Prospective Assessment of Premature Ventricular Contractions

Suppression in Cardiomyopathy (PAPS): A Pilot Study

CLINICAL INVESTIGATION PLAN

Sponsored by:
National Institute of Health (NIH)
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Principal Investigators
Jose F. Huizar, M.D. (Contact PI & Translational Research, McGuire VA Medical Center)
Carlos Morillo, M.D., (Tri alist, University of Calgary)
Teresa De Marco, M.D. (Heart Failure, University of California San Francisco)
Kenneth A. Ellenbogen, M.D. (Electrophysiologist, Virginia Commonwealth University)
Edward Gerstenfeld, M.D. (Holter Core lab, University of California San Francisco)
Gregory Hundley, M.D. (Magnetic Resonance Core lab, Wake Forest University)
John Gorcsan III, M.D. (Echo Core laboratory, University of Pittsburg)
Adam Sima, Ph.D. (Biostatistician, Virginia Commonwealth University)
## Contact information

<table>
<thead>
<tr>
<th>Role</th>
<th>Contact</th>
</tr>
</thead>
</table>
| **Clinical Contacts** | **Donna Sargent, RN**  
Research Coordinator  
McGuire VA Medical Center / McGuire Research Institute  
1201 Broad Rock Blvd, 3rd floor, Richmond, VA 23249  
Phone: 804-675-5466; Email: donna.sargent@va.gov |
|                       | **Jose F. Huizar, M.D.**  
Principal Investigator (Contact)  
Associate Professor of Medicine & Director, Arrhythmia and Device Clinic  
McGuire VA Medical Center / McGuire Research Institute  
1201 Broad Rock Blvd, 3rd floor, Richmond, VA 23249  
Phone: 804-675-5466; Email: jose.huizar2@va.gov; jose.huizar@vcuhealth.org |
| **Collaborating Centers** | 1. Mayo Clinic, Rochester, MN (Yong-Mei Cha, M.D.)  
2. University of California San Francisco Medical Center (E. Gerstenfeld, M.D.)  
3. University of California Los Angeles Medical Center (K. Shivkumar, M.D.)  
4. University of Pennsylvania Medical Center (Frank Marchlinski, M.D.)  
5. Vanderbilt University Hospital, Memphis, TN (Roy John, M.D.)  
6. Indiana University/Krannert Institute of Cardiology, Indianapolis, IN (John Miller, M.D.)  
7. McGuire VA Medical Center, Richmond, VA (Jose F. Huizar, M.D.)  
8. Virginia Commonwealth University, Richmond, VA (Kenneth Ellenbogen, M.D.)  
9. University of Calgary, Calgary, Alberta, Canada (Carlos Morillo, M.D.) |
| **Core Laboratories** |  
- **Echocardiography Core Laboratory**  
  John Gorcsan III, M.D.  
  University of Pittsburgh Medical Center, Pittsburgh, PA  
  Email: gorcsanj@upmc.edu  
- **Magnetic Resonance Core Laboratory**  
  Gregory Hundley, M.D.  
  Wake Forest Medical Center, Winston-Salem, NC.  
  Email: ghundley@wakehealth.edu  
- **Holter Core Laboratory**  
  Edward Gerstenfeld, M.D.  
  University of California San Francisco, San Francisco, CA.  
  Email: edward.gerstenfeld@ucsf.edu |
| **Data, Safety and Monitoring Board** |  
- Thomas A. Dewland, M.D.  
  (Cardiac Electrophysiologist)  
  Knight Cardiovascular Institute / Oregon Health & Science University  
  Portland, Oregon  
  Phone: (503) 494-7400; Email: dewland@ohsu.edu  
- Ryan J. Tedford, M.D.  
  (Heart Failure & Cardiac Transplantation)  
  Johns Hopkins School of Medicine / Division of Cardiology  
  1800 Orleans St. Rm 7125A, Baltimore, MD 21287  
  Phone 410-367-2149; Email: ryan.tedford@jhmi.edu  
- James C. Fang, M.D.  
  (Heart Failure & Cardiac Transplantation)  
  The University of Utah  
  50 North Medical Drive, Salt Lake City, Utah 84132  
  Phone 801-581-7715; Email: james.fang@hsc.utah.edu |
| **Adjudication Event Committee** | Joshua M. Cooper, M.D. (Cardiac Electrophysiologist)  
Temple University Health System  
3401 N. Broad Street, Philadelphia, PA 19140  
Phone: 215-707-7526; Email: [joshua.Cooper@tuhs.temple.edu](mailto:joshua.Cooper@tuhs.temple.edu) |
|Sean Pinney, M.D. (Heart Failure & Transplantation)  
Mount Sinai Health System  
One Gustave Levy Place, New York, NY 10029  
Phone 212-241-7300; Email: [sean.pinney@mountsinai.org](mailto:sean.pinney@mountsinai.org) |
|John P. Boehmer, M.D. (Heart Failure)  
PennState Hershey Heart & Vascular Institute  
500 University Drive, Hershey, PA 17033  
Phone: Email: [jboehmer@psu.edu](mailto:jboehmer@psu.edu) |
| **Vendors / Services** | - IRhythm Technologies Inc., San Francisco, CA  
Judith C. Lenane, RN, MHA (Chief, Clinical Officer & EVP, Operations)  
- Research Electronic Data Capture (REDCap)  
Tim Aro, Ph.D. Manage, Clinical Research Informatics  
Center for Clinical and Translational Research, VCU (Richmond, VA) |
## Protocol Synopsis

**PROSPECTIVE ASSESSMENT OF PVC SUPPRESSION IN CARDIOMYOPATHY (PAPS): A Pilot Study**

### Study / Objectives

**Aim 1.** Estimate the prevalence of cardiomyopathy (CM, LVEF ≤ 45%) and frequent premature ventricular contractions (PVCs ≥10%) in the overall population receiving ambulatory ECG Holter monitors.

**Aim 2.** PAPS pilot randomized trial: to assess the feasibility of enrolling, randomizing treatment strategies and retaining participants with frequent PVCs and associated CM.

### Interventions

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 patients with frequent PVCs.

### Study Design

Multicenter randomized prospective study

### Eligible patients

Patients with frequent PVCs (equal or greater than 10% burden) and cardiomyopathy with left ventricular ejection fraction (LVEF) ≤ 45%.

### Planned number of subjects

A total 36 subjects will be enrolled in the study – 3 subjects per center (enrollment completed within 18 months).

### Planned number of participating sites/countries

At least 9 centers in the United States and one in Canada

### Primary Endpoint(s)

1. *Improvement of LVEF after PVC suppression*. 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\(^1\)\(^-\)\(^3\). 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. 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 patients 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.

### Additional Endpoint(s)

1. *Efficacy of RFA vs AADs groups to achieve successful PVC suppression defined as a reduction of PVC burden greater than ≥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 patients with high PVC burden.

2. Composite end-point of adverse events, including worsening in NYHA functional class (I-IV), number of HF and cardiac-related admissions, RFA complications and AAD adverse effects and cardiovascular death.
3. **Composite end-point of arrhythmia burden**, including PVC recurrence, non-sustained (< 30sec) and sustained (> 30sec) ventricular arrhythmias and arrhythmic sudden cardiac death.

### Follow up Schedule

<table>
<thead>
<tr>
<th>Visit</th>
<th>Activities</th>
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<tbody>
<tr>
<td>Week 0</td>
<td>Screening, enrollment, consent and clinical evaluation</td>
</tr>
<tr>
<td>Week 10</td>
<td>ECG and ambulatory ECG recording</td>
</tr>
<tr>
<td>Week 12</td>
<td>Clinical evaluation and echocardiogram</td>
</tr>
<tr>
<td>Week 12-14</td>
<td>Initiation of intervention (RFA or AADs)</td>
</tr>
<tr>
<td>Week 20</td>
<td>Clinical evaluation</td>
</tr>
<tr>
<td>Every 3 months after RFA or AADs (week 38, 50 and 64)</td>
<td>Clinical assessment with occasional testing (echocardiogram and ambulatory ECG recording)</td>
</tr>
<tr>
<td>Week 64</td>
<td>Complete protocol.</td>
</tr>
</tbody>
</table>

All visits and testing are clinically indicated considered standard of care. Most of these patients receive this follow up regardless of participation on the study.

### Study Duration

Study duration is estimated 36 months. Each patient will be followed for at least 15 months, which includes a 3-month observation period and 12-month after intervention is initiated.

Enrollment and patient follow up of all patients is estimated to be completed within 3 years.

### Key Inclusion Criteria

- LV dysfunction (calculated LVEF ≤45%)
- Average PVC burden ≥ 10 % by 2-week Holter monitor
- Stable optimal medical therapy for at least 3 months

### Key Exclusion Criteria

- Current amiodarone use or within last 2 months
- Current use of any antiarrhythmic drug class I or III
- Contraindication to use amiodarone or any other antiarrhythmic class III
- Severely symptomatic PVCs while on optimal medical therapy (defined as incapacitating palpitations or pre-syncope) unable to complete a 3-month observation period
- Severe/ significant CAD with planned revascularization in the near future
- Complete AV block and pacemaker dependent
- Pacemaker or ICD with > 10% of right ventricular pacing
- Severe Valvular heart disease or planned valvular / cardiac surgery
- Uncontrolled or untreated endocrinopathies
- Uncontrolled HNT systolic BP > 160mmHg
- Hypertrophic cardiomyopathy
- Systemic infiltrative and immune disorders
- Family history of dilated CM in a fist degree relative
- Alcohol abuse or illicit drug use
- Contraindication to acute anticoagulation (due to possible randomization to RFA in the LV)
- Atrial fibrillation and flutter with Rapid VR with possible tachycardia-induced cardiomyopathy
- Pregnant or lactating women
- Possible infectious etiology of cardiomyopathy
### Statistical Methods

| Primary Statistical hypothesis | 1) The prevalence of CM (LVEF ≤ 45%) and frequent PVCs (≥10% burden) is largely under recognized in patients undergoing ambulatory ECG Holters.  
2) 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.  
3) The rate of responders (defined as improvement of LVEF ≥ 10% points) with HF medical therapy alone during observation period will be less than 15% in patients 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.  
4) 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. |
| Sample Size | 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%. 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 to enroll at least 20% (30 patients) of preliminary sample size estimation to understand feasibility and key aspects of patient enrollment, randomization and retention to properly power a large-scale randomized PAPS study. Sample size is increased by 15% (6 additional patients, 36 patients total – 18 patients in each treatment group) to take into account possible spontaneous improvement of LV dysfunction during 3-month observation period between treatment strategies. |
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PROSPECTIVE ASSESSMENT OF PVC SUPPRESSION IN CARDIOMYOPATHY (PAPS):
A Pilot Study

PROJECT SUMMARY / ABSTRACT

Premature ventricular contractions (PVCs) coexist in patients with heart failure (HF) and LV dysfunction. Frequent PVCs have shown to induce a reversible cardiomyopathy (PVC-CM). Yet, it is unclear why some patients 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 patients with PVC-CM is believed to carry significant benefits, improving quality of life (QOL), HF symptoms / admissions and life expectancy. Currently, these patients 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 prevalence of PVC-CM, feasibility and limitations of such a trial.

Research Design and Methods. We propose to screen 20,000 consecutive ambulatory ECG Holter monitors of all participating centers (2,000 per participating center) to identify all patients with probable diagnosis of PVC-CM (PVC burden >10% and LVEF <45%). In addition, we will conduct a clinical pilot study, enrolling 30 patients with frequent PVCs (burden >10%) and CM (LVEF <45%) and randomize them to either: 1) RFA or 2) AADs. Prior to treatment, baseline cardiac MR will be requested if clinically indicated followed by 3-month observation period (optimal HF medical therapy). We plan to follow change 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.

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 best treatment strategy for patients with PVC-CM. Treating and reversing this underestimated PVC-CM may improve patient’s health and subsequently decrease HF healthcare spending.
Rationale. Premature ventricular contractions (PVCs) are commonly associated with heart failure (HF) and cardiomyopathy (CM). Frequent PVCs have shown to induce a reversible cardiomyopathy (PVC-CM). Yet, it is unclear why some patients develop PVC-CM, while others do not. Recent publications have demonstrated an incidence of systolic HF of 62.8 (95% CI 61.2 to 64.4) per 1,000 patient 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 patients with PVC-CM is believed to carry significant benefits, improving quality of life (QOL), HF symptoms/admissions and life expectancy. Currently, these patients are offered radiofrequency ablation (RFA), antiarrhythmic drugs (AADs) or no treatment depending on physician’s experience and resources. Nevertheless, no randomized-prospective study exists to support the benefit of RFA. Thus, there is 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 patient 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.

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

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 ≥ 10% points) with HF medical therapy alone during observation period will be less than 15% in patients 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.

Methods. To test our hypotheses, we propose a clinical pilot study to prove the feasibility of a large-scale multicenter clinical trial (PAPS study) of patients with probable PVC-CM. This pilot study will enroll 36 patients with frequent PVCs (burden ≥10%) and CM (LVEF ≤45%) and randomize them to either: 1) RFA or 2) AADs. Prior to treatment, baseline cardiac MR will be performed if clinically indicated and be allowed a 3-month observation period (optimal HF medical therapy). 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 to assess for spontaneous improvement of PVCs and/or CM, and 2) active treatment to all patients, which will allow for easier patient 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 patients 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.
INTRODUCTION

Premature ventricular contractions (PVCs) are commonly associated with heart failure (HF), cardiomyopathy (CM), ventricular arrhythmias and sudden cardiac death (SCD)\(^4\-\!^7\,\!^9\,\!^10\). 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\(^4\,\!^5\,\!^11\-\!^13\). Moreover, case reports\(^14\,\!^15\) and retrospective studies \(^4\,\!^5\,\!^7\,\!^8\,\!^13\,\!^16\-\!^19\) have found a reversal of CM after elimination of PVCs; leading to the description of a reversible CM referred 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\(^7\,\!^20\). Yet, some patients do not develop a CM even with similar features. Thus, it is likely that other patient’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 patients with CM. Even if PVCs are the result of CM, PVCs may contribute and further worsen CM and HF symptoms\(^8\,\!^21\).

PVCs in a 60-second 12-lead ECG are found in 1% to 4% in patients 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)\(^8\). This can be explained due to a significant variability of PVC frequency with time\(^22\). It is not surprising that a 2-week ECG ambulatory recordings is ideal to determine more accurately the PVC frequency\(^23\).

A recent retrospective analysis of the Cardiovascular Health study (CHS)\(^10\) in patients 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 patients 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\(^7\) of 245 patients with non-ischemic CM and frequent PVCs (mean PVC burden 20 ± 13%) demonstrated improvement of LV function in 67% of patients after radiofrequency ablation (RFA). The mean improvement of LV function after RFA in most of studies ranges from ≥ 12-15%\(^7\,\!^20\,\!^24\). Similarly, a prospective study of 66 patients with LVEF <35% (ischemic and non-ischemic) with ICD indication and PVC burden >4% demonstrated that 24% of patients 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 patients (57 and 63%) at 6- and 12-month follow up, respectively\(^24\).

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\(^10\).

SIGNIFICANCE

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\(^2\). PVCs are highly prevalent in patients with CM and HF, and they have been recently identified as a potential cause of a reversible CM\(^6\). Most recent publications\(^5\,\!^6\) 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 patient 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\(^6\). At 40 years of age, the
lifetime risk of developing HF for both men and women is 1 in 5², and PVCs could well contribute to the development of some instances of CM and HF⁶.

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-CM⁵,⁸. 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.

Over the past few years it has become clear that comparative effectiveness trials to understand how to best treat patients with frequent PVCs and CM are needed¹⁰,²⁴. Thus, we propose a multicenter study to better understand the prevalence of frequent PVCs and CM, as well as and 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 devices⁶,²⁵, 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 patient’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 patients with PVC-CM⁶.

**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 patients with potential PVC-CM (>10% PVC burden and LVEF ≤ 45%) in the overall population receiving Holters in participating tertiary high volume centers.**

2) **Identifying demographics, rate and limitations of enrollment, rate of responders (defined as improvement of LVEF ≥ 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 to identify the best treatment strategy for patients with PVC-CM.

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**INNOVATION**

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 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 patient 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.

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**APPROACH – STUDY DESIGN**

**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 patients with possible PVC-CM, which is solely based on personal physician’s experience and availability rather than outcomes. This is demonstrated in the wide treatment variation in our clinical survey (discussed in Section: Preliminary data).

A. **Study Population and Eligibility**

This is a prospective randomized pilot study including 36 subjects with cardiomyopathy (CM) and high PVC burden with a likely diagnosis of PVC-CM\(^6\), where all patients with OMT 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 1drugs (AADs).

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 patient 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, 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 antiarrhythmic arm becomes positive during the 12-month follow up we will consider stopping antiarrhythmics and will be withdrawn from the study.

**Definitions:**

The *diagnosis criteria for PVC-CM* is based on LVEF \(\leq 45\%\) (by echocardiography) and average PVC burden \(\geq 10\%\) in a 2-week Holter monitor (Ziopatch) despite optimal medical therapy that meet the inclusion and exclusion criteria (Table 1), regardless of severity and time of onset.

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

All subjects should be on optimal medical therapy for at least 3 months prior to study enrollment. If screening confirms eligibility (LVEF \(\leq 45\%\) and PVC burden \(\geq 10\%\)), a baseline visit will be schedule to obtain patient’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 registry to follow their response and crossover to different treatment strategies.

Prior and during enrollment, all patients should meet and continue *optimal medical therapy* throughout the study. We define *optimal medical therapy* as 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\(^{26}\). 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 pro-arrhythmia.

Prior to intervention with either RFA or AADs, all subjects will have a 3-month observation period with optimal medical therapy (OMT) to 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 ≥ 10% and ≤ 45%, respectively. In such case, stratified randomization will be performed to assign to either RFA or AAD group. Based on our preliminary data, we expect that that around 30% of patients will have a PVC burden >20%. Thus, a stratified randomization based PVC burden (assessed by 2-week Holter) above and below 20% is needed to assure that patients 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 both PVC and/or LVEF criteria are not met after the observation period, the patient will be assigned to an optimal medical treatment alone and will be followed in a registry with assessment of PVC burden and LVEF as clinically indicated during the following 12-month study. These patients will continue treatment as recommended by their local clinical electrophysiologist.

Randomization will be performed at the time of enrollment (baseline visit, week 0). If a subject is randomized to 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 12-14). Crossover between PVC suppression strategies is not encouraged. If crossover is considered medically and/or ethically indicated, we will request to be performed only after 6 months of initiation of treatment, for which an intention-to-treat analysis will be performed.

Clinical Assessment and tests
Regardless of group assignment, all patients will undergo a series of clinical evaluation, tests and interventions as outlined in Table 2 and Figure 1:

* **12-lead ECG and 1 minute rhythm strip** will be performed in 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. 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.

* **Two-week Holter monitor** (Ziopatch, iRhythm, Inc). This Holter monitor will be provided directly by iRhythm to participating centers. The 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 observation period and treatment arms. Reports will be

Table 1. PAPS study – Inclusion & Exclusion criteria.

<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
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<tbody>
<tr>
<td>LV dysfunction (calculated LVEF ≤45%)</td>
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<tr>
<td>Average PVC burden ≥ 10 % by 2-week Holter monitor</td>
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<tr>
<td>Stable optimal medical therapy for at least 3 months</td>
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<table>
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<tr>
<th><strong>Exclusion Criteria</strong></th>
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<tbody>
<tr>
<td>Current Amiodarone use or within last 2 months</td>
</tr>
<tr>
<td>Current use of any antiarrhythmic drugs class I or III</td>
</tr>
<tr>
<td>Contraindication to use amiodarone or any other class III antiarrhythmic</td>
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<tr>
<td>Severe/ significant PVCs while on optimal medical therapy (defined as incapacitating palpitations or pre-syncope) unable to complete a 3-month observation period.</td>
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<tr>
<td>Severe/significant CAD with planned revascularization in the near future</td>
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<tr>
<td>Complete AV block and pacemaker dependent</td>
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<tr>
<td>Pacemaker or ICD with ≥ 10 % of right ventricular pacing</td>
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<tr>
<td>Severe valvular heart disease or planned valvular/cardiac surgery</td>
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<tr>
<td>Uncontrolled or untreated endocrinopathies</td>
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<tr>
<td>Uncontrolled HTN systolic BP &gt; 160mmHg</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td>Systemic infiltrative and immune disorders</td>
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<tr>
<td>Family history of dilated CM in a first-degree relative</td>
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<tr>
<td>Alcohol abuse or illicit drug use</td>
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<tr>
<td>Contraindication to acute anticoagulation (due to possible randomization to RFA in the LV)</td>
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<tr>
<td>Atrial fibrillation and flutter with rapid VR with possible tachycardia-induced cardiomyopathy</td>
</tr>
<tr>
<td>Pregnant or lactating women</td>
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<tr>
<td>Possible infectious etiology of cardiomyopathy</td>
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</table>
sent to the ECG/Holter core lab (noted above) for final interpretation. Similar to ECG, reader will be blinded to group assignment. Two-week Ziopatch monitor will allow us to assess long-term PVC burden and morphology and compare efficacy to achieve successful PVC suppression (defined as PVC reduction ≥ 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. Echocardiography. 2D-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. 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). A copy of the echocardiogram images will be sent to the Echo core laboratory (led by Dr. John Gorcsan, III) for final interpretation by cardiologist blinded to randomization arm. Assessment of LVEF by echocardiography will be repeated during observation and treatment arms in order to assess changes in LV function during observation period and between PVC suppression strategies.

d. Cardiovascular magnetic resonance (CMR). If clinically indicated, a delayed enhancement CMR will be performed in each center following a single protocol (approved by CMR core laboratory Director: Dr. Gregory Hundley, Winston-Salem, NC) and sent to CMR core lab for final interpretation. Similarly to other testing, CMR core lab and participants will remain blinded to group assignment. CMR will be obtained at baseline 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. 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 type of cardiomyopathy, and all sites have agreed to order CMR on enrolled patients.

e. 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 patient in their local institution. This will allow us to assess heart failure symptoms and change in quality of life during the

Table 2. Timeline of different tests and interventions during study (*, visit/intervention if clinically indicated).

<table>
<thead>
<tr>
<th>Test</th>
<th>Screen</th>
<th>Obs−V1 Baseline</th>
<th>Obs−V2 Visit 2</th>
<th>Obs−V3 Visit 3</th>
<th>Tx−V1 Baseline</th>
<th>Tx−V2 1-mo</th>
<th>Tx−V3 3-mo</th>
<th>Tx−V4 6-mo</th>
<th>Tx−V5 9-mo*</th>
<th>Tx−V6 12-mo</th>
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<tbody>
<tr>
<td>Consent</td>
<td>X</td>
<td>Week 0</td>
<td>Wk 10</td>
<td>Wk 12</td>
<td>Wk 12-14</td>
<td>Wk 20</td>
<td>Wk 26</td>
<td>Wk 38</td>
<td>Wk 50</td>
<td>Wk 64</td>
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<tr>
<td>H&amp;P/Med Rx</td>
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<td>X</td>
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<tr>
<td>Ziopatch</td>
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<td>X</td>
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<td>LVEF</td>
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<td>X*</td>
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<td>Randomize</td>
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<tr>
<td>CMR</td>
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<td>RFA or ADD</td>
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observation period and between both treatment groups. Questionnaires will be sent directly to 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).

Veteran participants who are evaluated by study staff and suspected to be depressed will be further evaluated by a psychiatrist or psychologist utilizing the Mental Health Consultation and Liaison Service at McGuire VAMC. Research study staff will page the C&L service at 351-1067 (Use *601 pager # 9198 after 4pm and on weekends) and then walk the participant to the C&L provider to facilitate the evaluation on the day that the participant presents as depressed.

**f. Complications, heart failure admissions and adverse events.** All events including mortality, hospital admissions and heart failure exacerbations and treatment-related complications will be documented in each patient throughout the observation and treatment periods. Each center will report any adverse events to the coordinating center (Mcguire VA Medical Center, Richmond VA) within a week of their 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, patient 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. [24].

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**Figure 1.** PAPS study design. A 3-month Observation (Obs) period allows each patient to serve as their own control to assess benefits of PVC suppression. After observation period, all patients 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).
B. Description of the intervention(s)/treatment(s).

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

Treatment or intervention arms will consist of:

i) Antiarrhythmic drug (AAD) therapy. AAD therapy of choice is amiodarone due to its proven safety in patients 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 ≥ 80% absolute reduction in PVC burden is achieved after a drug or intervention. Alternatively, sotalol and/or propafenone could be considered at discretion of electrophysiologists (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 patients with an implantable or external defibrillator (Lifestore). Optimal heart failure medical therapy should be continued in combination with AAD throughout the 12-month follow-up. Throughout 12-month follow-up, patients 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.

ii) Radiofrequency Ablation (RFA) of PVCs. RFA will be performed after 12 weeks of randomization (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 patients 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. RV or LV PVCs will be mapped/ablated as 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. Patients will be observed overnight in a telemetry bed and discharged home 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 continued throughout the 12-month follow-up. Practitioners will be asked to notify 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 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 (Ziopatch, IRhythm, Inc.) will be obtained 4 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 similar approach as in first intervention; however, epicardial mapping will be encouraged if considered appropriate. This subgroup of patients 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.
C. **Primary and secondary outcome measures.**

The choice of 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.** 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\(^1\)\(^-\)\(^3\). 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 (See rationale under Section "Definitions" in 3rd paragraph of Aim 2). 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 patients 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 defined as a reduction of PVC burden greater than \(\geq 80\%\) (regardless of LVEF change).** Understanding the success rate of PVC suppression between RFA and AADs will help better determine the best treatment to those patients with high PVC burden.

2. **Composite end-point of adverse events, 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 when patient’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.** 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.

D. **Data interpretation and analysis**

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

Patients are referred to tertiary centers for RFA of PVCs in patients 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. Patients that meet inclusion and exclusion criteria will be asked to participate. We plan to understand comfort level of patients participating in this clinical study. We will assess the rate and rationale of decline participation or withdrawal form 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 reason including those not related to study itself. Subjects that refuse enrollment, will be asked to participate in a registry to follow their response and crossover to different treatment strategies.

We hypothesize that patients and/or physicians will not object to participate due to 3-month observation period since most tertiary referral centers have significant procedure wait time for which usually they are schedule 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 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 patients will undergo a PVC suppression strategy. This pilot study will allow us to prove feasibility of the PAPS study with current study design including 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\textsuperscript{22,30}, 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 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. Patients that do not meet both inclusion criteria (LVEF ≤45% and PVC burden ≥10%) at the end of the observation period will not be randomized to either treatment groups, but rather they will be included in a registry. Based on preliminary data, we believe that less than 10% of patients 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.

Rate of responders to PVC suppression

Besides improvement in LV systolic function, no study has demonstrated any clinical benefits from PVC suppression, whether is 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\%\textsuperscript{7,20,24}. 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 LVEF = final LVEF – baseline LVEF) and 2) “responders” to PVC suppression (defined as change in LVEF ≥ 10\%). In addition, we will obtain QOL and NYHA functional class questionnaires (secondary end-point described above). Each patient 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 no therapy (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 in patients with PVC-CM is not known due to the lack of head-to-head comparison. 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. Yet, it is unknown the rate of responders, successful PVC suppression (defined as 80\% PVC reduction), adverse events and treatment crossover between these 2 treatment arms.
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 defibrillator. 

This pilot study will allow 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 it will allow us to properly design and power the large randomized PAPS study.

E. Data collection

Using a patient 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 observation and treatment period (RFA vs. AADs group) are outlined in Figure 1 and Table 2.

Data will be collected and recorded directly by research coordinator and local investigator and as per protocol. A common 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 (REDCap). All participating sites will comply with all applicable laws, regulations and provisions related to patient’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 patient’s research study forms to be completed by all centers, 2) review of patient’s data/forms as different 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, quality of echocardiographic, Ziopatch Holter monitors and CMR will be monitored by Echo, Holter and CMR core laboratories, respectively.

F. Limitations

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

1. Patients 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. Patients are excluded if symptoms preclude completion of 3-mo observation.

2. Limited or poor suppression of PVC suppression in randomized treatment (RFA or AAD) arm. These patients are encouraged to remain on the assigned arm. However, crossover to alternative treatment arm can be considered after 6 months only if considered medically indicated. If crossover were to be occur before 6 months, immediate notification and final evaluation with echocardiogram and 2-week Holter monitor should be obtained prior to crossover, and patient will be excluded from study and followed in a registry.

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 studying arrhythmias. Schmidt 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 (Ziopatch, IRhythm, Inc.) shown to be a better indicator of long-term PVC burden.

4. LV function assessment in ventricular bigeminy. Assessment of LVEF during frequent PVCs represents a challenge for all imaging modalities. Modified acquisition and post-processing methods have been developed to correct for R-R interval variability expected with frequent PVCs. In the event that the patient has persistent ventricular bigeminy at the time of scheduled echocardiography, we will request to postpone LV function assessment for 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 patients 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 this 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 al24. If an ICD is present or practitioner decide to implant ICD prior to completion of study; programming to VVI 40 or other pacing algorithm should be considered to ensure minimal ventricular pacing.

G. 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 calculated34. 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® 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 its 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 (ZioPatchTM, IRhythm Technologies, Inc.) and evaluated by Holter core lab (Dr. Gerstenfeld) to prevent differences in PVC detection algorithms. Finally, stratified randomization will ensure an equal distribution of patients 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 to enroll at least 20% (30 patients) of preliminary sample size estimation to understand feasibility and key aspects of patient enrollment, randomization and retention to properly power a large-scale randomized PAPS study. Sample size is increased by 15% (6 additional patients, 36 patients total – 18 patients in each treatment group) to take into account possible spontaneous improvement of LV dysfunction during 3-month observation period between treatment strategies.

H. Ethical / Regulatory Affairs

The study will be submitted for review to the local IRBs and registered on clinicaltrials.gov prior to commencement of study activity.

Event Adjudication Committee

We will establish a committee to evaluate each hospitalization event and determine the relationship to HF and/or PVC suppression treatment arm. The committee consists of three physicians: two heart failure
cardiologist and one cardiac electrophysiologists formed by 2 heart failure specialists (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 Heart Rhythm Society and FDA for the treatment of ventricular arrhythmias, respectively. Subjects assigned to RFA arm may have small risk of minor or major complications related to RFA of PVCs. However, these risks associated to 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 including 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 patient population with knowing complications and these adverse events. To minimize the potential risks with AADs, all subjects will receive additional safety laboratory analyses during treatment as recommended per guidelines based on AAD chosen (amiodarone - TSH, LFTs, PFTs, eye exam).

IRB should be notified of any serious adverse events (SAE) within 24 hours of such event. Additionally, SAE should be notified to PAPS research coordinator within 24-48 hours. The investigator must decide whether each incident meets the definition of a SAE.

**Data Safety Monitoring Plan and Board**

Serious adverse events and patient 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 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 document: Protection of Human Subjects and Data Safety Monitoring Plan.

I. **Timeline**

Timeline to enroll 30 patients in this prospective randomized clinical pilot study is summarized in Table 4. IRB submission and coordination will occur within the first few months. Enrollment in each center is planned to start as early as 2-months as soon as IRB approval is granted. We expect an average enrollment of 3 patients per center completing recruitment and follow-up in 18 and 36 months, respectively.

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J. **Enrollment**

We will engage clinicians / consultants to identify all patients 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 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 ≥ 10 PVC / hour. However, it is likely that most patients will be identified through Aim 1, where we will screen all ambulatory holters for PVC ≥10% and LVEF ≤45%. Refer to document Enrollment for further details.

REFERENCES


This population is the interest of our research study since PVCs are frequently found, and in general these patients 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 treat at least 3-4 patients within 2 years with diagnosis of PVC-CM. Thus, 10 participating centers should be able to enroll at least 36 patients 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 patients 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 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 > 10 PVC / hour and 6) screening of consecutive ambulatory Holter monitors (PAPS Pilot study - Part I).

Once identified, potential study patients will be engaged to participate in the PAPS study by: 1) engaging primary care providers to explain affected patients the relevance of participating and/or engaging and disseminating this important clinical trial; 2) sponsoring a PVC-CM & HF workgroup as mentioned above. This work group will be led by the principal investigator and/or research coordinator, who will present and update all patients/visitors the objective of the study, progress of the study as well as the importance of understanding the cardiovascular effects of PVCs. This will allow interaction between principal investigator and/or research coordinator and patients that would allow us to enroll and maintain engaged study subjects.

The enrollment and follow up plan will consist of different visits (see Research Strategy, Table 2 and Figure 1). Screening will consist on review of inclusion/exclusion criteria including optimal medical therapy for at least 3 months and if these two are met, then a 2-week Holter (contracted Holter monitor service) should be placed as part of the same screening visit to confirm PVC burden >10%. Baseline visit. If patient meets inclusion/exclusion and PVC burden, then a baseline visit will be requested to obtain baseline echo, NYHA assessment, quality of life questionnaire, ECG and randomization to either 1) RFA or 2) AADs groups. Visit 1. If patient is assigned to RFA, this procedure should be scheduled within 12 weeks (Visit 1). Coordinator will actively be engaged during RFA procedure and in recovery phase. If subject is randomized to AADs group, AAD can be only initiated after 3-month observation period.

After 12-month follow-up, we will encourage all patients to remain engaged by participating in PVC-induced CM & heart failure workgroup. 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 the trust from our patients.
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 complexes (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 patients 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 patients 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 a frequent PVCs (defined as PVC burden ≥ 10% in 2-week ambulatory Holter) and LV dysfunction (LVEF ≤ 45%) without any clear reversible cause of CM (outlined in Research plan: Table 1). All patients 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 thought, there is no evidence that age, gender or ethnic group will respond differently to treatment arm. While most patients 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 patients) or AAD therapy (70 patients) to assess differences between RFA and AAD treatments (see Sample size justification Section in Research Strategy). However, we propose a pilot study of 30 patients (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 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 patients undergoing a 24-, 48- and 2-week ambulatory ECG Holters for frequent PVCs (≥ 10% burden) and LVEF ≤ 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 from each participating subject. Inclusion and exclusion criteria are similar for all patients regardless of gender, age, race or ethnic group (See details in document: Research Strategy – Table 1). We plan to recruit study patients using different strategies and settings, but primarily by: 1) Engaging clinicians and consultants to identify patient 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 3) patients identified with frequent PVCs and CM during ambulatory ECG Holter screening (PAPS Pilot study – Part I).

As a retention strategy, we will request each participating center to maintain engaged active study patients through local heart failure work groups, monthly emails or phone calls. In addition, we will ask patients that have completed 12-months study to remain engaged throughout the 3-year duration of our proposed study in order to engage and support current active participants.

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 despite optimal medical therapy, 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 patients will have a PVC burden >20%, we plan a stratified randomization based PVC burden above and below 20% reported by 48-hour Holter. Stratified randomization will assure equal distribution of patients 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%.

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 10% PVC burden as inclusion criteria of our study as we believe these are patients with 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 vs. PVC suppression. 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 continue optimal medical therapy regardless of treatment randomization, they will be followed in every 3 months in order to assure compliance and assess potential side effects.

List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

We have involved a total of 9 nationally-renowned high-volume electrophysiology centers across the United States to participate in this study. All these institutions have agreed to participate in the PAPS study (see letters of support):

1. Virginia Commonwealth University, Richmond, VA (Kenneth Ellenbogen, M.D., Principal investigator – Clinical electrophysiologist).
2. McGuire VA Medical Center, Richmond, VA (Jose F. Huizar, M.D., Principal investigator – Translational research and Veterans Affair).
3. Hospital of the University of Pennsylvania, Philadelphia, PA (David Frankel, M.D., Frank Marchlinski, M.D., Co-investigator).
4. Indiana University / Krannert Institute of Cardiology, Indianapolis, IN (John Miller, M.D, Co-investigator).
5. Mayo Clinic, Rochester, MN (Yong-Mei Cha, M.D., Co-Investigator)
6. UCLA Medical Center, Los Angeles, CA (Marmar Vaseghi, M.D. and Kalyanam Shivkumar, M.D., Ph.D., Co-Investigator)
7. Vanderbilt University Medical Center (Roy John, M.D., Co-investigator)
8. McMaster University (Carlos Morillo, M.D., Principal investigator – Trialist)
9. UCSF Medical Center, San Francisco, CA (Edward Gerstenfeld, M.D., Principal Investigator – Holter core laboratory)

Each local investigator (co-investigator) will be responsible to obtain consent, follow research plan as outlined, report severe and non-severe adverse events within 24-48 hours, protect patient’s rights and welfare, securely store and submit accurate patient’s data, notify coordinating center of all IRB correspondence. Local IRBs at each local site are responsible of protecting safety and welfare of research subjects at their sites. All institutions will have in place instructions to store patient’s files and records in a secure locked location. Any questions from local investigators/collaborators and coordinators in regard patient enrollment, follow-up and/or termination should be addressed directly to the national research coordinator.

Each center will submit a Case Report forms via a secure encrypted data capture (REDCap) and/or 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 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 patient’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

Describe the research material obtained from living individuals in the form of specimens, records, or data. Describe any data that will be collected from human subjects for the project(s) described in the application.

We will record baseline patient 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, 2-week ambulatory Holter, echocardiogram and cardiac MR (if clinically indicated) as per protocol. All details related to 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 or 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 patients randomized to 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.
Indicate who will have access to individually identifiable private information about human subjects. Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

Data will be collected directly from patient, research coordinator and local investigator and as per protocol. This will be recorded by 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 common identifier will be given to each subject to identify subjects in the event that study provides important information that requires reach research subject. The common identifier and data collected in Case Report forms will be provided to coordinating center for analysis.

Each local investigator (collaborator) will be responsible to obtain consent, follow research plan as outlined, report severe and non-severe adverse events within 24-48 hours, protect patient’s rights and welfare, securely store and submit accurate patient’s data, notify coordinating center of all IRB correspondence. Local IRBs at each local site are responsible of protecting safety and welfare of research subjects at their sites. All institutions will have in place instructions to store patient’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 (REDCap, as described above) and/or 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 patient’s files and records (including identifiable private information) in a secure locked location.

c. Potential Risks
Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects. Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

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. Alternative treatments include use of antiarrhythmics and/or optimal medical therapy alone. Risks associated to 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-arythmic (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 3-month observation period (control). The risks of the subjects participating in this research proposal are considered small primarily because most of these patients 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 8-10 weeks 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 patients during their participation in this study. IRB in each institution will be notified of any serious adverse events within 24 hours of our knowledge of such event. Additionally, SAE should be notified to the coordinating center within 24-48 hours (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 patients using different methods and settings: 1) Engaging clinicians and consultants to identify patient 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) patients identified with frequent PVCs and CM during ambulatory ECG Holter screening (PAPS Pilot study – Part I). We plan to include only adults (greater than 18 year of age) and children will not be included as addressed in Section: Inclusion of Children (see below).

Potential study patients will be further introduce to the proposed study using different strategies: 1) Engaging primary care providers to explain affected patients the relevance of participating and/or engaging and disseminating this important clinical trial; 2) Sponsoring a PVC/CM/heart failure work group lead by the principal investigator and/or research coordinator, who will present and update objective of the study, progress of the study as well as the importance of understating the cardiovascular effects of PVCs; and 3) Requesting active study patients and clinicians to participate in the PVC/CM/heart failure work group, which will help assure new study patients and/or subjects considering participating in the study receive feedback from active study participants.

Once introduction to the health issue of cardiomyopathy and frequent PVCs occurs, the principal investigator, collaborators and/or research coordinators will personally approach patient in a 1:1 setting to further discuss the option to participate in this study. Personnel obtaining consent should explain in details aims and methodology of study and potential benefits and risks associated to study (described below). Only after patient is allowed to inquire any questions and they are all addressed, patient will be asked to sign informed consent if he is an agreement to participate in the study. We will recommend to all participating sites to preferably consent patient 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

Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.

In order to minimize potential risks, the proposed project will require IRB approval in 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 data of Human research participants. Completion of the CITI training is required to all research team members prior to issuing in proposed study.

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

Discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials must include a general description of the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.
All research performed under this study will conform to laws, regulations and Veterans Affairs (VA) policies and procedures pertaining to protections for human subjects. Collaborating centers and VA coordinating center shall immediately notify each other, and 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 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 or medical care could be directly affected by study results, VA (Coordinating center) shall send study subjects a written communication the content of which is subject to IRB approval.

Investigator and/or research coordinator in each participating center will be responsible for collecting data in regard adverse event. The investigator must decide whether each incident meets the definition of a SAE. 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 IRB on the required Significant Adverse Event Report Form (See form attached below) provided for this purpose. IRB in each institution will be notified of any serious adverse events within 24 hours of our knowledge of such event. Additionally, SAE should be notified to the coordinating center and NIH within 24-48 hours. If the adverse event results in the need to revise the informed consent, or other study documents, the PI must submit a study amendment to the IRB. An extensive Data Safety Monitoring Plan (DSMP) is described below.

Potential Benefits of the Proposed Research to Human Subjects and Others

**Discusses the potential benefits the research to research participants and others.**

The prevalence of frequent / high PVC burden and cardiomyopathy is key as it is likely that patients are under recognized. Furthermore,

Understanding the potential benefits of RFA of PVCs versus AAD therapy in patients with CM and frequent PVCs are particularly important to patients as we will try to understand 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 CM is paramount to properly target patients that are likely to respond to RFA of PVCs, and avoid this invasive procedure in patients that are less likely or do not have clinical benefit.

**Discuss why the risks to subjects are reasonable in relation to the 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 patients with frequent PVCs associated with cardiomyopathy supported only on retrospective and non-randomized observational studies with a relatively short 3-6 month follow up. 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 to 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-base treatment options in patients with frequent PVCs and LV dysfunction with or without heart failure, as we plan to compare RFA of PVCs vs. antiarrhythmic drug (AAD) therapy. **Patient’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 patients can be incorrectly considered or diagnosed with a persistent irreversible form of CM with
subsequent HF morbidity and mortality. Thus, patients 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 to HF and CM after elimination of PVCs with RFA. Moreover, these patients 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 to PVC-cardiomyopathy. This would lead to change in current practice as it will guide us to closely follow up those patients at risk to develop PVC-CM.

The proposed study will impact several aspects of patient care, such as: 1) evaluate clinical benefits of RFA of PVC in patients 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 patients likely to respond to RFA; and 4) decrease the financial burden associated with poor quality of life, heart failure symptoms and admissions, and ICDs in patients with frequent PVCs and CM.

Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

Risks associated to research subjects in this proposed study are considered small and acceptable since most of these patients would have been scheduled for RFA of PVCs without clear understanding of the benefits associated to RFA. In contrast, the risks related to those patients 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 patients should be referred to RFA of PVCs or initiate AADs. Until now, there are no randomized-controlled studies of patients with PVC-CM to clarify and answer these questions.

In summary, without clear evidence of benefit of RFA in patients with cardiomyopathy associated with frequent PVCs, we believe that the risk of withholding RFA is similar to the risk of those patients 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 patient safety. In addition to IRB, 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.

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 PI if requested by the Board. Data monitoring will focus on several areas: 1) Performance, which will allow us to assess sites performance with respect to subject recruitment, retention and follow-up, flow of data forms, protocol adherence and quality of data; 2) Safety, which allow us to assess the
magnitude of adverse events; and 3) Treatment, in order to monitor and assess treatment effects (described above under Section: Potential Risks).

**ClinicalTrials.gov Requirements**
As required, the PAPS pilot study we will be registered at www.clinicaltrials.gov within 21 days of obtaining national funding.

**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.
The PAPS Pilot study is national multicenter randomized control study to enroll a total of 30 subjects with cardiomyopathy associated with frequent PVCs. This phase III trial with moderate risk as participating subjects will be randomized to two different strategies (RFA versus AAD) commonly used in clinical practice to treat patients with frequent PVCs. We considered this study with a moderate risk since most patients 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 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 schedule visit and in between visits, patients will be asked and instructed to call in regard any event out of the ordinary. Those patients randomized to RFA group will be evaluated immediately, throughout the first 24 hours and 1-2 weeks after procedure by research team as standard follow up on any of these procedures. It will be responsibility of the investigator/coordinator to assess patient personally and request laboratory or any appropriate tests if needed. All adverse event including serious adverse events (SAE) will be monitored for all patients during their participation in this study.

a. Adverse event (AE) grading and attribution scale. The investigator will try to determine 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:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>No adverse event or within normal limits</td>
</tr>
<tr>
<td>1</td>
<td>Mild AE, not requiring treatment</td>
</tr>
<tr>
<td>2</td>
<td>Moderate AE, resolved with treatment</td>
</tr>
<tr>
<td>3</td>
<td>Severe adverse event (SAE) is any untoward medical occurrence that at any point during the study:</td>
</tr>
<tr>
<td></td>
<td>• Results in death</td>
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<tr>
<td></td>
<td>• 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.</td>
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<tr>
<td></td>
<td>• Requires in-patient hospitalization or prolongation of existing hospitalization – Hospital admission is usually interpreted as requirement at least one overnight stay in patients in the medical therapy arm or PVC suppression; whereas in subjects in the PVC suppression arm, a prolong 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.</td>
</tr>
<tr>
<td></td>
<td>• Results in persistent or significant disability/incapacity</td>
</tr>
<tr>
<td></td>
<td>• 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 of hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.</td>
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</table>

b. Reporting of Adverse Events (AE)

Investigator and/or research coordinator in each participating center will be responsible for collecting data in regard adverse event. 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 IRB on the required Significant Adverse Event Report Form (See form attached below) provided for this purpose. Supporting documents, including a copy of the Informed Consent, should also be attached. For reasons of
confidentiality, subject's names must not be included in the report. IRB in each institution will be notified of any serious adverse events within 24 hours of our knowledge of such event. Additionally, SAE should be notified to the coordinating center and NIH within 24-48 hours. If the adverse event results in the need to revise the informed consent, or other study documents, the PI must submit a study amendment to the IRB.

c. Annual Data and Adverse Events Report

This report will be prepared annually by PI and research coordinator at the coordinating center. This report will include number of patients actively enrolled, those that abandon and completed 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 12-month protocol. Data reports and interim analysis will be reviewed by IRB at coordinating center and DSMB during its convened meetings.

d. Data management and safety review

Collaborating centers and VA shall immediately notify each other, and VA shall promptly notify the IRB, upon identifying any aspect of the Protocol, including unanticipated problems involving risk and information discovered during 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 or medical care could be directly affected by study results, VA (Coordinating center) shall send study subjects a written communication the content of which is subject to IRB approval.

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 patient safety. In addition to IRB, 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.

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 PI if requested by the Board. Data monitoring will focus on several areas: 1) Performance, which will allow us to assess sites performance with respect to subject recruitment, retention and follow-up, flow of data forms, protocol adherence and quality of data; 2) Safety, which allow us to assess the magnitude of adverse events; and 3) Treatment, in order to monitor and assess treatment effects.

DSMB has the responsibility to make written reports of their findings and recommendations to the 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 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 patients 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 protocol with appropriate notification to collaborating centers. Similarly, if during a review or recommendation of Data Safety Monitor Board (DSMB) is made, all PIs will discuss and agree to modify or made appropriate changes to address concerns of 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 McGuire Research Institute IRB must be reported to the Human Protection Administrator (HPA) 804-675-5151. This form, along with a copy of the signed consent form should be submitted as soon as possible, 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: ________________________
PROJECT TITLE: ___________________________________________________________________
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: Sponsor 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: ____________

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Treatment date</th>
<th>Event</th>
<th>Onset Date</th>
<th>Outcomes (e.g. hospitalization, concomitant meds, study, status, etc.)</th>
</tr>
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<tbody>
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</table>

**Relationship**

- [ ] Definitely Unrelated
- [ ] Unlikely
- [ ] Possibly related
- [ ] Probably related
- [ ] Definitely related

**Description**

1. Event or problem
   - [ ] Resolved
   - [ ] Ongoing
   - [ ] Copy of SAE reported attached
   - [ ] Anticipated
   - [ ] Unanticipated

2. Was the subject withdrawn from the project
   - [ ] Yes on ____________
   - [ ] No
   - [ ] Not applicable

**Actions taken:**

1. Do you recommend modifications in the project (e.g. protocol changes, informed consent changes)?
   - [ ] Yes
   - [ ] No

2. Has the sponsor been notified of the event or problem?
   - [ ] Yes
   - [ ] No

3. Describe actions taken or will take to minimize risks:

   ______________________________________________________________________________________
   ______________________________________________________________________________________

   ___________________________ ______________________
   Investigator Signature     Date

   (Sub investigator may sign if the investigator is unavailable)
Prospective Assessment of PVC Suppression in Cardiomyopathy (PAPS): A Pilot Study

Adverse Events

Date: ________________________

<table>
<thead>
<tr>
<th>Subject</th>
<th>Adverse Event</th>
<th>Onset Date</th>
<th>Ending Date</th>
<th>Severity</th>
<th>Drug related</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

Codes:

<table>
<thead>
<tr>
<th>Severity</th>
<th>Drug Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – Mild</td>
<td>0 = Definitely Unrelated</td>
</tr>
<tr>
<td>2 = Moderate</td>
<td>1 = Unlikely</td>
</tr>
<tr>
<td>3 = Severe</td>
<td>2 = Possibly Related</td>
</tr>
<tr>
<td>4 = Life threatening</td>
<td>3 = Probably Related</td>
</tr>
<tr>
<td></td>
<td>4 = Definitely Related</td>
</tr>
</tbody>
</table>

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

Comments:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

________________________________________________________________________
________________________________________________________________________

Investigator Signature ___________________________ Date ___________________________
(Sub investigator may sign if the investigator is unavailable)
INCLUSION OF WOMEN AND MINORITIES

Based on observational non-randomized studies, PVC-cardiomyopathy does not appear to have a gender or age predisposition. Furthermore, no data has been published in regard 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 patients 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 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 to complete proposed clinical trial including women and minorities.

We intend to compare response to RFA and AADs between these different populations, however, PAPS study is not powered to compare between different populations since this would require several hundred patients. 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.

INCLUSION OF CHILDREN

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 patients 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 launch in the future, it could be the first prospective randomized trial to study the effects of catheter radiofrequency ablation in patients with PVC-induced cardiomyopathy. Particularly it could help us better identify patients that will benefit from PVC suppression with subsequent improvement in patient’s health, patient outcomes and narrow a gap in knowledge in regard in those patients with frequent PVCs and cardiomyopathy.

We understand the relevance of making available information that would allow any other researcher/colleague 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
2) Register our study at the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk./prospero/)
3) Describe of 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.