Research Protocol

FULL/LONG TITLE OF THE STUDY	Can MRI-based computational modelling of the heart be used to predict critical substrate in scar-dependent ventricular tachycardia ablation?
SHORT STUDY TITLE / ACRONYM	Multimodality assessment of ventricular scar arrhythmogenicity.
PROTOCOL VERSION NUMBER AND DATE	Version 1.1 (12/02/2021)
IRAS Number:	284337
JRES Reference Number	2020.0237
Funder Reference Number:	RES 20 21 001
ClinicalTrials.gov Reference Number	NCT04632394
This protocol has regard for the HRA guidance and order of content	

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Signature: Date: 04/12/2020

Name (please print): Sam Hollingworth

Position: Research Governance and Facilitation Officer, SGUL

Chief Investigator:

Signature: Date: 04/12/2020

Name: (please print): Magdi Saba

LIST of CONTENTS

KEY STUDY CONTACTS

KEY STUDY CONTACTS	
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Funder(s)	The AVATAR program fund under the direction of Dr Magdi Saba – administered by The St. George's Hospital Charity
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Committees	NA

FUNDING AND SUPPORT IN KIND

FUNDER	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
The AVATAR program fund under the direction of Dr Magdi Saba – administered by The St. George's Hospital Charity. Contact: Ms. Vivien Gunn Grant Manager Vivien.Gunn@stgeorges.nhs.uk	Full financial support to complete the MDRes degree in three years.

ROLE OF FUNDER

The funder will provide materials to facilitate the investigators in conducting the study, including access to computers for data storage and analysis and statistical analysis. The funder is paying the salary of the principal investigator – Dr Waight. The funder will not be involved in the design of the study, the collection or analysis of data, manuscript writing or dissemination of results.

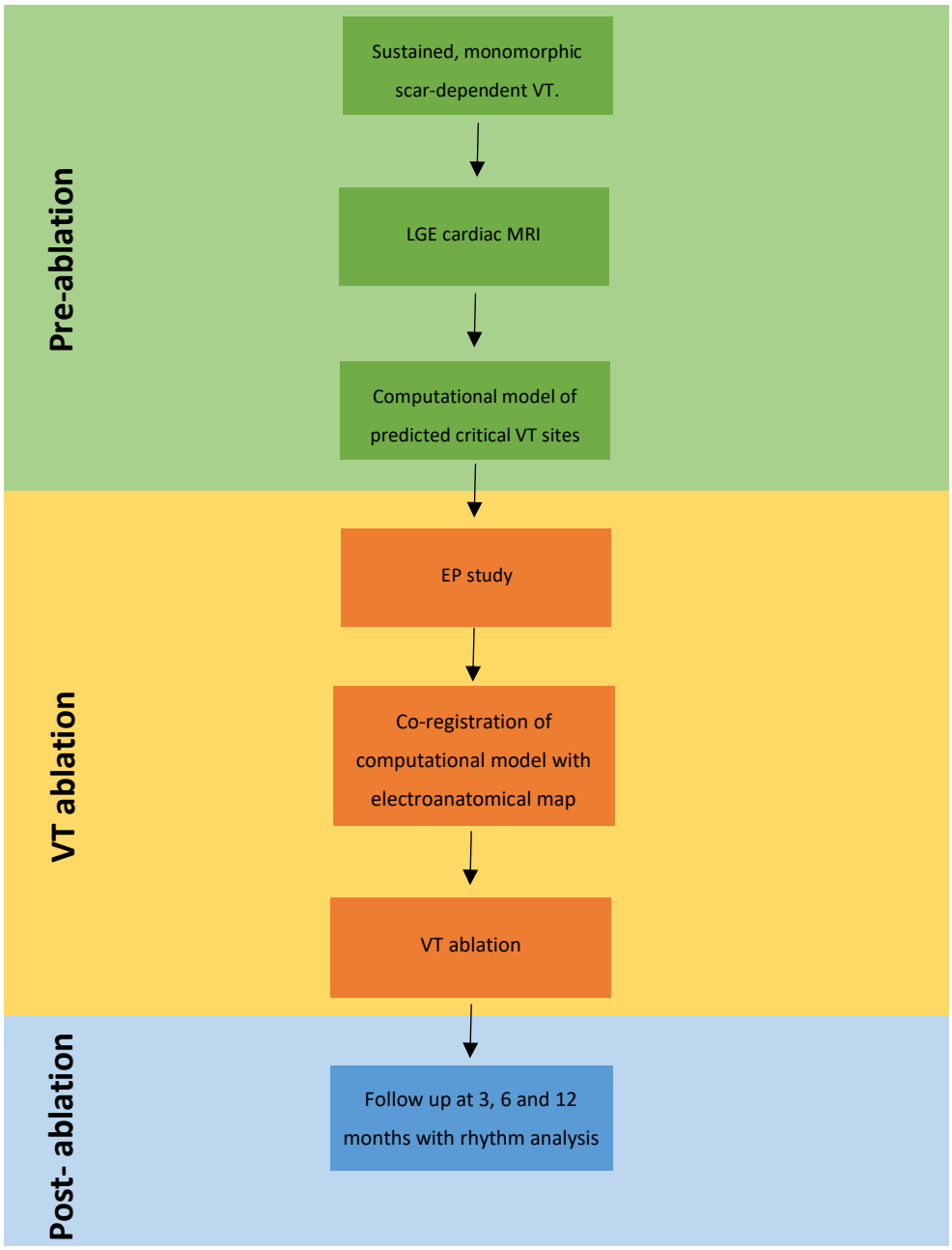
PROTOCOL CONTRIBUTORS

The protocol was developed by the named investigators as above:

- Dr Michael Waight
- Dr Anthony Li
- Dr Magdi Saba
- Professor Natalya Trayanova
- Dr Adityo Prakosa

The funder did not contribute to the production of this protocol.

STUDY Schematic



ABBREVIATIONS	
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SGUL	St Georges, University of London
SGHFT	St Georges, University Hospitals NHS Foundation Trust
JRES	(St Georges) Joint Research and Enterprise Services
VT	Ventricular tachycardia
MRI	Magnetic resonance imaging
ICD	Implantable cardioverter-defibrillator
LAVA	Locally abnormal ventricular activity
LGE	Late gadolinium enhancement
LAT	Local activation time
LV	Left ventricle
RV	Right ventricle

STUDY PROTOCOL

Can MRI-based computational modelling of the heart be used to predict critical substrate in scar-dependent ventricular tachycardia ablation?

1 BACKGROUND

Ventricular tachycardia (VT) is a life threatening rhythm disturbance of the heart, which is associated with a significant risk of mortality as well as morbidity. VT is particularly prevalent in patients with ischaemic heart disease. Over the past three decades, catheter directed ablation has emerged as an increasingly useful adjunct to the implantable cardioverter-defibrillator (ICD) as treatment for this rhythm disorder, especially if medications fail, or are prohibited by side effects or patient choice. Traditional catheter ablation of VT uses several different invasive mapping methods to analyse the ventricular myocardium in detail and aims to modify those areas which are thought to be critical for sustaining the arrhythmic circuit. Commonly used techniques include activation mapping, entrainment mapping, pace-mapping and substrate mapping.

Activation mapping is a technique which, in cases of focal VT, records the earliest ventricular activation to find areas which are key in the generation of the arrhythmia, or in cases of re-entrant VT, to identify the diastolic pathway which allows the perpetuation of the arrhythmia[1].

Entrainment mapping is a technique whereby critical parts of the arrhythmia circuit can be identified by pacing at different locations, in an attempt to enter the excitable gap and capture the arrhythmia circuit. Once the critical isthmus utilised by the circuit is identified, ablation in this area can lead to termination of the arrhythmia.[2]

Both activation and entrainment mapping require a stable VT which is haemodynamically tolerated, which is often not the case. Therefore other methods of invasively mapping VT have been devised, most notably substrate mapping. Substrate mapping can be performed with the patient in sinus rhythm and is based on the fact that arrhythmogenic substrate in the ventricle produces different EGM signals from healthy tissue. Features of interest include fractionated signals, low voltage, split or double potentials, mid-diastolic potentials, late potentials and locally abnormal ventricular activity (LAVA) [3,4].

For some patients, particularly in those with non-ischaemic cardiomyopathy, scar is predominantly epicardial or mid-myocardial, meaning that endocardial mapping and ablation may be of limited efficacy[5]. In these cases, accessing the epicardium via a subxiphoid incision and performing additional ablation on the epicardial surface has been shown to be of benefit [6,7].

Recently, data have emerged suggesting that computational modelling of a patient's heart based on 3D MRI reconstructions can enable prediction of optimal targets for VT ablation non-invasively. This has been confirmed in both retrospective and prospective studies.[8] This involves high resolution MRI imaging with late-gadolinium enhancement (LGE) to assess the three-dimensional geometry of the scar, followed by reconstruction of the patient's heart *in silico*[9,10]. Fibre orientation is established and overlaid onto this model[11]. Standard electrophysiological properties are applied to the different categories of tissue as defined by the LGE signal intensity, namely, normal tissue, scar and grey zone. Using computational modelling, this "virtual heart" is then analysed for different potential ventricular tachycardia circuits that are theoretically sustainable based on the information supplied. A virtual electrophysiology study with programmed stimulation is conducted by virtually pacing the heart model from various different locations[9]. An algorithm is used to predict optimal ablation sites to terminate all possible VT circuits in this model heart. The algorithm initially generates "primary sites", which are the initial locations which have the potential to sustain ventricular tachycardia in the patient's heart. The model then undergoes virtual VT ablation of these primary sites and the prediction algorithm is re-run. This may generate a new VT-sustaining substrate and give predictions of "secondary sites" which can sustain VT in the post-ablation heart. The process is repeated until the heart is no longer VT-inducible. [12]. In this way, not only should the patient's clinical VT be ablated, but all future potential ventricular tachycardias supportable by the substrate in its current form should also be avoided, reducing the need for repeat VT ablation.

2 RATIONALE

Current invasive substrate mapping techniques are time and labour intensive. The ability to identify arrhythmogenic from non-arrhythmogenic areas within the same scar is limited, leading to prolonged procedure time and the potential overuse of ablative energy. Activation mapping during ventricular tachycardia, the gold standard for defining the critical isthmus sustaining the arrhythmia, is significantly limited by hemodynamic instability.

Image-guided VT ablation has been shown to improve substrate definition and may underpin improved outcomes in certain patient populations[13,14]. Given the newly emerging field of personalised medicine and computation modelling this study will help to assess if an MRI-based, computer generated model accurately correlates to the invasive findings from an EP study with regards to targeting ablation in VT. If the model proves to be accurate, this will help to advance the process of *in silico* planning of VT ablation and potentially lead to improvements in outcomes of VT ablation, as well as reducing the need for repeated procedures. Results from the invasive studies can also be fed back into the computational model in an attempt to improve its accuracy. Furthermore, by assessing the electrophysiological properties of the computer generated predicted sites, we may learn which signals may indicate a critically important part of the VT circuit which traditional electroanatomical maps may miss.

3 THEORETICAL FRAMEWORK

As outlined above

4 RESEARCH QUESTION/AIM(S)

- To assess the accuracy of an MRI-based, computer-generated model of the heart in predicted sites which are particularly important in generating and sustaining ventricular tachycardia.
- What are the invasive electrophysiological properties of the sites which are predicted by the MRI-based computational model?
- Does ablation of the computer generated predicted sites lead to a change in the electrophysiological properties of distant sites?

4.1 Objectives

- To perform high resolution cardiac MRI prior to undergoing catheter-based VT ablation in order to non-invasively assess scar and provide data for computational modelling and prediction of likely VT circuits *in silico.*
- To assess the accuracy of the *in silico* predicted sites when compared to invasively obtained electrophysiological data.
- To assess the ventricular scar characteristics in patients with scar-dependent VT using high-definition invasive mapping.
- To invasively assess the *in silico* predicted sites in order to ascertain the electrophysiological properties which likely lead to their prediction as key sites for arrhythmogenesis.
- To corroborate the *in silico* predictions with the invasive findings during catheter-based VT ablation.

4.2 Outcome

- Assessment of the degree of validation of *in silico* computational modelling by invasive ventricular scar interrogation to see if the predicted sites match those sites which would have been determined as important from invasive mapping.
- Qualification of the electrophysiological characteristics of those sites which the computational model predicted in an attempt to see what it is about them that makes them likely to be key to maintaining the arrhythmia. With our mapping techniques, we can assess not only the amplitude and morphology

of the electrograms from these areas, but also the directionality of wavefronts to see if this is an important feature. With the additional benefit of the 3D computational model, we may be able to gain some insight into the 3D nature of channels which form part of the VT substrate.

- Assessment of the change in the invasive electrophysiological characteristics of distant sites following ablation of the primary predicted *in silico* sites. By ablating the predicted areas, it is possible that when we re-map distant points, they may be a change in their electrophysiological properties. There may be a change in variables such as the stim-QRS latency, the QRS morphology, the capture threshold and the nature of the exit site (e.g. multiple-exit site changing to single-exit site).
- Assessment of the frequency of ventricular arrhythmia, frequency of therapy delivered from an ICD (if applicable) and duration until first delivered therapy on serial heart rhythm monitors. Also assessment of patient's symptoms and adverse effects on clinical consultation.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

The study will be a single centre, prospective study based at St George's University Hospitals NHS Foundation Trust in London. Consecutive patients presenting to the hospital with an appropriate scar-dependent, sustained monomorphic ventricular tachycardia, requiring catheter ablation, will be screened for inclusion into the study. Full inclusion and exclusion criteria are listed below. Patients are likely to be predominantly outpatients, requiring elective VT ablation, however inpatients may also be included in the study.

If found eligible for the study, the patient will be approached by one of the study investigators and a Patient Information Sheet (PIS) will be offered. Written consent will be obtained if the patient is willing to proceed.

If included in the study, de-identified, anonymized MRI images from patient's routine scan will be transferred to Johns Hopkins University, Baltimore Maryland, for computational analysis. The patient's MRI images will be reconstructed, analysed and a 3D geometric model of the patient's heart formed. From this, a computer-generated model of the patient's heart will be created. As described above, a virtual EP study, VT ablation and generation of both primary and secondary sites will be generated. The computation model as well as the locations of these primary and secondary sites will again be stored securely and transferred back to the primary research centre.

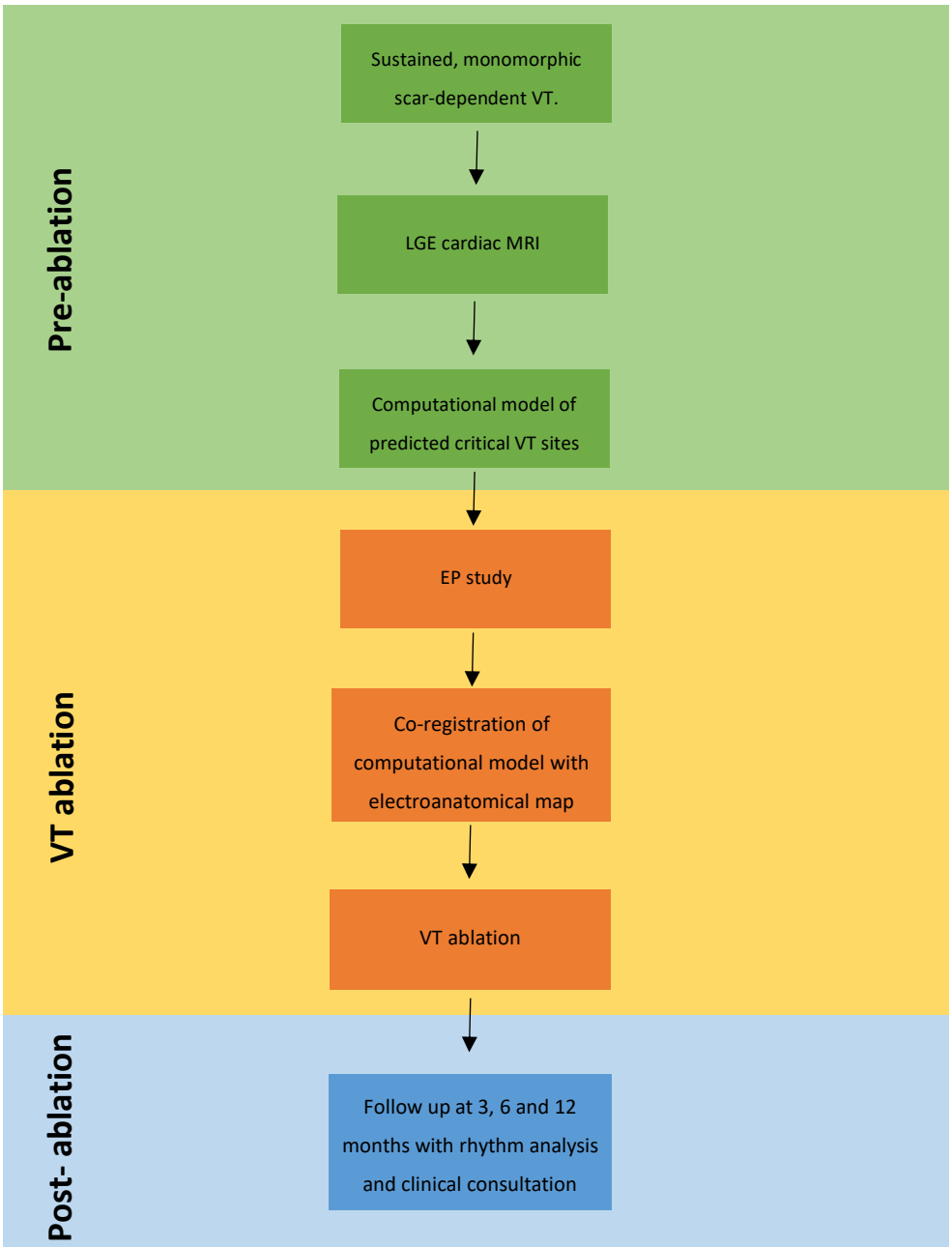
The patient will then undergo traditional endocardial, and in appropriate cases, epicardial, mapping and ablation of ventricular tachycardia, using the techniques previously described [1–3,7,15]. Patient preparation on the day of the procedure will be as for any other clinical VT ablation. Ablation technique will depend on whether or not there is a documented 12 lead ECG of the patient's clinical VT and also whether or not the VT is haemodynamically tolerated (stable) or not (unstable). This will be decided by the operator and will follow usual practice for VT ablation.

We will use a multipolar mapping catheter, in order to create a high-density map and gain as detailed information as possible about the substrate. Multipolar catheters are used as standard of care for VT mapping and ablation in our institution and most other high-volume specialised centres. The 3D computational model will be merged with the traditional 3D electroanatomical map generated during the VT ablation. Particular care will be taken when mapping the points of interest from the computational prediction to assess their particular electrophysiological properties. This will allow us to assess variables such as wavefront directionality, amplitude and morphology to see if they have a particular signal which marks them as important in sustaining the VT circuit and therefore conferring their importance in predicting potential sites for ablation. By overlaying the computer generated model onto the invasive map, we will be able to corroborate the predicted model's findings with traditional mapping techniques.

Ablation technique will be as per standard of care and the order of ablation will be guided by standard invasive mapping. However if we ablate at an area which the MRI-model also predicted to be important, we will re-map the surrounding myocardium to see if there has been an effect of the electrophysiological properties of these distant sites following ablation of the predicted sites.. The computer model will not alter the extent of ablation and will not lead to ablation of any areas which wouldn't otherwise be ablated using traditional mapping.

The patients will be followed up as standard of care at 3, 6 and 12 months following their procedure with ICD interrogation, or in the case of absence of an ICD an extended ECG monitoring period. We will use this to assess frequency and duration of recorded arrhythmias time to recurrence of ventricular arrhythmia as well as frequency of therapy delivered by the device. We will also use data from their clinical consultation to evaluate their symptoms and response to the procedure including any adverse events.

STUDY FLOW CHART



6 STUDY SETTING

The study setting is a large tertiary centre hospital in London, St George's University Hospitals NHS Foundation Trust which serves a population of around 1.3 million. It also receives referrals from district general hospitals around it including in London, Surrey and Sussex. The patient population is diverse and referrals are made to a

specialist arrhythmia clinic from which suitable patients can be identified. The majority of recruited patients are expected to be outpatients who are symptomatic from VT despite optimal medical therapy. This will allow sufficient time to perform the cardiac MRI and to generate the computational model. In some scenarios, emergency admissions with symptomatic VT may be included if they are suitable for inpatient VT ablation and there is sufficient time for the MRI and computation analysis to take place prior to the VT ablation. All patient recruitment, consent, imaging and ablation will be performed at the single study centre.

The MRI images will be transferred to Johns Hopkins University in Baltimore, Maryland, USA for computational analysis and predictive modelling. This information will be securely transferred and on completion will be transferred back to the investigators for analysis.

7 SAMPLE AND RECRUITMENT

7.1.1 Inclusion criteria

- Adult inpatients admitted to St George's Hospital London with sustained ventricular tachycardia or outpatients identified from the arrhythmia clinic with significant monomorphic ventricular tachycardia noted on cardiac monitoring who:
    - Have sustained, monomorphic scar-dependent ventricular tachycardia
    - Are symptomatic
    - Failed, unable or unwilling to tolerate anti-arrhythmic medications
    - Able to have a cardiac MRI
    - Have a life expectancy > 1 year
    - At least 40 days following a myocardial infarction

7.1.2 Exclusion criteria

- Patients under the age of 18
- Patients who are unable to give informed consent
- Pregnant patients
- Unable to have cardiac MRI
- Prohibitive procedural risk
- Unable to tolerate the ablation procedure due to haemodynamic instability

7.2.1 Size of sample

We aim to recruit at least 20 consecutive patients. This is larger than any previous study in this area and will provide sufficient numbers to assess if the computational modelling is accurate in predicting sites of myocardium critical to sustaining ventricular tachycardia.

The current frequency of ventricular tachycardia ablation is roughly one patient every two to three weeks. Allowing for incomplete patient uptake to the study, this should permit the required number of patients to be recruited within 20 months. This allows sufficient time for data analysis and writing up of the results.

7.2.2 Sampling technique

Given the low volume of patients presenting with the appropriate ventricular arrhythmia, and the small sample size being targeted, the sampling technique will be of consecutive recruitment over a period estimated to be 20 months.

7.3.1 Recruitment

Potential patients will be identified from two sources: first, those presenting to the arrhythmia clinic at the primary centre with findings of sustained ventricular tachycardia who are symptomatic despite medical therapy. Clinicians at this arrhythmia clinic will be members of the study team. Suitable patients identified in this way would be referred for ventricular tachycardia ablation as standard of care. These patients will be highlighted to the site research team who are also part of patient clinical team who will then proceed to perform eligibility screening using the inclusion / exclusion criteria. The patients will have the study discussed with them and if consent is gained, they will be enrolled.

The second group of patients are those who present acutely to hospital (either directly to the primary study centre or referred from a different hospital for further management). The study investigators will be involved in the care of these patients as standard of clinical practice. However, if for any reason the study investigators are not involved in the care of the particular patient, the patient's clinical team can highlight and approach these potential participants before referring them directly to the study investigators. The same inclusion / exclusion criteria would apply and the investigators may explain the study to them, offer enrolment and gain consent for inclusion whilst inpatients.

The investigations and procedures, including the cardiac MRI and mapping and ablation of the tachycardia, are considered standard of care. Therefore no extra journeys, follow up appointments or costs will be incurred by the patients who choose to participate in the study.

7.3.2 Consent

Informed consent will be obtained in writing after full discussion of the Patient Information Sheet. If necessary, the consent process may be remote, for example if the patient's initial consultation is via telephone. If this is the case, then the patient information sheet and consent form will be emailed or posted to patient and the PIS discussed by phone with patient. If happy, the patient will sign the consent form and consent will be documented in the notes. The patient will then email or post the partially signed consent form back to the study investigators, who will re-confirm consent over the phone and countersign the consent form. A copy of the fully signed consent form will be returned to the patient.

Consent will be required for the use, storage and sharing of the data collected from the MRI as well as the mapping and ablation data obtained at the time of catheter ablation. Written information about the objectives, methods and aims of the study will be provided and sufficient time will be allowed for the patient to make an informed decision, ask questions and consult a legal representative if requested. Only those patients deemed to have capacity will be approached for inclusion into the study.

Risks and benefits of the MRI as well as the ablation are obtained as standard of care for this group of patients by the clinical team.

7.3.3 **Data collection tool**

Each patient enrolled into the study will have a unique study trial ID number. This will allow the de-identification of all subsequent data associated with that patient. All subsequent data collection will be

transcribed next to this trial ID number in electronic format, through Microsoft Excel spreadsheets. There will be an electronic link document which will contain the patient identifiable information and the trial ID numbers, but no other data. This will be electronic and kept secure on password protected computers at St George's University, to which only the study investigators will have access. The link document will be kept until the results of the study have been analysed and written up. We anticipate that this will be complete within 3 years. The patient's consent will be kept in a locked area in the University.

Routine baseline demographics, risk factors and investigation results such as the patient's ECG and echocardiogram findings will be collected, de-identified and added to the Excel sheet. Primary data generated by the study will include the 3D computational model generated from the patient's cardiac MRI as well as data from the VT ablation including the baseline ECG, and electrograms during tachycardia and baseline rhythm. Individual data points from various endocardial and epicardial points will be collected by the mapping catheters which will contain information such as voltage, activation time, electrogram amplitude, directionality and morphology. Pacemaps and entrainment maps will be collected if these techniques are used. This data is generated by the cathlab software – Precision and Carto and will be de-identified, then transferred via USB stick to the password-protected excel spreadsheet with the appropriate trial ID number.

The data generated from the study will be stored for the duration of the study (3 years) and then archived onto secure, password-protected hard-drives. Paper documents will be archived with Iron Mountain for 5 years.

8 ETHICAL AND REGULATORY CONSIDERATIONS

The aims and methods of the research minimise extra investigations or procedures to the participant as well as confer no extra perceived risk by participating in the study. We believe that by using our study design the procedure will be lengthened by around 10% in duration, however due to our design, there will be no additional dose of ionising radiation above standard of care. The extra 10% duration (roughly 30 minutes) may slightly increase the risk of standard anaesthetic complications such as venous thromboembolism, pneumonia, confusion and allergic reaction. This will be mentioned on the PIS. The computational model will not influence the ablation set that the patient receives. We have set out clear inclusion and exclusion criteria to ensure that enrolled patients are appropriate and not coerced into taking part in the study. The interventions that the patient undergoes fall within internationally recognised guidelines for treatment of these patients. It has the support of the wider multidisciplinary team at the centre where it is being carried out.

8.1 Assessment and management of risk

The research protocol is predominantly within established standards for patients presenting with sustained monomorphic scar-dependent ventricular tachycardia. Undergoing a cardiac MRI and endocardial / epicardial

mapping and ablation for patients unresponsive to, intolerant of, or unwilling to use anti-arrhythmic therapy, is within the scope of international guidelines for these patients. Therefore, the protocol incurs no additional procedure for the patient. The extra time spent with co-registration of the computationally-generated virtual heart with the invasively-acquired 3D EAM, the extra mapping of the *in silico* predicted targets and remapping after ablation of the predicted sites, will mean that the procedure is only minimally extended beyond standard care, and by no more than a maximum of 10% of the usual duration. We propose that this does not generate a particular increase in risk compared to a standard VT ablation beyond the increased chance of complication from general anaesthetic. The overall goal of the ablation will remain the same whether the patient is included in the study or not – to render the patient non-inducible to VT. We will not ablate any area of the heart that wouldn't warrant it during a standard VT ablation and no area that is deemed important will be left un-ablated if the model does not predict it to be important. Therefore there is no expectation that they will be at higher risk of recurrence from participating in this study.

The data collection and sharing with Johns Hopkins University generates data protection requirements which will be met in accordance to the Data Protection Act of 2018. All patient information will be stored securely on restricted-access University storage and will be transferred securely only to the research team members directly involved in the study.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from an appropriate REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

For HRA- NHS REC reviewed research

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- It is the Chief Investigator's responsibility to produce the annual reports and submit the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- The Chief Investigator will notify the REC of the end of the study within one year after the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Regulatory Review & Compliance

The study has approval from the main study centre (St George's Hospital NHS foundation Trust).

For any amendment to the study, the Chief Investigator will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

Any amendments will be brought up with the HRA and SGREC in accordance with their policy and in writing. The funding body will also be notified. The decision to amend the protocol and whether it is substantial or non-substantial will be made by the chief investigator as well as the other contributors in the group in a collaborative fashion. The chief investigator will keep record of the amendment history.

8.3 Peer review

The protocol has been reviewed and agreed upon by two expert reviewers – Professor Elijah Behr and Dr Michael Papadakis.

8.4 Patient & Public Involvement

Other than patient participation, no public involvement is required in the design, management, undertaking, analysis or dissemination of this study. The trial is listed on ClinicalTrials.gov under trial ID: NCT04632394

8.5 Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

All protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

Data within this study will be compliant with the 2018 Data Protection Act as well as the EU General Data Protection Regulation (GDPR). Study data will be collected solely by the study investigators. When an individual is recruited to the study, we will assign them a trial ID number, against which all data collection will be recorded as an Excel spreadsheet. No patient identifiable information will be contained in this document. A link document will be created which will contain the trial ID number as well as the patient name and medical record number but no other data from the study. This will be password-protected, stored on secure computers and only accessible by the study investigators. We will collect demographic data from their medical records including age, gender, and ethnicity. We will also collect date regarding the patient's cardiovascular risk factors and pertinent cardiac investigations such as ECG and echocardiography results. Following the cardiac MRI, the files will be stored as DICOM (Digital Imaging and Communications in Medicine) images and de-identified image files will be sent with end-to-end encryption and stored securely at Johns Hopkins University. The computer generated model will be created and sent back to us with end-to-end encryption. Johns Hopkins University will securely retain the anonymised MRI-model for as long as is required to complete the study. The de-identified output from Johns Hopkins will be kept on secure, password protected computers. The outputs from the VT ablation (discussed above) will be downloaded from the cath lab software following the ablation. Again these will be stored in a database with the corresponding trial ID number assigned to the patient so that they remain anonymous. The results of the follow up 3, 6 and 12 month rhythm monitor will be added to the same database as well as an objective assessment of symptoms from the clinical consultation. Data will be stored securely on password protected University hard-drives to which only the study investigators will have access. Data will be sent and stored securely, with only necessary parties having access to the data. The data will only be stored as long as is necessary to complete the study, prior to being archived. The data custodian will be the Principal Investigator.

8.7 Indemnity

St George's University Hospitals NHS Foundation Trust sponsored research:

St Georges University Hospitals NHS Foundation Trust is party to NHS Litigation Authority (NHSLA) / NHS Resolution. As an NHS body it is 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.

8.8 Access to the final study dataset

The study investigators will all have access to the final dataset. A secondary analysis is not envisaged, but if required, would only be undertaken with the consent of the participants.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The data arising from the study will be owned by the study sponsor, who will have the right to publish the data. On completion of the study, the data will be analysed and tabulated and a Final Study Report generated, which will be accessible by means of peer-reviewed research articles as well as from the Chief Investigator. The funding body will be acknowledged within publication of the data. Participants in the study will be able to have access to the results of the study, once completed, if requested.

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

Before the official completion of the Trial,

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the **Steering Committee/the Funder** shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.

- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

9.2 Archiving Arrangements

Each site will be responsible for their onsite level study archiving. The trial essential TMF along with any central trial database will be archived in accordance with the sponsor SOP

9.3 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be granted to those who have had a significant contribution to the design, implementation and analysis of the study. No professional writers are expected to be required.

10 REFERENCES

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11.1 Appendix 1- Required documentation

CVs of research team – see separate attachment

Patient Information Sheet – see separate attachment

13 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	1.0	04/12/2020	Michael Waight Magdi Saba Anthony Li	First submission
1	1.1	12/02/2021	Michael Waight Magdi Saba Anthony Li	Revisions following REC meeting. Clarified that MRI-model does not alter order of ablation. Clarified that JHU will retain MRI model until study is complete. Clarified extra GA risks associated with longer procedure time