# Study Protocol and Statistical Analysis Plan: Characterising the Stable and Dynamic Left Atrial Substrate in Atrial Fibrillation

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**Study Title:** Characterising the stable and dynamic left atrial substrate in atrial fibrillation using high density contact and non-contact mapping

**Internal Reference Number / Short title:** CASDAF-HD

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There are no conflicts of interest

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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## 1. SYNOPSIS

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| **Study Title** | Characterising the stable and dynamic left atrial substrate in atrial fibrillation using high density contact and non-contact mapping | |
| **Internal ref. no. / short title** | CASDAF-HD | |
| **Study Design** | Prospective non-randomised mechanistic investigation | |
| **Study Participants** | Adults aged ≥18 with atrial fibrillation undergoing catheter ablation and 5 controls undergoing ablation of left sided accessory pathways | |
| **Planned Sample Size** | 35 (30 patients with AF and 5 supraventricular tachycardia (SVT)) | |
| **Planned Study Period** | 2 years | |
| | **Objectives** | **Outcome Measures** |
| **Primary** | To define the normal range of voltage amplitude identified using the Abbott EnSite Advisor HD grid (SE) catheter and HD wave solution and response to pacing cycle lengths using a control group with normal left atria | Mean and distribution of left atrial voltage amplitude across the whole chamber and by segments with lower limit of normal defined as the upper 95% value within the segment with the lowest mean amplitude at long pacing cycle length |
| **Secondary** | To characterise the left atrial electrophysiological substrate using electroanatomical voltage and activation mapping using the Abbott EnSite Advisor HD grid (SE) catheter during pacing using a basic cycle length and a single closely coupled extra-stimulus in a cohort of patients undergoing catheter ablation for atrial fibrillation. | A change in electrogram morphology from normal to abnormal (defined as ≥3 deflections lasting ≥50ms) between long and short pacing cycle length in regions of low (<0.5mV), intermediate (0.5-lower limit of normal defined from control group) and normal (defined from control group results) voltage amplitude. |
| | | Difference in single vector conduction velocity at long and short cycle lengths in regions of low, intermediate and normal voltage. |
| | **In a subgroup of 20 patients:**<br>To compare electroanatomic voltage mapping (EAVM) performed with a bipolar contact force guided ablation catheter to the Abbott HD grid using orthogonal wave analysis in sinus rhythm. | 1. Difference in voltage amplitude by each method in sinus rhythm<br>2. Surface area and proportion of points of scar (<0.05mV), low voltage (0.05-0.4mV), intermediate voltage and normal voltage (voltage cut-offs defined from control group). |
| | **In a subgroup of 10 patients:**<br>Correlate findings of high density | Correlate electrogram amplitude and morphology with regions of |

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| | contact mapping with AF propagation patterns using the AcQMap combined imaging and electrophysiological mapping system. | uniform, irregular, slow or rotational activation patterns during AF. |
| | To evaluate the distribution of late gadolinium enhancement on cardiac MRI relative to conduction properties identified using the HD grid (as above) | Electrogram amplitude, morphology and conduction velocities at long and short cycle length in regions with and without late gadolinium enhancement on cardiac MRI |
| | Correlate dynamic propagation patterns with distribution of atrial scar derived from cardiac MRI | Difference in distribution of late gadolinium enhancement in regions of predominant rotational and irregular activation during AF. |
| | Evaluate the effect of ablation on left atrial scar derived from cardiac MRI | Difference in burden of late gadolinium enhancement on pre- and post procedure cardiac MRI. |
| | **In 5 control patients:**<br>Evaluate the effect of cycle length on electrogram morphology in normal subjects | A change in electrogram morphology from normal to abnormal (defined as ≥3 deflections lasting ≥50ms), amplitude and duration between long and short pacing cycle length |

## 2. ABBREVIATIONS

| | |
|---|---|
| AF | Atrial fibrillation |
| CI | Chief Investigator |
| CRF | Case Report Form |
| EAVM | Electroanatomic Voltage Mapping |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| LGE-MRI | Late Gadolinium Enhanced – Magnetic Resonance Imaging |
| NHS | National Health Service |
| NRES | National Research Ethics Service |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| R&D | NHS Trust R&D Department |
| REC | Research Ethics Committee |
| SOP | Standard Operating Procedure |

## 3. BACKGROUND AND RATIONALE

Atrial fibrillation is a common condition resulting in significant morbidity and mortality. Catheter ablation based around a strategy of pulmonary vein isolation is increasingly used to maintain sinus rhythm.(1) However, particularly in patients with persistent atrial fibrillation, efficacy is limited with single-procedure success rates of <50%.(2-5) Although a number of techniques targeting non-pulmonary vein mechanisms have been explored, none has demonstrated superior efficacy in randomised controlled trials.(5) This is in large part due to a lack of understanding of AF mechanisms or subgroups of AF phenotypes and the contribution of identified conduction patterns to arrhythmia maintenance and propagation.

Assessment of atrial substrate is often performed through electroanatomical voltage mapping (EAVM) using multipolar or bipolar catheters. Regions of low voltage amplitude, used as a surrogate for fibrosis, predict worse outcomes following catheter ablation.(6-8) Prior studies have varied in the technology used to conduct EAVM and how low voltage areas are defined. They have largely focused on regions with bipolar amplitude <0.5mV with normal being defined as >1.1 or 1.3mV.(9, 10) The significance of regions with amplitude between these values (intermediate voltage) is poorly understood but there is some evidence that highly fractionated electrograms are seen in these areas(9, 10) which correlate with patchy enhancement rather than dense fibrosis on late gadolinium enhanced cardiac MRI (LGE-MRI). The presence of intermediate and low voltage areas is associated with AF recurrence following pulmonary vein isolation (PVI).(11, 12) Interestingly, a significant proportion of patients undergoing catheter ablation for persistent AF do not demonstrate regions of low voltage implying that it is not purely these regions that are important for AF maintenance.(7, 13) There also appears to be fairly poor correlation between AF duration and the presence of fibrosis, with some patients with longstanding AF demonstrating scar-free atria, whilst some with only brief episodes have highly scarred atria.(13, 14)

EAVM may significantly underestimate fibrosis when compared with MRI. One MRI study found >20% atrial fibrosis in 51% of patients and a second study found >10% fibrosis in 81%.(14, 15) Rolf's study assessing ablation of low voltage areas found these to be present in only 26% of patients.(7) This suggests that current strategies of EAVM fail to detect a significant proportion of fibrosis seen in MRI. This may be the result of regions of patchy fibrosis with relatively preserved voltage amplitude but abnormal conduction properties, important for AF propagation.

Studies have shown an increase in total atrial conduction time with increasing duration of AF and a corresponding slowing in conduction velocity.(10) Conduction velocities are significantly reduced in low voltage areas (<0.5mV) but are less thoroughly studied in regions of intermediate voltage.(16) Furthermore, the majority of this work has been undertaken in sinus rhythm. Conduction velocity and refractoriness are significantly affected by the interval between successive beats. Ectopic (premature) beats, usually originating in the pulmonary veins, commonly trigger AF. Therefore, although resting atrial conduction properties (and electrogram morphology) may appear normal, response to closely coupled ectopic activation could be impaired and contribute to the initiation and maintenance of fibrillation.

EAVM during AF is influenced by the effect of wavefront directionality on bipolar electrogram amplitude. The novel Abbott EnSite Advisor HD grid (SE) catheter uses orthogonal bipoles to reduce the

effect of wavefront direction (HD wave solution) and is therefore designed to facilitate more accurate substrate assessment compared to conventional bipolar mapping catheters. Appropriate voltage amplitude values representing the cut-off between normal and abnormal will vary with the catheter used (the result of electrode size and spacing) and has not been clearly defined with this technology.

The HD grid catheter is still a traditional "point by point" mapping system whereby small areas of the atrium are examined in sequence. Non-contact dipole density mapping facilitated by the AcQMap system from Acutus Medical allows real-time visualisation of whole chamber activation during AF and reveals complex propagation patterns. These patterns are highly variable between patients and their detailed analysis may identify important patterns related to the underlying electrophysiological substrate that may further our understanding of AF mechanisms and help guide effective ablation strategies.

This study therefore aims to conduct detailed EAVM using the Abbott HD grid catheter in 5 control patients undergoing ablation of left sided accessory pathways who are thought to have normal atria in order to define normal voltage amplitude and the response to changing activation rate. Detailed EAVM will then be performed in patients undergoing catheter ablation for AF in order to evaluate atrial properties at both long and short pacing cycle lengths. In 2 separate subgroups, the orthogonal HD grid mapping will be compared to either AcQMap propagation patterns or to a conventional bipolar ablation catheter with contact force. It is hypothesised that regions of intermediate voltage will demonstrate exaggerated slowing in conduction velocity and broadening of electrograms with shortening cycle length compared to regions of preserved amplitude, which will correlate with regions of slow and irregular propagation patterns during atrial fibrillation and late gadolinium enhancement on cardiac MRI. Furthermore, EAVM using the HD grid catheter will reveal higher mean electrogram amplitude compared to bipolar mapping with a lower surface area identified as low voltage (<0.5mV). The improved mapping resolution provided by the HD wave solution and HD grid catheter alongside use of varying activation times will facilitate greater understanding of the variable and patient specific AF substrate involved in AF maintenance. It is anticipated that combining this with non-invasive assessment of fibrosis distribution through cardiac MRI and AF propagation patterns visualised by panoramic mapping will provide pilot data with the potential to identify sub-groups of AF phenotypes. This data can then be applied to larger multi-centre studies of substrate mapping to better characterise the arrhythmic substrate and develop patient specific ablation strategies.

## 4. OBJECTIVES AND OUTCOME MEASURES

| **Objectives** | **Outcome Measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
|---|---|---|
| **Primary**<br>To define the normal range of voltage amplitude identified using the Abbott EnSite Advisor HD grid (SE) catheter and HD wave solution and response to pacing cycle lengths using a control group with normal | Mean and distribution of left atrial voltage amplitude across the whole chamber and by segments with lower limit of normal defined as the upper 95% value within the segment with the lowest mean amplitude at long pacing cycle length | During ablation procedure |

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| left atria | | |
| **Secondary:**<br>To characterise the left atrial electrophysiological substrate using electroanatomical voltage and activation mapping using the Abbott EnSite Advisor HD grid (SE) catheter during pacing using a basic cycle length and a single closely coupled extra-stimulus in a cohort of patients undergoing catheter ablation for atrial fibrillation. | A change in electrogram morphology from normal to abnormal (defined as ≥3 deflections lasting ≥50ms) between long and short pacing cycle length in regions of low (<0.5mV), intermediate (0.5-lower limit of normal defined from control group) and normal (defined from control group results) voltage amplitude. | During ablation procedure |
| | Difference in single vector conduction velocity at long and short cycle lengths in regions of low, intermediate and normal voltage. | During ablation procedure |
| **In a subgroup of 20 patients:**<br>To compare electroanatomic voltage mapping (EAVM) performed with a bipolar contact force guided ablation catheter to the Abbott HD grid using orthogonal wave analysis in sinus rhythm. | 1. Difference in voltage amplitude by each method in sinus rhythm<br>2. Surface area and proportion of points of scar (<0.05mV), low voltage (0.05-0.4mV), intermediate voltage and normal voltage (voltage cut-offs defined from control group). | During ablation procedure |
| **In a subgroup of 10 patients:**<br>Correlate findings of high density contact mapping with AF propagation patterns using the AcQMap combined imaging and electrophysiological mapping system. | Correlate electrogram amplitude and morphology with regions of uniform, irregular, slow or rotational activation patterns during AF. | During ablation procedure |
| To evaluate the distribution of late gadolinium enhancement on cardiac MRI relative to conduction properties identified using the HD grid (as above) | Electrogram amplitude, morphology and conduction velocities at long and short cycle length in regions with and without late gadolinium enhancement on cardiac MRI | During ablation procedure |
| Correlate dynamic propagation patterns with distribution of atrial scar derived from cardiac MRI | Difference in distribution of late gadolinium enhancement in regions of predominant rotational and irregular activation during AF | N/A |

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| Evaluate the effect of ablation on left atrial scar derived from cardiac MRI | Difference in burden of late gadolinium enhancement on pre-and post procedure cardiac MRI. | 3-6 months post procedure |
| **In 5 control patients:**<br>Evaluate the effect of cycle length on electrogram morphology in normal subjects | A change in electrogram morphology from normal to abnormal (defined as ≥3 deflections lasting ≥50ms), amplitude and duration between long and short pacing cycle length | During ablation procedure |

## 5. STUDY DESIGN

This is a prospective non-randomised mechanistic study of 35 patients including a control group of 5 patients with SVT and 30 patients undergoing elective AF ablation.

The 30 patients undergoing AF ablation will include 10 who are undergoing elective AcQMap guided procedures in order to correlate non-contact propagation patterns with contact substrate mapping. These 10 patients will also undergo cardiac MRI before and after the ablation procedure.

The remaining 20 patients will also undergo electroanatomical voltage mapping using a contact force guided bipolar ablation catheter in order to compare the two methods/technologies. This is a non-blinded comparison study.

The 5 control patients will be undergoing elective catheter ablation procedures for left sided accessory pathways. Additional left atrial electroanatomical mapping will be performed to define normal electrophysiological properties for comparison.

Participants will be identified in clinic or after listing for the procedure. Screening and formal recruitment will then be undertaken, with the research study conducted during the ablation procedure. No follow up is required but participants undergoing AcQmap guided ablation and cardiac MRI will undergo a repeat cardiac MRI within 6 months following the procedure.

## 6. PARTICIPANT IDENTIFICATION

### 6.1. Study Participants

Patients with atrial fibrillation undergoing an elective catheter ablation procedure and 5 patients undergoing elective left sided catheter ablation involving a trans-septal puncture.

### 6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18 years or above.
- Diagnosed with paroxysmal or persistent atrial fibrillation and planned for a catheter ablation procedure (AF ablation group only).

- Undergoing elective left sided catheter ablation procedure involving a trans-septal approach. (control group only)
- In the Investigator's opinion is able and willing to comply with all trial requirements.

### 6.3. Exclusion Criteria

- Previous cardiac surgery
- Medical history including any of: atrial fibrillation, atrial flutter, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, significant mitral valve disease (stenosis or regurgitation), pulmonary hypertension, obstructive sleep apnoea, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, structural heart disease (excluding known accessory pathway), congenital cardiac anomaly (excluding accessory pathway), previous left atrial ablation (catheter or surgical), cardiac surgery (control group only)
- Contradictions to MR scanning (such as metallic or electronic objects implanted in your body or history of severe claustrophobia) (AcQMap guided ablation group)
- Significantly impaired renal function (eGFR<30ml/min)
- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Participants who have participated in another research trial involving an investigational medicinal product in the past 12 weeks. (Involvement in *any* other research trial is not a contraindication per se.)

## 7. STUDY PROCEDURES

### 7.1. Recruitment

Potential study participants will be identified by medical staff in the outpatient clinic at the time of listing for catheter ablation, or by review of patients electronically listed for this procedure. If patients are in the clinic and give consent then a member of the research team may approach them at this stage. Some members of the clinical team are also part of the research team and therefore if identified by medical staff through listing for the procedure, they will be approached by telephone. An information leaflet will then be provided by post or email if this has not been provided in clinic with contact details for the research team. If willing to participate then formal screening and recruitment will follow. For most, this will take place at the time of attendance for standard pre-procedure assessment appointments or when attending for the elective procedure. Participants undergoing elective AcQMap guided procedures and

requiring cardiac MRI, formal recruitment and consent will take place prior to the initial study MRI scan. Information must have been provided with sufficient time for the potential participant to fully consider involvement prior to formal recruitment and consent (generally expected to be at least 24 hours).

### 7.2. Screening and Eligibility Assessment

As there is no randomisation, there is no time limit between screening and formal recruitment. It is anticipated that these will occur at the same visit to coincide with standard clinical care and avoid an extra patient journey. Screening procedures include a review of medical history and demographics and recording of height and weight.

### 7.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed. It is anticipated that this is done at the initial visit, which will serve as both the screening and baseline study visit.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant and a copy placed in the medical records. The original signed form will be retained at the trial site.

### 7.4. Baseline Assessments

Baseline assessments include medical history; current medications and any recently stopped medications (with particular reference to anti-arrhythmic drugs and anticoagulants), smoking history, alcohol use, and illicit drugs use. Measurements taken should include height, weight and body mass index.

Data collected from imaging performed as part of standard clinical care should include left ventricular ejection fraction, diastolic function (including average E/E’), significant valvular disease (defined as at least moderate stenosis or regurgitation), left atrial diameter, left atrial volume (including indexed for body surface area), and presence of significant coronary disease at angiography (invasive or CT)(if performed).

Laboratory test results recorded should include haemoglobin, urea, creatinine, and creatinine clearance (estimated by Cockroft and Gault formula).

A 12 lead ECG should be performed.

### 7.5. Pre-procedure cardiac MRI

Those participants who are undergoing elective AcQMap guided ablation will undergo a cardiac MRI (3 Tesla) within the 6 weeks prior to the catheter ablation procedure.

Patients will complete an MRI safety questionnaire (5 min) prior to the scan. An intravenous cannula will be inserted. Cardiac MRI will evaluate cardiac structure and function, with particular focus on the left atrium. For late gadolinium enhancement imaging, the total dose of gadolinium-based contrast will not exceed 0.2mmol/kg.

The total duration of the MR protocol will be ~60 min, considering ~50 min of scanning time, plus ~10 min for pre-/post-scan preparation.

### 7.6. Study visit (control group)

As part of standard care, a 12 lead ECG will be performed for all patients following arrival on the day of their procedure.

Venous access, placement of electrophysiology catheters, and completion of diagnostic electrophysiology study will be undertaken in line with standard clinical care. Trans-septal puncture for left atrial access will be undertaken and anticoagulation will be administered in line with standard protocols. Prior to any ablation, left atrial electroanatomical voltage mapping (EAVM) using the Abbott Advisor HD Grid (SE) mapping catheter using the orthogonal wave setting (HD wave solution) will then be undertaken. This will be conducted during bipolar pacing from the mid point of the coronary sinus catheter at a cycle length of 800ms for 4 beats followed by a single extrastimulus with coupling interval of 300ms. Care must be taken to keep the catheter in each position to record all 5 cycles before moving to acquire new points aiming for a minimum of 300 points in total with full and equal covering of the atrial surface. Interpolation threshold should be set to 7mm with points filtered to within 5mm of the surface anatomy (interior and exterior projection). Initial map collection should be specified as a CFAE map set to collect points with the catheter stationary for 5 seconds.

Following completion of the EAVM, the procedure continues in line with standard clinical practice. If, for any reason the EAVM is not performed then the patient will be removed from the study. If mapping has commenced but is incomplete then the data will still be used.

### 7.7. Study visit (excluding control group)

As part of standard care, a 12 lead ECG will be performed for all patients following arrival on the day of their procedure. In line with standard practice in this institution all procedures will be undertaken under general anaesthesia.

Venous access, trans-septal puncture and placement of standard electrophysiology catheters will be undertaken as per standard clinical care. Anticoagulation will be administered following trans-septal puncture in line with standard protocols.

Please see appendix A for detailed study flow chart.

**All patients**

All study patients will undergo electroanatomical voltage mapping (EAVM) using the Abbott Advisor HD Grid (SE) mapping catheter using the orthogonal wave setting (HD wave solution) in the same manner as described above. If in AF at the start of the procedure direct current cardioversion (DCCV) will be used to restore sinus rhythm. This can be repeated at the discretion of the operator if initially unsuccessful (including internal cardioversion if necessary). If unsuccessful then the patient will no longer be included in the study and the procedure should continue according to standard clinical care.

Mapping will then be undertaken during bipolar pacing from the mid point of the coronary sinus catheter at a cycle length of 800ms for 4 beats followed by a single extrastimulus with coupling interval of 300ms (or the shortest captured cycle length if longer). Atrial geometry can be acquired concurrently. Care must be taken to keep the catheter in each position to record all 5 cycles before moving to acquire new points aiming for a minimum of 300 points in total with full and equal covering of the atrial surface. Interpolation threshold should be set to 7mm with points filtered to within 5mm of the surface anatomy (interior and exterior projection). Initial map collection should be specified as a CFAE map set to collect points with the catheter stationary for 5 seconds. Subsequent analyses offline will use the Precision turbomap feature to adjust the data displayed. Ablation and the rest of the procedure can then be performed according to standard clinical practice.

Post procedure care including subsequent discharge will continue in line with standard clinical practice.

**Subgroup undergoing contact force guided mapping**

20 patients undergoing AF ablation will have a further map completed using a contact force guided bipolar irrigated ablation catheter (Abbott Tacticath) during the same pacing protocol. For all voltage maps a minimum of 300 points should be obtained with full and equal covering of the atrial surface, interpolation should be set to 7mm, and set to only include points with contact force between 5 and 50grams.

**Subgroup undergoing AcQMap guided mapping and ablation**

10 patients with persistent AF who are undergoing AcQMap guided elective catheter ablation procedures will be included in this sub-study. All patients will undergo the same main study mapping procedure outlined above. In addition, AcQMap recordings will also be obtained. Recordings will be made during pacing with the same main study protocol and two 30 second recordings will be undertaken during AF. HD grid contact recordings will then also be obtained in regions of prominent rotational and irregular conduction identified by AcQMap and ablation performed at the operator's discretion.

For patients presenting in sinus rhythm or AF, all required mapping should be completed in the presenting rhythm followed by either AF induction (using incremental burst atrial pacing) or DCCV respectively before completion of mapping procedures. Ablation in line with standard clinical care will be undertaken following completion of all mapping procedures.

For an outline of study procedures versus standard care and estimated time requirements, please see appendix B.

## 7.8. Follow up

Participants will be seen post procedure prior to discharge to exclude any adverse events. This will represent the end of the study. No further research follow up is required for most but routine clinical follow up will take place including participant access to arrhythmia specialist nurse practitioners. Participants undergoing AcQMap guided ablation and cardiac MRI will undergo a repeat cardiac MRI 3-6 months after the procedure. This will be planned wherever possible to take place at the same time as attending for routine clinical follow up after the procedure.

### 7.9. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- An adverse event which requires discontinuation of the catheter ablation or results in inability to continue to comply with trial procedures
- Withdrawal of Consent

If a patient is withdrawn or voluntarily withdraws from the trial prior to the study procedure then all study data collected will be excluded and they will be replaced in the study. If any event during the procedure results in necessary deviation from the study protocol on grounds of clinical necessity then any data collected up to that point will be analysed. It may be required to recruit additional patients if this occurs depending on the extent to which data had been collected. This is at the discretion of the chief investigator.

The reason for withdrawal will be recorded in the CRF.

### 7.10. Definition of End of Study

The end of the study is defined as the end of the study procedure for the last study participant.

## 8. SAFETY REPORTING

### 8.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

### 8.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

## 9. STATISTICS AND ANALYSIS

### 9.1. Description of Statistical Methods

This is a mechanistic study exploring a change in electrogram morphology. This will be expressed as a proportion of signals recorded within each amplitude bracket. Statistical comparisons using the chi-square tests of 2 proportions will be made to look for significant differences at long and short cycle length.

In the sub-study comparing voltage mapping methods, simple statistical analysis will be used to compare voltage amplitudes obtained by each method in sinus rhythm and in AF. Means will be compared using independent sample t-test.

Retrospective analyses may be conducted to explore trends in electrophysiological mechanisms identified and their relation to demographic, anatomical, or clinical features recorded and in line with secondary outcome measures.

### 9.2. The Number of Participants

The total number of participants will be 35; 30 with AF and 5 controls. Previous studies have revealed the presence of low voltage areas (<0.5mV) in approximately 35% of patients with persistent AF undergoing catheter ablation,(7) and in the one previous prospective study of patients without low voltage areas, intermediate amplitude regions were observed in 43%.(9) Our hypothesis is that conduction properties, and thus electrogram morphology will become abnormal at shorter cycle length. A sample of 35 is consistent with previous mechanistic exploratory studies and should include enough patients with regions of voltage amplitude <1.1mV according to prior results outlined above and allow comparisons between each cycle length. As this is an exploratory study we are not evaluating a specific intervention, formal power calculations have limited usefulness.

The control group will consist of 5 patients with presumed normal atria. Although this is a small number, a high number of points will be collected to allow good distribution of results. By analysing the combined total electrogram recordings and excluding patients with any risk factors for abnormal atrial substrate then this sample should provide adequate estimation of normal values.

## 9.3. Analysis of Outcome Measures

**Control group:**

All electrogram samples will be analysed at baseline (long) cycle length and classified as normal or abnormal (see above definitions in section 4). The same sampling points will then be analysed at short cycle length and classified in the same way. The proportion of electrograms changing from normal to abnormal will be recorded as will the change in electrogram amplitude and duration.

The whole chamber mean, median and distribution of voltage amplitude at long cycle length will be analysed. This will also be done for each atrial segment. The segment with the lowest mean amplitude will be identified and the cut-off for the value representing the upper 95% of recordings in that segment calculated. This will be used as the value representing the lower limit of normal for subsequent study analyses.

**All participants:**

All electrogram samples will be analysed at baseline (long) cycle length and classified as normal or abnormal (see above definitions in section 4). The same sampling points will then be analysed at short cycle length and classified in the same way. The proportion of electrograms classified as normal and abnormal at each cycle length will be calculated for the full sample set and according to baseline electrogram amplitude (<0.5mV, 0.5-lower limit of normal, and >lower limit of normal)(lower limit of normal defined above from analysis of the control group).

For each participant, conduction velocities will be analysed in regions of different baseline electrogram amplitude at both long and short cycle length. This will be done using the Turbomap feature in Precision to create an activation map (specified as measuring on maximum negative dV/dt). Conduction velocity will be calculated as a mean of 5 measurements using the difference in activation times between 2 points in a straight line at set distance through the region of least isochronal crowding. This will be done in regions of low, intermediate and preserved voltage at long and short cycle length.

The outcome measures will be assessed in all patients in whom the study procedure was performed.

**Voltage mapping subgroup:**

For all maps obtained in this subgroup using both the HD grid and ablation catheter, bipolar voltage amplitudes will be compared. Mean amplitudes will be compared for the entire chamber and each atrial segment (anterior, septal, inferior wall, posterior wall, roof, lateral wall). Each sampling point obtained using the ablation catheter in sinus rhythm/baseline pacing cycle length will then be compared to an equivalent nearest point obtained by the HD grid in sinus rhythm/baseline pacing cycle length to give a difference (+/-) in amplitude recorded. Mean differences will be compared for the whole atrium and each segment as outlined above.

The outcome measures will be assessed in all patients in whom the study procedure was performed.

**AcQMap subgroup:**

Qualitative and quantitative assessments of conduction patterns identified on AcQMap during AF will be made with regions of frequent focal firing, slow conduction, rotational activation or irregular activation identified (according to AcQTrack and visual interpretation of the operator in line with and according to

their prior experience). Contact electrograms using the HD grid will be recorded at these regions and classified according to their degree of fractionation. Regions identified as above by the operator will be compared to the rest of the atria according to sinus rhythm voltage amplitude and proportional change in electrogram morphology and conduction velocity with changing pacing cycle length.

The outcome measures will be assessed in all patients in whom the study procedure was performed.

## 10. DATA MANAGEMENT

### 10.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

### 10.2. Data Recording and Record Keeping

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file. A paper form assigning patient details to study codes will be kept in the study master file only.

Electroanatomical mapping data forms the majority of study data collected. Participants will be identified by their unique trial number on any data exported from the catheter laboratory computers. All clinical procedure data will be stored on secure trust servers in a password-protected folder in line with standard practice for all such clinical procedures. AcQMap data is stored on a designated ACUTUS workstation on which all clinical cases are stored. Study data for analysis will be exported at the time of the procedure in an anonymised form identifiable by study code onto separate computer workstations to allow analysis of the mapping data. Analysis work is done within the research office using these designated systems, which are password protected and accessible by the study team only.

Analysis results will then be recorded using a purpose designed Excel database.

Data will be retained for 5 years after the end of the study.

## 11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

## 12. ETHICAL AND REGULATORY CONSIDERATIONS

### 12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

### 12.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

### 12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

### 12.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

### 12.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

### 12.1. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

### 12.2. Cardiac MRI

MRI is a safe and non-invasive technique with no known risk when appropriately supervised. It does not involve ionizing radiation (X-rays). Potential participants with ferromagnetic objects in their bodies or with implanted devices which can be damaged by the CMR magnet will be excluded by carefully screening all participants for ferromagnetic objects, metal implants and other metal (e.g. shrapnel injury) every time prior to entering the scanner environment. OCMR is fully equipped for resuscitation (including defibrillation) in the unlikely event of a medical emergency during scanning. Either Advanced-Life-Support trained clinicians or Intermediate-Life-Support trained radiographers will be performing MRI scans in study participants.

While most people do not experience discomfort in a MRI environment, the enclosed space of the scanner can potentially feel uncomfortable. Discomfort from lying still for a long period of time will be minimized with comfortable padding and positioning. People with a history of claustrophobia would be excluded from participation in the study. Participants will be given a chance to see the scanner before the study starts. Whilst in the scanner, participants are able to use the alarm button or can squeeze a bulb placed in their hands if they wish to communicate with the operator or to interrupt the scanning at any stage of the scanning process. As the MRI scanner is noisy, participants would be fitted with ear-

plugs and/or acoustically shielded headphones to minimize the noise and aid communication between participants and investigators.

Once contraindications to magnetic resonance imaging are excluded by use of the facility's screening forms, the risks of undergoing a scan are minimal. A trained scanner operator or radiographer will go through a list of possible risks with the participant before scanning. The MRI scanner consists of a large powerful magnet. Magnetic resonance imaging uses no ionizing radiation. There are, however, potential hazards associated with MRI and the scanning of participants including the presence of surgical implants, participants' clothing, jewellery (such as body piercings) bodily habitus, or medical conditions. A comprehensive list of potential risks has been compiled, and the participant should be checked against this by the operator, prior to entering the controlled areas of the MRI scanners. Participants will be asked to wear a gown for the CMR scans that preserves their modesty while remaining loose in the scanner to avoid potential burns from synthetic clothing. To help maintain participant dignity they will be asked to leave their underwear on, so long as it is not made of synthetic material and has no metal parts (e.g. zips, bras clasps or studs). Participants will be asked to change in a changing room near to the scanner and will be given a locker to securely store their belongings. If they are unable to change into the gown by themselves a member of staff will be on hand to aid.

Gadolinium contrast is widely used for clinical indications in CMR and is safe. Occasionally it may cause a mild headache, nausea, itching and very rarely (< 1 in 5000) a more severe allergic reaction. It is cleared within hours by the body. Gadolinium has recently been associated with nephrogenic systemic fibrosis in patients with severe renal dysfunction; hence, as per departmental guidelines, based on Food and Drug Administration guidelines, all patients with glomerular filtration rate (GFR) < 30 ml/min (stage 3-5 renal disease) should not be given gadolinium. For this study, all potential participants with a GFR < 30 ml/min will be excluded (see Exclusion Criteria). It is known that small amounts of gadolinium deposits can remain in the body, including the skin, bones and the brain. There has been no scientific evidence to-date that these gadolinium deposits are harmful or lead to adverse health effects, although this is an active area of research.

The current study is wholly research-oriented, and the images of the heart are for specific research purposes only, and are not suitable for diagnostic opinions. However, although the images are not diagnostic scans, in the event of an abnormality of clear clinical relevance being noted incidentally, a designated clinical specialist would discuss the implications with the patient and arrange for further investigations as necessary.

## 13. FINANCE AND INSURANCE

### 13.1. Funding

Funding is secured through a competitive grant awarded by the Oxfordshire Health Services Research Committee (OHSRC) and through departmental research budgets (CRM Hub).

### 13.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

## 14. PUBLICATION POLICY

The results will be presented at scientific meetings and published in peer-reviewed scientific journals. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that The Oxfordshire Health Services Research Committee, part of Oxford Hospitals Charity, funded the study). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Participating patients will be offered a copy of any publications arising from the study.

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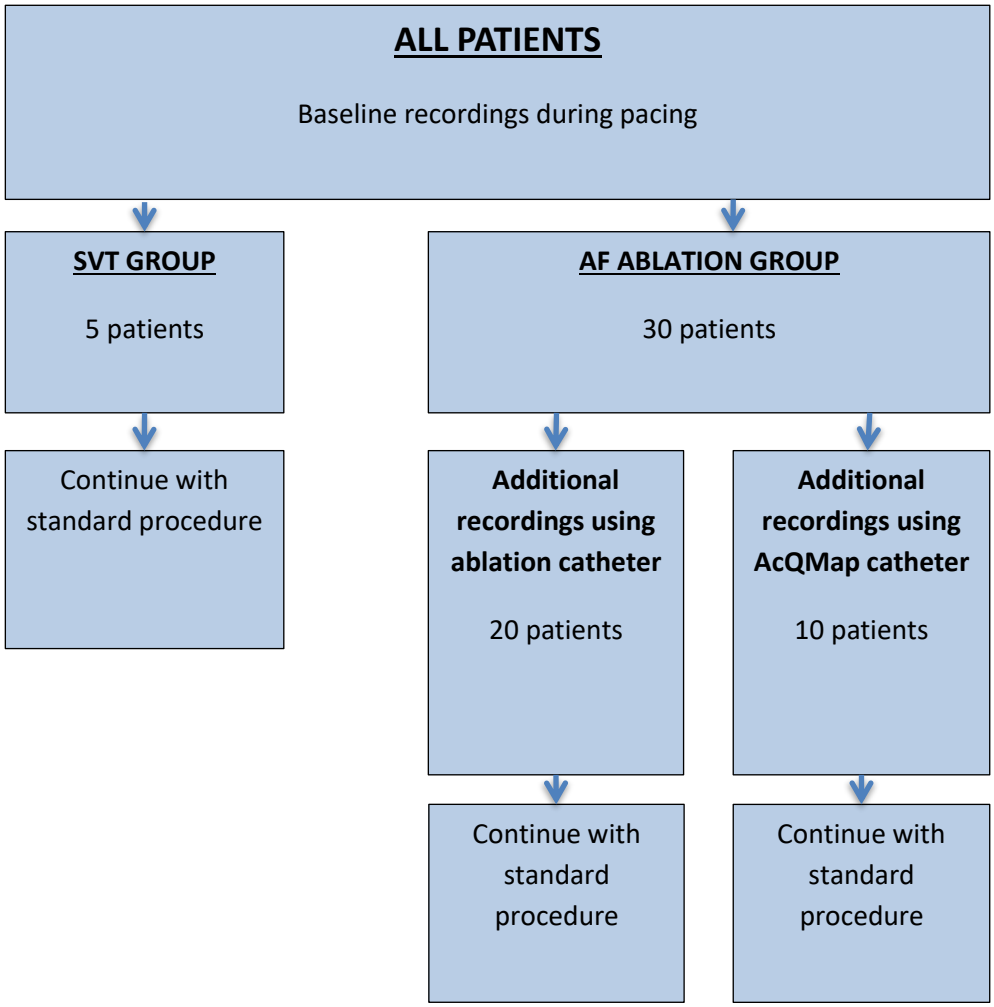
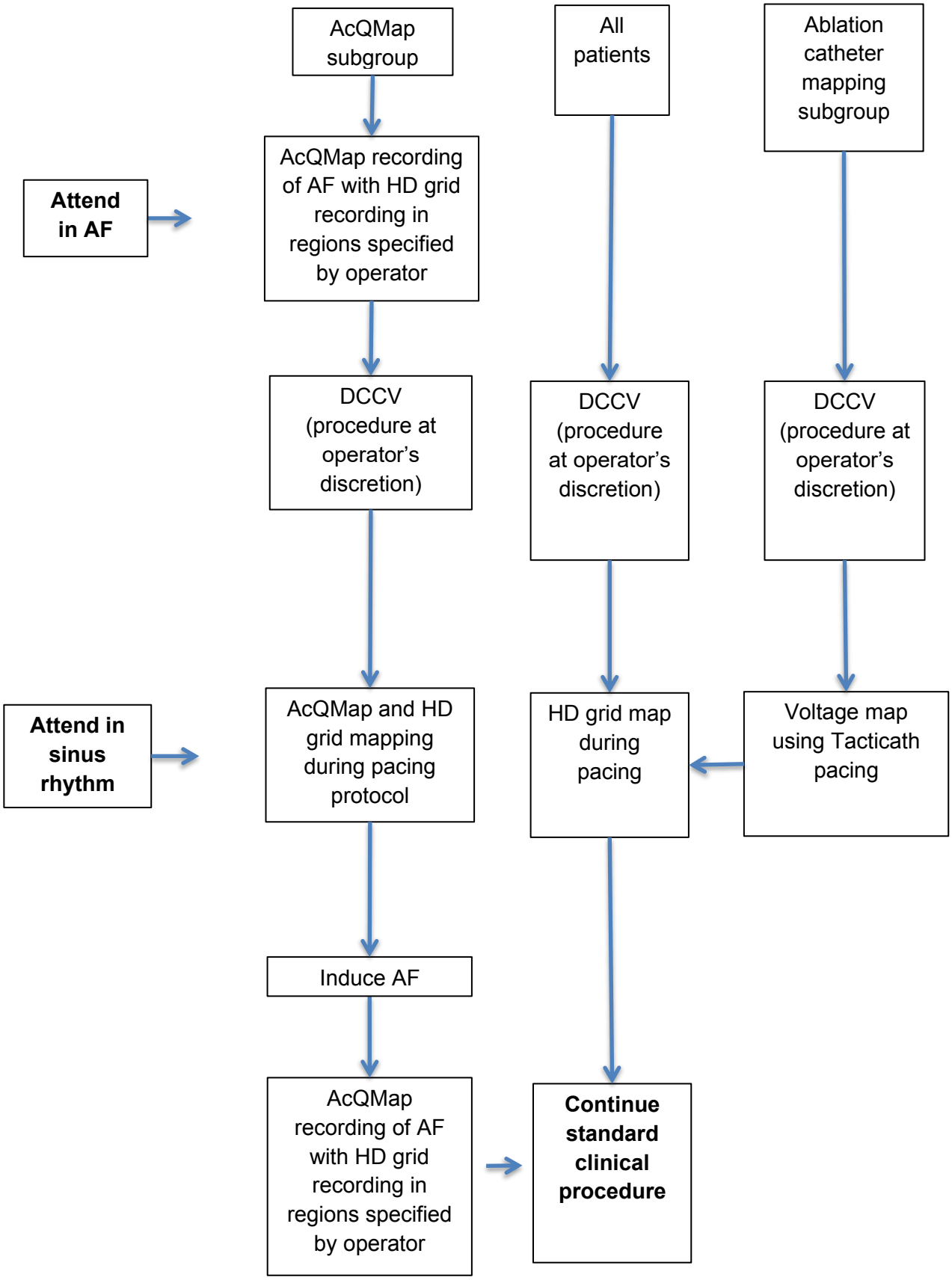
## 16. APPENDIX A: PARTICIPANT GROUP ALLOCATION AND STUDY FLOW CHART





## 17. APPENDIX B: Table distinguishing routine and study procedures and estimated additional time requirements

| **Standard care** | | | **Research procedure** | | | |
|---|---|---|---|---|---|---|
| **All elective AF ablation patients** | **AcQMap guided AF ablation patients** | **Left sided accessory pathway ablation** | **5 control patients** | **30 AF patients** | **Contact-force mapping subgroup** | **AcQMap guided subgroup** |
| Venous access and insertion of electrophysiological catheters and trans-septal puncture | Additional venous access and insertion of AcQMap catheter | Venous access and insertion of electrophysiological catheters | Specified left atrial 3-dimensional mapping using HD grid and specified study protocol (**Additional time estimate = 20 minutes)** | Specified pacing map during initial left atrial 3-dimensional mapping and geometry acquisition using HD grid **(Additional time estimate = 10 mins)** | Additional ablation catheter map during pacing (**Additional time estimate = 15 minutes)** | AcQMap recording during pacing **(Additional time estimate = 5 minutes)** |
| Standard 3-dimensional left atrial geometry acquisition and contact mapping using a multipolar mapping catheter | AcQMap mapping of AF (left +/- right atrium | Trans-septal puncture | | | | HD grid catheter evaluation of regions with specified activation patterns **(Additional time estimate = 10 minutes)** |
| Direct current cardioversion (if clinically required) | Additional left +/- right atrial ablation | Diagnostic EP study | | | | |
| Left atrial ablation including pulmonary vein isolation | | Accessory pathway mapping and ablation | | | | |
| **Total additional time estimates for each study group** | | | 20 minutes | 10 minutes | 15 minutes | 15 minutes |

## 18. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

| **Procedures (all participants)** | **Visits** | | | | | |
|---|---|---|---|---|---|---|
| | **Prior to procedure*** | | **Study visit** | | | |
| | **Screening** | **Baseline** | **Prior to procedure** | **During procedure** | **Prior to discharge** | **At ~3-6 months** |
| Informed consent | √ | | | | | |
| Eligibility assessment | √ | | | | | |
| Demographics | √ | | | | | |
| Medical history | √ | | | | | |
| Concomitant medications | | √ | √ | | | |
| Height, weight, BMI | | √ | | | | |
| Imaging results | | √ | | | | |
| 12 lead ECG | | √ | √ | | √ | |
| Laboratory test results | | √ | | | | |
| HD grid mapping at long and short cycle length | | | | √ | | |
| Adverse event assessments | | | | | √ | |
| **20 Ablation catheter mapping patients** | | | | | | |
| Additional mapping with HD grid and ablation catheter | | | | √ | | |
| **10 AcQMap patients** | | | | | | |
| AcQMap AF recording and HD grid contact electrogram acquisition | | | | √ | | |
| MRI Scan 1 | | √ | | | | |
| MRI Scan 2 | | | | | | √ |

***May be carried out when attending for the elective procedure but prior to the procedure taking place providing that all information has been provided to the prospective participant well in advance to allow them to fully consider involvement and they are not undergoing AcQMap guided procedures and cardiac MRI.**

## 19. APPENDIX C: AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| | | | | |