IdeNtification of SPecific EleCTrophenotypes in Atrial Fibrillation – INSPECT-AF

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the PHENOTYPE-AF study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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Glossary of Abbreviations

Abbreviation	Definition
ECG	Electrocardiogram
AF	Atrial fibrillation
pAF	Paroxysmal atrial fibrillation
PsAF	Persistent atrial fibrillation
ECGI	Electrocardiographic imaging
DCCV	Direct current cardioversion

Keywords
atrial fibrillation, ablation, electrophenotype, ECGI

Study summary

TITLE	Identification of specific electrophenotypes in human atrial fibrillation – INSPECT-AF
DESIGN	Single Centre, Observational Study
AIMS	1. Investigate the range of AF electrophenotypes and mechanisms in human AF and identify the important functional, structural and clinical determinar of the AF electrophenotype 2. Develop the use of non-invasive modalities to classify the underlying AF electrophenotype
OUTCOME MEASURES	1. Freedom from AF 2. AF burden 3. Quality of life
POPULATION	Patients with atrial fibrillation due to undergo first time atrial fibrillation ablatio or DCCV for under clinical grounds at Hammersmith Hospital
ELIGIBILITY	Adult patients 18-85 years, who are able to give informed consent,
DURATION	4 years

1. INTRODUCTION

1.1. Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults(1), with an estimated prevalence of 1% and is projected to become more prevalent (2, 3). AF is also a significant source of morbidity and mortality (4, 5) as well as reduced quality of life and exercise capacity in patients with AF-related symptoms, which can be improved with maintenance of sinus rhythm (6).

Limitations of current treatments and catheter ablation for AF

Catheter ablation is a commonly used to aid maintenance of sinus rhythm. We recently reported that pulmonary vein isolation (PVI) is markedly more effective than strategies not incorporating PVI (7), and PVI therefore remains the cornerstone of AF ablation. In patients with paroxysmal AF (PAF), PVI reduces AF recurrence in around 70-80% of patients (8), however in persistent AF (PsAF) the success rate of ablation is only 50% (9). The atrial substrate is an important determinant of recurrence in PsAF, this may explain the relatively poor outcomes of a PVI-only ablation approach. A wide range of adjunctive ablation strategies have been studied, however we have shown none conclusively improve success rates (10).

Lack of consensus on AF mechanisms - absence of mechanism-directed treatments

One major issue limiting the success of treatments for PsAF is the lack of mechanism-directed therapies. Although PsAF appears to be a heterogenous entity, ablation strategies for persistent AF centre around PVI. Adjunctive strategies are largely empirical with no tailoring of strategy towards patient-specific mechanisms. The absence of mechanism-directed treatments is due partly to the lack of consensus on the electrophysiological mechanisms that sustain AF. Two broadly contradictory hypotheses have been put forward. The “anarchical” model of AF proposes that AF is sustained by multiple self-perpetuating activation wavelets propagating randomly until extinguished(11). Importantly, this model is based on an absence of localised sources and would be best treated by lines of block to confine and extinguish wavelets (12, 13). Conversely, the “hierarchical” model proposes that AF is sustained by localised drivers or ‘rotors’ that may be stable or dynamic (14-16) however multi-centre studies of rotor guided ablation has demonstrated this approach to be ineffective (17, 18).

Concept of spectrum of different ‘electrophenotypes’ of AF

These apparently contradictory models may in fact prove to be a false dichotomy – the different proposed mechanisms may all be important in sustaining AF, with the predominant AF mechanism determined by the underlying atrial substrate. We recently described a spectrum of fibrillation ‘electrophenotypes’ in the ventricle (19), where patchy fibrosis favours VF sustained by stable rotational activity, while compact fibrosis is more prone to disorganised fibrillation with an intermediate electrophenotype caused be diffuse interstitial fibrosis. Our analysis of human persistent AF supports the hypothesis that a similar range of electrophenotypes exists in the atria (20). **Figure 1** (reproduced from Ng et al (21)) depicts our hypothesised electrophenotype spectrum for PsAF, proposing different AF mechanisms depending on the underlying substrate.

Mechanism-directed treatments based on identification of AF

electrophenotype
If the electrophenotype spectrum exists for human PsAF, and if the AF phenotype/mechanism can be reliably identified and classified in individual patients, a mechanism-directed approach may yield better success rates for AF ablation. For example, organised AF may be treated by mapping drivers while disorganised AF may be better treated with compartmentalisation of the atria with linear lesions or avoidance of ablation altogether.

Using non-invasive modalities to classify AF electrophenotype
Although we have shown that the identification of AF electrophenotype is possible using intracardiac electrograms, it would be preferable if the AF electrophenotype can also be discerned using non-invasive modalities, such as the ECG, electrocardiographic imaging (ECGI) and cardiac magnetic resonance imaging (CMR), all of which contain some information on the electrical and structural remodelling in the atria, and with which we have significant experience.

Surface ECG characteristics, including P wave duration and f-wave parameters have been used to predict success following catheter ablation and categorise AF (22-24). Because ECGI can provide detailed information in atrial conduction properties, it may also assist the classification of an individual's AF electrophenotype. ECGI is a non-invasive method to map epicardial electrograms across both ventricles and atria using 252 electrodes on the patient's chest and back (25).

Lastly, CMR has been used to quantify LA fibrosis (26), and based on our groups work in VF showing the important role of fibrosis pattern on determining VF mechanism (19), LA fibrosis maps from CMR may therefore be useful in complementing ECG and ECGI in helping to classify an individual's AF mechanism and electrophenotype. Our own analyses have described the distribution of scar within the left atrium and the effect of fibrosis on left atrial electrophysiological properties, with recent demonstrations that LA fibrosis as detected on CMR correlates with intracardiac electrograms voltage acquired in atrial fibrillation (27).

Recurrence of atrial arrhythmia after AF ablation
Current success rates following ablation for PsAF are only 50%. A significant proportion of these recurrences are due to the organised atrial arrhythmias atrial flutter and atrial tachycardia. Atrial flutter may be cavotricuspid isthmus (CTI) dependent or have a different mechanism. Ablation for CTI dependent flutter has a significantly higher success rate compared to ablation for atrial tachycardia. Additionally, knowledge of the tachycardia mechanism can be helpful to plan an ablation procedure; if the tachycardia originates in the right atrium the procedure can be undertaken under local anaesthetic without a transeptal puncture, while a left atrial tachycardia may require a general anaesthetic and transoesophageal echocardiography for transeptal puncture.

Biomarkers for atrial fibrillation

Proteomics profiling has been used to identify proteins independently associated with incident AF (28). MicroRNAs have similarly been associated with incident AF and cardiac remodelling (29). Machine learning (ML) has been incorporated with proteomics to yield new insights and outperform traditional techniques (30).

1.2. Rationale for current study

1. In human AF, there is a spectrum of different AF mechanisms (manifest as a

spectrum of 'electrophenotypes') that can sustain AF
2. The specific AF electrophenotype in each patient is determined by the underlying atrial substrate, and correlates to functional (e.g. conduction velocity), structural (fibrosis burden) and clinical characteristics (e.g. AF duration)
3. Analysis of surface ECGs, 252 lead ECGs and scar maps from MRI, in isolation or in combination, can provide an accurate non-invasive classification of AF electrophenotype, when compared to the gold-standard classification using intracardiac electrograms
4. Machine learning (ML) can be applied to ECGs, electrograms, 252 lead ECG and cardiac MRI to aid classification of electrophenotype

2. STUDY OBJECTIVES

Primary objectives

1. Investigate the range of AF electrophenotypes and mechanisms in human AF and identify the important functional, structural and clinical determinants of the AF electrophenotype

Secondary objectives

2. Develop the use of non-invasive modalities such as the surface ECG, 252 lead ECG and CMR, in isolation or in combination, to classify the underlying AF mechanism/electrophenotype

3. STUDY DESIGN

This is a prospective interventional study investigating invasive and non-invasive tools for determining AF electrophenotype. The study will last 2 years in duration and will recruit patients undergoing ablation or DCCV procedures for atrial fibrillation (AF). Patients will be recruited from secondary care clinics or pre-assessment prior to procedures at Hammersmith Hospital.

The study will be run at a single centre at the Hammersmith Hospital, Imperial College Healthcare NHS Trust. We will aim to enrol 300 patients.

3.1. Study outcome measures

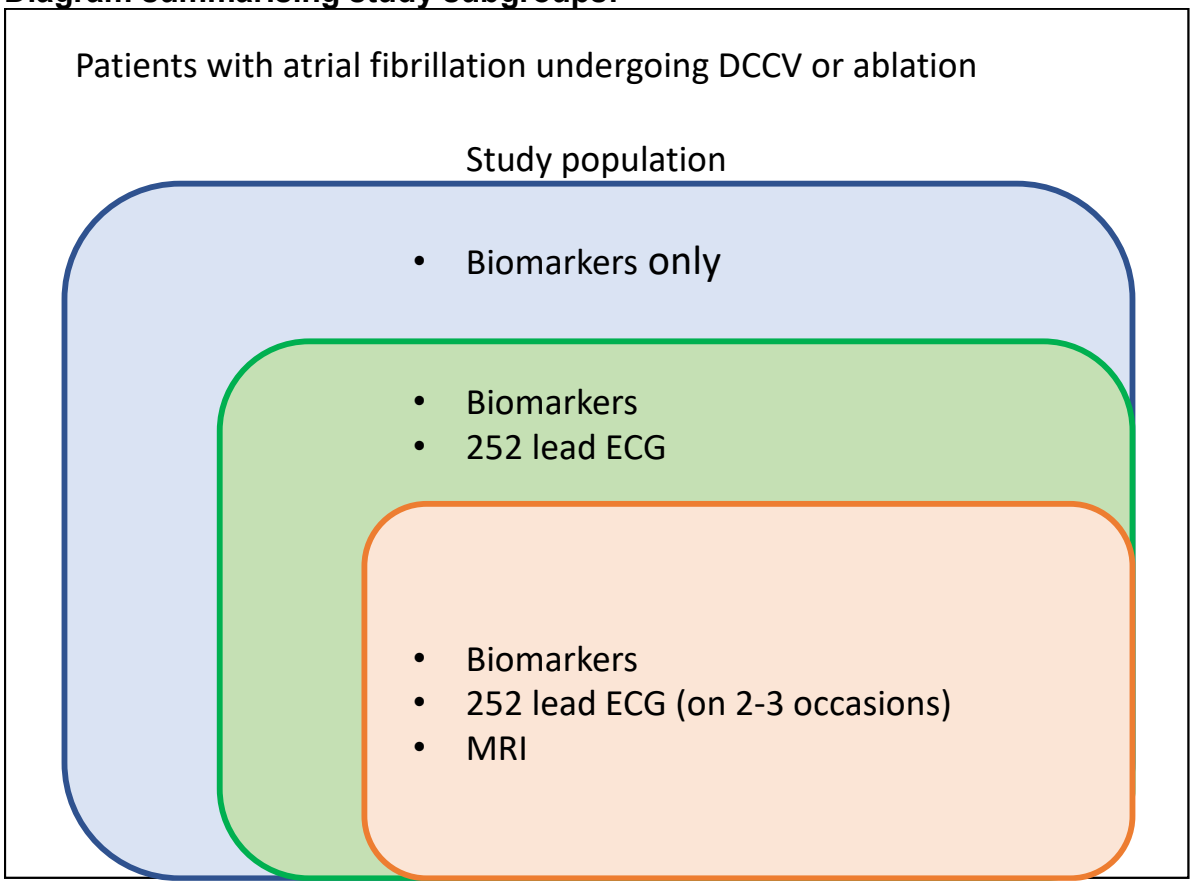
We will classify patients into electrophenotypes based on the invasive and non-invasive data collected. The primary outcome measure will be freedom from AF. Secondary outcome measures will be AF burden and quality of life.

3.2. Study protocol

Patients that suffer from AF and have been put forward for an ablation or DCCV, on clinical grounds as per current guidelines, will be recruited. Patients will be approached by a member of the clinical team by telephone from the Hammersmith Hospital waiting lists to discuss their interest in participating in the study. If the patient is interested, they will be provided with a patient information sheet, detailing information with regards to the study. The Investigators will subsequently consult with these patients to explain the study in greater detail and answer any further questions, in person, during an outpatient clinic visit or by phone. The consent form will include all information about the study and the mapping procedure.

All patient clinical data will be collected on a standardised electronic case report form.

Study groups
Diagram summarising study subgroups:



Biomarker protocol (all groups):
All patients will have blood samples taken to investigate for biomarkers that may correlate with electrophenotypes. In most cases this will be taken during the same blood draw as blood tests taken for clinical care or from sheaths in central veins that are placed routinely during an AF ablation. Rarely it may be necessary to perform an additional venepuncture in order to obtain the samples.

252 lead ECG protocol (green + orange groups):
A subgroup of 50-100 patients with persistent AF will have a 252 lead ECG. This will consist of up to 252 electrodes attached to the patient's front and back. A recording of up to 10 minutes will be taken before the AF ablation or DCCV procedure.

MRI protocol (orange group):
A subgroup of 10-30 patients who are undergoing ablation will undergo thoracic and cardiac MRI including administration of gadolinium intravenously. This will be performed on the day of their ablation procedure, prior to the ablation. This subgroup will have an additional 1-2 visits 1-2 weeks apart prior to their procedure date, where they will attend the hospital for 10 minutes of data collection with the 252 electrode device. This subgroup will have co-registration of the 252 electrode recordings taken on the day of the ablation with the MRI to allow reconstruction of the epicardial

electrograms through the inverse solution and Tikhonov regularisation steps.

DCCV protocol

1. **All patients will have up to 252 electrodes placed on their chest and back 2. Surface electrical data will be collected before the procedure and removed prior to the DCCV**
2. All patients will have sedation delivered by an Anaesthetist
3. Up to 3 synchronised shocks will be delivered in accordance with routine clinical practice
4. Patient recovery

AF ablation protocol

The AF ablation procedure will take place in the electrophysiology laboratory. The procedure routinely takes place under general anaesthetic. The procedure typically lasts 2-3 hours.

1. **All patients will have up to 252 electrodes placed on their chest and back, with gaps where necessary for patches/electrodes for clinical use**
2. **Surface electrical data will be collected throughout the procedure from the multiple electrodes**
3. **A subgroup of patients will have thoracic and cardiac MRI with gadolinium contrast**
4. All patients will be out under general anaesthetic by a Consultant Anaesthetist.
5. All patients will have a Transoesophageal echocardiogram to exclude LAA thrombus.
6. All patients have sheaths (small plastic tubes) inserted through their groin veins (femoral veins).
7. A transseptal puncture will be performed to gain access to the left atrium under heparin cover.
8. Cardiac ablation and mapping catheters (small plastic tubes with electrodes at the end) are advanced into the heart under fluoroscopic guidance.
9. A 3D model of the heart will be created to help guide ablation using clinical software (Ensite Precision, Abbott UK or CARTO, Biosense Webster).
10. **Electrical mapping data will be collected while the patient is in AF using a dedicated mapping catheter (Lasso or AFocusII/HD grid)**
11. **Adenosine will be administered through a central venous sheath to induce transient AV block, during which surface electrical data will be collected**
12. Pulmonary Vein Isolation ablation with radiofrequency energy will be completed as per standard of care.
13. **Electrical mapping data will be collected after pulmonary vein isolation if the patient has remained in AF.**
14. All patients will be cardioverted as part of the standard of care.
15. Heparin reversal with Protamine.
16. Sheath removal
17. End of procedure
18. Patient recovery

Steps in bold above will be additional to the standard of care.

After the procedure has finished and all devices have been removed from the patient, we will export each patient's pseudonymised data for further offline analysis

Patients undergoing AF ablation will be provided with an AliveCor device to use up to once per day and when they have symptoms to accurately monitor for recurrence of AF. They will also have holter monitoring and clinical follow up in line with routine clinical care. Patient's will be asked to complete symptom score/quality of life questionnaires up to once per month during follow up.

Patients undergoing DCCV will be followed as per routine clinical care.

Study participation will conclude after 300 patients have been recruited. Patients will be able to leave the study at any time they wish; they need only inform the research team.

4. PARTICIPANT ENTRY

4.1. Pre-registration evaluations

All patients enrolled in this study will have the usual standard of care NHS pre-procedural assessment for an ablation or DCCV for Atrial Fibrillation.

4.2. Inclusion criteria

Patients with atrial Fibrillation that have been put forward for an ablation or DCCV based on clinical grounds.

- Suitable candidate for catheter mapping/ablation or direct current cardioversion for atrial fibrillation
- Eighteen (18) to eighty-five (85) years of age
- Able to give informed consent

4.3. Exclusion criteria

- Severe cerebrovascular disease
- Moderate to severe renal impairment (eGFR < 30)
- Active gastrointestinal bleeding
- Active infection or fever
- Short life expectancy
- Significant anaemia
- Severe uncontrolled systemic hypertension
- Severe electrolyte imbalance
- Congestive heart failure - NYHA Class IV
- Recent myocardial infarction
- Bleeding or clotting disorders
- Paroxysmal Atrial Fibrillation
- Uncontrolled diabetes
- Inability to receive IV or oral Anticoagulants
- Unable to give informed consent (these patients would not be recruited)

- Pregnancy

4.4. Withdrawal criteria

- One of the exclusion criteria are fulfilled during the study period
- Patient wishes to withdraw from study

If criteria are fulfilled for exclusion during the study period patient will be withdrawn by investigators.

If patient wishes to withdraw, they can inform any staff involved in the study in writing or in person or any other mode of communication, and they will be withdrawn.

In call cases of withdrawal data will be kept and used in the study up to the time of withdrawal.

5. ADVERSE EVENTS

5.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2. Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1. Non-serious AEs

All such events, whether expected or not, should be recorded.

5.2.2. Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, recurrence of or death related to neurocardiogenic syncope, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the to the **[Placeholder for Ethics Committee]** where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs:
Please send SAE forms to: Dr Arunashis Sau: a.sau@nhs.net, Dr Fu Siong Ng: fusiong.ng@nhs.net and Imperial research governance and integrity RGIT@imperial.ac.uk

5.2.3. Incidental Findings

In the event an incidental finding is uncovered during the study, the relevant clinical team will be immediately notified. We will also inform the patient's GP, with the patient's permission (relevant clause is present on the informed consent form).

6. ASSESSMENT AND FOLLOW-UP

Patients undergoing AF ablation and the 252 lead ECG protocol will be provided with an AliveCor device to use up to once per day and when they have symptoms to accurately monitor for recurrence of AF. They will also be asked to complete symptom score (36-Item Short Form Survey Instrument
(SF-36) and Atrial Fibrillation Effect on QualiTy-of-life (AFEQT)) questionnaires up to once per month. They will have Holter monitoring and clinical follow up in line with routine clinical care.

Patients undergoing DCCV will be followed as per routine clinical care for 1 year.

The end of study is when the last patient has completed their last follow up visit.

7. STATISTICS AND DATA ANALYSIS

We will use the data collected to investigate the specific determinants of AF mechanism and electrophenotype. Patients will be classified into a range of AF mechanisms and electrophenotypes, ranging from organised AF sustained by localised drivers through to disorganised AF. The specific functional (e.g. atrial

conduction properties), structural (e.g. left atrial fibrosis burden) and clinical (e.g. AF duration) determinants of the AF electrophenotype will be investigated.

Intracardiac EGM data and 252 lead ECG
The 252 electrode device data will be analysed using a combination of established signal processing (dominant frequency, phase mapping and Shannon entropy) and machine learning techniques (unsupervised learning to cluster data into distinct phenogroups. For the subset of 10 patients with MRI data, we apply our 'in house' inverse solution and Tikhonov regularisation steps to reconstruct the epicardial electrograms.

Cardiac MRI
I will analyse burden of fibrosis and fibrosis distribution patterns and correlate these with the electrogram data.

AF electrophenotype will be determined using the analyses above. I will characterise each patient using both a regional and a global approach. The regional approach will analyse each sequentially collected 'kernel' of data from the RA and LA and assign a metric of organisation. The electrophenotype of a single patient therefore will be described by the number of organised/disorganised sites. The global approach will assign a global metric of organisation, including data from all collected kernels from both RA and LA. I will investigate the determinants of electrophenotype by correlating electrophenotype with clinical parameters including AF duration, co-morbidities and left atrial size on echocardiography. I will also compare intracardiac mapping pre- and post- PVI to investigate the impact of PVI on AF electrophenotype. I will investigate the degree to which the AF electrophenotype can predict outcomes compared to conventional clinical and echocardiographic predictors.

Biomarkers for identification of AF electrophenotype
We will look for differences in lipid metabolite levels, miRNA and protein expression between the electrophenotype groups, which may serve as biomarkers to non-invasively distinguish between these groups. I will analyse human serum using DNA barcode technology integrated with a nanopore platform to measure levels of these circulating miRNAs and proteins. Machine learning has been used effectively in proteomic studies (30). I aim to apply the biomarker data with electrical and imaging data using unsupervised machine learning to identify clinically relevant clusters (phenotypes).

Developing non-invasive methods to classify AF electrophenotype
Using simultaneously collected 252 lead ECG and intracardiac data, together with CMR LA fibrosis data, the surface ECG and biomarkers, I will develop tools to non-invasively classify AF electrophenotype.
Using the intracardiac data as the gold standard, I will continue to develop tools to determine the degree of global fibrillation organisation from surface ECGs, using band-power feature analysis and machine learning techniques. 252 lead ECG-derived biatrial maps in atrial fibrillation will then be analysed using both established (dominant frequency, phase mapping and Shannon entropy) and the novel (ML based analysis, including unsupervised machine learning) to further stratify patients into a spectrum of organised to disorganised electrophenotypes. Simultaneous

intracardiac and 252 lead ECG recordings will also allow further validation of 252 lead ECG in atrial fibrillation. I will use CMR data to correlate electrophenotype with anatomical data. LA fibrosis will be categorised by both degree and distribution of fibrosis and correlated with both intracardiac and non-invasively acquired electroanatomical data using linear regression models and ML. Invasive and non-invasive parameters will be combined and correlated with AF recurrence to create a tool using only non-invasive data to determine a patient-specific electrophenotype.

Outcomes

Freedom from AF, AF burden and quality of life outcome data will be correlated with electrophenotype groups (as defined by the above analyses) to investigate if certain groups benefit more from ablation than others.

Sample size is based on collecting sufficient data to detect differences in electrophenotypes using biomarkers and ECG parameters.

Data will be analysed by the chief investigator and the research team at the National Heart and Lung Institute, Imperial College London.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. Ethics approval

The Study Coordination Centre has obtained approval from Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

An approval from the National Research Ethics Committee (NRES) will be obtained before the start of any study related procedure and other relevant documents. All correspondence with the NRES will be retained in the Study Files.

8.2. Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. We will gain consent for participation in the study at Hammersmith Hospital. Consent for participation in the study can be gained by a consultant or registrar who is familiar with the study, clinical research fellow, or study nurse. Consent for the ablation procedure will be gained on the day of the procedure by the consultant performing the ablation or a specialty registrar who is familiar with the procedure, following normal clinical practice.
The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to

give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.
In case of loss of capacity during the study period, the participant will be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue will be collected, or any other research procedures carried out on or in relation to the participant. We will ensure informed consent is gained for use of collected data in case of incapacity, at a time when the patient has the capacity to make this decision.

8.3. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be pseudonymised

8.4. Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trust taking part in this study.

8.6. Funding

This study is funded by the British Heart Foundation Reference: FS/CRTF/21/24183

There will be no payments to research participants or researchers.

8.7. Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be coordinated by Dr Arunashis Sau clinical research fellow.

10. PUBLICATION POLICY

The investigators will publish the findings of the study at conference presentations and in peer-reviewed journals.

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