which will be held at least 5 half-lives prior to procedure. Beta blockers should be resumed after RFA.

EPS and RFA will be performed using standard techniques and protocols similar to those subjects that do not participate in this clinical study. Multipolar electrode diagnostic catheters will be inserted. If no ectopy is present at baseline, isoproterenol may be infused at rates up to 10mcg/min. If the ectopy is infrequent despite adrenergic stimulation, pace mapping will be performed at a pacing cycle length determined by coupling interval of the spontaneous ventricular ectopy<sup>5</sup>. RV or LV PVCs will be mapped/ablated at the discretion of the electrophysiologist. Coronary angiography and/or intracardiac echo will be performed as needed. RFA will be performed at the site of earliest endocardial activation or best pace map. RFA applications will be delivered for at least 30 seconds if adequate power at the electrode-tissue interface is achieved. RFA will be continued for at least 60-120 seconds in sites where PVCs are abolished within 30 seconds. After ablation of the PVCs, isoproterenol will be administered at 2-10 mcg/min as required to shorten sinus CL to 500ms to confirm that PVCs are not inducible by adrenergic stimulation. In the event of polymorphic PVCs, all morphologies are to be targeted for ablation<sup>5</sup>. Subjects will be observed overnight in a telemetry bed and discharged home the next day, as it is current standard of care.

During enrollment and immediately after RFA, baseline medical therapy (including ACE inhibitors/ARB, beta blockers) should be optimized or continued throughout the 12-month follow-up period. Practitioners will be asked to document any changes in medical therapy including rationale. All events, side effects as well as change or decrease of doses will be documented and rationale explained. Similar to the AAD group, subjects will have 5 follow-up visits (Visit 2 – 6, Table 2 and Figure 1) to assess changes in clinical status, arrhythmia burden including PVCs and LVEF.

A 2-week ambulatory ECG Holter (Zio Patch, IRhythm, Inc.) will be obtained 4-6 weeks after RFA to assess whether PVC suppression was successful (defined above). If successful PVC suppression is not achieved, subjects will be offered a second PVC-RFA procedure 3 months after initial randomization. Redo-RFA will be performed with a similar approach as the first intervention; however, epicardial mapping will be encouraged if considered appropriate. This subgroup of subjects will have a repeat 2-week Holter monitor within 2-4 weeks after redo-RFA to document successful or failure of PVC suppression. All events and complications in the PVC suppression arm related to RFA will be documented.

#### **E. Primary and secondary outcome measures.**

*The outcomes are divided in primary and secondary end-points (Table 3).*

*The primary end-points will consist of:*

1. *Improvement of LVEF after PVC suppression at 12-month follow-up.* This is chosen as primary-end point due to the known prognostic value of LVEF. The lower the LVEF, the higher the risk of sudden cardiac death and heart failure<sup>1-3</sup>. This will compare the overall improvement or change in LVEF between RFA and AAD groups. This end-point will support that either RFA or AADs have an overall better outcome due to significant improvement of LV function with potential impact on morbidity and mortality associated with PVC-CM.

2. *Responders to PVC suppression strategy at 12-month follow-up* (See rationale under Section “Definitions” in 3rd paragraph of Aim 2). Assessment of the number of responders (delta LVEF  $\geq$  10%) after PVC suppression strategies (RFA or AADs) will assess the effectiveness of RFA and AADs to reverse or improve cardiomyopathy induced by frequent PVCs. Evidence that either RFA or AADs is superior to improve or even reverse LV dysfunction in subjects with high burden PVCs could have significant impact of morbidity and mortality including future heart failure and ventricular arrhythmias, and also may avoid ICD implantation.

*The secondary end-points will consist of:*

1. *Efficacy of RFA vs AADs groups to achieve successful PVC suppression at 12-month follow-up, defined as a reduction of PVC burden  $\geq$ 80% (regardless of LVEF change). Understanding the success rate of PVC suppression between RFA and AADs will help better determine the best treatment to those subjects with high PVC burden.*

2. *Composite end-point of adverse events at 12-month follow-up, including worsening in NYHA functional class (I-IV), number of HF and cardiac-related admissions, RFA complications and AAD adverse effects and cardiovascular death.*

This adverse event composite end-point is chosen to understand the overall complications and adverse effects/events related to RFA and AADs. Worsening of NYHA functional class will be defined as when/if the subject’s functional status worsens by one NYHA class. Hospital admissions will be defined as any visit to ED or hospital admissions related only to a cardiovascular event such as heart failure, angina, pre/syncope and palpitations.

3. *Composite end-point of arrhythmia burden, including PVC recurrence, non-sustained (< 30sec) and sustained (> 30sec) ventricular arrhythmias and arrhythmic sudden cardiac death at 12-month follow-up.* This composite end-point of arrhythmia burden is chosen in order to understand the difference in arrhythmia recurrence between RFA and AAD therapy. PVC recurrence will be defined as reduction of PVC burden  $\leq$  80% at 6- and 12-months when compared to baseline (pre-treatment) PVC burden.

**F. Data interpretation and analysis**

**Barriers / limitations of enrollment, randomization and retention of participants in this clinical pilot study.**

Subjects are referred to tertiary centers for RFA of PVCs in subjects with associated CM in the hope to reverse LV dysfunction if the underlying cause is related to PVC-CM. Thus, it is important to understand that the observational period and randomization is acceptable and will not compromise enrollment. Subjects that meet inclusion and exclusion criteria will be asked to participate. We plan to understand the comfort level of subjects participating in this clinical study. We will assess the rate and rationale for declining participation or withdrawal from this study. Those individuals that decline or withdraw will be asked to provide one of the following rationale: 1) uncomfortable with observation/waiting period, 2) uncomfortable with AAD therapy, 3) unable/unwilling to commit for a long term follow up, 4) uncomfortable participating in any type of research, 5) other reasons including those not related to the study itself.

**Table 3. End-points for PAPS Pilot study**

Primary End-points
- Improvement of LVEF
- Responders to PVC suppression strategy (delta LVEF $\geq$ 10%)
Secondary End-points
- Successful PVC suppression ( $\downarrow$ PVC burden $\geq$ 80%)
- Composite end-point of adverse events <ul style="list-style-type: none"> <li>- Worsening NYHA functional class (I-IV)</li> <li>- Number of HF and cardiac-related Hospital admissions</li> <li>- RFA complications / AAD adverse effects</li> <li>- Cardiovascular death</li> </ul>
- Composite end-point of arrhythmia burden: <ul style="list-style-type: none"> <li>- PVC recurrence (PVC reduction &lt; 80 % after RFA or AAD)</li> <li>- Non-sustained and sustained ventricular arrhythmias</li> <li>- Arrhythmic sudden cardiac death.</li> </ul>

Subjects that refuse enrollment, will be asked to participate in a PVC-CM registry to follow their response and crossover to different treatment strategies (described above Section A.1)..

We hypothesize that subjects and/or physicians will not object to participate due to the 3-month observation period since most tertiary referral centers have significant procedure wait times for which usually they are scheduled between 8- to 12-weeks after clinical decision of PVC suppression is made. We have involved all participating centers, who agree that this is a common and acceptable scenario during which the observation period proposed could take place. In contrast to other clinical studies where RFA is being compared to placebo, we speculate that randomization of RFA vs. AADs will not be an enrollment limitation since all subjects will undergo a PVC suppression strategy. *This pilot study will allow us to prove feasibility of the PAPS study with the current study design including a 3-month observation period and treatment randomization.*

#### *Rate of spontaneous recovery of CM and PVCs suppression during the 3-month observation period and assess the recurrence of CM and PVCs during a 12-month follow up.*

Due to a known temporal variability of PVC burden over time<sup>24,32</sup>, it is unclear how often spontaneous variability of PVCs would lead to observing what appears to be spontaneous resolution of PVCs (e.g., without any intervention), which could in theory result in spontaneous improvement of LV dysfunction if CM is secondary to frequent PVCs.

We will assess and compare the PVC burden and LVEF between the time of enrollment and at the end of the 3-month observation period. *This pilot study will allow us to understand the degree and rate of spontaneous improvement of LVEF and reduction of PVCs (control phase) to properly power a large multicenter PAPS study.* Subjects that do not meet both inclusion criteria (LVEF  $\leq 45\%$  and PVC burden  $\geq 10\%$ ) at the end of the observation period will be considered a screen failure, and will be included in a PVC-CM registry if consent has been provided. Based on preliminary data, we believe that less than 10% of subjects will have spontaneous improvement of LVEF  $> 45\%$  and PVC  $< 10\%$ . Registry subjects will have PVC and LVEF assessment every 6 months for the remaining 12 months to understand the recurrence of CM and PVCs (see Section A.1).

#### *Rate of responders to PVC suppression*

Besides improvement in LV systolic function, no study has been designed to demonstrate clinical benefits with either RFA or AADs. Clinical benefits are implied based solely on the improvement of LVEF. Based on prior retrospective and observational studies, the rate of responders (improvement of LVEF) to PVC RFA is estimated at 50-65%<sup>7,22,26</sup>. Unfortunately, there is no recent data on antiarrhythmics due to the lack of recent studies. Our preliminary data from the CHF-STAT study demonstrates a response rate of 28% (Preliminary Data Section).

We plan to further identify the rate of responders after PVC suppression by obtaining the following primary end-points: 1) improvement in LVEF (determined by  $\Delta \text{LVEF} = \text{final LVEF} - \text{baseline LVEF}$ ) and 2) “responders” to PVC suppression (defined as change in LVEF  $\geq 10\%$ ). In addition, we will obtain QOL and NYHA functional class questionnaires (secondary end-point described above). Each subject will serve as its own control, since all data obtained will be compared between the end of 3-month observation period (control phase - prior to randomization) vs. 3-month after PVC suppression strategy, regardless of treatment randomization (RFA and AAD). We hypothesize that a PVC suppression strategy (RFA or AAD) is better than optimal HF medical therapy alone to improve LV function, HF symptoms, heart failure admissions, and avoid the need for defibrillator. *The PAPS pilot study will help us determine the rate of responders to PVC suppression strategy in order to properly estimate sample size and power the large randomized PAPS study.*

#### *Determine the efficacy to achieve successful PVC suppression and rate of adverse events between RFA and AAD treatment arms.*

The best PVC suppression strategy (RFA vs. AADs) in subjects with PVC-CM is not known due to the lack of head-to-head comparison. Moreover, The rate of responders, successful PVC suppression (defined as 80% PVC reduction), adverse events and treatment crossover between these 2 treatment arms is unknown. We plan to assess and compare clinical benefits (QOL, NYHA class, HF symptoms, morbidity and mortality, avoidance of device implants) and secondary end-points (composite adverse events,

composite arrhythmia burden and efficacy of PVC suppression) between RFA and AADs in a large randomized PAPS study.

After treatment randomization in the proposed PAPS pilot study, all data will be compared between RFA and AAD throughout the 12-month follow up to determine the change in PVC burden, clinical outcomes including adverse events and treatment crossover between both distinct treatments. We hypothesize that RFA is better than AADs to improve LV function, HF symptoms, while decreasing heart failure admissions, arrhythmia burden, heart failure admissions, and avoid the need for a defibrillator.

*This pilot study will allow us to determine the rate of successful PVC suppression (greater than 80% PVC reduction), adverse events and 6-month treatment crossover between both RFA and AADs, which in turn will allow us to properly design and power the large randomized PAPS study.*

### **G. Data collection**

Using a subject questionnaire and through medical records, we will obtain and record baseline demographics, including age, gender, race, ethnicity, duration of cardiomyopathy and prior LVEF, history of atrial fibrillation, and medical therapy including dosing prescription. All procedures and tests to be performed during the observation and treatment period (RFA vs. AADs group) are outlined in Figure 1 and Table 2.

*Data will be collected and recorded* directly by the research coordinator and local investigator and as per protocol. A unique identifier will be given to each subject. All participating institutions will be required to complete and submit all data directly to the Coordinating Center via a secure encrypted data capture system (REDCap). In addition, we will request all centers to scan a copy of all completed questionnaires and forms through REDCap. All participating sites will comply with all applicable laws, regulations and provisions related to the subject's privacy and data confidentiality (see details in Protection of Human Subjects).

*Data quality and consistency of intervention* (RFA of PVCs) will be facilitated and monitored by 1) standardized subject's research study forms to be completed by all centers, 2) review of subject's data/forms as study visits are completed, 3) complications/adverse events, and 3) effectiveness of PVC suppression by Data Safety Monitoring Board (DSMB) and during PAPS investigators annual meeting. In contrast, the quality of echocardiogram, Zio Patch Holter monitors and CMR will be monitored by Echo, Holter and CMR core laboratories, respectively.

### **H. Limitations**

The following limitations may arise during the development of this project:

1. Subjects with progression from mild and moderate to severely symptomatic PVCs (incapacitating palpitations and dizziness) will be encouraged to complete the 3-month observation period since PVC suppression will initiate immediately thereafter. Subjects are excluded if symptoms preclude completion of the 3-month observation.
2. Limited or poor suppression of PVC suppression in randomized treatment (RFA or AAD) arm. These subjects are encouraged to remain on the assigned arm. However, crossover to the alternate treatment arm can be considered after 6 months only if considered medically indicated. If crossover were to occur before 6 months, immediate notification and final evaluation with echocardiogram and ambulatory ECG Holter monitor (Zio Patch) should be obtained prior to crossover, and the subject will be excluded from study and followed in a PVC-CM registry if consent was provided (described above Section A.1).
3. PVC variability or spontaneous resolution of PVCs may limit pre vs post procedure comparison. PVC burden has significant temporal variability and it may be a major limitation in the study of arrhythmias<sup>24,32</sup>. Schmidt<sup>24</sup> demonstrated that an 80% absolute reduction of PVC burden is required to show a true drug effect. To minimize daily PVC variability, PVC evaluation in this study will be performed using a 2-week ambulatory ECG Holter monitor (Zio Patch, IRhythm, Inc.) which is shown to be a better indicator of long-term PVC burden<sup>33</sup>.
4. LV function assessment in ventricular bigeminy. Assessment of LVEF during frequent PVCs represents a challenge for all imaging modalities<sup>34</sup>. Modified acquisition and post-processing methods have been developed to correct for R-R interval variability expected with frequent PVCs<sup>35</sup>. In the event that the subject has persistent ventricular bigeminy at the time of the scheduled echocardiography, the LV function assessment should be postponed for a few hours or a later date when PVCs are less prominent (at least ventricular quadrigeminy).

5. Non-indicated clinical visits, ECGs and cardiac imaging. Due to limited funds provided by R34, the protocol relies mostly on clinically indicated follow up visits and cardiac imaging for subjects with HF and frequent PVCs undergoing PVC suppression strategy. Table 2 and Figure 1 detail the visits and procedures recommended for this study. However, some visits, testing and imaging may be considered outside of standard of care (noted on asterisk). It is left to the local PI to attempt to obtain/request these tests if considered clinically indicated. *This pilot study will also help us determine the number of visits, tests and imaging (echocardiograms and cardiac MR) that is clinically indicated to better plan a budget for the large-scale PAPS study.*

6. ICD implantation for primary prevention is not encouraged during the study as the CM may improve or even resolve after RFA of PVCs as recently shown by Penela et.al<sup>26</sup>. If an ICD is present or the practitioner decides to implant an ICD prior to completion of the study; programming to VVI 40 or other pacing algorithm should be considered to ensure minimal ventricular pacing.

### **I. Statistical analysis and sample size estimate**

All results will be reported according to the CONSORT guidelines. Specifically, all study data will be summarized by means and standard deviations or frequencies and percentages. Fisher's exact tests and Wilcoxon rank-sum tests will be used to compare demographic and baseline injury severity information between the treatment regimens to ensure proper randomization. The unadjusted relative risk between each potential predictors at each time point will be calculated<sup>36</sup>. An extended model will consider the change in the relative risk values over time while also assessing if the relationship between outcome and predictor depended on the baseline PVC burden. Similar analyses will be performed for each of the secondary outcomes. Lastly, the adverse events will be summarized separately for each treatment group using frequencies and percentages. Similar summaries will be provided for each of the PVC burden levels. The software SAS/STAT<sup>®</sup> Software (SAS Institute, Inc. Cary, NC) will be used for all statistical analysis.

#### Avoidance of bias

In order to avoid a high proportion of a single ethnic or racial group, we decided to involve multiple high-volume centers across the country. All participating centers will send all clinically indicated data (echocardiograms, CMR, ECG, and Holters) to the respective core laboratory, where the cardiologist will be blind to the assigned group, giving a final interpretation. All 2-week ambulatory ECG Holter monitors will be contracted to a single company (ZioPatch<sup>™</sup>, IRhythm Technologies, Inc.) and evaluated by the Holter core lab (Dr. Gerstenfeld) to prevent differences in PVC detection algorithms. Finally, stratified randomization will ensure an equal distribution of subjects between PVC burden above and below 20%.

#### Sample size justification.

*This has been estimated solely on primary end-point of improvement in LV ejection fraction after PVC suppression. We are planning to compare the improvement in LVEF between PVC suppression strategies (RFA vs. AADs groups). Due to the multiple random effects, a simulation study was conducted to estimate the number of subjects required for this study. Specifically, data was simulated according to a linear mixed-effects model with an unstructured error structure with a random site effect. It was assumed that subjects would have a LVEF level of 25% (SD=5%) in each of the groups at baseline and LVEF levels of 40% and 35% (SD=10%) in the RFA and AAD groups at 12 months, respectively. A within subject correlation of 0.25 was assumed along with an inter-site standard-deviation of 1%. *This model was fit assuming that, on average, 10% of the subjects would drop out randomly.* Approximately 140 total subjects (70 per group) should be enrolled to reject the null hypothesis that the mean LVEF between RFA and AAD groups are equal with probability (power) 0.8 and Type I error probability of 0.05. *As a pilot study we have determined the need to enroll at least 20% (30 subjects) of preliminary sample size estimation to understand feasibility and key aspects of subject enrollment, randomization and retention to properly power a large-scale randomized PAPS study. Sample size is increased by 15% (6-9 additional subjects, 36-39 subjects total – between 19-20 subjects in each treatment group) to take into account possible spontaneous improvement of LV dysfunction during the 3-month observation period between treatment strategies.**

## **J. Ethical / Regulatory Affairs**

The study will be submitted for review to your IRB of record and registered on clinicaltrials.gov prior to commencement of study activity.

### **Event Adjudication Committee**

We will establish a committee to evaluate each hospitalization event to determine its relationship to HF and/or the PVC suppression treatment arm. The committee consists of three physicians: 2 heart failure cardiologists (Drs. Sean Pinney and John Boehmer) and 1 cardiac electrophysiologist (Dr. Joshua Cooper) (see letters of support). Throughout the study and the adjudication process, the committee members will remain blinded to treatment allocation, as well as other information that may disclose allocation (TSH, LFTs).

### **Risk Benefit assessment**

All PVC suppression strategies (RFA and AADs), proposed in this grant application are approved by the Heart Rhythm Society and FDA for the treatment of ventricular arrhythmias, respectively. Subjects assigned to the RFA arm may have a small risk of minor or major complications related to RFA of PVCs. However, these risks associated with RFA of PVCs are acceptable and RFA of PVCs continues to be performed in clinical practice even though there is limited data to support benefit from this intervention. Risks associated with RFA are small (1-2%) including but not limited to stroke, myocardial infarction, coronary artery injury, bleeding, cardiac tamponade, pneumothorax, atrioventricular block with subsequent need for permanent pacemaker, and even death. Similarly, antiarrhythmic drugs (AAD) may have long-term risks/adverse effects based on the antiarrhythmic chosen (e.g. amiodarone has significant long-term effects including lung disease such as decrease in lung diffusion capacity, optical neuritis, abnormal thyroid and liver function, and pro-arrhythmic effects; see Section C in Protection of Human Subjects document for details). Yet, these treatment options are currently standard of care frequently offered to this subject population with known complications and these adverse events. To minimize the potential risks with AADs, all subjects should be considered for additional safety laboratory analyses during treatment as recommended per guidelines based on AAD chosen (amiodarone - TSH, LFTs, PFTs, eye exam).

A pregnancy test will be obtained on females of childbearing age that are assigned to the RFA treatment prior to procedure due to fluoroscopy exposure. In contrast, a pregnancy test will be performed on a monthly basis on those randomized to the antiarrhythmic treatment arm to confirm the lack of pregnancy throughout the 12-month follow up period. If a female on antiarrhythmic arm becomes pregnant during the 12-month follow up period, we will consider stopping antiarrhythmics and the subject will be withdrawn from the study.

The IRB should be notified of any serious adverse events (SAE) within 24 hours of such event or knowledge of the event. Additionally, the PAPS National Research Coordinator should be notified within 24 hours of the event or knowledge of the event. The investigator must decide whether each incident meets the definition of a SAE.

### **Data Safety Monitoring Plan and Board**

Serious adverse events and subject monitoring will be performed as stipulated in the Data Safety Monitoring Plan (DSMP). As required by NIH, this multicenter trial will also have a Data Safety Monitoring Board (DSMB) that will monitor the safety of the study. The DSMB will consist of 2 heart failure specialists (Drs. James Fang and Ryan Tedford) and a cardiac electrophysiologist (Dr. Thomas Dewland) (see letters of support). Further details of DSMP and responsibilities of IRB and DSMB as stated in the Section: Protection of Human Subjects and Data Safety Monitoring Plan.

## K. Timeline

The timeline to enroll between 36-39 subjects in this prospective randomized clinical pilot study is summarized in Table 4. IRB submission and coordination will occur within the first few months. Enrollment at each center will start as soon as central or local IRB approval is granted and proper training has been completed. We expect an average enrollment of 3 subjects per center completing recruitment and follow-up in 18 and 36 months, respectively.

**Table 4. Timeline of PAPS Pilot study**

Trimester (months)	Year 1			Year 2			Year 3		
	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	5 <sup>th</sup>	6 <sup>th</sup>	7 <sup>th</sup>	8 <sup>th</sup>	9 <sup>th</sup>
IRB submission	XX								
Coordination centers	XXXX								
Patient enrollment	XX	XXXX	XXXX	XXXX	XX				
Data Collection	X	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Data analysis							XXXX	XXXX	XXXX
R01 preparation									XXXX

## L. Enrollment

We will engage clinicians/consultants to identify all subjects with frequent PVCs and mild to severe CM, regardless of duration, symptoms and heart failure during the following visits: 1) primary care and cardiology clinics, 2) device clinic referral for ICD implantation; 3) non-invasive laboratory with documented LV dysfunction by transthoracic echocardiogram and a minimum of >10 PVC/hour on average on at least a 24-hour Holter; 4) HF clinic with systolic LV dysfunction with frequent PVCs; 5) hospital admission to cardiac telemetry due to HF symptoms and PVC frequency of  $\geq 10$  PVC / hour. However, it is likely that most subjects will be identified through Part II, where we will screen all ambulatory Holters for PVC  $\geq 10\%$  and LVEF  $\leq 45\%$ . Refer to document Enrollment for further details.

***Estimate the prevalence of CM (LVEF ≤ 45%) and frequent PVCs (≥ 10%) in the overall population receiving ambulatory ECG Holter monitors.***

To prove the feasibility of a large randomized clinical trial (PAPS study), we plan to better estimate the prevalence of patients with PVC burden ≥10% and associated CM (LVEF ≤ 45%) in all consecutive adult patients undergoing at least a 24-hr ambulatory ECG monitor (Holter).

**A. Study Population and eligibility**

All consecutive adult patients prospectively and retrospectively who have undergone or will undergo local ambulatory ECG Holters (at least 24 hr) will be scrutinized for the presence of PVC ≥10% and LVEF ≤ 45% by reviewing a recent LVEF assessment (echocardiogram, MUGA or cardiac MR within 6 months of Holter date). If no LVEF is available, LVEF assessment should be considered to rule out associated CM as this would be clinically indicated. The enrollment goal is 1,500 unique subjects per center in the first 2 years for a total of near 20,000. Waiver of consent and waiver of HIPAA is requested for this portion of the study.

Retrospective and prospective data collection of this Holter data will allow each center to identify patients with potential diagnosis of PVC-cardiomyopathy, which could potentially be candidates for treatment randomization (Part I) if inclusion/exclusion criteria is met. Sites will collect Holter data retrospectively starting with Holters placed in July 2018 and forward.

**B. Data Management / Collection**

We will request that all centers provide PVC burden and LV ejection fraction in all-comers that undergo placement of an ambulatory ECG Holter regardless of duration (at least 24 hours).

Only, if PVCs are >10% on Holter, will centers provide further data including:

- Ambulatory Holter: mean heart rate, number of different PVC morphologies, PVC coupling interval.
- Echocardiographic data: LV end-diastolic and end-systolic dimension, LA size, if available.
- Upload a 12-lead ECG with representative PVC if available.

Once information is collected and entered in REDCap, each subject will receive a unique case number.

**C. Data Interpretation**

By reviewing Holters and LVEF in all subjects undergoing Holters, we will be able to estimate the prevalence of CM (LVEF ≤ 45%) and frequent PVCs (PVC burden ≥10%) in this specific population. We will calculate the prevalence of PVC-CM by dividing the number of subjects with frequent PVCs and CM by the overall subjects receiving Holters. As noted in our preliminary data, we speculate that the prevalence of both CM and frequent PVCs is 0.6% in subjects undergoing Holters. If our hypothesis is proven correct, we could demonstrate the potential magnitude of this clinical entity and the feasibility of the large-scale multicenter PAPS study by having 3 subjects with a potential PVC-CM diagnosis per 500 Holters.

**D. Ethical / Regulatory Affairs**

The study will be conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki and US 21 CFR. Due to inaccessibility to some subjects, a waiver of informed consent and a waiver of HIPAA will be requested as some subjects may not be accessible for consent.

There is a possibility that during the screening of ambulatory ECG Holters and echocardiograms, we may find subjects with possible undiagnosed PVC-CM. Ethically, we would then be obligated to notify the primary care provider and/or cardiologist of a potential undiagnosed PVC-CM leaving it up to them to pursue further referral/interventions.



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## ENROLLMENT, RETENTION AND FOLLOW UP PLANS

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This population is the interest of our research study since PVCs are frequently found, and in general these subjects are not considered a “hard-to-reach” population. PVC-CM does not appear to have a gender predisposition, but the difference by race or ethnic groups is unknown. Refer to document: Inclusion of Women and Minorities, where we address different approaches to include all races and ethnic groups. All participating centers are high-volume ablation institutions. We estimate each center treats at least 3 subjects within 2 years with a diagnosis of PVC-CM. Thus, participating centers should be able to enroll between 36-39 subjects to complete this 3-year pilot trial. Therefore, we are confident that recruitment goals will be met. We will engage clinicians and consultants to identify all subjects with frequent PVCs and mild to severe CM, regardless of duration, symptoms and heart failure during the following visits: 1) primary care and cardiology clinics, 2) device clinic referral for ICD implantation; 3) non-invasive laboratory with documented LV dysfunction by transthoracic echocardiogram and a minimum of  $\geq 10$  PVC/hour on average on at least a 24-hour Holter; 4) HF clinic with systolic LV dysfunction with frequent PVCs; 5) hospital admission to cardiac telemetry due to HF symptoms and PVC frequency of  $\geq 10$  PVC / hour and most importantly by 6) screening of consecutive ambulatory Holter monitors (PAPS Pilot study - Part II).

Once identified, potential study subjects will be asked to participate in the PAPS study by engaging primary care providers to explain to affected subjects the relevance of participating and/or engaging and disseminating information regarding this important clinical trial.

The enrollment and follow up plan will consist of different visits (see Research Strategy, Table 2 and Figure 1). Screening will consist of review of inclusion/exclusion criteria Baseline visit (Observation-Visit 1). If the subject meets inclusion/exclusion, then a baseline visit will be scheduled to obtain subject consent and if agreeable obtain NYHA assessment, quality of life questionnaire, ECG and perform randomization to either 1) RFA or 2) AADs groups. If the subject is randomized to RFA, the subject should be scheduled 12-weeks ahead during which the 3-month observation period will take place. If the subject is randomized to the AAD group, we will ask that initiation of AAD be delayed, as there is a possibility of spontaneous resolution during a 3-month observation period. The observation period consists of 3 visits, while the treatment period consists of a total of 5-6 visits depending on whether successful PVC suppression is achieved with the very first intervention (Table 2).

We plan to retain enrolled subjects by active engagement by different strategies including: 1) informing primary care and heart failure providers of the relevance of this study due to the lack of evidence of best treatment strategy, 2) scheduled follow ups, which will allow us to present and update all enrolled subjects in regard to the objective of the study, progress of the study as well as the importance of understanding the cardiovascular effects of PVCs; and 3) encourage and engage all subjects during all scheduled visits, answering all questions in regard to the study and health condition in an effort to minimize drop out and noncompliance and successfully complete follow up.

We believe that this comprehensive enrollment and engagement plan will: 1) help us enroll and retain research subjects that are representative of the population with cardiomyopathy associated with frequent PVCs, and 2) achieve trust from our subjects.

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## PROTECTION OF HUMAN SUBJECTS

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This human research study involves an NIH-Defined Phase III clinical trial, which we will conduct according to Good Clinical Practice Guidelines, the Declaration of Helsinki and US 21 CFR.

### Risks to Human Subjects

#### **a. Human Subjects Involvement, Characteristics, and Design**

##### ***Involvement of human subjects in the work outlined in the Research Strategy section.***

Premature ventricular contractions (PVCs) are frequently found in cardiomyopathy (CM) and heart failure (HF). Recently, high PVC burden has been associated with a reversible left ventricular (LV) systolic dysfunction, so-called PVC-induced CM (PVC-CM). Animal models have proven the concept that frequent PVCs can induce CM, which is reversed after eliminating PVCs. A current clinical conundrum is to recognize when PVCs are responsible for the development of a CM or secondary to a CM. Furthermore, it is unclear why the majority of subjects with frequent PVCs have a benign course, whereas up to one third develop CM.

Radiofrequency ablation (RFA) is an accepted intervention to restore LV function in CM potentially induced by PVCs, based solely on limited small retrospective studies. RFA can have risks as any other invasive procedure. Antiarrhythmic drugs (AAD) therapy is an alternative therapy offered to eliminate PVCs if subjects or physicians feel appropriate; however, no randomized-prospective study exists to understand the clinical outcomes and benefit of RFA when compared to AAD therapy. Appropriate diagnosis and treatment of PVC-CM could impact HF morbidity, mortality and healthcare spending.

These clinical relevant questions cannot be addressed in animal models. Thus, we propose this prospective multicenter randomized trial of subjects with CM and high PVC burden with a likely diagnosis of PVC-CM. This pilot study intends to provide the basis to design and power a large clinical randomized trial to assess reversal of CM associated with frequent PVCs between RFA and AADs and compare clinical benefits (improvement in quality of life, NYHA class, heart failure symptoms and decrease in hospital admissions) between RFA and AADs in PVC-CM.

##### ***Characteristics of the subject population, including their anticipated number, age range, and health status if relevant.***

We will include subjects of any race, ethnic group, gender and adult age (18 years or older) with frequent PVCs (defined as PVC burden  $\geq 10\%$  by at least a 24-hr ambulatory Holter) ) and LV dysfunction (LVEF  $\leq 45\%$ ) without any clear reversible cause of CM (Study Design – Part I: Table 1). All subjects that meet inclusion/exclusion criteria will be offered participation in this study regardless of gender, age or ethnic background. We will attempt to have diversity in age, gender and ethnicity in our study by involving the general population treated in different University Hospitals, even though, there is no evidence that age, gender or ethnic groups will respond differently to treatment arms. While most subjects will be asymptomatic (no palpitations), the degree of heart failure symptoms will be variable (none to moderately severe). Based on sample size estimates, the full scale PAPS study will require 140 subjects randomized to either RFA (70 subjects) or AAD therapy (70 subjects) to assess differences between RFA and AAD treatments (see Sample size justification Section in Study Design – Part I). However, we propose a pilot study of 36-39 subjects (20% of subjects) to determine acceptability of treatment randomization of RFA versus AADs, rate of spontaneous recovery of CM and PVCs, responders, adverse events and treatment crossover, and to assess the feasibility of enrolling, randomizing and retaining participants. This pilot study will allow us to better design and power the large prospective PAPS study.

In addition, we propose to screen all consecutive subjects undergoing at least a 24-hr, ambulatory ECG Holter for frequent PVCs ( $\geq 10\%$  burden) and LVEF  $\leq 45\%$ . This has the intention to better estimate the prevalence of PVC and CM in this specific population.

No vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations will be enrolled in our study.

##### ***Sampling plan, recruitment and retention strategies and criteria for inclusion or exclusion of any subpopulation.***

A signed informed consent will be obtained from each participating subject. Inclusion and exclusion criteria are the same for all subjects regardless of gender, age, race or ethnic group (See details in document: Study Design – Part I: Table 1). We plan to recruit study subjects using different strategies and settings, but primarily by: 1) Engaging clinicians and consultants to identify subjects during visits to Primary care and cardiology clinics, Device and arrhythmia clinic, Non-invasive cardiac laboratory, heart failure clinic, and hospital admissions; 2) local heart failure service, and most importantly 3) screening of ambulatory ECG Holters that will allow us to identify subjects with frequent PVCs (Design Study – Part II). Due to inaccessibility to some subjects with previous Holters, a waiver of informed consent and a waiver of HIPAA will be requested for subjects in Part II as they may not be accessible for consent.

As a retention strategy, we will request each participating center to remain engaged with active study subjects through local heart failure groups and monthly emails or phone calls.

***Procedures for assignment to a study group. As related to human subject's protection, describe and justify the selection of an intervention's dose, frequency and administration.***

This is a *prospective randomized-controlled study* of subjects with CM and high PVC burden with a likely diagnosis of PVC-CM, where individual subjects will be assigned with a 1:1 random allocation to one of two un-blinded parallel groups (Figure 1): 1) PVC radiofrequency ablation (RFA) vs. 2) AADs. Since we expect about 30% of subjects will have a PVC burden >20%, we plan a stratified randomization based on PVC burden above and below 20% reported by at least a 24-hour Holter. Stratified randomization will assure equal distribution of subjects between PVC burden above and below 20%. Stratified randomization will be performed only at the Coordinating Center using biostatistics software and/or service (randomization.net). This stratified randomization will assure that both groups (RFA vs. AADs) are equally distributed between PVC burden above and below 20%.

A few small studies suggest that an overall PVC burden more than 20% may affect LV function and NYHA functional class. In contrast, PVC burden of less than 10% is less likely associated with impairment of LV function. Interestingly, a few studies with PVC burden as low as 10 PVCs per hour have shown some degree of improvement in LV ejection fraction after PVC suppression. Based on limited data, we chose  $\geq 10\%$  PVC burden as inclusion criteria for our study, as we believe these are subjects with a higher likelihood of a diagnosis of PVC-CM.

As proposed in this study, we have an observation period that would allow us to assess and compare no active intervention (3-month observation) vs. PVC suppression (treatment phase). Moreover, our study design will allow us to compare two PVC suppression strategies: 1) RFA versus 2) AADs. Successful PVC suppression is defined as a decrease in 80% of PVC burden after 2-4 weeks of procedure. Single RFA of PVCs has been shown to be successful in more than 80% of cases. As in current practice, we plan to repeat a second RFA after 4-6 weeks on those subjects with unsuccessful RFA (less than 80% decrease in PVC burden after RFA group). Since all subjects will start or continue optimal medical therapy regardless of treatment randomization, they will be followed approximately every 3 months in order to assure compliance and assess potential side effects.

***Collaborating sites and role of collaborating investigators in performing the proposed research.***

1. We have involved at least 9 nationally-renowned high-volume electrophysiology centers across the United States to participate in this study)

Each local investigator (co-investigator) will be responsible for obtaining consent, following the research plan as outlined, reporting severe and non-severe adverse events within 24-48 hours of knowledge of the event, protecting subject's rights and welfare, securely storing and submitting accurate subject data, notifying the Coordinating Center of all IRB correspondence. Central IRBs will be arranged for most institutions except VA Medical Centers. Each local site is responsible for protecting the safety and welfare of research subjects at their sites. All institutions will have in place instructions to store subject's files and records in a secure locked location. Any questions from local investigators/collaborators and coordinators in regard to subject enrollment, follow-up and/or termination should be addressed directly to the National Research Coordinator.

Each center will submit Case Report forms via a secure encrypted data capture system (REDCap) and/or scan/fax or special carrier service. A contractual agreement with REDCap (Research Electronic

Data Capture) will be established in order to perform encrypted electronic data capture of research subject's data throughout this 3-year national multicenter clinical trial. REDCap is a scalable, secure, enterprise-level application. Planning, configuration and end-user support for REDCap is provided by the VCU Clinical Center for Translational Research (CCTR). The REDCap platform at VCU is approved by VCU/VCUHS ISOs, has been extensively vetted and approved for capture of sensitive data (e.g. PHI), and is approved/recommended by the VCU IRB. The CCTR clinical research informatics group will provide project-specific training to all end users regarding access, permissions, reporting, data quality checks, audit trail, self-help options, database design considerations, export and reporting capabilities, etc. The software is delivered via 256 bit SSL-encryption, and features: 1) an intuitive interface for the creation of case report forms (CRFs) and validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) procedures for importing data from external sources; the ability to relate CRFs to study events and schedule them via a calendar function; and 4) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, STATA, R).

The Coordinating Center will store and protect subject's files and records in a secure locked location, while all electronic data will be secured in a secure (password-protected) encrypted server.

### **b. Sources of Materials**

We will record baseline subject demographics, including age (date of birth), gender, race, ethnicity duration of cardiomyopathy, calculated LVEF, history of atrial fibrillation, and medical therapy including dosing prescription. We will obtain a 12-lead ECG, Minnesota living with Heart failure QOL questionnaire and NYHA functional class, ambulatory ECG Holter, echocardiogram and cardiac MR (if clinically indicated) as per protocol. All details related to the observation period and treatment arms of RFA or antiarrhythmic drug (AAD) therapy will be recorded. Details related to RFA of PVCs will be obtained, including PVC morphology and location, different PVC morphology, number of RFA/cryo lesions, radiation exposure, peri- and post-ablation complications, fluoroscopy time, procedure duration and days of hospitalization related to RFA. Similar data will be collected from subjects randomized to the AAD arm if applicable. We will obtain case report forms (containing data above) from the Coordinating Centers as well as from the participating centers. This data will be sent via electronic data capture and/or fax in complete case report forms.

Data will be collected directly from the subject, research coordinator and local investigator as per protocol. This will be recorded by the investigator and/or research coordinators. All participating sites will comply with all applicable laws, regulations and provisions related to information privacy and data security in regard to individually identifiable private information. Local institutions will have only access to individual identifiable private information. A unique identifier will be given to each subject to identify subjects in the event that the study provides information that may affect the subject's willingness to continue participation in the study and that would require sites to reach the research subject.

Each local investigator (collaborator) will be required to obtain consent, follow the research plan as outlined, report severe and non-severe adverse events within 24-48 hours of becoming aware of the event, protect subject's rights and welfare, securely store and submit accurate subject data, notify the Coordinating Center of all local IRB correspondence (if applicable). Each local site is responsible for protecting the safety and welfare of research subjects at their sites. All institutions will have in place instructions to store subject's files and records in a secure locked location.

All participating institutions will be required to complete and submit all data directly to the Coordinating Center via a secure encrypted data capture system (REDCap, as described above) and/or scan/fax or special carrier service. The Coordinating Center will not require nor accept blood specimens from research subjects. All participating and coordinating institutions will have in place directives to store subject's files and records (including identifiable private information) in a secure locked location.

### **c. Potential Risks**

The study will be conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki and US 21 CFR. Current clinical practice offers radiofrequency ablation (RFA) plus optimal medical therapy to the population of interest (frequent PVCs associated with cardiomyopathy) supported only on retrospective and non-randomized observational studies with a relatively short (3-6 months) follow up period. Alternative treatments include use of antiarrhythmics and/or optimal medical therapy alone. Risks associated with RFA include cardiac tamponade, bleeding, stroke, AV block, myocardial infarction

and even death. Risks related to antiarrhythmic drugs include common significant drug-to-drug interactions and side effects depending on specific drugs, which commonly leads to poor compliance. Amiodarone for instance, as the primary proposed antiarrhythmic drug in this pilot study, can have significant side effects such as dizziness/lightheadedness, pro-arrhythmic (ventricular tachycardia, torsade de Pointes), thyroid disorders, elevated liver enzymes, optic neuritis, pneumonitis and lung disease depending on dosing. In contrast, optimal medical therapy alone is not considered to add any additional risks to the current illness, however, it is unclear if by not eliminating PVCs (either with RFA or antiarrhythmics) we are potentially withholding a beneficial intervention. Our study proposes to randomize these subjects to two groups: 1) RFA and 2) AAD only after a 3-month observation period (control). The risks of the subjects participating in this research proposal are considered small primarily because most of these subjects would undergo RFA as frequent yet unproven therapy. A 3-month observation period (control) is an ethical intervention since 1) no randomized controlled study has been performed to assess if RFA is better than optimal medical therapy 2) this elective procedure usually is scheduled 8-12 weeks after diagnosis in most high volume medical centers, and 3) it is unclear if PVCs would decrease with time and without intervention with subsequent improvement of LV function without the need for invasive procedures. Finally, our study would not impose any psychological, financial or legal issues.

Serious adverse events (SAE) will be monitored for all subjects during their participation in this study. The central IRB will be notified of any serious adverse events within 24 hours of our knowledge of such event. Additionally, SAEs should be reported to the Coordinating Center within 24 hours of the site becoming aware of the event (see details below Sections: Protection against risks and Data Safety Monitoring).

## **Adequacy of Protection against Risks**

### **a. Recruitment and Informed Consent**

#### ***Describe plans for the recruitment of subjects and the process for obtaining informed consent.***

The study will be conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki and US 21 CFR. We plan to identify study subjects using different methods and settings: 1) Engaging clinicians and consultants to identify subjects during visits to Primary care and cardiology clinics, Device and arrhythmia clinic, Non-invasive cardiac laboratory, heart failure clinic, and hospital admission; 2) local heart failure service and 3) subjects identified with frequent PVCs and CM during ambulatory ECG Holter screening (PAPS Pilot study – Part II). We plan to include only adults (greater than 18 years of age) Children will not be included as addressed in Section: Inclusion of Children (see below).

Potential study subjects will be further introduced to the proposed study by engaging primary care providers to explain to affected subjects the relevance of participating and/or engaging and disseminating information regarding this important clinical trial.

Once introduction to the health issue of cardiomyopathy and frequent PVCs occurs, the principal investigator, collaborators and/or research coordinators will personally approach the potential subject in a 1:1 setting to further discuss the option of participating in this study. Personnel obtaining consent should explain in detail the aims and methodology of the study and potential benefits and risks associated with the study (described below). Only after the subject is allowed to ask questions and they are all addressed, will the subject be asked to sign informed consent if he/she is in agreement with participating in the study. We will recommend to all participating sites to preferably consent the subject in the presence of a relative and/or witness. Signed written informed consent will be obtained from all subjects before protocol-specific procedures are carried out. Subjects will be informed of their right to withdraw from the study at any time.

### **b. Protections against risk**

In order to minimize potential risks, the proposed project will require IRB approval at all participating institutions. The professional qualifications and resources (including time, equipment, support services) of principal investigators and collaborators and research teams will be required to protect and minimize potential harm to participants. Research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges.

The Human Subjects CITI Online training including **Biomedical Research Investigators and Key Personnel (Basic Course Module) would be required** to minimize risks to privacy and confidentiality of

data of Human research participants. Completion of the CITI training is required of all research team members prior to participating in the proposed study.

Furthermore, a Data and Safety Monitoring Plan has been developed and will be submitted to the central IRB and NIH for approval prior to the accrual of human subjects (see details below).

***Medical or professional intervention in the event of adverse effects to the subjects.***

All research performed under this study will conform to laws, regulations policies and procedures pertaining to protections for human subjects. Collaborating centers and the Coordinating Center shall immediately notify each other, and the investigator shall promptly notify the IRB, upon identifying any aspect of the Protocol, including unanticipated problems involving risk and information discovered during site monitoring visits/remote site monitoring visits or in the study results that may adversely affect the safety, well-being, or medical care of subjects, or that may affect the willingness of subjects to continue participation in the research, may influence the conduct of the study, or may alter the IRB's approval to continue the study. When subject safety could be directly affected by study results, the Coordinating Center will notify participating sites who will provide written communication to affected subjects.

The Investigator and/or research coordinator at each participating center will be responsible for collecting data in regard to adverse events. The investigator must decide whether each incident meets the definition of a SAE. Once the local Principal Investigator (PI) determines that a serious adverse event meets reporting requirements, he/she must report the SAE, and related safety information, to the Coordinating Center on the required *Significant Adverse Event Report Form* (See form attached) provided for this purpose. Additionally, local SAEs should be reported to the Coordinating Center and IRB of record per policy. If the adverse event results in the need to revise the informed consent, or other study documents, the PI will submit a request for a modification through the Coordinating Center to the IRB of record. An extensive Data Safety Monitoring Plan (DSMP) is provided.

**Potential Benefits of the Proposed Research to Human Subjects and Others**

The prevalence of frequent/high PVC burden and cardiomyopathy is key as it is likely that subjects are under recognized. Furthermore, understanding the potential benefits of RFA of PVCs versus AAD therapy in subjects with CM and frequent PVCs are particularly important to subjects as we will try to understand the best treatment strategy to eliminate PVCs and if indeed both improve LV function, change quality of life, improve or even eliminate HF symptoms, morbidity and mortality, as well as avoid the need for implantable cardiac devices with all associated medical expenses. In addition, understanding the PVC features associated with CM is paramount to properly target subjects that are likely to respond to RFA of PVCs, and avoid this invasive procedure in subjects that are less likely or do not have clinical benefit.

***Risks versus anticipated benefits to research participants and others.***

The risks of the subjects participating in this research proposal are reasonable, since it is not clear if the benefits outweigh the risks of RFA. Even though risks of RFA are considered small, these can be serious (cardiac tamponade, bleeding, stroke, AV block, myocardial infarction) and even result in death. Current clinical practice offers RFA to subjects with frequent PVCs associated with cardiomyopathy supported only on retrospective and non-randomized observational studies with a relatively short 3-6 month follow up period. It is unclear if PVCs would decrease with time and without intervention with subsequent improvement of LV function without the need for invasive procedures. Thus, we believe that we need to further study the benefits of this invasive procedure to assure that it justifies the risks associated with it.

**Importance of the Knowledge to be gained**

**Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.**

The PAPS pilot study will help us understand the prevalence of PVC-CM and gather key information to better design and power a large randomized trial – the PAPS study. This large randomized study would aim to improve evidence-based treatment options in subjects with frequent PVCs and LV dysfunction with or without heart failure, as we plan to compare RFA of PVCs vs. antiarrhythmic drug (AAD) therapy.

Subject's health could be improved in those subjects with PVC-CM if subsequent normalization of LV function occurs after RFA of PVCs, avoiding heart failure and device implantation. Otherwise, these

subjects can be incorrectly considered or diagnosed with a persistent irreversible form of CM with subsequent HF morbidity and mortality. Thus, subjects with PVC-CM could have a significant improvement and/or normalization of quality of life, heart failure symptoms and NYHA class, while decreasing morbidity and mortality associated with HF and CM after elimination of PVCs with RFA. Moreover, these subjects would not require implantable cardiac devices.

Change in current clinical practice would occur if our study's hypotheses are proven correct, since Holter monitors would be routinely requested as standard of care to rule out PVC-CM in all the following subjects: 1) newly diagnosed CM with or without heart failure and 2) chronic LV dysfunction that demonstrate PVCs with or without heart failure and/or implantable cardiac devices. Furthermore, this study would attempt to understand predisposing factors and PVC features associated with PVC-cardiomyopathy. This would lead to a change in current practice as it will guide us to closely follow up those subjects at risk to develop PVC-CM.

The proposed study will impact several aspects of subject care, such as: 1) evaluate clinical benefits of RFA of PVC in subjects with suspected PVC-CM, by assessing changes in quality of life, HF symptoms and morbidity, 2) assess improvement in LV function after RFA of PVCs and/or AADs, which will in turn reduce the need for expensive implantable cardiac defibrillators (ICDs); 3) identify the PVC burden threshold required to induce CM, helping us to properly diagnose PVC-CM and target specific therapy, such as RFA of PVCs, to only those subjects likely to respond to RFA; and 4) decrease the financial burden associated with poor quality of life, heart failure symptoms and hospital admissions, and ICDs in subjects with frequent PVCs and CM.

#### Risks to subjects in relation to the importance of the knowledge that may be expected to result.

Risks associated with research subjects in this proposed study are considered small and acceptable since most of these subjects would have been scheduled for RFA of PVCs without a clear understanding of the benefits associated with RFA. In contrast, the risks related to those subjects undergoing RFA of PVCs are small but can be potentially severe (as described above).

Current gaps in knowledge include: 1) possible placebo effect of RFA as spontaneous resolution of PVCs could have occurred even without RFA of PVCs, 2) best treatment strategies, either RFA or AADs, to achieve successful PVC suppression, 3) unclear clinical benefits (quality of life, NYHA class, HF symptoms, HF morbidity and mortality, implantable cardiac devices) of RFA of PVCs or AADs in the setting of PVC-CM, and 4) PVC features required to induce CM, in which subjects should be referred to RFA of PVCs or initiate AADs. Until now, there have been no randomized-controlled studies of subjects with PVC-CM to clarify and answer these questions.

*In summary, without clear evidence of the benefit of RFA in subjects with cardiomyopathy associated with frequent PVCs, we believe that the risk of withholding RFA is similar to the risk of those subjects undergoing an invasive procedure such as RFA of PVCs.*

#### **Data and Safety Monitoring Plan (DSMP)**

A detailed Data and Safety Monitoring Plan (DSMP) will be submitted to the IRB and NIH (funding institution) for approval prior to the accrual of human subjects. The Data Safety Monitoring Plan is written to ensure the safety of the participants and verifying the validity and integrity of the data (see details in document: Protection of Human Subjects). Details are expanded on document: Data Safety Monitoring Plan.

A Data and Safety Monitor Board (DSMB) will consist of 2 heart failure specialists (Drs. James Fang and Ryan Tedford) and a cardiac electrophysiologist (Dr. Thomas Dewland) (see letters of support) that have no direct investment in the study to prevent jeopardizing subject safety. In addition to the Coordinating Center and central IRB, the DSMB will review the research protocol and plans for data safety and monitoring, evaluate the progress of the trial with periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and reports from related studies.

The DSMB will meet every 4 months to review data and adverse event reports. Additionally, they will meet to review interim analysis when available. This will be performed in a closed session with open access to the PI if requested by the Board. Data monitoring will focus on several areas: 1) Performance, which will allow us to assess site performance with respect to subject recruitment, retention and follow-up, flow of data forms, protocol adherence and quality of data; 2) Safety, which will allow us to assess the magnitude

of adverse events; and 3) Treatment, in order to monitor and assess treatment effects (described under Section: Potential Risks).

### **ClinicalTrials.gov Requirements**

As required, the PAPS pilot study has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT03228823).  
<https://clinicaltrials.gov/ct2/show/NCT03228823?term=NCT03228823>

### **Inclusion of Women, minorities and children**

As per instructions, these aspects are detailed in separate documents:

- 1) Inclusion of Women and Minorities.
- 2) Inclusion of Children.



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## DATA SAFETY MONITORING PLAN

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The PAPS Pilot study is a national multicenter randomized control study to enroll between 36-39 subjects with cardiomyopathy associated with frequent PVCs. This is a phase IV trial with moderate risk as participating subjects will be randomized to two different strategies (RFA versus AAD) commonly used in clinical practice to treat subjects with frequent PVCs. We consider this study to be moderate risk since most subjects with a suspected PVC-CM would undergo RFA as a common clinical practice (as discussed above). All research performed under this study will conform to laws, regulations and VA policies and procedures pertaining to protections for human subjects.

In addition to Coordinating Center and central IRB oversight, a Data Safety Monitoring Board (DSMB) will be organized according to the FDA recommendations to review all serious adverse events as well as study progress (including all adverse events) every 4 months after study initiation. The DSMB will be integrated by faculty members from institutions without active enrollment in the study and without a vested interest in the proposed research that have different expertise (see DSMB section in Protection of Human Subjects document). The members of the DSMB will have full access to all study records and will have the authority to discontinue the study at any time. Please consult the Protocol in Appendix for additional details.

A detailed Data and Safety Monitoring Plan (DSMP) will be submitted to the IRB and NIH (funding institution) for approval prior to the accrual of human subjects. The Data Safety Monitoring Plan is written to ensure the safety of the participants and verifying the validity and integrity of the data.

During each scheduled visit and in between visits, subjects will be asked and instructed to call in regard to any event out of the ordinary. Those subjects randomized to the RFA group will be evaluated immediately, throughout the first 24 hours and 1-2 weeks after the procedure by the research team as standard follow up on any of these procedures. It will be the responsibility of the investigator/coordinator to assess the subject personally and request laboratory or any appropriate tests if needed. All adverse events including serious adverse events (SAE) will be monitored for all subjects during their participation in this study.

a. Adverse event (AE) grading and attribution scale. The investigator will try to determine the relationship of adverse event to RFA and/or AAD therapy as not related, possibly related, or definitely related using standard criteria for clinical trials. All grades of toxicity will be noted.

The following grading and attribution scale will be employed:

- 0 = No adverse event or within normal limits
- 1 = Mild AE, not requiring treatment
- 2 = Moderate AE, resolved with treatment
- 3 = Severe adverse event (SAE) is any untoward medical occurrence that at any point during the study:
  - Results in death
  - Life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
  - Requires in-patient hospitalization or prolongation of existing hospitalization – Hospital admission is usually interpreted as requirement of at least one overnight stay in subjects in the medical therapy arm or PVC suppression; whereas in subjects in the PVC suppression arm, a prolonged hospital stay will be defined if more than two days of hospital stay is required after RFA ablation. Treatment and release from an emergency department generally does not qualify as a hospitalization, unless the event qualified as an SAE based on other criteria.
  - Results in persistent or significant disability/incapacity
  - Considered medically significant by the investigator or requires intervention to prevent any of the outcomes above. Medically significant are those events considered important in the investigator's opinion and which may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

b. Reporting of Adverse Events (AE)

The Investigator and/or research coordinator at each participating center will be responsible for collecting data in regard to adverse events. The investigator must decide whether each incident meets the definition of a SAE.

*Reporting Requirement:* Once the local Principal Investigator (PI) determines that an adverse event meets the IRBs' reporting requirements, he/she must report the SAE and related safety information to the Coordinating Center on the required *Significant Adverse Event Report Form* (See form attached) provided for this purpose. Supporting documents, including a copy of the Informed Consent, should also be emailed/submitted through REDCap. For reasons of confidentiality, subject's names must not be included in the report. Additionally, local SAEs must be reported to the IRB of record per policy. If the adverse event results in the need to revise the informed consent, or other study documents, the PI will submit a request for a modification through the Coordinating Center to the IRB of record.

c. Annual Data and Adverse Events Report

This report will be prepared annually by the PI and research coordinator at the Coordinating Center. This report will include the number of subjects actively enrolled, those that abandon and complete the research protocol, as well as, all side effects and adverse events in both groups.

In addition, an interim analysis or treatment monitoring will be performed by VCU Research Incubator. Due to a small risk related to RFA (estimated 2-3%), this interim analysis will be performed once the first 15 subjects (half of sample size) have completed a 15-month protocol. Data reports and interim analysis will be reviewed by the IRB at the Coordinating Center and DSMB during its convened meetings.

d. Data management and safety review

Collaborating centers and the Coordinating Center shall immediately notify each other, and the Coordinating Center shall promptly notify the IRB, upon identifying any aspect of the Protocol, including unanticipated problems involving risk and information discovered during site monitoring visits/remote monitoring visits or in the study results that may adversely affect the safety, well-being, or medical care of subjects, or that may affect the willingness of subjects to continue participation in the research, may influence the conduct of the study, or may alter the IRB's approval to continue the study. When subject safety could be directly affected by study results, the Coordinating Center will notify participating sites who will provide written communication to affected subjects.

A Data and Safety Monitoring Board (DSMB) will consist of 2 heart failure specialists (Drs. James Fang and Ryan Tedford) and a cardiac electrophysiologist (Dr. Thomas Dewland) (see letters of support) that have no direct investment in the study to prevent jeopardizing subject safety. In addition to the IRB, the DSMB will review the research protocol and plans for data safety and monitoring, evaluate the progress of the trial with periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and reports from related studies.

The DSMB will meet every 4 months to review data and adverse event reports. Additionally, they will meet to review interim analysis when available. This will be performed in a closed session with open access to the PI if requested by the Board. Data monitoring will focus on several areas: 1) Performance, which will allow us to assess site performance with respect to subject recruitment, retention and follow-up, flow of data forms, protocol adherence and quality of data; 2) Safety, which allows us to assess the magnitude of adverse events; and 3) Treatment, in order to monitor and assess treatment effects.

The DSMB has the responsibility to make written reports of their findings and recommendations to the Coordinating Center, IRB, NIH/NHLBI (funding institution) and investigators concerning continuation or conclusion of the trial if it considers that RFA has a significantly higher benefit or increased risk as compared to the control arm. Annual data safety, adverse event reports and interim analyses may result in the need to revise the informed consent, or other study documents, for which the PI must submit a study amendment to the IRB. This could result in early study termination only if continuation will not produce benefit to subjects or if the treatment outcome is known to have benefit.

In accordance with the terms of the Federal Wide Assurance, the Office for Human Research Protections (OHRP) and the Federal Drug Administration (FDA) will be notified in a timely manner of 1) serious or continuing noncompliance; 2) significant adverse events involving risk to participants or others; or 3) suspension or termination of IRB approval for a study.

Governance plan, administrative, technical and scientific responsibilities of PIs and research coordinators are detailed in the document: Leadership plan. If an unexpected scenario was to occur, all PIs will have to be in agreement in order to change or deviate from the protocol with appropriate notification to collaborating centers. Similarly, if during a review or recommendation of the Data Safety Monitor Board (DSMB) is made, all PIs will discuss and agree to modify or make appropriate changes to address concerns of the DSMB.

**Prospective Assessment of PVC Suppression in Cardiomyopathy (PAPS): A Pilot Study**

**REPORT OF SIGNIFICANT ADVERSE EVENT**

Serious and unexpected events that are related to research under the supervision of the local IRB must be reported to the Human Protection Administrator (HPA) in your institution. This form, should be submitted as soon as possible to your IRB and coordinating Center (McGuire VA Medical Center), but **NO LATER THAN 24-48 WORKING HOURS** after first awareness of the problem. Refer to the **IRB Guidelines for Reporting Significant Adverse Events** for more information.

PRINCIPAL INVESTIGATOR: \_\_\_\_\_ DEPARTMENT: \_\_\_\_\_  
INSTITUTION: \_\_\_\_\_  
SUBJECT'S INITIALS: \_\_\_\_\_ AGE: \_\_\_\_\_ DATE OF INCIDENT: \_\_\_\_\_  
**RESEARCH PROCEDURE INVOLVED:** \_\_\_\_\_

**DESCRIBE IN DETAIL THE NATURE AND TIMING OF EVENT(S) (A Letter Explaining Any Other Details Should be Attached if Needed.):** \_\_\_\_\_

**The Likelihood The Injury Was Caused By The Study Is:**

Definitely Unrelated \_\_\_\_\_ Unlikely \_\_\_\_\_ Possible \_\_\_\_\_ Probable \_\_\_\_\_

**Event Appears To Be:**

Directly \_\_\_\_\_ Indirectly \_\_\_\_\_ Not Related To Research Treatment \_\_\_\_\_

**Check All That Apply:**

Resulted in Hospitalization \_\_\_\_\_ Resulted in Disability \_\_\_\_\_ Required Supportive Treatment \_\_\_\_\_ Subject Remains on the Study \_\_\_\_\_ Subject Died \_\_\_\_\_

**DESCRIBE TREATMENT OF THE INJURY:**

By Whom: \_\_\_\_\_ Where: \_\_\_\_\_

**DID PI REPORT THIS INCIDENT TO:** Coordinating Center \_\_\_\_\_ Co-Investigator(s) \_\_\_\_\_ Other \_\_\_\_\_

**Signature of PI:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Printed Name of PI:** \_\_\_\_\_ **Phone:** \_\_\_\_\_

**Signature of Person Reporting:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Printed Name of Person Reporting:** \_\_\_\_\_ **Phone:** \_\_\_\_\_

**DOES THIS EVENT REQUIRE REVISION TO THE PROTOCOL? Yes \_\_\_\_\_ No \_\_\_\_\_**

**DOES THIS EVENT REQUIRE REVISION TO THE CONSENT? Yes \_\_\_\_\_ No \_\_\_\_\_**

*If YES to Either, Please Submit Appropriate Paperwork.*

**REMINDER:** *If there is any new information contained in this report that might have an impact on issues of risk connected with this study a revision must be made to the protocol and/or consent.*

# **Prospective Assessment of PVC Suppression in Cardiomyopathy (PAPS): A Pilot Study**

## **Serious Adverse Events**

Date: \_\_\_\_\_

<b>Subject</b>	<b>Age</b>	<b>Treatment date</b>	<b>Event</b>	<b>Onset Date</b>	<b>Outcomes (e.g. hospitalization, concomitant meds, study, status, etc.)</b>

### **Relationship**

- Definitely Unrelated       Unlikely       Possibly related  
 Probably related       Definitely related

### **Description**

- Event or problem  
 Resolved       Ongoing       Copy of SAE reported attached  
 Anticipated       Unanticipated
- Was the subject withdrawn from the project  
 Yes on \_\_\_\_\_ (date)  
 No       Not applicable

### **Actions taken:**

- Do you recommend modifications in the project (e.g. protocol changes, informed consent changes)?  
 Yes      If yes, submit a Modification of Approved Research IRB submission Form  
 No
- Has the sponsor been notified of the event or problem?  
 Yes       No       Not applicable
- Describe actions taken or will take to minimize risks:  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Investigator Signature  
(Sub investigator may sign if the investigator is unavailable)

\_\_\_\_\_  
Date

**Prospective Assessment of PVC Suppression in Cardiomyopathy (PAPS): A Pilot Study**

**Adverse Events**

Date: \_\_\_\_\_

Subject	Adverse Event	Onset Date	Ending Date	Severity	Studyrelated Yes or No?	Action	Outcome

**Codes:**

Severity	Drug Related
1 – Mild	0 = Definitely Unrelated
2 = Moderate	1 = Unlikely
3 = Severe	2 = Possibly Related
4 = Life threatening	3 = Probably Related
	4 = Definitely Related

Action (taken)	Outcome
0 = None	1 = Resolved
1 = Dose Modification	2 = Recovered with minor sequelae
2 = Counteractive Medication	3 = Recovered with major sequelae
3 = Medical / Surgical intervention (specify under comments)	4 = Condition still present and under treatment
4 = Hospitalization	5 = Condition continues to worsen
5 = Treatment/drug permanently discontinued	6 = Subject died
6 = Other (specify under comments)	

Comments:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_  
Investigator Signature  
(Sub investigator may sign if the investigator is unavailable)

\_\_\_\_\_  
Date

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## **INCLUSION OF WOMEN AND MINORITIES**

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Based on observational non-randomized studies, PVC-CM does not appear to have a gender or age predisposition. Furthermore, no definite data has been published in regard to the prevalence of PVC-CM and/or degree of response to radiofrequency ablation (RFA) or antiarrhythmic drugs (AADs) by gender, race or ethnic groups.

As outlined in the Research Strategy Section, all subjects that meet inclusion/exclusion criteria will be offered participation in this study regardless of gender, age, race, ethnicity, geographic, or clinical status. We will attempt to have diversity in age, gender, race and ethnicity in our study by involving the general population treated in high-volume referral University Hospitals across the country. We expect to have a wide range of age groups and an even proportion of gender in this proposed study. However, we cannot describe or predict the goals of race and ethnic groups.

We will request each collaborating/participating center to identify local referrals with a high percentage of women and minorities. In addition, we will request collaborators to directly approach primary care providers in several forms on a regular basis (every quarter) to make them aware of the relevance and importance of completing the proposed clinical trial including women and minorities.

We intend to compare response to RFA and AADs between these different populations; however, the PAPS study is not powered to compare between different populations since this would require several hundred subjects. Findings of the PAPS study could potentially provide the basis for designing future studies properly powered to assess differences in response between gender and minorities.

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## **INCLUSION OF CHILDREN**

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The prevalence of premature ventricular contractions (PVCs) is generally age-dependent, ranging from <1% in children < 11 years to 69% in subjects >75 years. Furthermore, frequent PVCs in children appear to have minor impact on LV function with few cases of PVC-induced cardiomyopathy.

Children (defined as individuals under 18 years of age) will be excluded from the proposed research since PVC-induced CM is extremely rare in children. Furthermore, the risk of complications with invasive procedures in this population may be unwarranted given the unknown benefits. An attempt to enroll children would result in a significant delay to complete the proposed study with a need to expand this study for several years.

### Data Sharing Plan

*Note: The requirement for a data-sharing plan applies only to studies that are requesting funding at a level greater than \$500,000 in direct costs in any project year.*

Our proposed study does not require funding greater than \$500,000 in direct costs in a year, for which this section does not apply to our proposal. This grant application is solely to initiate a pilot study of frequent PVCs and cardiomyopathy. Results of this preliminary data will not provide final definitive data, yet we will make it available. However, we will make clear that this pilot data is not intended to answer benefits of different PVC suppression strategies to avoid misinterpretation or inaccurate conclusions based solely on our preliminary data.

### Replication of Research Findings

The PAPS pilot study is a multidisciplinary prospective multicenter collaborative randomized-controlled trial to be performed in a broad population of subjects with cardiomyopathy associated with frequent PVCs. If funding is granted, this pilot data will provide a better estimate of the prevalence of frequent PVCs and cardiomyopathy, as well as pave the way for the PAPS trial, a large-scale multicenter randomized clinical trial.

Thus far, only retrospective and observational non-randomized studies have been performed. If the PAPS study were to be launched in the future, it could be the first prospective randomized trial to study the effects of catheter radiofrequency ablation in subjects with PVC-induced cardiomyopathy. Particularly it could help us better identify subjects that will benefit from PVC suppression with subsequent improvement in subject's health, subject outcomes and narrow a gap in knowledge in regard to those subjects with frequent PVCs and cardiomyopathy.

We understand the relevance of making available information that would allow any other researchers/colleagues to further develop or expand other relevant knowledge in this important area. Thus, upon receiving funding, we plan to pursue the following steps:

- 1) Register the trial at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- 2) Register our study at the International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/prospero/>)
- 3) Describe study datasets, including code books, meta-data related to datasets, and documented programming code used for creating the final study population, for creating variables, and for conducting all outcomes analysis. This information will be provided within 3 months of the end of the final funding year.
- 4) Submit a manuscript to a major peer-review journal such as Circulation, Heart Rhythm Journal or The Journal of American College of Cardiology that describes study population and detailed methodology including study population, data definitions, main objectives, hypothesis, preliminary findings of pilot study, future directions of the study including primary and secondary outcomes, studied variables and analysis plan. This would be submitted for publication within 12 months of receiving funding.



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