PROTOCOL SYNOPSIS

Title of Study:
Catheter Ablation versus Anti-arrhythmic Drugs for Premature Ventricular Complexes (CAAD-PVC): A Randomised Controlled Trial

Study Duration
12 weeks

Clinical Phase
III

Objectives
To determine in patients with premature ventricular complexes (PVCs) if catheter ablation is more efficacious than medical therapy to reduce PVC burden and improve symptoms, and quality of life.

Primary Hypothesis
Catheter ablation is more effective at reducing PVC burden and associated symptoms, improving quality of life compared to medical therapy alone.

Planned Participants
50

Study Design
A randomised, open label randomised controlled trial of patients with PVCs who will be randomised in a 1:1 manner to receive either catheter ablation or medical therapy and followed up for 12 weeks.

Selection and Enrolment

Inclusion Criteria
Patients will be eligible for inclusion if they have:

1. PVC burden of ≥10% as determined by ≥24-hour heart rhythm monitoring,
2. Normal left ventricular ejection fraction (ejection fraction ≥ 50%)
3. Aged ≥18 years.

Exclusion criteria

1. Unable or unwilling to provide informed consent or comply with study requirements including study investigations, follow-up, medical adherence and completion of the assigned intervention.
2. Women who are pregnant or breastfeeding.
3. Life expectancy ≤ 12 months.
4. Ventricular tachycardia (VT) defined as spontaneous VT lasting ≥30 seconds, haemodynamically unstable VT of any duration, inducible sustained VT during any electrophysiology study or ≥10 episodes of non-sustained VT (>5 consecutive beats lasting ≤30 seconds) within 24 hours on heart rhythm monitoring.
5. Previous catheter ablation for ventricular arrhythmia.
6. Coronary artery disease defined as a history of myocardial infarction, prior coronary revascularisation, inducible ischaemia on functional testing or obstructive coronary artery

disease on coronary imaging. Any type of coronary assessment is permitted although computed tomography coronary angiography is encouraged.

7. Moderate or greater valvular heart disease.
8. Known non-ischaemic or ischaemic cardiomyopathy or evidence of myocardial scar on cardiac magnetic resonance imaging suggestive of structural heart disease.
9. Known cardiac channelopathies including catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome and long- or short- QT syndrome.
10. In the opinion of the investigator or responsible physician, participation would not be in the patient's best interest or the patient would be unable to complete study procedures because of concomitant illness, physical impairment or mental condition.

Outcome measures and outcome assessment

Primary Outcomes:

1. Reduction in PVC burden by at least 80% as measured by ≥24 hour heart rhythm monitoring at 12 weeks.

Secondary Outcomes:

1. Change in PVC burden at 12 weeks as measured by ≥24-hour heart rhythm monitoring
2. Reduction in PVC burden by at least 99% at 12 weeks.
3. Quality of Life score as measured by QoL questionnaires, including the ASTA,[1] DASS21[2] and EQ-5D-5L.[3] The ASTA will be the primary quality of life measure.
4. Tolerability of medical therapy (adherence, adverse events)
5. Tolerability of catheter ablation (complications, adverse events)
6. Health service utilization (hospital admissions)

These secondary endpoints will permit an assessment of other potential benefits of either medical therapy, or ablation for PVCs. They will also help us to understand the findings if the trial does not demonstrate a difference between treatment allocations.

Safety outcomes

Serious Adverse Events (SAE) and Adverse Events of Special Interest (AESI) will be recorded throughout the trial from immediately post randomisation.

a. AESI related to effects of catheter ablation.
b. AESI related to medical anti-arrhythmic drug therapy.

Study Intervention

All participants who meet the eligibility criteria for the study will be randomised to:

a. Catheter ablation for PVC within 2 weeks of randomisation

OR

b. Anti-arrhythmic drug (AADs) at maximally tolerated dose. These could include beta blocker, calcium channel blocker, sotalol or Class 1C agents (if structural heart disease ruled out). Choice of AADs will be up to treating physician, if no preference, trial will suggest sotalol or class 1 AADs.

1. DETAILED PROTOCOL

1.1 Aim

To examine in a randomised trial in patients with premature ventricular complexes (PVCs), if catheter ablation (CA) compared to medical therapy with anti-arrhythmic drugs (AADs) results in reduced PVC burden, improved quality of life.

1.2 Hypothesis

Catheter ablation will be superior to anti-arrhythmic drug therapy in reducing PVC burden and associated symptoms as well as improving quality of life compared to AADs alone.

1.3 Background

Premature ventricular complexes (PVCs) are extra, abnormal heartbeats arising from the ventricles of the heart and are the most common ventricular arrhythmia. Estimates of the prevalence of PVCs in the general population depend on the duration of monitoring. In the ARIC (Atherosclerosis Risk In Communities) study examining a multi-ethnic population of men and women between the ages of 45 and 64, PVCs were seen in 1.8% of the population as captured by a single 10 second electrocardiogram (ECG)[4]. In comparison community based 24 hour Holter monitor demonstrated that 69% of participants aged between 25 and 41 had at least a single PVC[5]. One in every five hundred (0.2%) of Californian residents seen in ED, hospitals or outpatient surgery centres had health-care code billing for PVCs[6].

Many people with PVCs are asymptomatic, however there are some individuals who develop significant symptoms including palpitations, chest discomfort, light-headedness, shortness of breath and fatigue. These symptoms can lead to significantly impaired quality of life. In a prospective study of 37 patients referred for CA of PVCs, 35% had severe or disabling symptoms (European Heart Rhythm Association AF score 3 or 4) and low baseline scores in mental health and vitality domains in the Short Form – 36 questionnaire[7]. Furthermore, in some patients, PVCs can cause life-threatening heart rhythms, sudden death, and heart failure. Higher burden of PVCs are associated with reduced heart function, increased heart failure and increased mortality[8]. PVCs can worsen normal heart function, leading to a condition known as PVC-mediated cardiomyopathy. Moreover, treatment of PVCs through either catheter ablation or AADs has shown to improve cardiac function.[9]

Patients with PVCs are often investigated for underlying heart disease including assessment of their heart function with a transthoracic echocardiogram (TTE) and assessment for coronary artery disease and other forms of structural heart disease. The burden (percentage of total heart beats which are PVCs) can be calculated by ambulatory ECG monitoring, most commonly a Holter Monitor. Some patients require an electrophysiology study (EPS) to determine if these PVCs herald an increased risk of sudden cardiac death. During an electrophysiology study, tiny electrical wires are navigated into the heart from the groin veins and the patient undergo systematic electrical stimulation testing to provoke the PVCs or any sustained life-threatening ventricular rhythms (called ventricular tachycardia (VT). Patients deemed to be high risk of developing VT due to other non-invasive tests e.g. cardiac magnetic resonance imaging, genetic testing, family history, may also receive a primary prevention implantable cardioverter defibrillator (ICD) implant.

Treatment of PVCs can involve conservative monitoring (if symptoms are tolerated and heart function is not impaired), medical therapy with AADs or catheter ablation (CA), where an electrophysiology study is performed and then the tissue from which PVCs arise is burned with heat-emitting electrodes.

For patients with symptoms, AADs are often used. These can include beta blockers, calcium channel blockers, sotalol or Class 1C agents such as flecainide. Despite this AADs have variable efficacy in reducing PVC frequency. They can themselves be pro-arrhythmic and have significant side-effects, especially if used long term. Further AADs are also not always well tolerated, particularly in young patients. CA offers potentially curative therapy for their PVCs. Although head-to-head studies are lacking, observational studies have generally demonstrated that CA exhibits superior effectiveness to AADs but may have greater upfront risks.[10] Complications of catheter ablation procedures for PVCs are observed in approximately 0%-5% of cases including hematoma, pseudoaneurysm, atrioventricular fistula, aortic dissection, atrioventricular block, myocardial infarction, cardiac tamponade, and stroke.

We conducted a systematic review of the literature comparing AADs and CA (De Silva et al. 2023).[10] This described one RCT for only right ventricular outflow tract PVCs, [11], one prospective non-randomised study where treatment allocation was up to patient preference[12], one cross-over open label trial where patients were randomised to different AADs and those failing AADs were offered CA[13] and three retrospective studies[9,14]. CA appeared superior to AADs for PVC recurrence, frequency, and burden. One study reported long term symptoms and showed CA to be superior. Quality of life or cost effectiveness were not reported. Complication and adverse event rates were 0-5.6% (CA) and 9.5-21% (AADs). The right ventricular outflow tract is the easiest location to treat PVCs by CA and there are no RCTs evaluating CA of other locations.

Clinical guidelines offer some recommendations on CA vs AADs for treatment of PVCs however consensus opinion is based on limited evidence. American College of Cardiology (2017) guidelines suggest that CA is useful in patients with symptomatic PVCs arising from the outflow tracts of the heart for whom AADs are not preferred by the patient, are ineffective or not tolerated (Class 1 B-NR)[15]. Although the RCT comparing CA and AADs for patients with PVCs arising specifically from the right ventricular outflow tract likely drove this recommendation, there are no other RCTs comparing these two approaches in PVCs from other (more technically challenging) locations. Available studies to date do not reflect the now standard state-of-the-art CA protocols that are employed. Notably, the tools routinely used for catheter ablation have continued to improve and evolve; indeed, much of the effectiveness and complication rates reported earlier arose before the routine use of ultrasound-guided vascular access, intracardiac echocardiography, deflectable long sheaths, and irrigated catheters with contact force sensing.

1.4 Summary of rationale

There is a substantial need for randomised trial evidence to guide therapy for PVCs for several reasons:

- Available data comparing CA and AADs which have informed the current consensus guidelines by the American Heart Association/American College of Cardiology/Heart Rhythm Society have only one single randomised controlled trial specifically investigating treatment of a specific (technically more accessible) location of PVC (RVOT).[15] The optimal approach to the asymptomatic patient with a high burden of PVCs and a normal LVEF remains unknown.[20] This will be the first trial which will comprehensively compare CA and AADs in this population (burden, LVEF, QoL).
- Upcoming published trial protocols comparing CA and AADs will not answer our research question. The ECTOPIA trial establishes highly controlled and somewhat artificial conditions,

mandating particular AADs where standard clinical practice would involve trialling multiple drugs. It also has a crossover design which will contaminate each arm for measurement of longer term outcomes.[16] The PAPS pilot study does not assess quality of life which is a significant reason patients may prefer CA to AADs.[17] The CAT-PVC trial compares CA to amiodarone which whilst an effective drug has significant long term side-effects and is seldom used for PVCs[18]. Similar to Ling et al. 2014, the AVATAR trial restricts CA to outflow tract only.[19]

- There has been a great improvement in the technique of mapping and ablation of PVCs which have not been examined in any recent clinical trials. Updated evidence exploring CA for PVCs is required.[7,21-23]

This trial will attempt to clarify the optimal management of patients in a real-world scenario by including all forms of PVCs. As described, there is limited evidence to guide clinicians either toward pharmacologic therapy with effective but potentially toxic drugs, or CA. An RCT is needed.

2. Trial/Study Design

2.1 Study Design:

This will be an investigator initiated single centre, parallel group, two arm, unblinded, superiority randomised controlled trial running over 1 to 2 years enrolling 50 patients with high burden PVCs who will be followed for 12 weeks after randomisation.

2.2 Assignment of interventions and randomisation

Randomisation of interventions will be in the ratio 1:1. Randomisation will occur in variable block sizes from 2-6 and will be performed using a secure, password-protected web portal (REDCap), managed by Western Sydney Local Health District.

The randomisation allocation will be open to all participants and clinicians although statisticians will be blinded to allocation during the final analysis. Outcome investigations of heart rhythm monitoring will be analysed in a blinded fashion.

3. Methods: Participants, Interventions and Outcomes

3.1 Study Setting and Recruitment

This study will take place out of Westmead Hospital. The study will be presented to referring cardiologists and primary care physicians to assist in identifying potentially eligible patients through outpatient clinics, presentations, admissions and diagnostic investigations, from local and external referrals. After referral, eligibility will be assessed by a member of the study team.

Eligible patients will then be provided with information about the study through the Participant Information Form and through verbal discussion, and if needed, written correspondence. This information will include the reasons for conducting the study, the impact of randomisation on their ability to choose, and the potential risks and benefits of the study. Potential participants will be given ample opportunity to consider the study and whether they wish to be involved and will be ensured that they are able to withdraw from the study at any time.

If the patient wishes to enrol in the study, they will be required to sign the Participant Consent Form prior to undergoing randomisation. The consent form will also be signed by a designated member of the study.

We will only randomise patients that meet eligibility criteria and provide informed consent.

The trial methodology is summarised in Figure 1.

3.2 Eligibility Criteria

3.2.1 Inclusion Criteria

Patients will be eligible for inclusion if they have:

1. PVC burden of ≥10% as determined by ≥24-hour heart rhythm monitoring,
2. Normal left ventricular ejection fraction (ejection fraction ≥ 50%),
3. Aged ≥18 years.
4. Symptoms due to PVCs according to the judgement of the treating physician.

3.2.2 Exclusion criteria

1. Unable or unwilling to provide informed consent or comply with study requirements including study investigations, follow-up, medical adherence and completion of the assigned intervention.
2. Women who are pregnant or breastfeeding.
3. Life expectancy ≤ 12 months.
4. Ventricular tachycardia (VT) defined as spontaneous VT lasting ≥30 seconds, haemodynamically unstable VT of any duration, inducible sustained VT during any electrophysiology study or ≥10 episodes of non-sustained VT (>5 consecutive beats lasting ≤30 seconds) within 24 hours on heart rhythm monitoring.
5. Previous catheter ablation for ventricular arrhythmia.
6. Coronary artery disease defined as a history of myocardial infarction, prior coronary revascularisation, inducible ischaemia on functional testing or obstructive coronary artery disease on coronary imaging. Any type of coronary assessment is permitted although computed tomography coronary angiography is encouraged.
7. Moderate or greater valvular heart disease.
8. Known non-ischaemic or ischaemic cardiomyopathy or evidence of myocardial scar on cardiac magnetic resonance imaging suggestive of structural heart disease.
9. Known cardiac channelopathies including catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome and long- or short- QT syndrome.
10. In the opinion of the investigator or responsible physician, participation would not be in the patient's best interest or the patient would be unable to complete study procedures because of concomitant illness, physical impairment or mental condition.

3.3 Interventions

The intervention of this study is the randomisation process itself. Both catheter ablation and AADs are considered standard of care.

3.3.1 Study Treatment

Patients in both arms will be managed with appropriate, clinically indicated medical therapy by their usual medical practitioners. This will include medications to manage blood pressure and other cardiovascular risk factors as required.

3.3.2 Medical therapy: Anti-arrhythmic drugs

Patients randomised to the control arm will be managed with medical therapy alone by their usual medical practitioners. The objective of this arm is that it replicates what would constitute standard of care for patients with PVCs managed with a non-interventional approach.

Standard clinical care would usually encompass patients who have symptoms and have not previously been prescribed AADs, being commenced on AADs. Choice of AADs will be left to primary physician however if this is deferred to the trial team, the study protocol recommends up to sotalol 80mg twice daily – a common medication that has both AAD and beta blocker properties. It is recommended that patients start at 40 mg twice daily and uptitrate to 80 mg after at least one week. The minimum total daily dose will be 40 mg and the maximum will be 320 mg.If sotalol is contraindicated or not tolerated, patients will be recommended metoprolol, starting at 25 mg twice daily and uptitrating to the maximum total daily dose of 300 mg.

Clinicians may consider alternative AADs if there is a contraindication to a beta-blocker. For example, a non-dihydropyridine calcium channel blocker e.g. verapamil or diltiazem may be initiated if patient has concurrent asthma. If coronary artery disease and structural heart disease is ruled out, flecainide (class I anti-arrhythmic agent) can also be used.

As consistent with clinical practice, AADs can be changed at any time depending on clinical response.

PVC ablation will be discouraged but not prohibited as part of the trial for patients allocated to medical therapy. Should the patient's treating physician decide to perform a PVC ablation during the time-course of the trial, the occurrence and time point of this cross-over will be recorded. Data analysis will be performed as an intention to treat analysis.

3.3.3 Catheter ablation

Patients randomised to the intervention arm will be expected to have the CA procedure within 2 weeks post randomisation.

Medical therapy can be used as a temporising measure before CA, as is standard of care. If the patient is drug-naïve, initiation of sotalol is recommended, but not mandated, as per the control arm. Post ablation, all PVC medical therapy should be discontinued.

Halting medical therapy for PVCs before a CA is standard practice: for patients already medicated for PVCs prior to CA, an additional heart rhythm monitor may be performed after at least 5 half-lives without any medical therapy to establish baseline burden.

CA procedures will be performed in the standard fashion, as accepted by international guidelines. Procedures will be performed under conscious sedation or general anaesthesia, as per the operator preference. This will include venous and/or arterial femoral vascular access, advancement of electrode catheters to the coronary sinus, right ventricle and/or the left ventricle. If the PVCs are arising from the left ventricle, access will be obtained via either transeptal puncture or retrograde aortic access at the operator's discretion. Where available, pre-procedural imaging with cardiac MRI or cardiac CT will be integrated with the electroanatomic mapping system to aid procedures. Intracardiac echocardiography will be encouraged but not mandated. Ablation will be guided by a combination of standard mapping techniques, as per standard practice. Preference will be given to "activation mapping" of the PVCs (which may be stimulated by administration of intravenous isoprenaline) using a three-dimensional electroanatomic mapping system. If there is paucity of PVCs, then "pace-

mapping" will be performed. Acute success will be defined as elimination of PVCs during the procedure.

Induction of ventricular tachycardia (VT) with programmed electrical stimulation (PES) will also be attempted during the procedure, as a standard practice to aid risk patient risk stratification. PES will be performed from the right ventricular apex, using a well validated stimulation protocol.

Intravenous heparin will be given at the beginning (bolus) and during the procedure, especially if endocardial left ventricular access is planned to prevent risk of systemic and/or venous thromboembolism. Further heparin boluses will be given to maintain an activated clotting time >300s, as per published guidelines. If the patient is on anticoagulation, the procedure may be performed on uninterrupted warfarin and/or dabigatran, or bridging therapy with intravenous heparin or subcutaneous enoxaparin, as per the operator discretion. Post procedural anticoagulation for 6 weeks is recommended, but not mandated if extensive ablation (RF time ≥10 minutes) is performed.

Post procedure, medical therapy, if the patient was receiving it, will be stopped. Repeat ablation procedures will be discouraged for the 12 weeks of monitoring.

Occasionally, patients may experience a random episode of PVC quiescence, leading to an absence of PVCs on the day of CA. This can be a result of changes in medication, stress, hormones, electrolytes and can be unpredictable. As at least one PVC occurring with the patient in the procedural area is required to perform a CA, an episode of PVC quiescence on the day of the procedure that inhibits the ablation from taking place will not preclude the patient from having a repeat attempt at the CA within two weeks.

3.4 Control of bias

Blinding of patients is not possible as one of the interventions is invasive and a sham procedure would be considered unethical without further scientific data available. We will institute the following to minimise the potential for bias:

1. Maximise adjunctive non-arrhythmic drug therapy as much as tolerated.
2. Ensure adequate management of new onset or decompensated heart failure with maintenance of euvolemic state.
3. Optimisation and maintenance of electrolytes.
4. Personnel analysing heart rhythm monitors will be blinded to intervention allocation. Similarly, statistical analysis will be performed whilst blinded to group assignment.

These measures will reduce the possibility of contamination and co-intervention effects. In addition, a Clinical Event Committee blinded to treatment allocation will be used to objectively adjudicate the events associated with the primary and secondary endpoints. We will offset the inability to blind subjects or investigators by using a blinded Clinical Events Committee.

3.5 Study Risks and Deviation from Usual Care

This study is comparing two established methods of treating PVCs, both of which are considered standard of care. The intervention in the study is the randomisation process itself, wherein a participating patient will have the decision about which treatment they undergo made for them. There is a risk of participants feeling that they have a lack of control or empowerment with this model, however, they will be assured that they can withdraw from the study at any time. There is a risk that

the allocation may not work for them, and they would have chosen the other outside the context of the study, potential delaying the positive benefit of a working treatment. However, any benefit from particular therapy is subject to individual variability and at the current state of scientific knowledge is difficult to predict. To alleviate these risks, cross-over for CA or AADs will be afforded for patients with ongoing symptoms. Cross-over numbers and reasons for cross-over will be recorded.

Medical therapy and CA are valid and established methods for the management of PVCs. Current guidelines suggest that CA is superior to AADs in treatment of symptomatic PVCs originating from the right ventricular outflow tract (Class 1). For other PVCs, CA is indicated when medical therapy has failed, is not tolerated due to side effects, or as primary treatment, if patients prefer not to take medications. The primary goal of PVC treatment in a structurally normal heart is symptom management, and prevention of remodelling. Hence, both medical therapy and CA are common clinical approaches, and there is considerable clinical equipoise between them, as we demonstrated in our systematic review.[10]

Investigations commonly used in clinical practice for the evaluation of structural heart disease aetiology and its severity may include one or more of heart rhythm monitoring, TTE, coronary angiography, cardiac MRI, cardiac CT scanning, biopsy, cardiac positron emission tomography (PET) scan, genetic testing for familial dilated cardiomyopathies, and blood work to evaluate renal, thyroid and hepatic function. In this trial, withholding of AADs is recommended for measurement of baseline PVC burden which may expose patients to additional arrhythmic risks. However, this practice is routine and almost universally performed in the leadup to catheter ablation. Furthermore, if the treating clinician feels that withholding drugs is unsafe for a particular patient, it is not mandated.

Routine clinical follow-up at 6-monthly intervals is considered clinical standard of care. The study will not mandate any of these tests beyond what is considered clinically relevant by the treating physician.In addition to routine clinical follow-up, participants in this study will also undergo in person or telemedicine review as part of the study at 6- and 12-weeks to complement routine follow-up.

3.5.1 Study Benefits

The benefits available to potential study participants are modest and subtle. Participants may experience benefits such as improved clinical outcomes and positive healthcare experiences from increased attention in a clinical trial setting. However, it is possible that patients may experience the same level of benefit from not enrolling in the study and undergoing the standard treatment of their choice.

3.6 Study Outcomes

3.6.1 Primary Outcome

1. Reduction in PVC burden by at least 80% as measured by ≥24 hour heart rhythm monitoring at 12 weeks.

3.6.2 Secondary Outcomes

1. Change in PVC burden at 12 weeks as measured by ≥24-hour heart rhythm monitoring
2. Reduction in PVC burden by at least 99% at 12 weeks.
3. Quality of Life score as measured by QoL questionnaires, including the ASTA,[1] DASS21[2] and EQ-5D-5L.[3] The ASTA will be the primary quality of life measure.

4. Tolerability of medical therapy (adherence, adverse events)
5. Tolerability of catheter ablation (complications, adverse events)
6. Health service utilization (hospital admissions)

These secondary endpoints will permit an assessment of other potential benefits of either pharmacologic therapy, or ablation for PVCs. They will also help to understand the findings if the trial does not demonstrate a difference between treatment allocations.

3.6.3 Safety outcomes

Serious Adverse Events (SAE) and Adverse Events of Special Interest (AESI) will be recorded throughout the trial from immediately post randomisation.

a. AESI related to effects of catheter ablation.
b. AESI related to medical anti-arrhythmic drug therapy.

3.7 Methods for Follow-up

Patients will be followed until the end of the trial (6 12 weeks) or death, with a . Patients will be evaluated at baseline, 6 weeks and 12 weeks. Trial follow-up will complement, without replacing, routine clinical follow-up with the primary cardiologist or primary care physician. The primary outcomes will be assessed through heart rhythm monitoring at 12 weeks by a ≥24 hour monitor.

Trial follow-up will take place as per the patients' preference of in-person or telehealth, unless in-person attendance is required for follow-up investigations (e.g. heart rhythm monitoring), or the study team has reasonable concern about the patient's welfare.

Effects of treatment on PVC burden will be assessed by heart rhythm monitor analysis.

Quality of Life questionnaires will be completed by participants either by hand or through REDCap survey portal created for this trial, as per the participants preference, at baseline, 6-weeks and 12-weeks.

3.7.1 Participant Timeline

All eligible participants will be randomised and followed up for a period of 12 weeks. At enrolment, if patients have not had a ≥24 hour heart rhythm monitor and TTE in the past year they will undergo these tests. They will complete quality of life questionnaires. At 6-weeks post randomisation, patients will undergo quality of life questionnaires. At 12-weeks, participants will undergo repeat quality of life questionnaires and a ≥24 hour heart rhythm monitor. The schedules and nature of the data collection required during the study period is illustrated in Table 1.

3.7.2 Screening and Enrolment Process

≥24 hours heart rhythm monitoring demonstrating PVC burden of ≥10% must be performed within 1 year before randomisation and be off AADs, including beta blockers. If monitoring needs to be performed, it should be performed within 2 weeks and before the initiation of the trial intervention. Repeat heart rhythm monitoring is only required if heart rhythm monitoring was performed more than 1 year prior to randomisation or monitoring was completed whilst the patient was on AADs. If baseline heart rhythm monitoring needs to be performed, AADs should be stopped for at least 5 half-

lives prior to commencement of monitoring (Table 2). In the case of the CA arm, withholding medications would usually be part of routine medical care in the leadup to the ablation, and monitoring may be performed at this time. If the treating clinician feels that this is unsafe or not in the patient's interest, this is not mandated in either arm.

As with other common medical investigations (e.g., blood tests, medical imaging), heart rhythm monitoring is routinely performed by hospitals, community cardiologists and primary care physicians; therefore, heart rhythm monitoring is permitted to occur at non-study sites.

All participants screened will be recorded by the study team and entered in the trial screening log. If the patient is not eligible the main reason as to why a participant is excluded will be recorded on a screening log.

If the patient is eligible then initial contact may be via telecommunication or in-person. Initial screening activities will include a brief verbal assessment of the potential participant's medical history, their willingness to participate, and current medications. If the member of the study team determines that the potential participant is suitable for the study an invitation package including a copy of the Participant Information and Consent Form will be provided to the potential participant to review.

3.7.3 Baseline visit

For baseline assessment, the information listed in Table 1 and Appendix 1 will be collected from each participant. This will include details of medical history, concomitant medications, results of blood tests and baseline imaging. The recordings from the heart rhythm monitors will be downloaded and details regarding PVCs documented (duration, frequency, burden). All baseline and subsequent follow-up will be recorded in pre-formed, WSLHD REDCap database.

3.7.4 Randomisation

Randomisation to catheter ablation or medical therapy will be 1:1. Randomisation will be by a computerised system that will allow for variable block sizing (2-6). Randomisation will be performed by using a secure, password-protected web portal (REDCap).

3.7.5 Subsequent visits

Information shown in Table 1 and Appendix 1 will be collected on subsequent visits at 6- and 12-weeks. This will include heart rhythm monitoring and quality of life surveys. Any intervening events or hospitalisations will also be reviewed.

As above, heart rhythm monitoring is commonly performed at healthcare centres. To aid participants, follow-up heart rhythm monitoring may be performed by their primary cardiologist or primary care physician,

3.7.6 Premature withdrawal and early study termination

If a participant wishes to withdraw or the study team / responsible physician decides it is in the best interest of the participant to withdraw from the study, every effort should be made to conduct all assessments until the date of the last follow-up. Withdrawal will be formalised by signing of the Withdrawal Form, within the Participant Information and Consent Form

3.7.7 Retention

The study team will retain all study records in accordance with applicable regulatory requirements in a secure and safe facility for a minimum period of 5 years

5. Statistical Considerations

5.1 Sample size calculations

Multiple studies have shown a significant reduction in PVC burden for CA vs AADs with a reduction in PVC burden in 85% of all patients undergoing PVC ablation[25] compared to 43% undergoing drug therapy.[26] With a significance level alpha of 0.05, power of 90% and two groups, a total sample size of 50 patients is required according to the Chi squared test. It is estimated that crossover and loss to follow up will be minimal (see below) so the target recruitment will be 50 patients.

5.2 Recruitment Rate

Approximately 40 patients with structurally normal hearts present to Westmead Hospital each year for catheter ablation of PVCs. There are an existing 26 patients followed in the Westmead public cardiology clinic who also have high burden PVCs. The study and availability of treatment will be advertised to general cardiologists. Given this figure, we anticipate that recruitment will take 12 months. Patients are referred to Westmead Hospital from primary care physicians, cardiologists and emergency departments for PVC investigations; recruitment will be encouraged through promotion of the trial to healthcare staff.

5.3 Cross over rates

As PVCs may be well tolerated, there is short trial follow-up and there is clinical equipoise, we anticipate a low cross over rate. Sample size impact, therefore, should be minimal.

5.4 Loss to follow-up

We anticipate that <2% of patients will be lost to follow-up. This patient group is closely engaged with care providers. Ling et al. (2014) had only 1.5% of patients lost to follow-up in a similar trial.

4.5 Subgroup analysis

The following subgroups will be used: sex, age (above or below the median), ejection fraction (above or below the median), beta blocker (excluding sotalol) only arrhythmic or not, PVC morphology (only suspected outflow tract or elsewhere) and presence of multiple PVC morphologies on heart rhythm monitoring.

6. Data management, Statistical Methods and Analysis

6.1 Data Management

All paper forms including consents and follow-up information will be locked in secure filing cabinets in locked areas of the Cardiology Department, Westmead Hospital. Electronic data will be stored in an electronic database that will be accessible only to designated individuals and password locked. A random sample of 10% of key data entered will be examined against source documents. We will run statistical quality checks, e.g. to check for out-of-range values.

6.2 Statistical Methods

Detailed statistical methodology is detailed in the Statistical Analysis Plan. Statistical analysis will be performed blinded to allocation.

6.2.1 Demographics

Clinical demographic information collected is described in Appendix 1. These will be summarised with standard statistical methods. based on intention-to-treat populations.

6.2.2 Primary Analysis

The primary analysis will be an intention to treat and will compare the primary outcome (80% reduction in PVC burden at 12 weeks) in catheter ablation compared to medical therapy. Outcomes will be compared with a Chi-squared test with confidence intervals for risk differences determined by the Wald method.

6.2.3 Secondary Analysis

Secondary outcomes will be analysed on an intention to treat principle and will compare the change in PVC burden with regression, the change in echocardiographic parameters with ANCOVA, the change in quality of life scores with ANCOVA and healthcare utilisation with Mann-Whitney U. The full details are in the statistical analysis plan.

7. Trial Committees

7.1 Trial Steering Committee

The steering committee will form the principal leadership structure of the study. Members of the steering committee will be the listed PIs on this application. The steering committee will be responsible for the overall conduct of the trial, its conception and termination, and interpretation and publication of the results.

7.2 Trial Management Group

The Trial Management Group will compose of people at the coordinating or principal site, who oversee the day-to-day conduct of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. This group will include the key individuals responsible for the everyday management of the clinical trial, such as the Site Principal Investigator, trial coordinator, data manager.

7.3 Events Committee

An events committee (EC) will be appointed. This committee will be blinded to treatment allocation of enrolled patients and will review de-identified data and source documents including heart rhythm monitoring reports, TTEs and redacted hospitalisation records, and will primarily adjudicate on endpoints. The EC will individually examine the validity of noted events using available records of events. Consensus will be sought to classify an event as accurate or not.

8. Adverse Events

Any adverse event occurring as a result of standard medical therapy or catheter ablation will be recorded. An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose or a medical procedure that does not necessarily have to have a causal relationship with this treatment. A list of adverse events is shown in Appendix 2.

Procedure-related adverse event is any adverse event that, in the investigator's opinion, is a complication of the catheter ablation procedure and occurs within 48 hours of catheter insertion.

Adverse Reaction will be defined as a harmful and unintended response to an approved and marketed health product. This includes any undesirable patient effect suspected to be associated with health product use. Unintended effect, overdose, interaction (including drug-drug, and drug-food interactions) are all considered to be reportable adverse events in this study.

Serious Adverse Event (SAE) will be defined as any untoward medical occurrence that:

1. Results in death.
2. Is life threatening in the opinion of the attending clinician (i.e. the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe).
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation (Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria).
4. Results in persistent or significant disability or incapacity.
5. Is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above.

An adverse event that meets the above categories between when the informed consent form is signed, the end of study at follow-up (12 weeks) will be reported as an SAE. All SAEs will be reported to the trial sponsor (the local health district) within 24-hours of the study team first becoming aware of the event. The SAE will also be required to be reported to the relevant HREC within the timeframe specified in the relevant committee guidelines. Adverse events which do not fall into these categories are defined as non-serious.

The following events are not considered to be SAEs:

- Planned hospitalisations for pre-existing condition.
- Hospital admission for interventions or procedures required by the study protocol.
- Emergency department presentation, without admission, for non-cardiovascular events.

Suspected Unexpected Serious Adverse Reaction (SUSAR). An unexpected adverse reaction (UAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. A Suspected Unexpected Serious Adverse Reaction is any UAR that at any dose meets the definition of an SAE. Any event that meets the definition of a SUSAR between when the informed consent form is signed and the end of study will be reported to the local HREC and the relevant regulatory authorities as per local requirements and ICH Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Questionnaire-related events: If a person is deemed as at risk for depression from the questionnaires, particularly the Depression, Anxiety, and Stress Scales-21 (DASS21) questionnaire, this will be discussed with the patient in the context of assisting them with locating supportive resources, including but not limited to, liaising with the patients general practitioner and services such as Beyond Blue. Whilst not anticipated, these services will also be provided to any patient that feels their

involvement in the research study is causing them distress, along with reminders of their option to withdraw.
If there is immediate concern for the patient's welfare, or absent or failed collaboration with GP or external services, the patient may be advised to present to an Emergency Department.

8.1 Risk assessment and management plan

The intervention of this study is the randomisation process, with both treatment allocation arms being considered standard of care. As such the risk of adverse events occurring is low. However, efforts will be made to mitigate any long-term effects or increasing of severity of adverse events by the study team. Before enrolling into the study, patients will have to understand that there are risks of adverse events associated with all medications, and that the risk of serious adverse events for catheter ablation procedure is around 1%, whilst minor adverse events, such as bruising, may be as high as 5%. Critically, participants will need to understand that these risks are the same whether they participate in the study or not.

If a participant is allocated to the catheter ablation arm and experiences an adverse event, they will undergo clinical review by the treating cardiologist. If the treating cardiologist is not available, another cardiologist from the study team will step in and review the patient. Adverse events occurring in hospital will be managed as per established protocols. Adverse events occurring following discharge will be discussed with a study doctor and if required the participant will be asked to present to hospital for treatment. If no presentation is required, a follow-up appointment at the Rapid Access Cardiology Clinic in the subsequent days will be arranged. If no follow-up appointment is required, the participant may require reassurance, and a repeated check-in at a shorter time interval as clinically indicated.

If the participant is allocated to medical therapy and experiences an adverse event related to their prescription, this will be discussed with the treating cardiologist. If the treating cardiologist is not available, a cardiologist from the study team will assist and review the event.
As the adverse events related to medications range from minor to major, the participant may be advised to reduce their dose, change their dose, cease the medication or present to the hospital for review. If the patient is unable or unwilling to present to hospital, an appointment will be made in the Rapid Access Cardiology Clinic.

Participants will always be advised that when at home or in the community, should they experience severe symptoms or symptoms that concern them, they should call an ambulance or present to their local medical centre.

9. Auditing

The study may be audited by the third parties and inspected by government regulatory authorities. CRFs, source documents and other study files must be accessible at the time of auditing and inspection during the course of the study and after the completion of the study.

10. Ethics and Dissemination

10.1 Regulatory and Ethical Compliance

This study protocol was designed and shall be implemented and reported in accordance with the ICH Guidelines for Good Clinical Practice, NHMRC National Statement on Ethical Conduct in Human Research, applicable local regulations including European Directive, US Code of Federal Regulations

Title 21, Therapeutics Goods Administration (TGA), and with the ethical principles laid down in the World Medical Associations (WMA) Declaration of Helsinki.

The protocol and the proposed informed consent form and any subsequent modifications will be reviewed and approved by the Human Research Ethics Committee before any participant is enrolled.

Prior to study start, investigators are required to sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, HRECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Western Sydney Local Health District immediately that this request has been made.

10.2 Informed Consent

Potential participants may only be included in the study after providing written informed consent. The associate investigator will issue the information sheet and consent forms and will obtain consent from participants. Before the start of the study, a member of the study team will have the participant information sheet and consent form that will be provided to the participants reviewed and approved by the HREC. This review and approval will be documented and stored with other study documents. The associate investigator must fully inform the participant of all relevant aspects of the trial. During the consultation with participants, the associate investigator will explain the details of the study, and provide an information sheet detailing the aims, methodology, and possible outcomes of the research proposal. Participants will be given information about their rights to refuse consent, right to confidentiality, right for their information to be secured in a locked facility if they choose to participate in the study. Participants will be given opportunity to communicate their choice of participating or not at the time of initial consultation and once again 1 week after consultation. During this time, support will be provided to answer any questions or comments arising from the consent process. A copy of the signed written informed consent will be given to the participant. The participant must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. Participants will have 2 weeks to consider participation. The participant must sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted, including screening procedures. If the participant is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature. If the participant is unable to speak or read in English, an interpreter will be used to explain the study to them. Interpreter services are readily available. Ample time will be provided to these participants, along with repeated sessions to explain the study, as with any other participant, if required.

10.3 Confidentiality

Every precaution will be taken to respect the privacy of participants in the conduct of the study. Only de-identified data will be entered in the central study database to maintain participant confidentiality. In the course of monitoring data quality and adherence to the study protocol, the monitor will refer to medical records at the participating study site. This information will be included in the PICF. All individual and site information will be de-identified in reporting data and results to protect the confidentiality of participants. For the purpose of tracking of clinical and adverse events however, a log will be kept separately from the study database containing information about the participant number and their corresponding clinical details in a re-identifiable format.

10.4 Trial Sponsorship

The primary investigator (A/Prof. Saurabh Kumar) is a staff specialist within the Western Sydney Local Health District (WSLHD), therefore WSLHD will be the trial sponsor.

10.5 Ancillary and post-trial care

Patients that are enrolled into the study are covered by indemnity for negligent harm through their participating primary care practice and participating research staff and investigators. WSLHD has insurance to cover for non-negligent harm associated with the protocol. This will include cover for additional health care, compensation or damages whether awarded voluntarily by the Sponsor, or by claims pursued through the courts. Incidences judged to arise from negligence (including those due to major protocol violations) will not be covered by study insurance policies and will be covered by the insurance of responsible individual(s), if applicable.

10.6 Dissemination Policy

Publication of the main results from the study will be in the name of the CAAD-PVC Investigators. Full editorial control will reside with a Writing Committee approved by the Steering Committee (SC). Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship that follow:

a. Authors must make substantial contributions to the conception and design of the study, acquisition of data, or analysis of data and interpretation of results.
b. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors.
c. Authors must provide approval of the final draft version of the manuscript before it is submitted to the journal for publication.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per ICMJE guidelines for acknowledgement.
De-identified study data may possibly be made available for future research such as meta-analyses.

11. Funding

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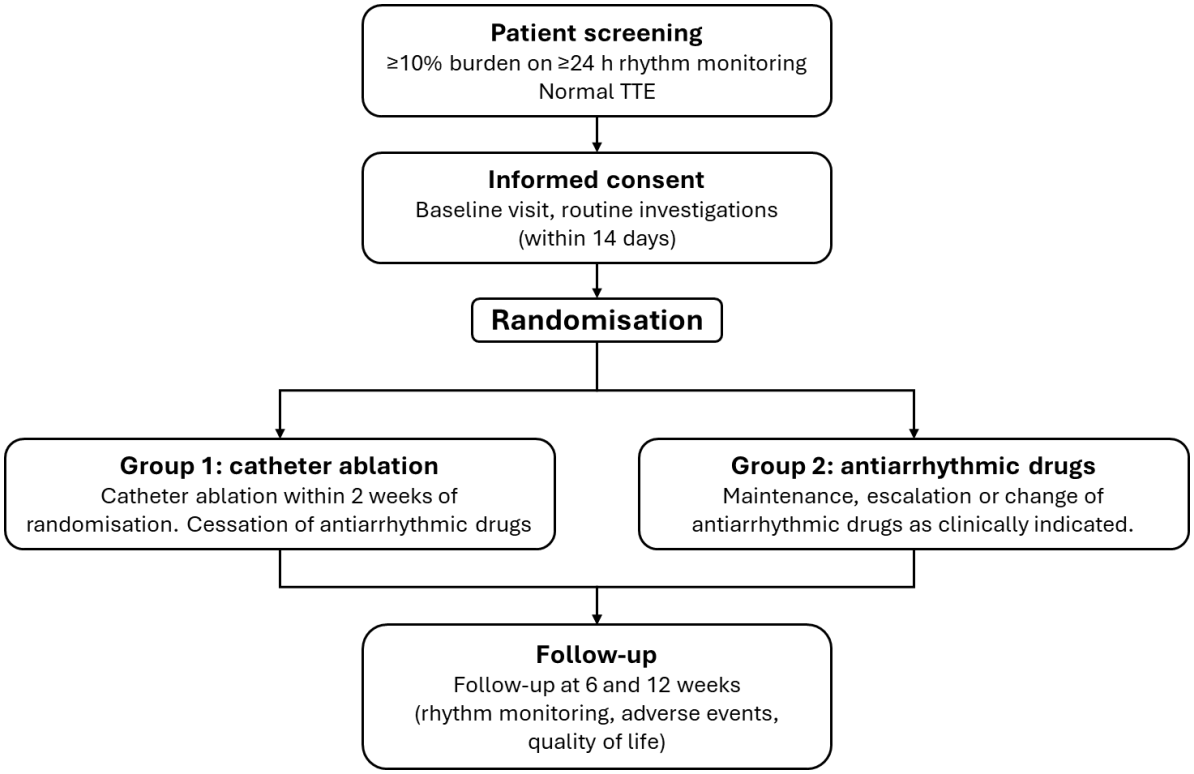


Figure 1. Trial Schema

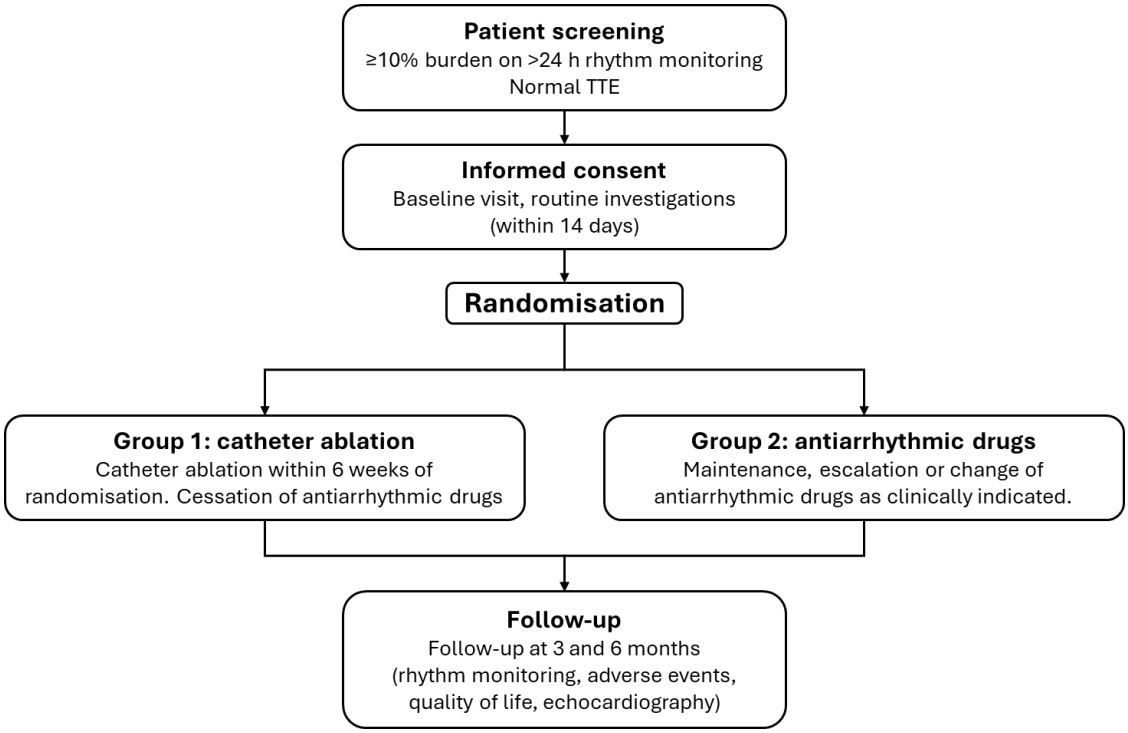


Table 1. Timetable of Trial Procedures and Follow-up

Study Periods	**Baseline**	**Randomisation**	**Treatment**	
Study week	N/A	0	6	12
Study Visit Window	±14 days	N/A	±14 days	±14 days
Evaluation				
Inclusion/exclusion criteria	X			
Informed consent	X			
Clinical History (demographics, medication, comorbidities, history)	X			
Randomisation		X		
≥24 hour heart rhythm monitoring	X*			X
Quality of Life Questionnaires (ASTA, DASS21, EQ-5D-5L)	X		X	X
Adverse Events			X	X

*Heart rhythm monitoring may be performed up to 2 weeks after randomization, provided it occurs before initiation of AADs or CA. Heart rhythm monitoring results may be used if they were performed less than 1 year prior to randomisation.

Table 2. Half-lives and washout periods of standard anti-arrhythmic drugs

	Half-life (hours)	Washout period (days)*
Amiodarone	63 (days)	315
Atenolol	7	1.5
Bisoprolol	10	2.1
Carvedilol	8	1.7
Digoxin	39	8.1
Diltiazem ER	12	2.5
Diltiazem IR	8	1.7
Flecainide	20	4.2
Ivabradine	11	2.3
Metoprolol ER	8	1.7
Metoprolol IR	3	0.6
Mexiletine	12	2.5
Nadolol	22	4.6
Propafenone	6	1.3
Quinidine	7	1.5
Sotalol	15	3.1
Verapamil	5	1.0

* Washout period is 5 half lives[27]

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APPENDICES
APPENDIX 1: DATA COLLECTION

Referral source

- Referral source (direct to Westmead, or free text)

Demographics and clinical history

- Age
- Sex
- Cardiovascular co-morbidities
    - Diabetes mellitus
    - Hypertension
    - Hypercholesterolaemia
    - Chronic kidney disease
    - Smoking history
    - Alcohol use
    - Implantable cardioverter defibrillator
    - Atrial fibrillation or flutter
    - Previous electrophysiology study
    - Race or ethnic group (white, black, Asian, Middle-Eastern, indigenous, other, unknown)
    - BMI
- Medication Data
    - Medication prescribed
    - Dose
    - Frequency
- Symptomatic PVCs?

Baseline Investigations

- >24 hour heart rhythm monitoring
    - PVC burden (percentage)
    - Count per 24 h
    - Percentage
    - Duration of monitoring
- Transthoracic echocardiography
    - Left ventricular function
    - LVEF%
    - GLS%
    - LV end diastolic dimension
    - LV septal thickness
    - TAPSE
    - Visual systolic function assessment
    - Valvular assessment (free text comments of any valvular dysfunction)
- Quality of Life and Symptom surveys
    - ASTA
    - DASS21
    - EQ-5D-5L
- 12-lead ECG
    - Morphology of PVC: outflow tract or other

    - Coupling interval of PVC
    - Cardiac Rhythm: sinus or atrial fibrillation/flutter or other
    - PR interval
    - QRS duration
    - QTc
    - Axis
- Lab tests (as required)
    - Renal
    - Thyroid (TSH and T4)
    - Liver function
    - Electrolytes (Na, K, Mg)
    - Full blood count (Hb)

Catheter Ablation procedural data

- Anaesthesia type
    - Sedation
    - General
    - Inhalational
    - Total intravenous anaesthesia (TIVA)
- Localisation site of PVCs
    - Pace-mapping results
        - Location
        - Correlation (%)
        - Characteristics
    - Activation mapping results
        - Location
        - Earliest activation time (msec)
        - Electrogram characteristics
    - Ablation data
        - Sites of ablation
        - Total ablation delivered in duration
        - Number of PFA lesions
- Electroanatomic mapping characteristics
    - Normal substrate distribution
    - Abnormal substrate distribution
- Inducibility of VT
    - VT morphology and cycle length
    - VT ablation
    - Induction method
    - Coupling intervals
    - Isoprenaline
- Acute success (elimination of PVCs during the procedure)

Post-Procedure Follow-Up Data (at 6- and 12-weeks)

- Adverse events
- PVC burden from >24 hour heart rhythm monitoring
    - Count
    - Percentage
    - Documentation of VT

    - Duration of monitoring
- Quality of Life and Symptom surveys
    - ASTA
    - DASS21
    - EQ-5D-5L
- Changes to clinical history
- Current Medications
    - Failure to adhere to anti-arrhythmic medical therapy
    - Medication prescribed
    - Dose
    - Frequency
- Health care utilisation (hospital admissions)

APPENDIX 2: ADVERSE EVENTS

Adverse events will be adjudicated by the Events Committee within the following categories:

Death

- All cause
- Cardiac
- Non-cardiac

Cardiac events

- Arrhythmic
- Non-arrhythmic e.g. heart failure

Complications related to catheter ablation

- Procedure related death (30-day mortality)
- Retroperitoneal haemorrhage
- Other major vascular injury (requiring surgical repair or a blood transfusion > 1 unit of packed cells)
- Sepsis / bloodstream infection
- Access site infection
- Pneumothorax
- Anaesthesia related complications
- Acute kidney injury
- Thromboembolism
- Stroke
- Transient ischaemic attack
- Deep vein thrombosis
- Embolism to limb or peripheral organs
- Cardiac bleeding
- Tamponade requiring percutaneous or surgical drainage
- Valve injury
- New onset valvular regurgitation in follow -up
- Temporary or permanent complete heart block
- Myocardial ischaemia or infarction defined by rise and fall of cardiac biomarkers with one of:
- Symptoms of ischaemia,
- New ST changes or new LBBB,
- Development of Q waves
- Evidence on imaging of new loss of viable myocardium or new regional wall motion abnormality
- Acute heart failure occurring within 48 hours of catheter ablation
- Complications of epicardial access and/or ablation
- Pericardial bleeding
- Injury to subdiaphragmatic vessels or organs
- Coronary artery injury
- Phrenic nerve injury
- Severe pericarditis or pleuritic pain requiring hospitalisation >72 hours
- Inability to perform CA due to PVC quiescence

Complications related to AADs use prompting discontinuation due to perceived side-effects

Beta blockers

- Heart failure
- Fatigue
- Symptomatic bradycardia
- Rash
- Intolerable gastrointestinal disturbances namely nausea, vomiting, indigestion, flatulence, cramps, diarrhoea, constipation, ulceration
- Sexual dysfunction including reduced libido or impotence
- Hypotension

Amiodarone

- Interstitial pneumonitis
- Hypothyroidism
- Hyperthyroidism
- Hepatic dysfunction
- Symptomatic bradycardia
- Torsades de pointes
- Skin adverse event
- Photosensitivity
- Skin discoloration
- Severe cutaneous adverse reactions
- Tremor
- Ataxia
- Insomnia
- Peripheral neuropathy
- QT prolongation
- Visual symptoms (decreased vision, blurring, halos)
- Optic neuropathy / optic neuritis
- Vortex keratopathy
- Transaminitis

Sotalol

- Heart failure
- Torsades de pointes
- Symptomatic bradycardia
- Fatigue
- Rash
- Intolerable gastrointestinal disturbances namely nausea, vomiting, indigestion, flatulence, cramps, diarrhoea, constipation, ulceration
- Intolerable sensory disturbances namely paraesthesia, visual changes, taste or hearing abnormalities, abnormal physical weakness or lack of energy

- Intolerable central nervous system effects including sleep changes, depression, mood changes, anxiety
- Sexual dysfunction including reduce libido or impotence
- QT prolongation

Mexiletine

- Intolerable gastrointestinal disturbances namely nausea, vomiting, indigestion, flatulence, cramps, diarrhoea, constipation, ulceration
- Intolerable central nervous system effects including sleep changes, depression, mood changes, anxiety, light headedness, tremor or involuntary muscle movements, confusion or delirium
- Intolerable sensory disturbances namely light headedness, paraesthesia, visual changes, taste or hearing abnormalities, tremor or neurological abnormality, physical weakness or lack of energy
- Hepatotoxicity

Flecainide

- Shortness of breath, wheezing, laboured breathing
- Burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- Dizziness, faintness, or light-headedness when getting up suddenly from a lying or sitting position
- Bradycardia
- Cardiac arrhythmias
- Vertigo
- Headache