Endocardial mapping of atrial fibrillation in patients with sinus node disease

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust (s), regulatory authorities, and members of the Research Ethics Committee.

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1. SYNOPSIS

Study Title	Endocardial mapping of atrial fibrillation in patients with sinus node disease
Short title:	How does sinus node disease maintain atrial fibrillation?
Study Design:	Observational cohort study
Study Participants:	Patients who are due to undergo a clinically indicated ablation for atrial fibrillation, pacemaker implantation or supraventricular tachycardia ablation.
Sample size:	40 in total (10 with persistent atrial fibrillation alone = Group 1; 10 with persistent atrial fibrillation + sinus node disease = Group 2; 10 with supraventricular tachycardia (no atrial fibrillation or sinus node disease) = Group 3; and 10 with sinus node disease alone (No AF) requiring pacemaker implantation = Group 4)
Study duration:	: 1st May, 2019 – 31st October, 2023
Primary Objective:	To understand how the mechanisms of atrial fibrillation differ in patients with sinus node disease meaning the arrhythmia is harder to treat successfully.
Secondary Objective:	To see whether there are electrical markers within the atria that mean patients with sinus node disease should not be exposed to the risk of an ablation because the chance of successful outcome is reduced.
Inclusion Criteria:	• Patients aged 18 - 60 undergoing first elective EP study and/or catheter ablation, groups will be age matched • For the study groups: supraventricular tachycardia, documented persistent (up to 1 year) atrial fibrillation ± sinus node disease requiring ablation or sinus node disease requiring pacemaker implantation
Exclusion Criteria:	• Under 18 or over 60 years of age • Longstanding persistent AF • BMI >35 • Inadequate understanding of spoken English • Intubated/ventilated patients • Unwilling to give consent to participation OR advised by consultee that this would be against the patient's wishes. • Diabetes Mellitus • Intravascular implanted cardiac device or prior device extraction • Prior cardiac surgery • Participation in a clinical trial of an investigational medicinal product (CTIMP) • Inability or unwillingness to discontinue antiarrhythmic medication prior to procedure • Ischaemic heart disease (documented myocardial infarction, angiographic evidence of functionally significant coronary disease, ischaemia on non-invasive testing) • Uncontrolled stage II or III Hypertension (Diastolic BP >100 mmHg or Systolic BP > 160 mmHg) on repeated readings or ambulatory monitoring • Previous catheter or surgical ablation procedure for AF • Unwillingness or inability to complete the required follow-up arrangements • Structural cardiac abnormality including moderate or severe heart valve disease, severe left atrial dilatation, ASD • Infiltrative or inherited cardiomyopathy

	• Left ventricular systolic dysfunction (ejection fraction <50%) • Pregnancy
Setting(s):	Study participants will be recruited from the Cardiology services at the participating NHS Trusts.
Study procedures:	Recording of additional electrical signals from the heart using catheters that are in place for the clinically indicated procedure. Some patients will have atrial fibrillation induced by pacing from these catheters and may require DC cardioversion if the atrial fibrillation does not spontaneously terminate.
Data analysis:	Qualitative and descriptive analysis of the AF patterns will be performed, numerical quantitative data will be compared using unpaired T-Test or ANOVA. Categorical data will be analysed by Chi square.
Outcomes:	Comparison of the incidence and distribution of AF activation patterns thought to be active drivers of AF

2. ABBREVIATIONS

AF	Atrial Fibrillation
CI	Chief Investigator
CRN	Clinical Research Network
CTIMP	Clinical Trial Investigation Medicinal Product
EPS	Electrophysiological study
ICH - GCP	International Conference on Harmonisation Good Clinical Practice
MFT	Manchester University NHS Foundation Trust
MRI	Manchester Royal Infirmary
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
SAN	Sinoatrial Node
SVT	Supraventricular Tachycardia
SR	Sinus Rhythm

3. BACKGROUND AND RATIONALE

To date the specific role of sinus node disease (SND) in atrial fibrillation (AF) has not been investigated. It is known that SND frequently co-exists with atrial fibrillation (AF), and the presence of SND is a predictor of poor success rates of catheter ablation treatment for AF.[1] ***We know that AF can cause SND,[2] but can SND cause AF by altering the electrical properties of the right atrium to act as a driver domain that maintains AF?*** This project is part of a larger project that will elucidate the electroanatomical properties of the normal and diseased sinoatrial node (SAN) with respect to mechanisms that can promote and maintain AF. I will also investigate whether intervention to prevent electrical remodelling of the SAN in the presence of AF can prevent SND and increase the chance of successfully restoring normal sinus rhythm (SR).

AF is the commonest sustained cardiac arrhythmia in humans, the UK prevalence is 4.7% in people aged over 65[3] and AF is present in around 5% of all acute medical admissions to hospital.[4] Currently available drug therapy has poor efficacy in maintaining SR, therefore catheter ablation of AF has been developed.[5] This method involves removal of initiating foci via pulmonary vein isolation (PVI) and is successful for ~90% of patients with paroxysmal AF and is recommended in the European Society of Cardiology and NICE guidelines.[6]

However, in longer lasting 'persistent' AF (episodes lasting more than one week) PVI alone maintains SR in less than 60% of patients[7] and more extensive catheter treatments have not been robustly proven to have any additional benefit.[7] Catheter ablation of Persistent AF is challenging because, unlike paroxysmal AF, in addition to the pulmonary vein triggers there is widespread structural and electrical remodelling of the atrial muscle substrate. This promotes initiation and maintenance of AF independent of the pulmonary vein triggers that are important for paroxysmal AF.[8] The exact nature of this remodelling is unknown. There is an ongoing search for methods to treat persistent AF, clinical technology for endocardial mapping of AF is rapidly evolving, but there is an important need to understand the additional atrial substrate that maintains persistent AF to allow targeted ablation treatment. There are multiple theories regarding AF 'drivers' and most of these relate to areas of structural and electrical abnormalities in the atria. These electrical abnormalities may manifest as 'complex fractionated electrograms' (CFAE). Another example is the presence of fast vortex like re-entry in the atrial muscle around minuscule cores (rotors). The importance of rotors for maintaining persistent AF is highlighted by reports that ablation of rotors improves catheter ablation success rates.[9] Rotors cluster in stereotyped anatomical locations throughout the atria and may be anchored to anatomic structures or areas of fibrosis.[10] An important observation is that 30-50% of patients with PersAF have rotors in the superior aspect of the right atrium raising the possibility that these rotors are anchored at, or dependent on a diseased sinus node pacemaker complex.[10,11]

Mechanisms of persistent atrial fibrillation

There is widespread acceptance of the importance of the pulmonary veins as the main source of focal triggers that initiate AF. After initiation, AF may be sustained even on removal of the focal PV trigger but little is known about factors involved with this maintenance of AF. Detailed mapping in humans is difficult; therefore much knowledge comes from animal models and broadly speaking there are two main theories as to the underlying wave dynamics operative in the maintenance of PersAF:

1) The multiple wavelet hypothesis, a passive process. In this theory, multiple randomly propagating wavelets form, extinguish and re-form in a constant dynamic process.[12]

2) Focal drivers, an active process. In contrast, other animal studies have suggested that within the fibrillating atria, there may be areas of fast, highly organised activity that act as focal active drivers maintaining AF.

Using high-resolution video to examine sheep models of AF, these drivers corresponded to rotors.[13] The centre of the rotors displayed rapid and regular activation (demonstrated by the highest dominant frequency, DF).

Endocardial mapping and body surface potential mapping have suggested a high prevalence of rotors as driver domains in patients with AF.[9,10] However, these have low spatial resolution and the electrodes on the basket catheter used for endocardial mapping are separated by 2-3 cm. The activation patterns are created by interpolated animations and body surface potential mapping produces activation maps based on mathematical derivation from surface ECGs. High-resolution epicardial mapping studies have not confirmed the existence of ***sustained*** rotors in human AF; indeed mapping during cardiac surgery has yielded conflicting results with evidence for both multiple unstable wavefronts[14] and for sustained *active driving* focal sources.[15] In one study during prolonged recordings of PersAF activation patterns were varied, the most common pattern was simultaneous multiple narrow wavefronts; rotors were seen but remained transient.[15] Multiple wavelets with longitudinal block have also been demonstrated.[14]

What is clear is that there is overt electroanatomical remodelling of the *atrial muscle* during persistent AF that promotes stability of atrial fibrillation. There are demonstrable changes in atrial refractoriness, action potential duration, calcium handing, ion channel expression and gap junction expression.[8] Taking forward this concept, it is important to consider the role of the SAN pacemaker complex in persistent AF. Like the remodelled atrial muscle described above, the SAN is an area that is electrically and functionally distinct from normal atrial myocardium. For example cell coupling is poor via low conductance gap junctions and there is cellular automaticity throughout.[16] Even in the absence of SND, the SAN plays an important role in atrial arrhythmia; for example as an area of conduction block in atrial flutter, and through focal automaticity in atrial tachycardia.[17,18] With the development of SND there are significant alterations in the calcium handling, ion channel expression and function of the SAN.[16] These changes may promote initiation and maintenance of AF and explain why persistent AF is so difficult to treat in the presence of SND, but this has not been investigated.

For the purposes of this study, persistent AF, longstanding persistent AF and sinus node disease definitions are as follows:

Persistent AF (as defined by European Society of Cardiology guidelines) is AF that lasts for longer than 7 days, including episodes that are terminated by cardioversion, either pharmacologically or electrically, after 7 days or more.

Longstanding persistent AF (as defined by European Society of Cardiology guidelines) is persistent AF that continues uninterrupted for 1 year or more.

Sinus Node Disease will be defined as the presence of at least two of the following criteria:

- Corrected sinus node recovery time (CSNRT) of >550ms in the absence of reversible causes (e.g. rate limiting medication and cardiac ischaemia)
- Post-AF shock sinus recovery time >1200ms (>1.2 seconds) in the absence of reversible causes (e.g. rate limiting medication and cardiac ischaemia)
- ECG evidence of sinus pause >3 seconds when awake in the absence of reversible causes (e.g. rate limiting medication and cardiac ischaemia)

- ECG evidence of sinus rates <45 beats per minute for more than 1 minute when awake in the absence of reversible causes (e.g. rate limiting medication and cardiac ischaemia)
- Evidence of chronotropic incompetence on maximal exercise stress test (defined as reaching <80% of age-predicted maximal heart rate at maximal exercise) in the absence of reversible causes (e.g. rate limiting medication and cardiac ischaemia).

4. OBJECTIVES

4.1 Primary objective:

To characterise the role that SND plays in maintaining AF.

4.2 Secondary objective:

To identify electrical markers that might identify patients at risk of a poor rhythm control outcome after AF ablation.

5. METHODS

5.1 Study overview

Detailed high resolution electrical recordings will be taken from the SAN area of patients during clinically indicated ablation for AF or SVT. The recordings will be analysed to determine whether there are AF driver regions in this region due to remodelling caused by SND. The data will be correlated with animal data and human surgical data collected in parallel.

5.2 Participating centres

Lead site will be Manchester Royal Infirmary (MRI), which is part of Manchester University NHS Foundation Trust. Other participating sites will include Wythenshawe Hospital (also under Manchester University NHS Foundation Trust), Barts Health NHS Trust, Glenfield Hospital, Liverpool Heart and Chest Hospital and Royal Papworth Hospital.

5.3 Trial Participants

5.3.1 Overall Description of Trial Participants

Patients referred to the Cardiac Clinical service at participating centres will be screened for study participation at the discretion of their treating physician. Only participants referred for catheter ablation will be screened for study eligibility. No payment will be offered for participation.

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise, as stated below:

5.3.2 Inclusion criteria

- Patients aged 18 - 60 undergoing first elective EP study and catheter ablation, groups will be age matched

- For the study groups: supraventricular tachycardia, or documented persistent (up to 1 year) atrial fibrillation ± sinus node disease requiring ablation or sinus node disease requiring pacemaker implantation

5.3.3 Exclusion criteria (pre-procedure)

- Under 18 or over 60 years of age
- Longstanding persistent AF
- BMI >35
- Inadequate understanding of spoken English
- Intubated/ventilated patients
- Unwilling to give consent to participation OR advised by consultee that this would be against the patient's wishes.
- Diabetes Mellitus
- Intravascular implanted cardiac device or prior device extraction
- Prior cardiac surgery
- Participation in a clinical trial of an investigational medicinal product (CTIMP)
- Inability or unwillingness to discontinue antiarrhythmic medication prior to procedure
- Ischaemic heart disease (documented myocardial infarction, angiographic evidence of functionally significant coronary disease, ischaemia on non-invasive testing)
- Uncontrolled stage II or III Hypertension (Diastolic BP >100 mmHg or Systolic BP > 160 mmHg) on repeated readings or ambulatory monitoring
- Previous catheter or surgical ablation procedure for AF
- Unwillingness or inability to complete the required follow-up arrangements
- Structural cardiac abnormality including moderate or severe heart valve disease, severe left atrial dilatation, ASD
- Infiltrative or inherited cardiomyopathy
- Left ventricular systolic dysfunction (ejection fraction <50%)Pregnancy
- Concurrent medical or surgical illness likely to impact on interpretation of the data

5.3.4 Exclusion criteria (post-procedure)

- Concurrent clinical problem likely to interfere with participation or completion of the study
- Research mapping protocol not completed due to safety concerns or other clinical concerns at the discretion of the lead clinician performing the ablation or pacemaker procedure

5.4 Study Procedures

5.4.1 Participant screening

Patients attending arrhythmia clinics at participating centres will be approached and screened for study participation by local clinicians and nurses who will also be working as part of the research team. Any approaches made to patients regarding the study will not delay or interfere with clinical care. It is hoped the study will be adopted onto the National Institute for Health Research Clinical Research Network (NIHR-CRN) portfolio and as such will benefit from local support for the identification of potential participants.

Study participants will be identified by one of the following methods:

- Screening of the waiting list for electrophysiology studies (EPS) or cardiac ablation procedure. This will be performed by members the direct care team, including the cardiology research practitioner; who undertakes this duty as part of their role. Initial approach to those identified as potentially eligible will be made by letter from the clinician responsible for their care. The letter will contain brief description of the study, together with contact information for the research team.
- Referral from a clinical Cardiology colleague from a participating centre. Patients seen at these clinics and who are identified as potentially eligible to participate will be asked by their clinician for verbal permission to pass their contact details to the research team. The research team will then send out a letter with the patient information sheet.
- Participants may also be recruited from poster advertisements in arrhythmia clinics at these sites.

Patients expressing interest will then be sent the study patient information sheet (PIS) and any additional supporting information to allow them to understand the study. The information sent will include contact details for the research team so that the patient can contact the research team to express an interest in participating in the study, or ask any questions they may have about the study. If no response is received within one week, the patient will again be contacted by the research team by letter to provide the information and establish interest. All potential participants will be advised that participation in the research is voluntary and declining participation will not affect their clinical care.

The potential participant will have until the date of their clinical visit (pre-admission) to decide on study participation. Depending of the date of pre-admission visit, potential participants will have between 24 hours and 8 weeks from the time the study information is sent out until the date of the pre-admission visit, to decide on study participation. If patients cannot be contacted and express interest in participating in the study at the pre-admission appointment they will still be given the opportunity to take part, but would need to return for a clinic discussion for consent or could discuss by telephone prior and consent on the day of the procedure. If patients are unable to decide whether they wish to participate in the study prior to the procedure, they will no longer be considered for study participation.

5.4.2 Recruitment and consent

Patients who are willing to participate after receiving the study information will be met at their pre-admission appointment by a member of the research team, and patients will be informed this may extend the duration of the visit by up to 30 minutes. Before a patient's participation in the study is permitted, it is the PI's or his designee's responsibility to obtain written informed consent from the participant.

A member of the research team will fully explain the study, answer any questions about the study that the patient may have, and establish the patient's eligibility to take part in the study. With verbal consent from the potential participant to access clinical examination data, the researcher will confirm there are no concomitant conditions that would, in the opinion of the local investigator, prevent inclusion in the study e.g. clinical indicators of respiratory or cardiovascular disease requiring further investigation including murmurs, wheeze and blood pressure. Following written consent a research assessment will take place which will include medical history and clinical examination. Data will be collected from either medical records or by repeat questioning or examination by a medically qualified researcher or research nurse. The informed consent procedure will be performed by a trained, delegated member of the research team at the local site. We will continue to recruit patients across the study sites until we have a total of 10 participants in each group (40 in total).

5.4.3 Durations and timing of study

Following consent, the participant will undergo a number of assessments, and non-invasive investigations as part of study participation, which is in addition to usual clinical care. Descriptive clinical data will be collected by the research team (see section 5.4.4). All study participants will undergo the cardiac ablation procedure and standard follow up at 3-4 months post procedure as part of clinical care.

5.4.4 Assessment and data collection

Baseline Assessment:

Following written consent, the study participant will have a 24 hour ECG holter monitor only if they have not had one as part of their clinical workup within the previous 3 months. The following data will be collected from either the participant or the medical records or by repeat examination by a medically qualified researcher or research nurse and recorded in a paper case report form (CRF):

1. Past medical history including prior ablation procedures, prior cardiac surgery, thyroid disease, hypertension, smoking status, alcohol intake, comorbidities, prior cardiac arrhythmia, allergies, prior implanted cardiac device or device extraction, hypertension, $CHADS_2$ VA_2Sc score, current medication, diabetes, ischaemic heart disease.

It is the responsibility of the local PI to confirm participant safety prior to cardiac mapping. The participant may be withdrawn from the study at the time of clinical procedure at the discretion of the operator (see post-procedure exclusion criteria)

Schedule of Assessments:

For all patients

- Written Informed Consent
- 24 hour ECG holter if not performed clinically in last 3 months
- Re-confirmation of eligibility prior to cardiac mapping
- Follow up 24 hour ECG holter at 3 months post procedure to be performed as research if not performed for clinical indication

AF patients (with or without Sinus Node Disease). Groups 1 and 2

- Intraprocedural recording of additional electrograms using standard clinically available electrophysiology catheters.
- Atrial pacing using catheters already in place for clinical procedure.
- No additional procedure time (research protocol to be performed during clinical waiting period post-ablation prior to confirming PV isolation).
- 1-2 min additional low dose fluoroscopy at 4-5 frames per second (usual overall procedural mean fluoroscopy time for AF ablation is between 20-30 min depending on operator).
- It may be necessary to reclassify patients between these two groups following their procedure. For example, a patient felt to have AF without sinus node disease pre-procedure is found to have intraprocedural electrophysiological criteria of sinus node dysfunction, then they would need to be reclassified as having AF with sinus node disease post-procedure and analysed within this group.

SVT patients. Group 3

- Intraprocedural recording of additional electrograms using standard clinically available electrophysiology catheters.
- If AF has not been induced as part of the diagnostic electrophysiology assessment; induction of acute AF by pacing through catheters already in place for clinical procedure (no clinical risk from very short episodes of AF, this is often used as part of the electrophysiology assessment)
- No additional procedure time (research protocol to be done during clinical post ablation waiting period)
- 1-2 min additional low dose fluoroscopy at 4-5 frames per second (usual overall procedural mean fluoroscopy time for SVT ablation is between 5-20 min depending on operator).

Pacemaker insertion. Group 4

- Intraprocedural recording of additional electrograms using standard clinically available electrophysiology catheters requiring additional femoral venous puncture that is not part of the usual pacemaker implantation procedure.
- Induction of acute AF by pacing through catheters (no clinical risk from very short episodes of AF, this is often used as part of an electrophysiology assessment)
- Predicted 30 min additional waiting time
- 1-2 min additional low dose fluoroscopy at 4-5 frames per second (usual overall procedural mean fluoroscopy time for pacemaker implantation is between 5-10 min depending on operator).

All study participants will receive standard follow up at 3-4 months post procedure as part of clinical care.

6. STATISTICS

6.1 Description of Statistical Methods

This is a mechanistic study and so much of the analysis will be qualitative and descriptive. For quantitative data the study design is simple and therefore statistical analysis requires only the use of T-test or ANOVA to detect statistically significant changes. Where categorical variables are assessed Chi-square test will be used.

6.2 Number of Participants

We will continue to recruit patients across the study sites until we have a total of 10 participants in each group (40 in total).The endpoint event rates are not known. Prior studies of similar design have used groups of 10. The frequency of observed changes between groups is unknown given the novelty of mapping the SAN in PersAF. Previous human mapping studies have used samples of 10 per group to demonstrate valid findings. Our study is exploratory, seeking to provide initial comparisons between three different groups, with a view towards hypothesis generation. Therefore we intend to use a similar structure, recruiting 40 patients, 10 per group.

7. ETHICS

7.1 Declaration of Helsinki

The Chief Investigator will ensure that the study is conducted in full conformity with the current revision of the Declaration of Helsinki (Edinburgh, 2008) or with the regulations and guidelines set out in the Research Governance Framework for Health and Social Care Version 2, whichever affords the most protection for the patient.

The CI will be responsible for the submission of reports and application for extensions of permission from the HRA, REC and other regulatory bodies and committees.

7.2 Informed consent and withdrawal of consent

The study protocol complies with the requirements of ICH-GCP and The Declaration of Helsinki (2008).

Before a patient's participation in the study is permitted, it is the PI or their designee's responsibility to obtain written informed consent from the participant.

A record of the informed consent process and the patient's inclusion in the study will be documented in the participant's medical notes (paper or electronic) and this will be treated as source data. The consent form should be signed and personally dated by the patient and by the person conducting the informed consent discussion. The original signed informed consent form will be retained in the Investigator Site File, with a copy stored in the patient's medical notes, and a copy provided to the patient.

Participants may withdraw from the study at any time without any effect on their subsequent care. In addition, the CI or designee may withdraw a participant from the study should they think it is in the patient's best interest to do so. In the event that it no longer becomes feasible to continue with the study or the study is stopped for other reasons, all participants will be contacted and informed of this as soon as possible.

7.3 Guidelines for Good Clinical Practice

The study will be undertaken in accordance with Good Clinical Practice (GCP). All staff will receive appropriate Good Clinical Practice Training. A Study Management Committee, and Data and Safety and Monitoring Board will be appointed for the study. Each recruiting site will have a designated Principal Investigator. Obtaining consent and recruitment to the study and CGM training, will be undertaken by appropriately trained members of the local teams. A delegation log will be held at each site listing the responsibilities of staff members. The sponsor will put in place monitoring arrangements appropriate for the study.

7.4 Approvals

All study documentation including the protocol will be submitted to the Health Research Authority and an appropriate Research Ethics Committee to obtain HRA approval for the study. All study documentation will also be submitted to the host institution(s) for confirmation of capacity and capability prior to any study activity taking place at these sites. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

It is hoped the study will be adopted onto the National Institute for Health Research Clinical Research Network portfolio and as such will benefit from local support for the identification of potential participants.

7.5 Confidentiality

The Chief Investigator will ensure that the participants' anonymity is maintained. All study participant information recorded in the paper Case Report Form will be treated as source data and stored in a locked cabinet within a locked room at each participating site. No patient identifiable information will be included in the paper CRF. All data from the CRF will be transcribed into an electronic data system (RedCap) by the researcher at each site. Each subject will be assigned a unique study number by which they will be identified (see 7.6). Consent forms will be retained and archived at sites on completion of the study.

7.6 Data Handling and Record Keeping

Study documentation will be completed and stored in accordance to the Medical Research Council's guidelines for Good Clinical Practice in clinical trials (MRC, 1998) and other applicable local guidelines.

Personal Identifiable Data will be collected from participants by the research team and kept at the individual hospital with access restricted to the treating clinical team and study team only. Patients will be assigned a unique study identification number on enrolment and all data entered into the RedCap electronic research dataset will be pseudo-anonymised using this number.
The key that links the case number to the patient will be password protected and encrypted on an NHS computer at each participating site which will be password protected and accessible by only the local research team.

At the end of the study, the anonymised Redcap dataset will be transferred to the CI at the University of Manchester where it will be stored on the secure network.
Anonymised procedural mapping data will be transferred between collaborating sites and MFT using encrypted, password-protected physical storage media by a Boston Scientific representative and given to the chief investigator at MFT for analysis. Each subject will have been assigned a unique, sequential study number on entering the dataset. At the end of the study, this link will be destroyed and the dataset will be fully anonymized.

7.7 Retention of Records

All essential documentation will be retained by the institution for 5 years. Investigators will be responsible for ensuring that participant's clinical records will be available for the retention period. The Chief Investigator will be classified as the data guardian. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor of the study in writing of the new responsible person and/or the new location.

In keeping with the guidance for the Research Governance Framework, the information arising from the study will be made available to the study population that it affects, the clinical community who may use the information and also to anyone who may benefit from the study's findings. In order to achieve this, all participants will be asked whether they wish to receive a summary of the study's findings at study entry, regular presentations will be made to clinicians and the study will be submitted for presentation at scientific

and clinical meetings and for publication in peer reviewed periodicals. Anonymised data will be kept for 5 years.

7.8 Finance and Insurance

The study is being funded by the British Heart Foundation. Standard NHS indemnities will apply.

7.9 Publication policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2004), which states:

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

When a large, multi-centre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate proportions of the content.

8. APPENDICES

Copies of all information sheets, informed consent forms, GP letter, invitation letters and posters will not be included in the protocol.

9. REFERENCES

1 Park, J. *et al.* Post-shock sinus node recovery time is an independent predictor of recurrence after catheter ablation of longstanding persistent atrial fibrillation. *Int J Cardiol* **168**, 1937-1942, doi:10.1016/j.ijcard.2012.12.095 (2013).

2 Elvan, A., Wylie, K. & Zipes, D. P. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Electrophysiological remodeling. *Circulation* **94**, 2953-2960 (1996).

3 Sudlow, M., Thomson, R., Thwaites, B., Rodgers, H. & Kenny, R. A. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet* **352**, 1167-1171, doi:10.1016/S0140-6736(98)01401-9 (1998).

4 Zarifis, J., Beevers, G. & Lip, G. Y. Acute admissions with atrial fibrillation in a British multiracial hospital population. *Br J Clin Pract* **51**, 91-96 (1997).

5 Jais, P. *et al.* Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* **118**, 2498-2505, doi:10.1161/CIRCULATIONAHA.108.772582 (2008).

6 European Heart Rhythm, A. *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* **12**, 1360-1420, doi:10.1093/europace/euq350 (2010).

7 Verma, A. *et al.* Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* **372**, 1812-1822, doi:10.1056/NEJMoa1408288 (2015).

8 Nattel, S., Burstein, B. & Dobrev, D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circulation. Arrhythmia and electrophysiology* **1**, 62-73, doi:10.1161/CIRCEP.107.754564 (2008).

9 Narayan, S. M. *et al.* Treatment of Atrial Fibrillation by the Ablation of Localized SourcesCONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) Trial. *Journal of the American College of Cardiology* **60**, 628-636, doi:10.1016/j.jacc.2012.05.022 (2012).

10 Haissaguerre, M. *et al.* Driver Domains in Persistent Atrial Fibrillation. *Circulation* **130**, 530-538, doi:10.1161/circulationaha.113.005421 (2014).

11 Lemes, C. *et al.* P1583. Location of rotors in patients with atrial fibrillation:use of a novel body surface mapping system. *Europace* **17**, iii237 (2015).

12 Allessie, M. A., Lammers, W. & Bonke, F. I. in *Cardiac Electrophysiology and Arrhythmias* (eds D. P. Zipes & J. Jalife) 265-275 (Grune and Stratton, 1985).

13 Mandapati, R., Skanes, A., Chen, J., Berenfeld, O. & Jalife, J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* **101**, 194-199 (2000).

14 Allessie, M. A. *et al.* Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circulation. Arrhythmia and electrophysiology* **3**, 606-615, doi:10.1161/CIRCEP.109.910125 (2010).

15 Walters, T. E. *et al.* Temporal Stability of Rotors and Atrial Activation Patterns in Persistent Human Atrial FibrillationA High-Density Epicardial Mapping Study of Prolonged Recordings. *JACC: Clinical Electrophysiology* **1**, 14-24, doi:10.1016/j.jacep.2015.02.012 (2015).

16 Morris, G. M. & Kalman, J. M. Fibrosis, electrics and genetics. Perspectives in sinoatrial node disease. *Circ J* **78**, 1272-1282 (2014).

17 Fedorov, V. V. *et al.* Complex interactions between the sinoatrial node and atrium during reentrant arrhythmias in the canine heart. *Circulation* **122**, 782-789, doi:CIRCULATIONAHA.109.935288 [pii] 10.1161/CIRCULATIONAHA.109.935288 (2010).

18 Kalman, J. M. *et al.* "Cristal tachycardias": origin of right atrial tachycardias from the crista terminalis identified by intracardiac echocardiography. *J Am Coll Cardiol* **31**, 451-459, doi:S0735-1097(97)00492-0 [pii] (1998).