VIVO™ non-invasive Time Assessment Protocol

Short Study Title/Acronym: VIVO™ mapping Protocol

REC Reference: Insert REC Reference
IRAS Reference: 257755

CHIEF INVESTIGATOR:

Dr Sabine Ernst, Consultant Cardiologist and Reader in Cardiology, Lead for Electrophysiology Research for the Royal Brompton Hospital

Royal Brompton Hospital (RBH)

Sydney Street

London SW3 6NP

Phone: 00442073518612
Email: s.ernst@rbht.nhs.uk
Fax: 00442073518131

SPONSOR REPRESENTATIVE:

Mr Patrik Pettersson
Royal Brompton and Harefield NHS Foundation Trust (RB&HFT)
Royal Brompton Hospital (RBH)
Research Office
Chelsea Wing, Level 2
Sydney Street
London SW3 6NP

Phone: 0207 352 8121 ext. 8736
Email: P.Pettersson@rbht.nhs.uk
Fax: 0207 351 8829

Signature Page

The Chief Investigator (CI) and the Research Office have discussed and agreed this study protocol. The investigators agree to perform the investigations outlined in this study protocol and to abide by this protocol except in the case of medical emergency that will be notified to the Research Office.

The Investigator agrees to conduct the study in compliance with the study protocol and/or any subsequent amendments approved by the Sponsor and HRA, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent as applicable), the Research Governance Framework for Health & Social Care, 2nd Edition (2005), the Sponsor's SOPs, and any other applicable regulatory requirements.

This protocol has been written in accordance with the Sponsor's guidance for writing non-CTIMP protocols.

Table of contents

1. LIST OF ABBREVIATIONS

VT	ventricular tachycardia
PVC	premature ventricular contraction
HR	heart rate
LV	left ventricle
RV	right ventricle
RVOT	right ventricular outflow tract
RF	radiofrequency current
EAM	electroanatomical mapping
EGM	electrogram
TOE	transesophageal echocardiography
TTE	transthoracic echocardiography
ECG	electrocardiogram
CT	computer tomography
F/U	follow-up
EP	electrophysiology
QoL	quality of life
PI	principal investigator
CMR	cardiac magnetic resonance imaging
VTK	visualization toolkit
RB&HFT	Royal Brompton and Harefield NHS Foundation Trust
AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event

2. STUDY PERSONNEL AND FACILITIES

Principal Investigator (PI): Dr Sabine Ernst
Consultant Cardiologist and Reader in Cardiology Lead for Electrophysiology Research for the Royal Brompton Hospital
Royal Brompton Hospital (RBH)
Sydney Street
London SW3 6NP

E-mail: s.ernst@rbht.nhs.uk
Phone: 00442073518612
Fax: 00442073518131

Co-Investigators: Dr Ilaria Cazzoli
Clinical and Research Fellow
Royal Brompton Hospital (RBH)
Sydney Street
London SW3 6NP

E-mail: I.Cazzoli@rbht.nhs.uk

Additional electrophysiology consultants at the Royal Brompton Hospital and Specialist registrars in Electrophysiology.

Statistician: Mr Winston Banya
Royal Brompton and Harefield NHS Foundation Trust (RB&HFT)
Royal Brompton Hospital (RBH)
Research Office

Royal Brompton & Harefield NHS
NHS Foundation Trust

Chelsea Wing, Level 2
Sydney Street
London SW3 6NP

E-mail: W.Banya@rbht.nhs.uk
Phone: 00442073512707

Routine local laboratories: Royal Brompton Hospital

Central Laboratory: Royal Brompton Hospital

Pharmacy: Royal Brompton Hospital

3. STUDY SYNOPSIS

Full study title:	VIVO™ non-invasive Time Assessment Protocol
Short study title:	VIVO™ mapping Protocol
Study R&D number:	VIVO-RBH01
Chief Investigator:	Dr Sabine Ernst
Medical condition/disease under investigation:	Patients undergoing PVC/VT Ablation with structurally normal hearts
Study duration:	9 months
Primary Objective:	*Safety:* • Absence of acute adverse events due to the use of VIVO system during PVC/VT ablation • Safety endpoint of the entire mapping and ablation strategy *Efficacy:* • To assess the efficacy of VIVO to decrease procedure time as compared to standard of care ablation procedures.
Secondary Objective:	• To assess clinical outcome (suppression of reduction of PVCs burden/VT at 3-month F/U) • To assess economical outcome (cost reduction per case)
Study population:	VIVO Cohort – 15 patients presenting for PVC/VT ablation with structurally normal heart Control Cohort – Retrospective review of historical matched patients within the physician's database that had PVC/VT ablations with structurally normal hearts
Recruitment Target	15 patients
Recruitment Window (Months)	6 months
Methodology:	The study is a non-randomized, single-centre, study designed to evaluate the procedural efficacy of VIVO as compared to standard of care ablation procedures. Up to 15 patients will be enrolled.
Eligibility criteria:	***Inclusion criteria:*** 1. Subjects who are at least 18 years or older 2. Subjects who are scheduled for PVC/VT ablation procedure 3. Subjects who have signed an IRB/EC approved Informed Consent Form and applicable subject privacy protection authorization per local law 4. Subjects will be selected without regard to gender or age (unless precluded by local regulatory requirements) 5. Subjects with or without cardiac structural disease
	Exclusion criteria: 1. Reversible causes of PVC/VT 2. Subjects with recent (within 3 months) acute coronary syndrome 3. Subjects who are contraindicated for CT or MRI (must be able to get one)

	4. Subject whose MRI or CT scan does not comply with the requirements of this protocol 5. Subjects who are contraindicated for an electrophysiology procedure and/or fluoroscopy: 6. INR > 3.5 7. Active infection 8. Pregnancy: Females of childbearing potential with a positive pregnancy test. 9. Existing mechanical heart valve 10. Subjects with structural cardiac disease
Study treatment: *(i.e. dose and mode of the study drug administration if applicable)*: **NA**	

4. INTRODUCTION

4.1 BACKGROUND

Accurate localization of the origin of focal ventricular arrhythmias is a prerequisite to successful catheter ablation[1]. Nevertheless, mapping and determining the arrhythmic foci is time consuming, invasive and difficult. Catheter ablation guided by VT activation mapping has evolved to treat scar-related arrhythmias with up to 75% success rate after successful mapping procedures. However, non-sustained, non-inducible, or hemodynamically unstable VTs cannot be mapped with this technique. Alternatively, EP substrate mapping during sinus rhythm (SR) identifies the scar EP substrate based on low voltage and the presence of fractionated EGMs and late potentials (LPs). Conventionally, pre-procedural diagnosis and localization of cardiac arrhythmias has been done by the 12 lead ECG [2]. However, 12-lead ECG arrhythmia-origin algorithms have limitations and may negatively influence ablation outcomes. For example, erroneous identification may result in unnecessary mapping and failure to identify the treatable target [3].

VIVO was developed to easily determine the location of PVC/VT foci and to reduce mapping/identification time. VIVO improves upon the non-invasive 12 lead ECG by combining the ECG data with an already acquired CT/MR image and a 12 lead ECG to create a patient specific model, thus improving the localization accuracy [4-10].

4.2 PRE-CLINICAL DATA/CLINICAL DATA

4.2.1 Early Development Study

First in man studies were conducted at the University of California, Los Angeles using the initial VIVO software and algorithm. During the study, the software capabilities and algorithm were fine tuned to improve the accuracy of PVC and VT foci.

The study enrolled 20 patients and had no complications or safety concerns. VIVO correctly identified 100% of the PVC, VT, or stimulation sites to the correct region. Publications from this study are in Attachment A.

4.2.2 Clinical Validation

Previously, 22 patients were enrolled and analysed in a study at Johns Hopkins University Hospital (Baltimore, Maryland) without complications related to VIVO (Satish Misra et al, 2018). Prior to the procedure, imaging (contrast enhanced CT or MRI) was acquired based on the institution's protocol. In addition, a 3D image (to determine ECG lead placement) and ECG data (extracted from CardioLab) were also acquired pre-procedure. Image segmentation, surface electrode registration, and PVC/VT analysis was performed post-procedurally using the VIVO analysis software. VIVO identification of PVCs and VTs was then compared to invasive electro-anatomical mapping (EAM). A PVC location was defined as a site of earliest activation during electroanatomic mapping and/or site of successful ablation. VT was defined as (a) operator defined exit site (b) area of successful ablation.

Results of the study are below:

- 22 patients
- 19/22 locations determined by VIVO were a match to standard mapping systems
- No safety concerns
- Zero complications

A further trial for FDA approval is currently underway with US and European centres contributing.

4.3 Study Rationale and risk/benefit analysis

4.3.1 Mapping PVC/VT

Outflow tract ventricular tachycardia or frequent premature ventricular tachycardia (PVCs) often occur in the absence of structural heart disease and account for 10% of all ventricular tachycardia (VT). The majority of these originate from the right ventricular outflow tract and the remainder from the left ventricular outflow tract, including cusps of the aortic valve 10. Eighty to 90% of tachycardia in normal hearts originate from the right ventricle, most commonly the right ventricular outflow tract (RVOT)[11].

Especially in ischaemic patients, but not only, scar-related re-entry ventricular arrhythmia may involve the endocardium, mid-myocardium, and epicardium. Importantly, the presence of epicardial VT circuits (in about 32% of patients with post-myocardial infarction scars) is considered one of the reasons for failure of a subset of endocardial ablations. Consequently, epicardial mapping via subxyphoidal puncture has evolved as an essential procedure for mapping epicardial scar EP substrate and guiding epicardial ablation, especially in ischaemic cardiomyopathy patients with failed endocardial ablation. Epicardial mapping is associated with procedural complexity and risk of complications. In some cases, catheter access to the epicardium is limited by the presence of pericardial adherence. Non-invasive mapping of epicardial EP substrate and VT activation is therefore a highly desirable procedure. It could aid in deciding whether endocardial or epicardial approach should be used and provide important information for the pre-procedural planning of epicardial ablation. With regards to

endocardial foci, a precise anatomical localization of the "clinical" PVC/VT morphology is critical for the success of the ablation procedure, especially in the setting of hemodynamically poorly tolerated arrhythmias. Over the recent years, the only non-invasive electrocardiographic imaging mapping system validated in the EP laboratory was the CardioInsight (Medtronic, MN, USA), whose accuracy in distinguishing endocardial from epicardial or papillary muscles arrhythmia origin is however limited (margin of error ~6mm).
Unlike other existent systems, Vivo™ non-invasive mapping system offers an easier and more accurate localization of PVC/VT foci, allowing to distinguishing endo- from epicardial foci with a high accuracy even with regards to more complex or smaller structures (i.e. anterior from posterior aspect of a papillary muscle, or aortic cusps). The use of such system in a pre-procedural phase can therefore not only increase the success rate of the ablation itself, but also potentially decrease the procedural time (resulting ideally in a reduction of the procedural costs) and radiation exposure time, without adding any risk to the overall procedure.

4.3.2 Procedure Requirements

4.3.2a Prior to EP Procedure

Prior to the procedure the subject will undergo cardiac and thoracic imaging. This can be in the form of a MRI or CT scan, based on physician preference. Specific MRI and CT scan protocols do not significantly differ from the protocols already in use at the Brompton for pre-procedure roadmap scan. The recorded DICOM images should be provided the physician to upload into VIVO for future segmentation. The Mortara 12-lead Holter will be used to record the patient's PVCs templates (with their respective frequency of presentation). The recorded files will be then imported into Vivo analysis software for the analysis and localization on the pre-reconstructed model. Likewise, the analysis will be done with templates from the Sensis software in the catheter laboratory.

The 3 D Camera will be used to take a 3D image of the patient's torso after ECG lead placement. This will be merged with the cardiac anatomy from the 3D scan.

4.3.2b During the EP procedure

The EP procedure will be completed per the Institution's standard of care using a 3D electroanatomical mapping system (CARTO, Biosense Webster).
The information from VIVO analysis will be integrated in the 3D mapping process such that the ablation procedure will be provided with this information, or in post-processing to establish the accuracy of the localization.
Pacing locations can be selected at any time during the procedure based on the physician's preference.

4.3.2c Registration of EAM to Imaging

Left sided ablations: A Carto mapping catheter will be used to generate a complete fast anatomic map (FAM) anatomic shell of the left ventricle for identification of cardiac structures related to imaging. Imaging should be acquired at End Diastole. Landmarks will include those that are required for the individual procedure, including the papillary muscles if pacing is planned on the papillary muscles.

Right sided ablations: A Carto mapping catheter will be used to generate a complete fast anatomic map of the entire right ventricle and right ventricular outflow tract. Landmarks will include those that are required for the individual procedure.

4.3.2d Identifying the location of PVC or VT Origin

Identification with VIVO: Identifying the location of the PVC or VT foci with VIVO will be done prior to the patient's procedure.

Identification with CARTO: Identifying the location of the PVC or VT foci with Carto can be done at any time during the procedure based on physician preference. Once determined this point should be acquired in CARTO and tagged as Site of Origin. If the Site of Origin cannot be determined by Carto, the "best guess" location will be identified at the discretion of the physician.

4.3.2e Pro-procedure / Post-procedure processing

We will generate a screenshot of each pacing site and the clinical PVC/VT in an orientation that allows adequate visualization of the pacing and arrhythmia locations.
The physician in charge of the analysis will generate a screen shot of the final VIVO analysis for comparison to the Carto screenshots. This will be reviewed with the physician to determine if the VIVO analysis location matches the location identified by Carto.
An electronic copy of the screenshots will be placed in the patient's study file.

4.4 MANAGEMENT OF POTENTIAL STUDY RISKS

Risks

There is no additional risk onto the already well-established risks of catheter ablation of PVC/VT/VF.

CT scan (only if patient has a contra-indication for CMR scans)

The scan is acquired in a single breath hold during expiration from the level of the acromial processes to the dome of the diaphragm and starts with the 80 mls injection of contrast agent with Omnipaque 350 mg/ml followed by 20 mls of saline at a flow rate of 5 mls per second.

Cardiac CT performed on retrospective ECG gated CT imaging (end diastole) using tube modulation technique and adjusting the kvp according to BMI (100 kvp if BMI<30 and 120 kvp if BMI >30 kg/m2). There could be adverse reactions to the intravenous contrast agent. Patients with renal impairment would be excluded from this study.
Clinical protocols are in place to manage anaphylaxis which is however very rare.

Mapping with VIVO system and catheter ablation

We anticipate that mapping with Vivo™ system will not prolong the overall procedure duration or any technical aspect of the catheter ablation. As it is a non-invasive system intended to provide an accurate localization of the arrhythmia foci, most part of the work will be carried out in a pre-procedural phase (anatomy reconstruction from the pre-acquired scan, ECG template acquisition and arrhythmia foci localization on the virtual model). Also, the radiation exposure time for operator and patient is overall comparable to conventional procedures.

We will use an amended version of the already routinely used consent form for PVC/VT ablation used in the Trust to outline the inherent risk of an ablation for PVCs/VT/VF.

5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

Our hypothesis is that patients with PVCs/VT who must undergo catheter ablation can benefit from a VIVO non-contact mapping and guided ablation in terms of efficacy to decrease the procedural time of the ablation and acute success.

5.2 SECONDARY OBJECTIVES

We will assess the efficacy of Vivo non-invasive mapping system guided ablation with regards to safety and clinical outcome. Furthermore, we will assess if the precise 3D a priori knowledge of the arrhythmia exit site shortens the procedure and how large thereby the reduction of costs per single case is, as compared to historic controls.

6. STUDY DESIGN

6.1 OVERALL DESIGN

This is a prospective, single arm, observational and feasibility study, which will recruit 15 non-selected patients, with structurally normal heart, with a conventional indication for catheter ablation of PVCs/VT. The follow up will be of three months. The study will also include another retrospective cohort, including age & gender matched patients, without cardiac structural disease, with a conventional indication for catheter ablation of PVCs/VT from the last 5 years' database of the same operator. For this second retrospective cohort there will be no follow-up.

6.2 TREATMENT AND RATIONALE

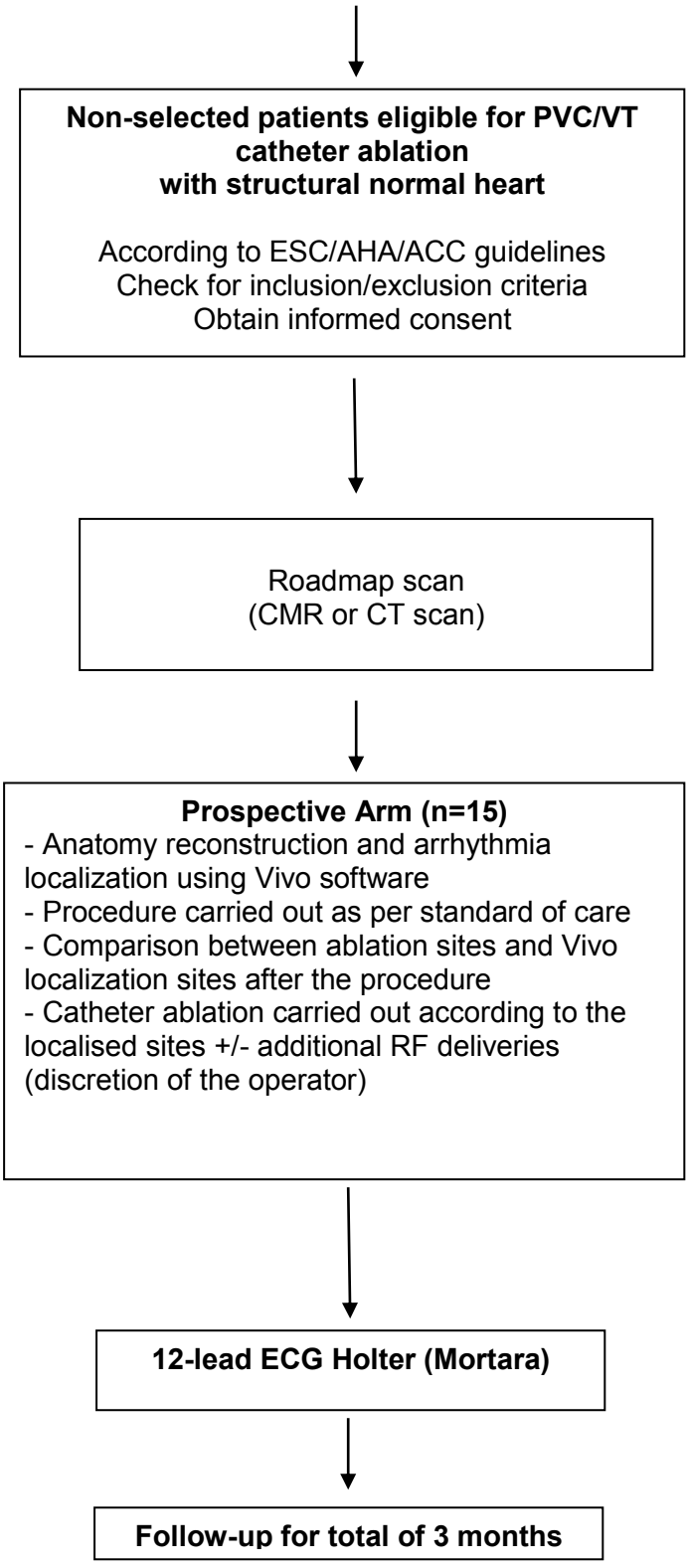
A three month follow up period after ablation of PVC/VT is a long enough time frame which allows us to assess the effect of the ablation on suppression/reduction of arrhythmia burden. Patients will be followed-up at 3 months following the ablation procedure. Early recurrences will be treated by uptitrating/changing/addition of anti-arrhythmic medication and/or DCCV if persistent arrhythmia. If further arrhythmia occurs despite these measures, a re-ablation procedure will be offered. If further episodes occur, patients can be offered a second ablation procedure or continuation of medical management.

6.3 SCHEMATIC OF STUDY DESIGN

	Pre-ablation	Pre-discharge	3 months
12 lead ECG		X (routine)	X (routine)
Telemetry	X (routine)		
Contrast CT scan or non-contrast CMR for roadmap	X (routine)		
TTE		x (routine)	
Symptom questionnaire	X (research)		X (research)
Clinic Visit			X (EP OPC)
ECG Holter (Mortara)	X (research)		X (research)

VIVO™ non-invasive Time Assessment Protocol

(Vivo protocol)


Non-selected patients eligible for PVC/VT catheter ablation with structural normal heart
According to ESC/AHA/ACC guidelines
Check for inclusion/exclusion criteria
Obtain informed consent
Roadmap scan
(CMR or CT scan)
Prospective Arm (n=15)
- Anatomy reconstruction and arrhythmia localization using Vivo software
- Procedure carried out as per standard of care
- Comparison between ablation sites and Vivo localization sites after the procedure
- Catheter ablation carried out according to the localised sites +/- additional RF deliveries (discretion of the operator)
12-lead ECG Holter (Mortara)
Follow-up for total of 3 months

7. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

- Subjects who are scheduled for PVC/VT ablation procedure, without structural heart disease
- Age >18 years old and ≤ 80 years
- Fulfil established clinical criteria for catheter ablation of PVC/VT
- Subjects who are at least 18 years or older
- Subjects who have signed an approved Informed Consent Form and applicable subject privacy protection authorization
- Subjects will be selected without regard to gender or age

7.2 EXCLUSION CRITERIA

- Reversible cause of PVC/VT
- Recent cardiovascular event including TIA
- Structural heart disease
- Intolerance or unwillingness to oral anticoagulation with Warfarin
- Bleeding disorder
- Contraindication to CT scan
- Presence of intracardiac thrombus
- Vascular disorder preventing access to femoral veins
- Severe, life threatening non-cardiac disease
- Active malignant disease and recent (<5 years) malignant disease
- Unable or unwilling to comply with F/U requirements
- Renal impairment
- Pregnancy

7.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

There are no major additional hazards related to the use of Vivo mapping system to guide the ablation, and the rest of the procedure is carried on using an established ablation strategy. The only difference is in the pre-procedural phase, when Vivo software will be used to localise the ablation targets. Therefore, we do not expect that patients will develop major

side effects related to the intervention tested in this study to warrant withdrawal. However, if patients present with acute medical conditions non-related to the study or new diagnosis are made during the follow-up period, such as active malignant disease, they can be withdrawn from the study. Additionally, patients can be withdrawn on their own request. The patients thus withdrawn from the study will continue to be followed-up regularly in the arrhythmia clinic. There are no major foreseeable circumstances under which the trial will need to be stopped prematurely, other than technical limitations.

8. SUBJECT/PATIENT RECRUITMENT PROCESS

Patient recruitment at a site will only commence once the *study* team has ensured that the following approval/essential documents are in place:

1. HRA approval,
2. Local Site Delegation of Duties and Signature Log is completed (if applicable).

The Royal Brompton Hospital is the single site participating in the trial and will be asked to provide a copy of the following:

1. Signed Clinical *study* Site Agreement (CSSA) (if applicable)
2. Confirmation of capacity and capability

All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator (CI), Principal Investigator or Co-Investigator.

We will recruit patients from those with PVC/VT who have already an indication for catheter ablation according to the current guidelines or have recurrent PVC/VT after previous catheter ablation(s). Patients will be offered participation in the study during the visit in the outpatient clinic. Only one centre will be involved in recruitment of the patients. All electrophysiology consultants in each Trust will be familiar with the protocol and be involved in selection of the patients.

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

Informed consent will be obtained by the Chief Investigator (CI), Principal Investigator (PI) and/or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log. Only those members of the study team who have clinical responsibility for the care of

patients under the care of the general medical service will be permitted to undertake informed consent.
Due to the complexity and novelty of the Vivo study, a senior nurse or an SHO cannot take consent for this study. All individuals taking informed consent will have received consent training. Patients will be provided with the information necessary to consider their participation at least 24 hours before the procedure.

Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. Likewise, periods longer than 24 hours will be permitted should the patient request this. The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one field in the Trial Master File (TMF)). A copy of the consent form will also be given to the patient.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

9.2 RANDOMISATION PROCEDURE

This section does not apply.

9.3 EMERGENCY UN-BLINDING

This section does not apply.

10. STUDY ASSESSMENTS

10.1 SCREENING ASSESSMENTS

Screening

Fifteen patients with PVC/VT and an indication for catheter ablation will be prospectively recruited. The screening visit will involve the following:

- Inclusion and exclusion criteria assessment
- Detailed past medical history including first diagnosis of PVC/VT and related symptoms
- Details of any previous catheter ablation for PVC/VT
- Physical examination
- ECG
- Evaluation of PVC/VT related symptoms
- Standard echocardiography (new or up to 12 months before the procedure)
    - LVEF, LV/RV volumes, LVOT obstruction

10.2 BASELINE ASSESSMENTS

- Detailed past medical history including first diagnosis of PVC/VT and related symptoms
- Physical examination
- ECG
- Evaluation of PVC/VT related symptoms
- Standard laboratory tests
- ➢ complete blood count
- ➢ coagulation studies
- ➢ serum creatinine and electrolytes
- ➢ liver function tests
- ➢ CRP

10.3 TREATMENT PROCEDURE

Using the roadmap 3D image information of the CMR or CT scan a standard three-dimensional (3D) reconstruction will be performed (CARTO software package). The CMR or CT scan will be also imported into the Vivo anatomy software to reconstruct the patient's model, necessary for the following localization analysis.

Before the start of the ablation procedure, when still in the ward, the patient will undergo a 12-lead ECG recording (Mortara) while contemporarily on telemetry in order to record the templates of the different PVC/VT morphologies, with also regards to their frequency. Should the patient present no ventricular arrhythmia, a challenge with exercise bike or

intravenous administration of isoprenaline or atropine could be chosen. Finally, a picture of the patient's chest will be taken and imported in the software to match the ECG electrodes' position.

Mapping Vivo non-contact system and ablation procedure

Once the different templates are acquired, they will be imported into the VIVO analysis system, and a final model with foci localization will be generated. The information will be integrated into the 3D mapping system prior to starting the procedure.

After venous vascular access has been gained using an ultrasound-guided approach, an octapolar catheter (InquiryTM, Saint Jude Medical) will be positioned in His-RV position, while a mapping/ablative catheter will be used both for mapping and RF delivery. In case of arrhythmias originating from the LV, it is the operator's choice to use either an arterial femoral access for a retrograde approach or a transseptal access route. In case of left-sided access, as per institutional standard, ACT measurements will be carried out every 30 min with bolus injections of Heparin to achieve an ACT of ≥350 sec.

The whole ablative procedure will be carried out according to international guidelines and as for operator expertise and discretion. Achievement of PVC/VT suppression will be documented for all patients for 30 minutes after last RF delivery, with or without IV drug provocation challenge. DCCV may be carried out at the discretion of the operator during the procedure if needed.

Removal of sheaths will be performed as per institutional standard (+/- protamine).

10.4 SUBSEQUENT ASSESSMENTS

Follow-up

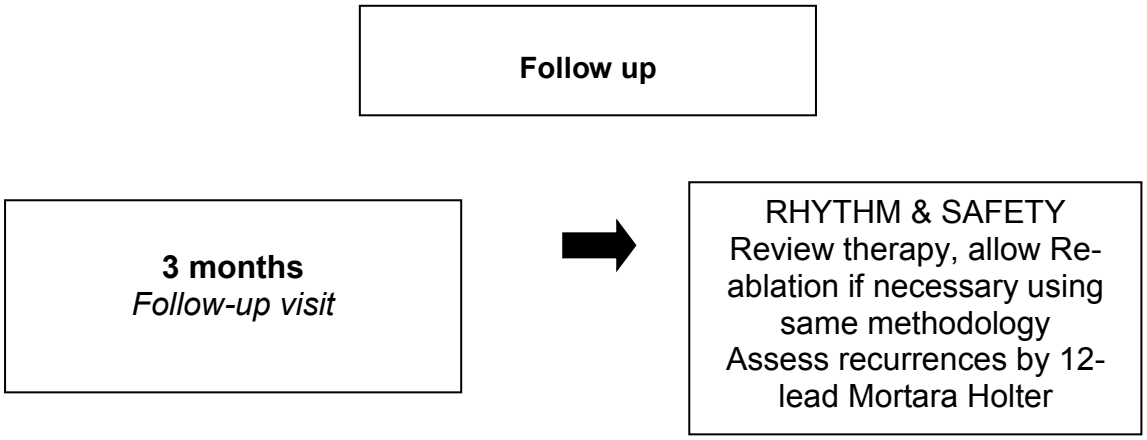
3 months *(follow-up visit – study completion - endpoints assessment)*

The next scheduled follow-up visit after discharge will be at approximately three months post PVC/VT ablation. The following assessments will take place:

- Patient's symptoms (questionnaire) and clinical assessment
- Review of medication
- 12-lead ECG
- 12-lead Holter (Mortara)
- If high PVC/ VT burden at 3 months, either therapy change or repeat ablation (according to patient and physician preference).

10.5 SUMMARY CHART OF STUDY ASSESSMENTS

	Pre-ablation	Pre-discharge	3 months
12 lead ECG		X (routine)	X (routine)
Telemetry	X (routine)		
Contrast CT scan or non-contrast CMR for roadmap	X (routine)		
TTE		x (routine)	
Symptom questionnaire	X (research)		X (research)
Clinic Visit			X (EP OPC)
ECG Holter (Mortara)	X (research)		X (research)



11. METHODS

11.1 Laboratory Procedures

We will not take specific blood or tissue samples. Routine bloods will be taken at admission for the ablation and pre-discharge.

11.2 Radiology or any other procedure(s)

All patients will undergo a cardiac CMR or CT exam to be used as a roadmap during the ablation procedure. The CT exam will comprise of a standard-of-care contrast-enhanced scan to visualise the cardiac chambers. This pre-procedure imaging is necessary in order to define the spatial anatomical relationship of the cardiac chambers.
In the event that the ablation procedure needs to be repeated during follow-up, the roadmap scans can be re-used.

As part of a conventional PVC/VT ablation procedure, the patient is exposed typically to about 2 mSv of ionizing radiation, occasionally increasing to 10 mSv or more, per procedure. If radiation is necessary to be used during any of the study procedures than efforts will be made to lower the exposure to as low as reasonably achievable including the re-use of the CT or CMR scan for 3D image integration during the ablation procedure(s).

- ***Techniques and Interventions***

The technique of mapping the ventricular chambers/epicardial space in order to guide the PVC/VT ablation is a conventional procedure which is carried out routinely in the catheter labs using different mapping system according to operators' experience and confidence. The here proposed study will use the Vivo™ (Catheter Precision, Inc., USA) in the pre-invasive phase in order to guide ablation.

- ***Tools***

All tools used for the ablation procedure will include standard materials for ablation of PVC/VT. The Vivo™ Anatomy and Analysis software and the Kinect Camera are fully CE marked.

- ***Study Drugs***

This section does not apply.

11.3 Definition of the End of Study

The end of trial will be considered the last patient last visit (hospital visit).

12. SAFETY REPORTING

12.1 Definitions

Adverse Event (AE) — any untoward medical occurrence in a patient or clinical study subject who is administered a treatment and which does not necessarily have a causal relationship with this treatment (*i.e.* any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).

Serious Adverse Event (SAE) – is defined as an untoward occurrence that:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
- Is otherwise considered medically significant by the investigator.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

12.2 Recording Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes and Case Report Form (CRF).
If the Investigator suspects that the disease has progressed faster due to the administration of the study treatment/procedure, then he/she will report this as an unexpected adverse event to the Sponsor and the REC as detailed in Section 12.3.

12.2 Assessment of SAEs

Principal Investigator (PI) at all sites must report all SAEs to the Chief Investigator (CI) or a delegated individual in the research team. The CI and his research team at RBH are responsible for reporting events to the Research Office immediately and/or within 24 hours of becoming aware of the event using the Sponsor's SAE Reporting Form.

Classification and causality of Adverse Events (AEs) will be conducted by local PIs and reviewed by CI. The CI cannot downgrade the site PI's classification and if there is disagreement which cannot be resolved during formal discussion then the assessment of the site PI will be accepted. The CI, can however, upgrade the seriousness of an event without consultation with the site PI.

12.3 Reporting of SAEs to the Sponsor and the REC

All AEs that are to be reported to the Research Office must be recorded, signed and dated by the Investigator at site. Research Office accepts study specific SAE forms, HRA SAE Form or RB&HFT template SAE Reporting Form available here.

Information can be submitted in electronic format:

- E-mail: research.reporting@rbht.nhs.uk
- Fax: 0207 351 8829.

An SAE occurring to a research participant will be reported to the Research Ethics Committee (REC) that gave a favorable opinion of the study (the 'main REC'), the study Sponsor (RB&HFT Research Office) and the local R&D Office where in the opinion of the CI/PI the event was:

- **'related'**: that is, it resulted from administration of any of the research procedures; and
- **'Unexpected'**: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted within 15 days of the CI/PI becoming aware of the event; using the SAE reporting form for non-CTIMPs published on the HRA website and entitled non-CTIMP safety report to REC. The form should be completed in typescript and signed by the Chief Investigator (CI) prior to submission to the REC.

Reports of SAEs in double-blind studies should be un-blinded.

The coordinator of the main REC will acknowledge receipt of safety reports within 30 days. It is the responsibility of the CI and his/her research team to send a copy of the SAE notification and acknowledgement receipt to the Research Office.

The research team also has the responsibility to report SAEs occurring in a certain period (28 days) after a patient completes the study. Any SAEs reported to the Investigators during this phase must be documented in the patient's medical notes and submitted via an SAE form

12.4 THE TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER AEs

The type and duration of follow-up care for subjects following an SAE will be as follows: 6-12 months following phrenic nerve palsy, valve damage; 3-6 months following vascular complications or pericardial effusion (usually these complications are promptly treated without major long-term consequence).

12.5 PREGNANCY

Pregnant patients will be excluded from the study. However, if pregnancy occurs after inclusion into the study, we will record and notify pregnancies occurring during the study period to the Sponsor.

Follow-up of pregnant subject:

- No further ablation procedure will be undertaken during the pregnancy period in order to avoid radiation exposure and hazards to the foetus.
- Medication contraindicated during pregnancy will be withdrawn.
- No additional investigations involving radiation exposure such as CT, X ray will be performed, unless clinically urgent.

Follow-up of child born to a pregnant trial subject, including male trial subject who is the partner of the pregnant woman:

Children born to a pregnant subject are unlikely to be affected by the participation of the parent in the study. For safety reasons, a specialised paediatric team will follow children for 1 year.

12.6 ANNUAL PROGRESS REPORTS (APRS)

The Chief Investigator will prepare the APR for the study. It will be reviewed by the RO and sent to the REC by the CI within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the study is declared ended.

12.7 REPORTING URGENT SAFETY MEASURES

The Sponsor and/or the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazard to their health or safety. If safety measures are taken, REC approval is not required before the measure is taken.

The Investigator will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and the study Sponsor of the measures taken and the circumstances giving rise to those measures.

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore the CI/PI must report any urgent safety measures to the REC directly, and in parallel to the Sponsor. The REC coordinator will acknowledge receipt of urgent safety measures within 30 days.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act 1998, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, 2nd Edition (2005), and the condition of the REC approval.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, Date of Birth (DOB) and study Identification Number (ID), will be used for identification.

13.2 DATA COLLECTION TOOL

Case Report Forms (CRF) will be designed by the CI and the final version will be reviewed and discussed with the study Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all study personnel responsible for data collection, entry, handling and managing the database.

Data will be firstly recorded into source documents (i.e medical notes) (medical history, baseline investigations) and then recorded onto the CRF (with the addition of the procedure specific data).

Methods used to maximise completeness of data will include telephoning subjects who have not attended the planned follow-up visit.

13.3 DATA HANDLING AND ANALYSIS

- Excel software will be used for data entry.
- In order to ensure validity and quality of data we will use cross validation
- Data will be stored and backed up on 2 additional hard drives on two different sites in order to allow recovery of data in case of a disaster such as fire/flooding/ theft. The PI and their collaborators/co-workers will be responsible for data entry and quality of data collection. Analysis will be performed by the study investigators and reviewed independently of data entry by the statistical team.
- Every patient will receive a numerical patient identifier and all data that is transferred outside the primary hospital will exclusively be identified by this study number.
- The study database will be held at a server at the Royal Brompton Hospital.

13.4 ARCHIVING ARRANGEMENTS

The study documents (including the Study Master File (SMF), Case Report Forms (CRFs), Informed Consent Forms along with the study database) will be kept for a minimum of five years. They will be stored in locked offices within the Royal Brompton and Harefield NHS Foundation Trust (RB&HFT). The CI is responsible for the secure archiving of study documents. The study database will also be kept electronically on the RB&HFT computer network, for a minimum of five years.

The approved repository for longer retention of local materials for studies that involve RB&HFT patients is Box-It Storage UK. The study documentation will be prepared for archiving by the research team in line with the Research Office Archiving SOP and the transfer will be arranged by the Research Office.

Patient anonymised data may be exported for the purpose of offline review and to perform the image merge as part of the study and also to further develop the technology.

14. STATISTICAL DESIGN

This is a prospective, non-randomised, observational study which will recruit 15 non-selected patients with PVC/VT eligible for catheter ablation, without structural heart disease.
Procedural outcomes will be compared to age & gender matched procedures of the same operator from the last 5 years' database.
The statistical design was decided in collaboration with the study PIs and will be descriptive only.

14.1 SAMPLE SIZE AND RECRUITMENT

This is a feasibility pilot study, which will test the feasibility of PVC/VT foci mapping with Vivo system and catheter ablation in unselected patients without structural heart disease, eligible for PVC/VT ablation. Therefore, no power calculation has been done and the number of patient recruited will be of 15 which are deemed sufficient by the CI and Co-PIs on a clinical basis.

The estimated recruitment period for the trial will be of 6 months. We estimate that this sample size is attainable in practice, as the number of PVC/VT ablation procedures per year performed within the Trust is around 100. We also included patients with previous PVC/VT ablation in order to maximise chances of recruitment. This pilot is performed with the intention to plan a prospective multi-operator/multicentre trial which is adequately powered.
We will aim to compare the procedure parameters as well as the outcome of this trial to age & gender matched procedures of the same operators from the last 5 years' database.

14.2 ENDPOINTS

14.2.1 Primary endpoints

Safety:

- Absence of acute adverse events due to the use of VIVO system during PVC/VT ablation
- Safety endpoint of the entire mapping and ablation strategy

Efficacy:

- To assess the efficacy of VIVO to decrease procedure time as compared to standard of care ablation procedures.

14.2.2 Secondary endpoints

- To assess clinical outcome (suppression of reduction of PVCs burden/VT at 3 months F/U)
- To assess safety
- To assess economical outcome (cost reduction per case)

14.3 STATISTICAL ANALYSIS PLAN

Descriptive statistic data with regard to baseline and procedural variables will be reported; continuous variables will be expressed by mean ± standard deviation or median and interquartile range (25^{th}, 75^{th} percentile), depending on the normality of distribution; categorical variables will be summarized by frequencies and percentages. The outcome of radiofrequency ablation on the entire cohort of patients will be presented in the form of percentage of patients free from symptomatic or documented arrhythmia or with only mild symptoms related to arrhythmia recurrence.

Depending on the severity of symptoms and documentation of tachycardia during follow-up, patients will be divided into two groups (success/recurrence). Baseline characteristics and procedural variables will be compared between these two groups by student t-tests, Mann Whitney U tests, or Fisher's exact test where appropriate in order to identify those variables associated with better mid/long term outcomes. A two-tailed p value <0.05 will be considered statistically significant. Intra-patient improvement from baseline to 6 months follow-up visit will be assessed by McNemar's test. Freedom from PVC/VT will be assessed as a time-dependent variable using Cox proportional hazard models.

To judge if ablation strategy using Vivo mapping system is as successful in achieving the clinical endpoint, we will compare the procedure parameters as well as the outcome of this trial to age & gender matched procedures of the same operator from the last 5 years' database.

To measure the strength of association between the acute successes (PVC/VT suppression at the end of the ablation) and outcome, a McNemar test will be performed. Data will be analyzed using SPSS version 18 (IBM Corporation).

14.4 RANDOMISATION

Not applicable

14.5 INTERIM ANALYSIS (IF APPLICABLE)

Not applicable

14.6 OTHER STATISTICAL CONSIDERATIONS

None

15. COMMITTEES INVOLVED IN THE STUDY

Trial Management Group (TMG) - normally includes those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Monitoring and auditing

The requirement for study monitoring or audit will be based on the internal Research Office risk assessment procedure and applicable Standard Operating Procedures (SOPs). It is the responsibility of the RO to determine the monitoring risk assessment and explain the rationale to the study research team.

Study monitoring and/or audit will be discussed with the CI before arrangements are made to conduct the visit.

16. DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the study protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the Health Research Authority (HRA) which includes Research Ethics Committee (REC)

approval if applicable, prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for HRA approval prior to implementation.

Before site(s) can enrol patients into the study confirmation of capacity and capability must be issued by the institution hosting the trial (unless HRA specifically has confirmed in the HRA approval letter that this is not required). It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approvals by the participating site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.
Within 90 days after the end of the study, the CI will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply a final summary report of the clinical study to the REC and the Sponsor in parallel within one year after the end of the study.

18. FINANCE

The therapeutic procedure follows the normal clinical pathway for treatment of ventricular arrhythmias. The additional cost incurred due to the participation in the Vivo mapping protocol per patient will be sponsored by Catheter Precision. In addition, any non-routine clinical investigations incurred as part of the clinical protocol will be financially sponsored by Catheter Precision. A financial agreement will be in place between Royal Brompton Hospital and Catheter Precision to enrolments.

19. INSURANCE AND INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm should be stated to the participant.

20. PUBLICATION POLICY

Data ownership rights will lie with the institution. The sponsor agrees that employees of the Trust and the investigator, Dr Sabine Ernst, shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, these or dissertation, or otherwise of their own choosing, methods and results of the clinical investigation.

21. STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by HRA and according to RGF standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and HRA except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and the REC as soon as possible.

22. LIST OF PROTOCOL APPENDICES

Appendix 1 *Summary Chart of Study Assessments*

23. REFERENCES

1. Wissner, Erik, et al. Radiofrequency ablation of premature ventricular contractions originating from the aortomitral continuity localized by use of a novel noninvasive epicardial and endocardial electrophysiology system. *Heart Rhythm,* (2016); 2, 255-257.

2. Erkapic, Damir, et al. Clinical Impact of a novel three-dimensional electrocardiographic imaging for non-invasive mapping of ventricular arrhythmias – a prospective randomized trial. *Europace* (2015); 17, 591-597.

3. Erkapic, Damir, Neumann, Thomas. Ablation of Premature Ventricular Complexes Exclusively Guided by Three-Dimensional Noninvasive Mapping. *Cardiac Electrophysiology Clinics* (2015); 7, 109-115.

4. van Dam, P., Tung, R., Shivkumar, K., Laks, M. Quantitative localization of premature ventricular contractions using myocardial activation ECGI from the standard 12-lead electrocardiogram. *Journal of Electrocardiology,* (2013); 12*, 574-579.*

5. van Dam, P., Gordon, J.P., Laks, M. Sensitivity of CIPS-computed PVC location to measurement errors in ECG electrode position: the need for the 3D Camera. *Journal of Electrocardiology,* (2014); 47, 788-793.

6. Van Dam, P., et al. Electrocardiographic imaging-based recognition of possible induced bundle branch blocks during transcatheter aortic valve implantations. *Europace* (2014); 17, 750-757.

7. van Dam, P., et al. Development of new anatomy reconstruction software to localize cardiac isochrones to the cardiac surface from the 12 lead ECG. *Journal of Electrocardiology* (2015); 48 959 – 965.

8. Oosterhoff, P., Meijborg, V., van Dam, P., van Dessel, P., Belterman, C., Streekstra, G. de Bakker, J., Ruben, C., Oostendorp. F. Experimental Validation of Noninvasive Epicardial and Endocardial Activation Imaging. *Circulation Arrhythmia and Electrophysiology*, (2016); 9, e004104.

9. van Dam, P. et al. Localization of premature ventricular contractions from the papillary muscles using the standard 12-lead electrocardiogram: a feasibility study using a novel cardiac isochrone positioning system. *Europace*, (2016); 18, iv16–iv22.

10. Jamil-Copley, Shahnaz, et al. Noninvasive electrocardiographic mapping to guide ablation of outflow tract ventricular arrhythmias. *Heart Rhythm*, (2014); 11, 588-594.

11. Nathani, P., et al. Ventricular Tachycardia in Structurally Normal Hearts: Recognition and Management. *Supplement of JAPI*, (2007); 55, 33-55.

Appendix 1

Summary chart of study Assessments (Template)

Please note that the summary chart below should only be used as guidance and ensure that the list of procedures in the chart as well as treatment and follow up timelines relate to procedures in your study.

	Pre-ablation	Pre-discharge	3 months
12 lead ECG		X	X
Telemetry	X		
Contrast CT scan or non-contrast CMR for roadmap	X		
TTE		x	
Symptom questionnaire	X		X
Clinic Visit			X
ECG Holter (Mortara)	X		X