*C*atheter *A*blation Versus Thoracoscopic *S*urgical *A*blation in Long Standing Persistent *A*trial *Fi*brillation (CASA-AF)

Short Study Title/Acronym: CASA-AF

REC Reference: 15/SC/0023
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1. LIST OF ABBREVIATIONS

AAD	Anti-Arrhythmic Drugs
AE	Adverse Event
AF	Atrial Fibrillation
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Catheter Ablation
CFAE	Complex Fractionated Atrial Electrogram
CI	Chief Investigator
CMR	Cardiac Magnetic Resonance Imaging
CRF	Case Report Form
DMC	Data Monitoring Committee
ECG	Electrocardiograph
eCRF	Electronic Case Report Form
EHRA	European Heart Rhythm Association
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
ICF	Informed Consent Form
ILR	Implantable loop recorder
ISF	Investigator Site File
ISRCTN	International Standard Randomised
KCTU	Kings Clinical Trials Unit
LAA	Left Atrial Appendage
LSPAF	Long Standing Persistent Atrial Fibrillation
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
RFA	Radiofrequency Ablation
SA	Surgical Ablation
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SR	Sinus Rhythm
SSA	Site Specific Assessment
TDI	Tissue Doppler Imaging
TMG	Trial Management Group
TSC	Trial Steering Committee
V_{minLA}	Volume of atrium at end atrial systole
V_{pLA}	Volume of atrium at onset of P wave

2. STUDY PERSONNEL AND FACILITIES

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3. STUDY SYNOPSIS

Full study title:	Catheter Ablation *versus* Thoracoscopic Surgical Ablation in Treating Long Standing Persistent Atrial Fibrillation
Short study title:	CASA-AF
Study R&D number:	2014CI005B
REC ID	15/SC/0023
IRAS ID	155944
UKCRN ID	18834
ISRCTN number	ISRCTN18250790
Chief Investigator:	Dr Tom Wong
Medical condition/disease under investigation:	Long-standing persistent Atrial Fibrillation (LSPAF)
Study duration:	48 months
Clinical phase:	N/A
Primary Objective:	The primary efficacy end-point is freedom from atrial arrhythmias after a single procedure without anti-arrhythmic drugs (AADs) within 12 months (as assessed from the end of the 3 months blanking period to 12 months).
Secondary Objectives:	1. Safety end-point is the intervention-related major complication rate defined as permanent injury or death, requires unplanned intervention for treatment, or prolongs or requires unplanned hospitalization for more than 48 hours. 2. Clinical success - defined as a 75% or greater reduction of AF burden assessed by implantable loop recorder (ILR) during 12 months follow-up with or without AADs. 3. Freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up. 4. Identify changes in atrial anatomy and function following ablation as assessed by echocardiography and CMR imaging using tissue Doppler and strain. 5. Change in AF symptom score (EHRA score) and quality of life assessments (EQ5D5L, AFEQT) 6. Quality Adjusted Life Years (QALYs) accrued during 12-month study period

	7. Cost-effectiveness (Incremental Cost per QALY gained) for surgical ablation (SA) compared with catheter ablation (CA) estimated over the 12-month study period ('within trial' analysis) and over a lifetime horizon ≥ (estimated by modelling).
Study population:	Adults with persistent atrial fibrillation referred for ablation
Methodology:	Prospective, open-label, multi-centre randomised controlled trial
Eligibility criteria:	***Inclusion criteria:*** 1. Age≥ 18 yrs. 2. LSPAF (> 12 months' duration) 3. EHRA > 2 4. Left ventricular ejection fraction ≥ 40% 5. Suitable for either ablation procedure
	Exclusion criteria: 1. Valvular heart disease with severity greater than mild 2. Contraindication to anticoagulation 3. Thrombus in the left atrium despite anticoagulation in therapeutic range 4. Cerebrovascular accident within the previous 6 months 5. Previous thoracic or cardiac surgery (including surgical interventions for AF) 6. Prior left atrial catheter ablation for AF 7. Unable to provide informed written consent 8. Active malignancy, another severe concomitant condition or presence of implanted intracardiac devices that would preclude patient undergoing study specific procedures 9. Pregnant or breast-feeding, or women of childbearing age not using a reliable contraceptive method.
Study treatment: *(i.e. dose and mode of the study drug administration if applicable)*: **N/A**	
There are two treatment arms of the study: 1. Catheter ablation 2. Thoracoscopic surgical ablation	

4. INTRODUCTION

4.1 BACKGROUND

Atrial fibrillation (AF) is the commonest heart rhythm disturbance, affecting 1-2% of the population. Its prevalence increases with age, from 0.5% at 40-50 years to 5-15% at 80 years. With an ageing population, AF will affect an increasing proportion of the population [1]. In the UK alone, NHS admissions have risen 60% over 20 years, with total cost to the NHS of £2.2bn a year, and projected to double by 2050 [2,3].

AF is characterised by an irregularly irregular pulse, loss of atrial contractile function and attendant loss of active ventricular filling, and risk of thromboembolic stroke. In addition to prevention of stroke with anticoagulants, there are two principal therapeutic strategies for treatment of AF: rhythm control (to restore sinus rhythm) and rate control (to accept AF and simply control the ventricular rate). Rhythm control is preferred in symptomatic, especially younger, more active patients with symptoms *despite* adequate rate control. Traditionally, rhythm control is attempted with antiarrhythmic drugs (AADs) and direct current (DC) cardioversion. Long-term efficacy is poor, and it is associated with drug side-effects and risk of proarrhythmia. Consequently, there has been an increasing impetus particularly over the last two decades to advance non-pharmacological approaches to AF management.
Clinically, AF is categorised into three types: paroxysmal AF (recurrent fibrillation that terminates spontaneously within 7 days), persistent AF (lasting longer than 7 days or successfully terminated before with cardioversion) and longstanding persistent AF (arrhythmia persisting for more than a year) [4].

Interventional treatments (surgical or catheter) have evolved over the years and nowadays allow reliable clinical success in treating paroxysmal AF, albeit with repeat procedures necessary in a proportion of patients. However, the best strategy for achieving sinus rhythm (SR) in patients at the most severe end of the AF spectrum, namely longstanding persistent AF (LSPAF), has not been fully elucidated.

4.1.1 Percutaneous catheter ablation

Since the seminal work by Haissaguerre in 1997 highlighting the importance of pulmonary vein (PV) triggers in the initiation of AF [5], percutaneous techniques to electrically isolate the PVs have developed into an important interventional therapy for AF. The growth of percutaneous AF

ablation has been rapid, with a 2010 worldwide survey describing 20,825 percutaneous AF ablation procedures performed between 2003 and 2006 at 521 centres [6, 7].

However, PV isolation (PVI) alone is inadequate in treating non-paroxysmal AF [8, 9]. Additional modification of the remaining atrial substrate is necessary to achieve lasting freedom from persistent forms of AF [10, 11]. Techniques used for atrial substrate modification include creation of linear lesions and targeting areas exhibiting Complex Fractionated Atrial Electrograms (CFAEs). The benefit of linear lesions has been highlighted in a randomised controlled trial [12] whilst the benefit of CFAE ablation has been confirmed by meta-analysis, when added to PVI in non-paroxysmal AF [13].

Single procedure success rates of catheter ablation are low in LSPAF. In LSPAF cohort undergoing PVI and CFAE ablation, but without linear lesions, single procedure success rate was only 27% at 40 months, with overall success increasing to 79% after a median of 2.3 procedures [14].

4.1.2 Surgical AF ablation

The first interventional treatment for AF, developed in the 1980s, was surgical. Using a cut-and-sew technique, linear lesions were created whilst on cardiopulmonary bypass *via* median sternotomy. The lesion set was modified over time, culminating in the Cox-Maze III procedure. Excellent long-term results were reported with 80% maintenance of sinus rhythm, off AADs, in a mixed group of patients (64% paroxysmal, 36% persistent) beyond 5 years. This became the gold standard of interventional AF treatment for over a decade [15, 16]. However, this extensive and technically complex procedure was associated with significant mortality (1.8%) and morbidity (10.7%), including re-operations for bleeding (2.7%), renal failure (1.8%), intra-aortic balloon pump placement, mediastinitis, and need for a permanent pacemaker in approximately 8% of cases [16].

The advent of better surgical ablation tools in the late 1990s led to the development of less invasive thoracoscopic surgery without midline sternotomy and on a beating heart. Early thoracoscopic procedures used a simpler lesion set than the Cox-Maze III, *via* mini-thoracotomy incisions. Wolf *et al.* then described a video-assisted thoracoscopic technique of epicardial AF ablation. On a beating heart, PVI was performed using a bipolar radiofrequency (RF) device and the left atrial appendage (LAA) as excised with a staple device [17]. In 2009 Edgerton *et al.* published a series of 114 patients who underwent thoracoscopic PVI, ganglionic plexi ablation

and LAA excision. At 6 months, SR rates off AADs were 71% for paroxysmal, 47% for persistent and 32% for LSPAF [18]. Although these early reports described a 'minimally invasive' approach, the majority still used muscle splitting mini-thoracotomy incisions. In 2008, the first totally thoracoscopic approach (without mini-thoracotomy incisions) was published detailing a series of 9 patients with paroxysmal AF [19]. A subsequent retrospective study described 32 persistent AF patients who had undergone totally thoracoscopic ablation [20]. In this study, in addition to PVI and ganglionic plexi ablation, three connecting linear lesions were added and attempts made to verify linear lesion block with an electrophysiology catheter. At 6 months follow-up, 87% of patients were in SR off AADs. Other groups then published further totally thoracoscopic case series with success rates of 92% in treating paroxysmal AF and 47-80% in treating non-paroxysmal AF at 6-12 months follow-up [21,22].

RF energy remains the only energy source that is available for a totally thoracoscopic surgical ablative procedure. The bipolar radiofrequency ablation devices that we will use in this study have been shown in animal models to consistently produce transmural lesions both acutely and longer term [23]. Bipolar radiofrequency energy is also the most tested thoracoscopic ablation modality [24].

4.2 PRE-CLINICAL DATA/CLINICAL DATA

4.2.1 Catheter ablation versus totally thoracoscopic surgical ablation (FAST study)

Data comparing catheter and thoracoscopic AF ablation is limited to a single two-centre randomised controlled trial published in 2011 [25]. The study randomised patients to thoracoscopic surgical ablation (n=61) or catheter ablation (n=63). It included both paroxysmal (59%) and non-paroxysmal (41%) AF cases, and most patients had previously failed catheter ablation (60% in catheter arm vs. 74% in surgical arm). There were twice as many persistent AF cases in the catheter ablation arm as in the surgical arm (42% vs. 21%). The catheter ablation protocol consisted of PVI with or without additional linear ablation, depending on the centre. In the surgical arm, the lesion set also varied by centre, but included PVI in all patients. Ablation in Waterston's groove, ganglionic plexi ablation and linear ablation varied between centres and patients. The primary endpoint, freedom from atrial arrhythmia at 12 months, off AADs, was significantly greater in the surgical group compared to the catheter ablation group (65.6% vs. 36.5%, p=0.0022). The procedural adverse event rate was significantly higher in the surgical group (23.0% vs. 3.2%; p=0.001).

Thus, while the study suggested an important difference in the primary efficacy endpoint, its results need to be interpreted with caution for a number of reasons:

1. It enrolled a mixed cohort of paroxysmal and persistent patients.
2. There was a two-fold difference in the proportion of non-paroxysmal patients in the two arms.
3. Most patients had undergone prior catheter ablation at the time of enrolment.
4. Lesion sets were not uniform, and this affected both the surgical and catheter ablation arms.

Thus, while the FAST trial was an important contribution to the literature, hinting at a potentially very important difference in procedural efficacy, it was limited by several methodological flaws. A further study is required. Catheter and thoracoscopic surgical ablation require comparison in a rigorous randomised trial conducted in a uniform population and employing uniform lesion sets. The proposed study amongst patients with LSPAF will define the best treatment strategy for this important subset of therapy-resistant AF patients.

4.2.2 CASA-AF Pilot Study Data

The Royal Brompton and Harefield NHS Foundation Trust (RB&HFT) are currently conducting a pilot study as a precursor to this proposed randomised controlled trial. The pilot is a prospective, non-randomised study comparing thoracoscopic surgical AF ablation versus catheter AF ablation in LSPAF. The ablation lesion sets in both arms are almost identical to those proposed in the current application.

To date 24 patients have undergone thoracoscopic surgical ablation and 25 patients' catheter ablation. In the surgical arm, 20 patients have completed 6 months' follow-up of whom 16 patients (80%) were free from atrial arrhythmias off AADs following a single procedure. In the catheter ablation arm, 22 patients have completed 6 months' follow-up with 11 patients (50%) free from atrial arrhythmia following a single procedure off AADs.

4.3 STUDY RATIONALE AND RISK/BENEFIT ANALYSIS

4.3.1 Study Rationale

AF is the commonest arrhythmia in humans and is related to significant detrimental effects on quality of life [36], morbidity (5 fold increase stoke, 3 fold increase in heart failure) and mortality (2-fold increased fatality) [37].

It is perhaps logical and now well-recognised that patients, who are symptomatic from AF, will benefit from the restoration of normal SR. Furthermore, there is now a body of evidence (from 10 randomised controlled trials) showing that catheter ablation of AF is more effective than AAD therapy in achieving and maintaining normal SR [38-47].

That said, although conventional catheter ablation can reliably achieve respectable clinical success rates in treating paroxysmal AF (up to 78%) [8], the outcome in ablating the more challenging spectrum of AF, LSPAF, is less encouraging [32-40%] and often requires more than one procedure to increase success rates [11,48].

The advent of minimally invasive thoracoscopic surgical AF ablation opens the possibility of ablating AF under direct vision using radiofrequency energy with concomitant exclusion of the left atrial appendage without the need of midline sternotomy. The early experience in comparing surgical thoracoscopic AF and catheter ablation was reported in a single randomised controlled trial (FAST trial) showing that the surgical approach is more effective (65.6% *vs.* 36.5% clinical success, P=0.0022) [25] which is consistent with the pilot data that we have been collecting in the past two years (refer to section 4). However, the FAST trial had important caveats in the study design in terms of a heterogeneous study population (including paroxysmal and persistent AF in both *de novo* and repeat cases) and non-uniform lesion set in both the catheter and surgical ablation arms.

Catheter ablation has become a widely accepted and effective therapy for paroxysmal AF, but results for persistent, and particularly LSPAF, are suboptimal. Traditional drug-based approaches also remain unsatisfactory. The best interventional treatment for symptomatic, LSPAF is yet to be defined. The encouraging results achieved with thoracoscopic surgical ablation in several cohort studies [20-22] in persistent AF and LSPAF are also echoed by our pilot study results (see section 4.2.2). These warrant further investigation in a properly powered randomised controlled trial amongst patients with a single AF type (LSPAF) and employing uniform lesion sets. The proposed trial will resolve this question, determining single and multiple procedure success rates, as well as the relative morbidity associated with each technique, the effect on quality of life and the cost effectiveness, in a rigorously designed and conducted study.

4.3.2 Risks of Catheter AF Ablation

The potential risks of catheter AF ablation are well studied. A worldwide survey from Cappato *et al.* in 2010 included 20,825 AF ablation procedures from 521 centres [6]. The overall major complication rate was 4.5% and consisted of the following; death 0.15%, stroke 0.23%, transient ischaemic attack 0.71%, cardiac tamponade 1.31%, pulmonary vein stenosis requiring intervention 0.29%. In our pilot study, amongst the 25 index catheter AF ablation procedures and 8 repeat ablations, there have been no major procedural complications.

4.3.3 Risks of Thoracoscopic Surgical AF Ablation

The risks of thoracoscopic surgical AF ablation, as a relatively new operation, are less well characterised. The major complication rate in the relatively small case series published so far range from 0 to 39% [35]. The key randomised controlled study (FAST Study) reported a procedural major adverse event rate of 23%, including pericardial effusion 1.6%, cerebral embolic event 1.6%, pneumothorax 9.8%, haemothorax 1.6%, rib fracture 1.6%, sternotomy for bleeding 1.6%, pneumonia 1.6%, permanent pacemaker insertion 3.3% [25]. In our pilot study, amongst the 21 thoracoscopic surgical AF ablations, there were 4 (16%) major adverse events: pleural effusion requiring drainage in 1 (4%), phrenic nerve palsies in 2 (8%) and PV stenosis (without intervention) in 1 (4%). There was no pericardial effusion, stroke, TIA, pneumo- or haemo- thorax, sternotomy, pacemaker implant or death.

4.4 BENEFITS OF THIS STUDY

Patients recruited into this trial will be those who would otherwise be offered conventional catheter ablation to treat symptomatic LSPAF on clinical grounds outside of the clinical trial setting. The interventions in both arms of the study will be performed in selected high-volume cardiothoracic centres by experienced operators. All patients will benefit from comprehensive pre-procedural assessments and post-procedural rhythm monitoring as well as optimised follow up with specialist arrhythmia care during the course of the study. The research fellow and research nurse will be available for contact as necessary: this may facilitate rapid onward referral for other heart or medical problems as needed.

Our proposed study will be the only randomised controlled study, to our knowledge, focusing on a specific challenging type of AF (symptomatic LSPAF) with clearly defined lesion sets comparing catheter ablation to thoracoscopic surgical ablation. The findings will improve understanding of how best to treat LSPAF. The trial will facilitate a broadening of the interventional options

available for treating LSPAF, if not a paradigm shift in the management of this condition both nationally and internationally.

4.5 MANAGEMENT OF POTENTIAL STUDY RISKS

Any potential complications arising from the study interventions will be managed as per best practice standard of care at local treating centre and will be individualised as per patient needs.

5. OBJECTIVES

5.1 PRIMARY OBJECTIVE

1) The principal objective of this industry-independent, multi-centre randomised controlled trial is to identify the most effective arrhythmia intervention for treating LSPAF by comparing thoracoscopic surgical AF ablation to conventional percutaneous catheter ablation.

2) The primary hypothesis is that thoracoscopic surgical ablation is more effective than percutaneous catheter ablation in LSPAF with regards to freedom from atrial arrhythmia within 12 months follow-up (as assessed from the end of the 3 month blanking period to 12 months) after a single procedure without anti-arrhythmic drugs.

5.2 SECONDARY OBJECTIVES

1) To evaluate and to compare the safety of the arrhythmia interventions. The safety end-point is the intervention-related major complication rate defined as permanent injury or death, requires unplanned intervention for treatment, or prolongs or requires unplanned hospitalization for more than 48 hours.

2) To evaluate and to compare the clinical success from the arrhythmia interventions (distinct from arrhythmia-free survival) - defined as a 75% or greater reduction of AF burden assessed by implantable loop recorder during 12 months follow-up with or without AADs.

3) To evaluate freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up.

4) To identify changes in atrial anatomy and function following ablation as assessed by echocardiography and CMR imaging using tissue Doppler and strain.

5) To evaluate and to compare the effects of the arrhythmia interventions on the patients' symptoms and quality of life as assessed by change in AF symptom score (EHRA score) [49] and quality of life assessments (EQ5D, AFEQT) from baseline to follow-up [50,51].

6) To evaluate Quality Adjusted Life Years (QALYs) accrued during 12-month study period

7) To evaluate Cost-effectiveness (Incremental Cost per QALY gained) for surgical ablation compared with CA estimated over the 12-month study period ('within trial' analysis) and over a lifetime horizon ≥ (estimated by modelling).

The objectives of this study are in line with questions defined as important in the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF [4]:

- To identify the most effective ablation strategy in treating patients with LSPAF.
- To relate the effectiveness of the ablation techniques to quality of life using validated general and disease-specific tools.
- To assess the cost-effectiveness of interventional techniques by performing a comprehensive health economic assessment.

6. TRIAL DESIGN

6.1 OVERALL DESIGN

6.1.1 Design

A prospective, non-commercial, industry independent, open-label, multi-centre, randomised clinical trial.

6.1.2 Blinding

It is not possible to blind patients to the procedure as the mode of access will be obvious (incisions at the side of chest in thoracoscopic ablation *vs.* small punctures in the groin for percutaneous ablation).

6.1.3 Methods used to maintain standardisation

The following systems will be put in place to ensure that all interventions, in both the surgical arm and the catheter ablation arm, are standardised between operators' at all three sites:

1. Only named operators involved in the design of this trial will perform the interventions in both the surgical and the catheter ablation arms. This protocol and the lesion sets have been agreed by all operators beforehand and demonstrated to be clearly achievable in our pilot study.

2. A member of the research team (as defined by those who sign the delegation and responsibility log), in addition to the named operator, will be present for every procedure to ensure that the agreed standardised protocol is followed and that the case template is completed in a point-by-point contemporaneous manner.

3. A case template form developed for each arm requires sequential documentation of every step of the protocol in addition to research data points being collected during treatment. All members of the team understand the need to complete this meticulously.

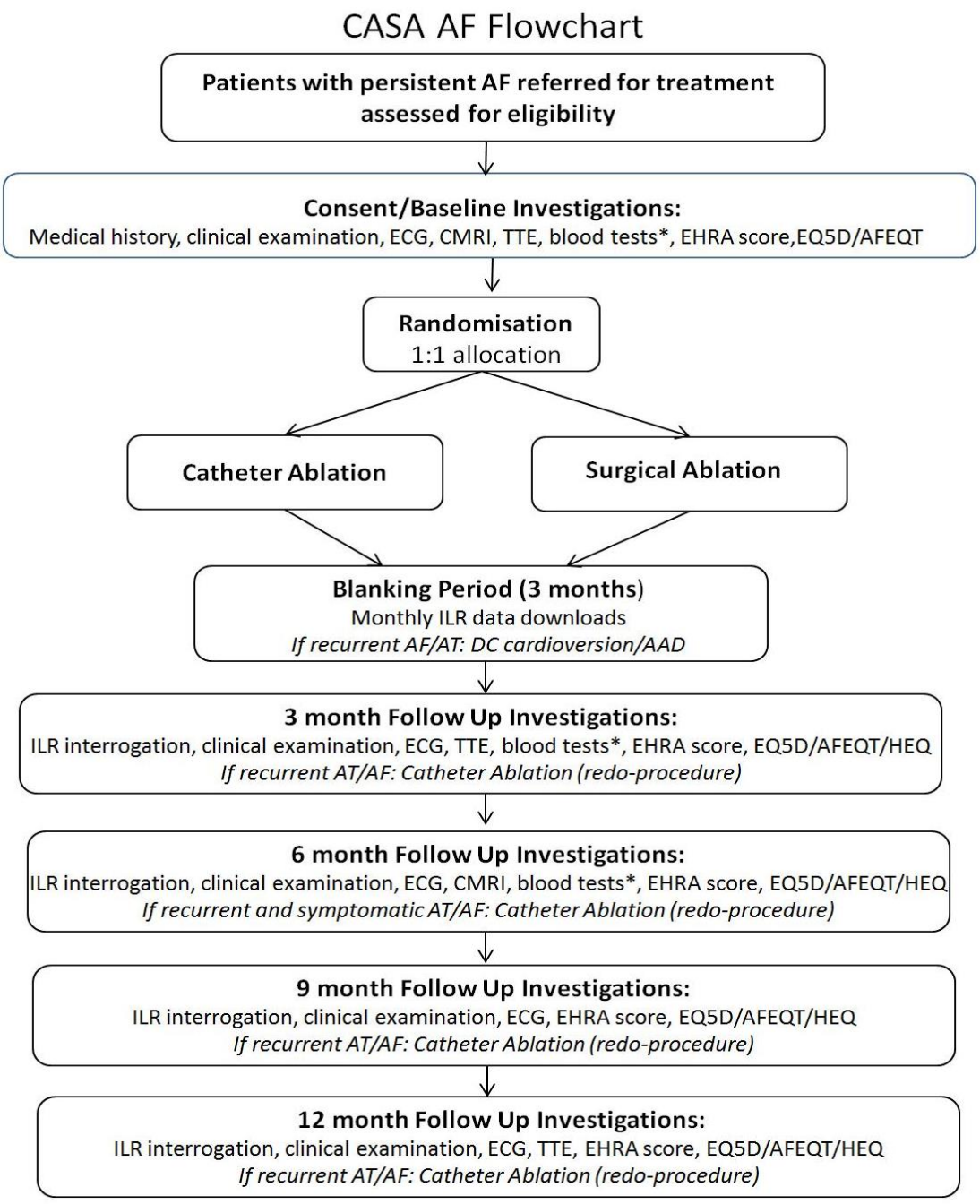
6.2 TREATMENT AND RATIONALE

6.2.1 Catheter and Surgical AF Ablation Protocol

The arrhythmia interventions (both catheter and surgical ablation) in this study are standardised in terms of equipment used, ablation lesions, procedural end-points and follow-up, to allow meaningful comparison of outcomes. Lesion sets are almost identical to the pilot study to provide close estimation of the appropriate sample size calculations.

Detailed description of each procedure is given in section 10.3.

6.3 SCHEMATIC OF TRIAL DESIGN



Key to abbreviations:

AAD = anti-arrhythmic drug
AF = atrial fibrillation
AT = atrial tachycardia
AFEQT = AF Effect on QualiTy of life survey questionnaire
CMRI = cardiac magnetic resonance imaging
ECG = 12 lead electrocardiogram
EHRA =European Heart Rhythm Association
EQ5D = EQ5DTM questionnaire
HEQ - health economic questionnaire
ILR - implantable loop recorder
TTE = transthoracic echocardiogram

**** comprising: full blood count, electrolytes and renal function, coagulation profile, liver function tests, thyroid function tests, C-reactive protein, tests for diabetes (HbA1C) and lipids profile***

5. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

i. Age ≥ 18 years
ii. Long-standing persistent AF (>12 months' duration)
iii. EHRA symptom score >2 (see Appendix 1)
iv. Left ventricular ejection fraction ≥ 40%
v. Suitable for either ablation procedure

7.2 EXCLUSION CRITERIA

i. Valvular heart disease with severity greater than mild
ii. Contraindication to anticoagulation
iii. Thrombus in the left atrium despite anticoagulation in therapeutic range
iv. Cerebrovascular accident within the previous 6 months
v. Previous thoracic or cardiac surgery (including surgical interventions for AF)
vi. Prior left atrial catheter ablation for AF
vii. Unable to provide informed written consent
viii. Active malignancy, another severe concomitant condition or presence of implanted cardiac devices that would preclude patient undergoing study specific procedures
ix. Pregnant or breast-feeding, or women of childbearing age not using a reliable contraceptive method.

7.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

7.3.1 Withdrawal of Subjects

Patients will be randomised as close as possible to the time of the intervention (within four weeks), reducing the risk of post-randomisation or pre-intervention dropouts. Individual participants who are randomised into the trial will be followed up as per protocol.

Participants have the right to withdraw from the study at any time and for any reason. The investigator also has the right to withdraw participants from the study in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations or other reasons. Should a participant

decide to withdraw from the study, they will be asked for a reason for withdrawal but are at liberty not to disclose it.

Should a participant withdraw from the study intervention, efforts will be made to continue to obtain follow-up data, with the permission of the participant. Subjects who refuse follow up data collection will be encouraged to return to the study site for early termination assessments, and those who agree to continued data collection will have follow-up for 12 months.

7.3.2 Stopping rules

The DMC will review data quality and accumulating safety data throughout the trial. There is no expectation of the use of formal statistical stopping rules in this trial, but if there is any change to this plan, the DMC will document this via the DMC charter.

7.3.3 Discontinuation

The study may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Chief Investigator, Data Monitoring and Ethics Committee (DMC) and/or Trial Steering Committee (TSC), Sponsor or Research Ethics Committee (REC) concerned.

8. SUBJECT/PATIENT RECRUITMENT PROCESS

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

1. The main REC approval,
2. Final sponsorship and/or R&D approval (NHS Permission),
3. Local Site Delegation of Duties and Signature Log is completed.

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA)
2. Host site (R&D approval) NHS Permission.

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

Trained staff at participating centres will be responsible for identifying eligible patients and obtaining written informed consent. Informed consent will be obtained by the Chief Investigator (CI), Principal Investigator (PI), research team member (including clinical research fellow, and research nurse) and/or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log. All individuals taking informed consent will have received appropriate consent training.

Patients referred to outpatient clinics or those on catheter ablation waiting lists will be screened for eligibility for inclusion in the study. Those who fulfil the criteria will be provided with detailed study information, including its nature, purpose, risks, burdens and potential benefits, at least twenty-four hours prior to written informed consent being sought. Potential participants will be allowed to specify the time they wish to spend deliberating, usually up to two weeks. Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. This process has been defined with the support of our patient advisory group and is based on feedback from participants in our pilot study who took on average 48 hours to decide whether to take part. With permission from the patient's clinical team the clinical research fellow will contact patients who have been approached about the study but did not respond after a 4-week period.

The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (filed in the Investigator Site File), a copy will be filed in the medical notes and another will also be given to the patient.

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

9.2 RANDOMISATION

9.2.1 Randomisation Method

Randomisation will be *via* a 24 hour bespoke web based randomisation system hosted by the KCTU on a secure server. See section 14 for more information on the method of randomisation.

9.2.2 Randomisation Procedure

A Patient Identification Number (PIN) will be generated by registering the patient on the MACRO eCRF system (InferMed Macro), after consent has been signed. This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study.

Authorised site staff will be allocated a username and password for the randomization system. Once a patient is consented, all baseline data collected and eligibility confirmed (usually within a week from date of consent), the staff member will log into the randomization system (www.ctu.co.uk) and click 'randomisation – advanced' and select CASA- AF and enter the patients details (including MACRO PIN). The 'help' section of the system has video demonstrations to aid new staff in using the system. Once randomized, the system automatically generates confirmation emails to key staff, with or without treatment allocation information, depending on their role in the study.

Patients that withdraw will not be replaced; levels of attrition have formed part of the sample size calculation to accommodate this.

10. STUDY ASSESSMENTS

10.1 BASELINE SCREENING ASSESSMENTS

- Medical history (including cardiac risk scoring and concomitant medications)and clinical examination, EHRA AF symptom score assessment (see Appendix 1)
- Quality of life questionnaire (EQ-5D-5L and AFEQT)
- 12 lead ECG
- Transthoracic echocardiogram
- Cardiac MRI (with prior rate control adjustment as needed to achieve resting HR <80bpm)

- Blood Tests: *Routine*: full blood count, electrolytes and renal function, coagulation profile, liver function tests, thyroid function tests, C-reactive protein, tests for diabetes (HbA1C) and lipid profile (HDL, LDL)

  Research: cardiac biomarkers.

At this point patients will be asked if they are willing to donate surplus blood samples to NIHR supported Cardiovascular Biobank at the Royal Brompton Hospital (RBH) for future research.

10.2 PRE-INTERVENTION

If patients fulfil criteria for enrolment following baseline screening assessments they will be randomised and formally enrolled in the trial.

If there is a significant delay between completion of baseline assessments and randomisation (i.e. greater than 12 weeks) patients will need to be re-consented and baseline tests repeated to ensure they are still fit to undergo the intervention. Cardiac MRI and transthoracic echocardiograms however should not be repeated in order to reduce the burden on the patient. It is reasonable to expect that the results of these two tests will not significantly change in our patient population within 6 months. It is also not necessary to collect additional samples for biomarkers and biobanking if they were collected when the patient was originally consented.

In some circumstances, clinicians may require additional tests (i.e. chest x-ray. CT scan) before the patient is considered fit to undergo ablation procedure. Patients will be fully informed about the type of test necessary and why it is needed.

To minimise post-randomisation, pre-intervention dropout, patients will be scheduled for their procedure within 4 weeks post randomisation.

10.2.1 Anticoagulation

According to current guidelines, it is recommended that patients randomised to catheter ablation remain on uninterrupted warfarin treatment unless different strategy is outlined by the operator. If patients are treated with NOACs they can be either:

a) converted to warfarin treatment for 4 weeks before the catheter ablation procedure or

b) continue with NOACs but stop the therapy 24-36 hours before the ablation procedure (depending on the type of NOAC).

For patients randomised to surgical ablation it is recommended to stop warfarin therapy 5 days before procedure and have anticoagulation bridging with enoxaparin at a dose of 1.5 mg/kg once daily on day -4,-3,-2. The patients will therefore not have any anticoagulation a day before they have the procedure.

NOAC treatment will also discontinue for patients randomised to surgical ablation. The timing of discontinuation will depend on the type of drug and renal function but in general NOACs should be stopped 2-5 days before surgery.

Patients who discontinued NOAC treatment but experience a delay with surgical procedure may be treated with enoxaparin if assessed as necessary. Enoxaparin treatment should be stopped for at least 24 hours before the procedure.

Anticoagulation protocols may be altered as guidelines are updated and local practices change.

10.2.2 Anti-Arrhythmia Drugs

Patients will remain on prescribed AADs (i.e. flecainide, procainamide, amiodarone or sotalol) for a maximum duration of 3 months post intervention (during blanking period only). Whenever possible the AADs therapy will be stopped 2 months post-ablation.

10.3 TREATMENT PROCEDURE

10.3.1 Experimental Intervention - Thoracoscopic Surgical AF Ablation

Patients randomised to the surgical arm will receive thoracoscopic surgical AF ablation. Details of the operation are as described previously by Yilmaz and others [19, 22]. However, we will also include a cardiac electrophysiologist to ensure conduction block is tested and achieved for all lesions. Cardiac surgeons participating in this study will have to have conducted at least 20 thoracoscopic ablations as the primary operator.

In brief, under general anaesthesia, transesophageal echocardiography will exclude left atrial thrombus and left atrial structure and function analysis will be documented. Three thoracoports will be introduced on each side. PVI will be performed from the epicardial surface using the Lumitip dissector and a bipolar radiofrequency ablation clamp (AtriCure, Inc, West Chester, Ohio) using overlapping applications around each PV. PVI will be confirmed as entrance and exit block during pacing. Further ablation will be performed if PVI is incomplete. An Isolator multifunctional pen (AtriCure) will then be used to ablate ganglionic plexi located by high-frequency stimulation. Additional linear lines will be undertaken using the Isolator Cool Rail tool (AtriCure) connecting the contralateral superior PVs (roof line) and the inferior PVs (inferior line)

to create a posterior box lesion. Sensing and pacing manoeuvres will then be used to verify electrical isolation of the posterior box in sinus rhythm. The left atrial appendage will then be excluded using the Atriclip LAA excluder system (AtriCure). If AF persists, then sinus rhythm will be restored by external electrical cardio version. The ILR will be implanted at the end of the procedure. Patients will be extubated in the operation room, and post-operative management will be according to standardised hospital protocol. Later management, follow-up and data collection will be identical between arms.

10.3.2 Summary of Thoracoscopic Surgical AF Ablation Lesion Set

- PV electrical isolation
- Ganglionated plexi ablation
- Linear ablation connecting the contralateral superior PVs (roofline) with conduction block
- Linear ablation connecting the contralateral PVs (inferior line) with conduction block
- Left atrial appendage exclusion
- Base of left atrial appendage to the upper left pulmonary vein

10.3.3 Control Intervention - Catheter AF Ablation

Patients randomised to the control arm will receive catheter AF ablation. The details of the catheter ablation protocol have been described by our group and others [52,53]. In brief, under general anaesthesia, transoesophageal echocardiography will exclude left atrial thrombus and guide trans-septal puncture. Left atrial structure and function will be assessed. Patients will be heparinised to maintain an activated clotting time between 300 - 350 seconds. The CARTO 3 three-dimensional electroanatomical mapping system (Biosense Webster, Diamond Bar, California) will be used to create the left atrial geometry with a twenty-pole circular mapping catheter (Lasso 2515 NAV, Biosense Webster, USA). Ablation will be conducted with a 3.5mm irrigated-tip catheter (Biosense Webster, Diamond Bar, California). A stepwise ablation strategy will be used to electrically isolate the PV at the antral level, then linear ablation at the left atrial roof and the mitral isthmus, followed by the ablation of posterior line (to create a 'box lesion'). If AF persists, then sinus rhythm will be restored by external cardioversion. Then finally ablation at the cavotricuspid isthmus ablation will be performed to prevent atrial flutter. Electrical isolation of the PVs will be confirmed through testing of both entrance and exit block with the circular catheter. The integrity of the linear lesions will be assessed by differential pacing manoeuvres. If block is not attained, further ablation will be performed to achieve bi-directional block across the

linear lesions. If atrial tachycardia occurs at any point, it will be mapped and ablated to SR when possible. The ILR will be implanted at the end of the procedure once the activated clotting time (ACT) has been reversed. Patients will then be extubated in the cardiac catheterisation laboratories.

10.3.4 Summary of Catheter AF Ablation Lesion Set

- Antral PV electrical isolation (WACA)
- Linear ablation between the contralateral superior PVs (roofline) to achieve conduction block across the linear lesion.
- Linear ablation between contralateral inferior PVs (posterior line) to achieve conduction block across the linear lesion and create a 'box lesion')
- Cavotricuspid isthmus line to achieve conduction block across the line.
- Linear ablation at the mitral isthmus to achieve conduction block across the linear lesion.
- Mapping and ablation of atrial tachycardia that occurs at any point of the procedure.

10.3.5 Post-operative management

Post-operatively the patients will be managed according to standardised hospital protocols described briefly below. Local practices may differ slightly.

10.3.5.1 Post-operative analgesia

Participants in surgical ablation arm will receive intercostal nerve block at each port site (Marcaine or similar agents; dosage depending on patient size and tolerance), paracetamol (1g, QDS, IV/PR and then PO) and codeine (30-60 mg/QDS). If patient is still fasting they can also be given tramadol (50 mg I/M). In the first 24 hours post-procedure the patient will be on patient controlled analgesia using fentanyl or morphine or other opioids depending upon the anaesthetist's requirements in keeping with clinical practice. Opiates should be reduced 12 hours post-operatively.

A day after surgery if patients have normal renal function, analgesia could be provided by NSAIDs for 1 week with optional opiates.

On discharge the patients will have a supply of analgesics for 28 days to be taken as needed and can take conventional analgesics over the counter if required.

Participants in catheter ablation arm will be treated with paracetamol and codeine as required.

10.3.5.2 Postoperative anticoagulation

After the ablation (surgical or catheter) patients will restart warfarin (or NOACS) the day after the procedure if there are no contraindications. Anticoagulation will continue for the duration of the trial follow up.

10.3.5.3 Postoperative AADs

AADs therapy (flecainide, procainamide, amiodarone or sotalol) will continue for maximum of 3 months after the ablation procedure at which point it should be terminated. Drugs that may have an effect on heart rhythm but are used to treat other conditions (like hypertension) will continue to be administered (i.e. beta blockers and calcium channel blockers) as clinically indicated.

10.3.5.4 Postoperative antibiotic prophylaxis

In both treatment arms patients will usually receive one dose of antibiotic on induction of anaesthesia, one dose at the end of the procedure, and two to five doses post-operatively, depending on local practices

10.3.5.5 Early post-operative discharge period

Following discharge, study participants will be contacted by the research team once a week for a month to assess their health status. They will be asked about pain management, cough, raised temperature, difficulties swallowing and any other symptoms that may be early indications of possible complications. In addition, patients will be advised to contact the study team if they have concerns regarding their health for the duration of the study. If deemed appropriate the patients will be brought back to the study centre for full assessment, evaluation and treatment of health issues even if the likelihood of those issues to be related to study procedures is remote.

10.4 SUBSEQUENT ASSESSMENTS

Following index ablation procedure there will be monthly ILR data assessments after ILR implantation in addition to the following hospital visits:

10.4.1 Three Month Follow-Up - (3M F/up hospital visit)

- Remote ILR interrogation included
- EHRA AF symptom score
- Quality of life (EQ-5D-5L and AFEQT) and health economic questionnaire (HEQ)
- 12 lead ECG

- Transthoracic echocardiogram
- Blood tests – as per baseline investigations.

10.4.2 Six Month Follow-Up – (6M F/up hospital visit)

- Remote ILR interrogation included
- EHRA AF symptom score
- Quality of life (EQ-5D-5L and AFEQT) and Health Economic Questionnaire (HEQ)
- 12 lead ECG
- Cardiac MRI
- Blood tests – as per baseline investigations.

10.4.3 Nine Month Follow-Up – (9M F/up hospital visit)

Remote ILR interrogation included

- EHRA AF symptom score
- Quality of life (EQ-5D-5L and AFEQT) and health economic questionnaire (HEQ)
- 12 lead ECG.

10.4.4 Twelve Month Follow-Up – (12M F/up hospital visit)

- Remote ILR interrogation included
- EHRA AF symptom score
- Quality of life (EQ-5D-5L and AFEQT) and health economic questionnaire (HEQ)
- 12 lead ECG
- Transthoracic echocardiogram

Blood tests – as per baseline investigations.

10.5 RHYTHM ASSESSMENT USING THE IMPLANTABLE LOOP RECORDER

The primary and secondary efficacy end-points, in terms of freedom and burden of atrial arrhythmias, will be assessed by implantable loop recorders (ILR) with specific AF detection algorithms. For patients in the catheter ablation arm the ILR will be implanted immediately after the index ablative procedure during the same procedural setting with reversal of heparin related anticoagulation with protamine. For patients having surgical ablation the ILR will be implanted at the end of the surgical procedure. Unlike catheter ablation, anticoagulation is not an issue as

patients will be free from any anticoagulation the day before and day of the procedure. Remote home monitoring system will be set up with all patients, which will allow remote download of data to the Medtronic Carelink secure server which will then be accessed centrally by the cardiac physiologist(s) at Royal Brompton & Harefield NHS Foundation Trust for analysis.
Prior to discharge from either procedure the patients will be trained on setting up home monitoring system and initiation of manual data downloads according to local pacing clinics practices. The study team will be in regular contact with patients to ensure data downloads are not missed and no data is lost (i.e. when the device approaches full memory capacity).

The timing of rhythm assessment is summarised in the flow chart. In essence, after the index procedure, the ILR data will be downloaded remotely (by the patient at home) on a weekly basis. There will be no direct contact between the cardiac physiologist (assessor of primary endpoint) and the patient. At the 6 month follow-up visit, the ILR data will need to be downloaded before the MRI scan (to prevent damage/loss of data). The data collected during the MRI scan will need to be cleared after the scan to minimise MRI-induced artefacts.

10.6 MANAGEMENT OF ATRIAL ARRHYTHMIA RECURRENCE

The recurrence of atrial arrhythmia is defined as the AF, atrial flutter or atrial tachycardia of at least 30 seconds in duration after 3 months' blanking period following AF ablation as per recommendation from HRS 2012 HRS/EHRA/ECAS Expert Consensus Statement Guidelines [4].

Management of recurrent atrial fibrillation will be guided by ILR data and patients' symptoms. During and up until the 3 months' blanking period (including attendance at the 3 month follow-up), if patients are found to have recurrence of atrial arrhythmia, they will be offered treatment by DC cardioversion +/- AADs as per normal clinical practice. If atrial arrhythmia recurs after the 3 months, patients may be offered a catheter re-ablation procedure regardless of the type of the index ablation procedure. It is not desirable to undergo a second thoracoscopic surgical ablation procedure as the access would be very difficult due to fibrosis at the pericardial space. There will be no maximum number of repeat procedures that can be offered but as seen in our pilot study, 2 is generally the maximum number undertaken in a 12-month period. Management of recurrent atrial fibrillation will be individualised in discussion between the patient and their clinical care team. The longevity of implanted loop recorders allows for heart rhythm monitoring for up to three years in patients who agree to keep the loop recorders beyond the study follow up term of 12 months

10.7 INTERPRETATION AND MANAGEMENT OF ILR DATA – PRIMARY ENDPOINT

ILR data analyses will be performed monthly after the procedure and within the first 3 months will be used to direct any management required in the blanking period (i.e. DC cardioversion, AAD therapy).

The rhythm primary endpoint data will be assessed monthly after the 3 month blanking period until the 12-month follow-up. The interpretation and analysis of this data will be conducted by an independent cardiac physiologist(s) blinded to all research-related information including which arm of the study the patient is in.

Patients will be asked not to reveal which arm of the study they are in to pre-empt any unforeseen circumstances where they might meet the cardiac physiologist(s) although this eventuality is extremely unlikely.

The named physiologist in core lab will manually assess the anonymised ILR device data (taking into account the device's automatic algorithm assessment of atrial arrhythmias). The number of episodes of atrial arrhythmia (atrial fibrillation, atrial tachycardia) and the duration of each episode will be recorded on a study specific data form which will then be passed to the Trial Manager and the research fellow together with the PDF version of the downloaded data file.

All the raw data from each download for every patient, regardless of site, will be on the Carelink (Medtronic) secure server. These data will be accessed (via a unique username and password) and reviewed centrally (*i.e.* by the cardiac physiologist at RB&HFT which will act as the core lab) although provision will be made for emergency access by a member of the research team should the need arise. If an atrial arrhythmia (or any other arrhythmia lasting ≥ 30 seconds) is detected from the ILR data downloads by the centrally located cardiac physiologist then this will be communicated appropriately to the research team at the relevant site. Local researchers will discuss these findings with patients and establish if treatment for arrhythmia is required.

To ensure the highest degree of accuracy in data interpretation, an additional senior independent cardiac physiologist will provide on-going quality assurance of data by performing frequent and regular spot checks centrally on 30% of the data downloads.

In the event of discrepancies identified during quality checks or if data requires further clarification (*e.g.* whether true atrial arrhythmia or not) a blinded panel of 3 expert cardiologists will be given anonymised data to adjudicate upon.

Although it would be preferable that all members of the research team are blinded to the patients' intervention arm, in practice this is not achievable. It should be noted, however, that the primary endpoint is such that it cannot be altered by the researcher knowing which arm of the study the patient is in. In addition, a need for further intervention and/or anti-arrhythmic drug use outside of the 3 month blanking period will constitute a fail in the primary endpoint.

10.8 LEFT ATRIAL ASSESSMENT

The left atrial anatomy and function will be assessed by CMR and echocardiography before and after the arrhythmia intervention.

10.8.1 Cardiac Magnetic Resonance Imaging (CMR)

LA area and length will be traced on the atrial systolic and atrial diastolic frames of the complete cine CMR (Steady State in Free Precession, SSFP) acquired in the left ventricular vertical and horizontal long axes. LA end-diastole will be defined as the phase with the largest volume on visual assessment, and end-systole as the phase with the smallest volume/dimension. Maximum (LA max) and minimum (LA min) LA volumes will be calculated using the biplane area-length method for ellipsoid bodies. LA emptying fraction (active LA function) will be calculated using the following equation: LA max – LA min / LA max x 100 [54, 55]. Measurements will be uploaded onto the study database by the research team. Images will be stored on the MRI imaging database at the respective sites. LA scar will be assessed with DE-MRI and uploaded at a later stage of the trial to Matlab software for analysis of location and quantification of fibrosis. The software is currently in the development phase.

CMR images will be used to establish absence of thrombus in LA which is one of the exclusion criteria for the study.

10.8.2 Echocardiography

Conventional left atrial echo parameters such as analysis of transmitral flow from pulsed-wave Doppler are limited by the influence of loading conditions. Newer techniques such as tissue Doppler imaging (TDI) measurement of myocardial velocities and left atrial strain and strain rate are less load dependent measures [56].

Colour TDI will allow simultaneous assessment of velocities of several atrial segments but is not able to distinguish atrial contraction from mitral annular and ventricular motion. Left atrial deformation imaging by TDI has excellent site specificity as each manually-defined segment of left atrial wall is analysed on a frame-by-frame basis throughout the cardiac cycle, but it is limited by being angle dependent (the atrial wall segment must be parallel to the interrogating Doppler beam) and it is extremely time-consuming [57].

The echocardiography protocol for left atrial assessment will include the following assessments:

1. Assessment of atrial volumes at end-systole and end-diastole by area-length, Simpson's MoD and 3D volume methods.
2. Left atrial systolic function (V_{PLA} - V_{minLA})
3. Pulse wave Doppler of transmitral flow
4. Pulse wave Doppler of pulmonary venous flow and calculation of the peak outflow velocity systolic fraction
5. Myocardial velocities assessed by TDI
6. Atrial deformation (strain and strain rate) imaging by analysis of myocardial velocities and also by 2D speckle tracking method.

Measurements will be uploaded onto the study database by research team. Images will be stored on the echocardiography imaging database at the respective sites.

Echocardiography data will be used to assess whether ejection fraction is at required level (≥40%) and to measure diameter of LA (one of the stratifying variables for randomisation)

10.8.3 SUMMARY CHART OF STUDY ASSESSMENTS

Study Procedures	Baseline Screening	3 month Follow up	6 month Follow up	9 month Follow up	12 month Follow up
Informed consent	✓	N/A	N/A	N/A	N/A
History and clinical examination	✓	✓	✓	✓	✓
ECG	✓	✓	✓	✓	✓
Echocardiogram	✓	✓	✗	✗	✓
CMR Scan	✓	✗	✓	✗	✗
Questionnaires	✓	✓	✓	✓	✓
Blood tests	✓	✓	✓	✗	✓
ILR remote interrogation	✗	✓	✓	✓	✓

11. METHODS

11.1 LABORATORY PROCEDURES

Samples collected during the trial are processed and reported as per normal routine NHS practice except for cardiac biomarker samples (*i.e.*TGF-beta), which will be spun down and stored in a freezer at an appropriate temperature. These samples will then be transported to the RB&HFT at the end of the study for analysis.

11.2 RADIOLOGY OR ANY OTHER PROCEDURE(S)

11.2.1 Catheter Ablation - Radiation Exposure

Radiation exposure (X rays) during catheter ablation is a necessary part of the procedure even with non-fluoroscopic mapping equipment. X rays provide additional real-time information to the operator about the positioning of multiple catheters in the heart and are vital when accessing the chambers of the heart (e.g. trans-septal puncture). Total radiation dose will be minimised by using pulsed, low frame rate fluoroscopy and the virtual 3D mapping system. Therefore, their use is justified in order to maximise safety of the patient.

The radiation dose delivered during an RF catheter ablation procedure is very variable. It depends on the subject's clinical condition, x-ray equipment used and skill of the operator. The estimated procedure dose that has been quoted is an upper figure, which takes into account these parameters.

The total effective dose arising from this research protocol will be approximately 10mSv for about half of the subjects in the study who will undergo 1 intervention, and 20mSv for some subjects who may undergo up to 2 catheter ablation interventions. The entire radiation dose delivered to the subject in this study will arise from routine clinical care. A total radiation dose of 10mSv is equivalent to about 4 years' worth of natural background radiation.

The risks associated with this amount of radiation are: cancer induction and skin injury as redness similar to sunburn.

The risk associated with this amount of radiation is cancer induction. If a cancer is induced there will be a delay before it becomes evident, i.e. there is a latency period (2 - 20 years typically). The chance of a cancer being induced in a healthy 40-year-old by a total dose of 10 mSv is estimated as 1 in 2000, using the risk coefficient of 5x10-5 per mSv. For comparison, the natural cancer mortality rate in the UK is 1 in 4.

Skin injuries will not occur if the radiation dose delivered per procedure is less than 10 mSv or 2 Gy entrance dose. The entrance dose displayed during the procedure and the operator must take all reasonable steps to ensure that the entrance dose threshold of 2 Gy is not exceeded.

11.2.2 CMR Imaging – DE-MRI sub-analysis

The CMR protocol will evaluate the changes in LA structural remodelling pre- and post-ablation, assessment of pulmonary vein patency (pre- and post-ablation). In addition (at RB&HFT only) left atrial myocardial scar using delayed enhancement MRI (DE-MRI) will be assessed. DE-MRI is an important and growing technique analysing the distribution and quantification of scar in the left atrium and has been shown to predict ablation outcomes and also reconnection sites (gaps in ablation lines) responsible for AF recurrence post ablation [58]. The latter is particularly important in post ablation patients who have a recurrence of atrial arrhythmia as it provides a non-invasive assessment of potential sites of pulmonary vein (PV) reconnection after the ablation procedure and may help to guide repeat procedures. The objectives of DE-MRI imaging are as follows

1. Investigate pre- and post- ablation scar distribution and quantification,
2. Identify gaps in ablation lines
3. Correlate the above with prediction of ablation success. This additional DE-MRI technique and analysis will be undertaken only at RB&HFT.

At present, the number of centres (worldwide) that are able to conduct this DE-MRI technique to successfully analyse LA scar remains low.

We propose to undertake this DE-MRI sub-analysis only at the RB&HFT centre, as this is where this particular expertise lies. All patients will have a pre-procedural and 6 month follow-up MRI but the RB&HFT patients will have an additional DE-MRI sequence during the scan to enable left atrial scar burden to be quantified and correlated with clinical outcomes. In addition, correlation with electro-anatomical voltage data will be possible with those who have undergone an index procedure of catheter ablation.

11.3 QUESTIONNAIRES

11.3.1 EQ-5D Questionnaire

EQ-5D is a standardised instrument for use as a measure of health outcome. It is applicable to a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. EQ-5D has been specially designed to complement disease-specific measures.

EQ-5D is designed for self-completion by respondents and will be conducted at baseline and all follow-up visits. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

11.3.2 AFEQT

The AFEQT questionnaire was developed to assess the impact of AF and its treatment on three domains: patients' symptoms, functioning and treatment concerns. It is designed for self-completion using a 4-week recall frame with 20 questions on a seven point Likert scale ranging from the most severe limitation/symptoms to no limitation/symptoms. The survey takes about five minutes to complete.

11.3.3 Health Economic Questionnaire (HEQ)

A tailored questionnaire has been developed to collect information from patients about their use of health and social care during the follow-up period. This will complement data collected from electronic records and medical notes at the recruiting centre for costing purposes: providing additional information about any attendances at other hospitals and use of out of hospital services that are related to AF or adverse effects. The HEQ will be administered at 3, 6, 9 and 12 month follow-up assessments. On each occasion, patients will be asked about their use of services related to AF during the previous three months, including: hospital emergency department attendances, admissions, outpatient clinic visits, tests and procedures, medications, contacts with general practitioner, primary care nurse other healthcare professionals outside hospital, and use of social services.

11.4 DEFINITION OF THE END OF TRIAL

The formal end of the trial will be defined as 'Last Patient Last Visit' (LPLV) to the hospital 12 months after their index ablation procedure.

12. SAFETY REPORTING

12.1 DEFINITIONS

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

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

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)

- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
- Is otherwise considered medically significant by the investigator.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.
Planned hospitalisation for DC cardioversion or re-ablation will be reported as adverse events only unless these procedures lead to additional complications that merit reporting as SAE.

12.2 RECORDING AND COLLECTION OF ADVERSE EVENTS (AES)

All Adverse Events (AEs), serious and non-serious, occurring during the course of the clinical trial (*i.e.* from signing the Informed Consent onwards through the observational phase) will be collected, documented and recorded by the research team in patient's medical hospital notes and the study eCRF.

12.2.1 Serious Adverse Events (SAEs)

Major intra and perioperative complications listed in the Patient Information Leaflet (PIL) and the table of expected adverse events (section 12.5 below) will be recorded as Serious Adverse Events when they lead to permanent injury or death, require additional intervention for treatment, or prolong or require hospitalization for more than 48 hours (See Section 5.1 that outlines safety end points of the study).

12.3 ASSESSMENT AND REPORTING OF ADVERSE EVENTS (AES)

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

All other AEs must be reported to the Sponsor by the research team in the Annual Progress Report (APR).

Classification and causality of Adverse Events (AEs) will be conducted by local PIs and reviewed by CI. The CI cannot downgrade the site PI's classification and if there is disagreement which cannot be resolved during formal discussion then the assessment of the site PI will be accepted. The CI, can however, upgrade the seriousness of an event without consultation with the site PI. The Data Monitoring Committee (DMC) will then assess the safety data and will make recommendations to the Trial Steering Committee (TSC).
For quality assurance the research team will seek expert opinion on classification of SAE from appointed independent clinicians (one thoracoscopic surgeon and one EP cardiologist).
All Adverse Events that are to be reported to the Research Office must be on signed and dated AE form completed by the Investigator.
Information can be submitted in electronic format:

- Email: safetyreporting@rbht.nhs.uk or
- Fax: 0207 351 8829.

The research team also has the responsibility to report SAEs occurring in a certain period (28 days) after a patient completes the trial. Any SAEs reported to the Investigators during this phase must be documented in the patient's medical notes and submitted *via* an SAE form and on the eCRF.
Adverse event data will be recorded in the eCRF system, exported and tabulated by the trial statistician for the DMC reports in order to allow the Committee to evaluate any emerging between-group difference in safety. Tables of data for the open and closed DMC reports will be agreed at the first DMC meeting.

12.4 Reporting of SAEs to the REC

A Serious Adverse Event (SAE) occurring to a research participant should be reported to the Research Ethics Committee (REC) that gave a favourable opinion of the study (the 'main REC') and the study Sponsor (RB&HFT Research Office) where in the opinion of the CI/PI the event was:

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

Reports of related and unexpected SAEs will be submitted to the REC within 15 days of the CI/PI becoming aware of the event, using the form below. The form will be completed in typescript and signed by the Chief Investigator (CI).

- NRES Report of Serious Adverse Event Form, V3.

The coordinator of the main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt should be sent to the Research Office.

12.5 TABLE OF EXPECTED ADVERSE EVENTS IN THE STUDY

Adverse Events	Serious Adverse Events
Bruising, hematoma, vascular injury not requiring intervention	Vascular complications requiring blood transfusion or intervention
Pericardial/ pleural effusion (observation only)	Symptomatic pericardial/pleural effusion or requiring intervention
Broken rib	Stroke (TIA)
Pneumothorax requiring observation	Pneumothorax requiring chest drain
Infection (i.e. pneumonia)	Empyema
Pulmonary oedema	Myocardial infarction
Temporary phrenic nerve damage	Permanent phrenic nerve damage
Pain near surgical sites	Pulmonary vein stenosis (>50% reduction in diameter from baseline)
	Requirement to insert PPM (with or without prior conduction tissue damage)
	Cardiac trauma requiring surgical intervention
	Radiation induced skin damage
	Oesophageal atrial fistula
	Death

12.6 THE TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER AES

All AEs will be reviewed by the local PI and followed through to resolution or until the investigator attributes the AE/SAEs to a cause other than the study intervention or assesses them as chronic or stable. Patients experiencing AE during hospital stay for the trial intervention will be treated according to standard medical care at the participating site.

12.7 ANNUAL PROGRESS REPORTS (APRS)

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

12.8 REPORTING URGENT SAFETY MEASURES

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

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

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

All urgent safety measures reported by PIs from participating sites will also be forwarded to the relevant local REC.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

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

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

13.2 DATA COLLECTION TOOL

Source data worksheets and electronic CRFs will be used and they will be designed with input from the CI, study statistician and relevant co-applicants.

The database has a robust audit trail such that when anyone attempts to change data – the CTU can tell who made the change, when, and how the data values changed.

Written informed consent will be obtained prior to screening and any other study specific procedures are performed.

For data collected, source data worksheets will be used for each patient and data will be entered onto the eCRF database. Source data worksheets will be reconciled at the end of the trial with the patients NHS medical notes in the recruiting centre. During the trial, critical clinical information will be written in the medical notes to ensure informed medical decisions can be made in the absence of the study team. Trial related clinical letters will be copied to the medical notes during the trial. The Principal Investigator will provide an electronic signature for each patient Case Record Form once all queries are resolved and immediately prior to database lock.

It will be the responsibility of the PI and his team to ensure the accuracy of all data entered in the worksheets in accordance with Good Clinical Practice. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database. The Principal Investigator will be responsible for ensuring that source data worksheets are filed in a suitably secure location to ensure source data verification can be undertaken throughout the study.

13.3 DATA HANDLING AND ANALYSIS

All study data and site files will be kept at site in a secure location with restricted access.

The study will employ an eCRF created using the InferMed MACRO database system. Data will be managed via this system. The eCRF will be created in collaboration with the trial statistician and the CI and maintained by the KCTU. It will be hosted on a dedicated secure server within KCL.

This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive) and will have a full audit trail, data discrepancy functionality, database lock functionality, and supports real time data cleaning and reporting.

The Trial Manager will be responsible for providing usernames and passwords to permitted local study personnel. Only those authorised by the Trial Manager will be able to use the system. Data entry will be conducted primarily by the clinical research fellow, research nurse,

cardiac physiologist(s) and the trial manager.

Database Website Address:

Go to www.ctu.co.uk and click the link to MACRO EDC V4 on the lower right hand side of the screen.

13.4 QUALITY ASSURANCE

The study incorporates a range of data management quality assurance functions. The eCRF system will contain a range of validations that will alert sites to inconsistencies in the data being entered which will be monitored by the Trial Manager. The Trial Manager will provide study training, on-going study support and will conduct regular monitoring visits at each centre, checking source data for transcription errors. Any necessary alterations to entered data will be date and time stamped within the eCRF.

A detailed monitoring plan and data management plan will be developed and updated as the trial progresses, detailing the quality control and quality assurance checks to be undertaken.

13.5 DATABASE LOCK

Prior to database lock, the Trial Manager will review any outstanding warnings on the eCRF and resolve or close these as appropriate before database lock. Local study personnel should resolve any queries that arise promptly. Once all queries have been resolved no further changes will be made to the database unless specifically requested by the Study Office in response to the statistician's data checks. The study PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data will be formally locked for analysis. At the end of the trial, each centre will be supplied with the eCRF for their centre on a CD-ROM. This will be filed locally for any future audit or inspection.

13.6 ARCHIVING ARRANGEMENTS

The study documents (including the Trial Master File (TMF), Case Report Forms (CRFs), Informed Consent Forms along with the trial database) will be saved to CD/DVD and kept for a minimum of five years. They will be stored in locked offices within the Royal Brompton and Harefield NHS Foundation Trust (RB&HFT). The CI is responsible for the secure archiving of trial

documents. The trial database will also be kept electronically on the RB&HFT computer network, for a minimum of five years.

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

Essential documents held by the KCTU will be returned to the Chief Investigator for archiving by the Sponsor organisation at the end of the study. eCRF data will also be exported and provided to the Chief Investigator for archiving.

14. STATISTICAL DESIGN

14.1 SAMPLE SIZE AND RECRUITMENT

14.1.1 Sample Size

The sample size calculation is based on updated data obtained from our pilot study. In the Surgical Ablation group 76% of patients (13/17) at 6 months are free of AF and AADs compared with 44% patients (8/18) in the Catheter Ablation group. Using these data a sample size of 48 per group will be required to achieve this effect size at 90% power for 5% significance.

It should be noted that compared with serial 7-day continuous ambulatory ECG monitoring, the implantable loop recorder has been shown to have a tendency to detect a higher number of patients with AF recurrences (31 vs. 24%; P = 0.125), although this was not statistically significant [63]. This implies that slightly more failures would be detected than our current method of serial 7-day continuous ambulatory ECG monitoring used in the pilot study. As the sample size calculation is based on the serial 7-day holter method, it may be that the success rates fall in each group; however, this would mean that the actual sample size might rise. We therefore have built in a significant safety margin to our sample size calculation as detailed below.

14.1.2 Compliance

No patients dropped out of our current pilot study due to patient compliance issues. This may reflect the fact that the design and follow-up schedule of the pilot study incorporated significant input from patients to ensure that the follow-up schedule was not too arduous. As this proposed

study follows a very similar format we feel that a 10% attrition (drop-out) rate is sensible. Also, given that the percentage success rates in the pilot study are based on small numbers this may translate into a degree of uncertainty in our estimates. Therefore the final sample size has been calculated with a 25% margin of error (which includes the 10% drop-out rate) and gives a final sample size figure of 120 patients.

14.1.3 Recruitment rates

The final sample size calculation is a total of 120 patients. This equates to a required recruitment rate of 5 patients per month from the 3 named centres.

We have designed a recruitment strategy that incorporates two tiers to ensure recruitment targets are met. The first tier encompasses the three large ablation centres described in the original application. We have now added a second tier of two other large centres that will act as Patient Identification Centres (PICs) if required, and as confirmed in the enclosed letters of support:

- The Heart Hospital, University College London (UCL)
- St George's Hospital, University of London

The 3 main sites have a large throughput, having conducted approximately 1050 AF ablations in the last 12 months. In addition, during our pilot study at just two sites (Royal Brompton & Harefield), 52 patients were recruited over 20 months despite choosing to recruit slowly during the initial phase of the pilot study. These figures show that recruitment may be anticipated at a rate of approximately 5 patients per month between the 3 main centres proposed. Furthermore, the two second tier recruitment centres have conducted approximately 650 AF ablations in the last 12 months and thus if recruitment rates fall below target, there will be a large reserve which can be tapped if required according to the findings of monthly monitoring of the recruitment rate and cumulative total. Thus, although our pilot experience indicates that recruitment should be possible from the 3 main centres, the inclusion of these two second tier patient identification centres should mitigate any concerns about recruitment rates.

We have carefully considered the roles of these additional centres and resolved that they will only act to identify patients for treatment in a named study centre, to ensure that complete compliance with the ablation protocol in each arm of the study is maintained.

This study is a research priority at both Trusts with both clinical and research teams fully informed and committed to recruitment. Due to the specific AF cohort being studied (LSPAF), it is not in direct competition with any existing or future planned studies.

14.1.4 Likely attrition rate

There are no patients that have dropped out of our current pilot study due to patient compliance issues. This may reflect the fact that the design and follow-up schedule of the pilot study incorporated significant input from patients to ensure that the follow-up schedule was not too arduous. As this proposed study follows a very similar format we feel that a 10% attrition (drop-out) rate is sensible. Also, given that the percentage success rates in the pilot study are based on small numbers this may translate into a degree of uncertainty in our estimates. Therefore the final sample size has been calculated with a 25% margin of error (which includes the 10% drop-out rate) and gives a final sample size figure of 120 patients.

14.2 ENDPOINTS

14.2.1 Primary endpoint

The primary efficacy end-point is freedom from atrial arrhythmias after a single procedure without AADs within 12 months (as assessed from the end of the 3 months blanking period to 12 months).

14.2.2 Secondary endpoints

1. To evaluate and to compare the safety of the arrhythmia interventions. The safety end-point is the intervention-related major complication rate defined as permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours.

2. To evaluate and to compare the clinical success from the arrhythmia interventions (distinct from arrhythmia-free survival) - defined as a 75% or greater reduction of AF burden assessed by implantable loop recorder during 12 months follow-up with or without AADs.

3. To evaluate freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up.

4. To identify changes in atrial anatomy and function following ablation as assessed by echocardiography and CMR imaging using tissue Doppler and strain.

5. To evaluate and to compare the effects of the arrhythmia interventions on the patients' symptoms and quality of life as assessed by Change in AF symptom score (EHRA score) [49] and quality of life assessments (EQ5D, AFEQT) [50,51].

6. To evaluate Quality Adjusted Life Years (QALYs) accrued during 12-month study period

7. To evaluate Cost-effectiveness (Incremental Cost per QALY gained) for surgical ablation compared with CA estimated over the 12-month study period ('within trial' analysis) and over a lifetime horizon ≥ (estimated by modelling).

14.3 STATISTICAL ANALYSIS PLAN

The primary outcome of the trial is to establish the proportion of AF patients undergoing ablation that are free from atrial arrhythmias within 1 year after a single ablation procedure with surgical ablation showing superiority over catheter ablation. Rhythm status data will be assessed using the ILR downloaded data monthly and at 3, 6, 9 and 12 months post-ablation follow-up visits. The proportion of patients meeting the end point criteria at 1 year will be compared using the chi-squared or Fisher's exact test. A Logistical regression model will be developed to estimate the probability of being free from AF at 1 year. The model will include a flag indicating whether the patient is in the surgical group. The will enable us to ascertain the odds ratio of being AF free for the surgical group after the other factors in the model have been controlled for. The baseline data will be presented as percentages or means (SD) or median (IQR) depending on the type and distribution of the individual variables.

Binary secondary outcomes will be analysed in the same manner as the primary outcome using a combination of Fisher's exact test and logistic regression. Continuous outcomes will be analysed by either paired t-test, Wilcoxon test as appropriate. In addition regression models will be built to control for the effects of other factors. All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive and no hypotheses testing are planned. Data will be analysed at regular, pre-specified intervals by the DMC. The statistical analysis will be carried out using R statistical software Version 3.0.2 (or higher).

14.3.1 Primary endpoint analysis

As mentioned in section 10.4, the analysis of the primary outcome measure (and all other ILR data) will be conducted by cardiac physiologist(s) based centrally at RB&HFT, which will act as the core lab. The cardiac physiologist(s) will be blinded to the patients' mode of intervention.

As mentioned in Section 14.3, the primary measure to be reported is the odds ratio of being AF free for the surgical group after the other factors in the model have been controlled for. The flag indicating treatment arm will be strictly based on intention to treat. Sensitivity analysis will be used to explore the impact of missing data, non-compliers, spurious data and withdrawals in analysis. Sub group analysis will be avoided.

14.3.2 Secondary endpoint analysis

1) To evaluate and to compare the safety of the arrhythmia interventions. The safety end-point is the intervention-related major complication rate defined as permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours.

Continuous outcomes will be analysed by either paired t-test, Wilcoxon test as appropriate.

2) To evaluate and to compare the clinical success from the arrhythmia interventions (distinct from arrhythmia-free survival)- defined as a 75% or greater reduction of AF burden assessed by implantable loop recorder during 12 months follow-up with or without AADs.

A Logistical regression model will be developed to estimate the probability of achieving a 75% or greater reduction of AF burden. The model will include a flag indicating whether the patient is in the surgical group. The will enable us to ascertain the odds ratio of being AF free for the surgical group after the other factors in the model have been controlled for.

3) To evaluate freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up.

A Logistical regression model will be developed to estimate the probability of achieving freedom from atrial arrhythmia. The model will include a flag indicating whether the patient is in the surgical group. The will enable us to ascertain the odds ratio of being AF free for the surgical group after the other factors in the model have been controlled for.

4) To identify changes in atrial anatomy and function following ablation as assessed by echocardiography and CMR imaging using tissue Doppler and strain.

The analysis of the secondary end-points of change in left atrial anatomy and function using echocardiography and CMR will also be conducted by members of the research team blinded to the mode of intervention. Continuous outcomes will be analysed by either paired t-test, Wilcoxon test as appropriate.

5) To evaluate and to compare the effects of the arrhythmia interventions on the patients' symptoms and quality of life as assessed by change in AF symptom score (EHRA score) [49] and quality of life assessments (EQ5D, AFEQT) [50,51].

See health economic analysis below.

6) To evaluate Quality Adjusted Life Years (QALYs) accrued during 12-month study period

   See health economic analysis below.

7) To evaluate Cost-effectiveness (Incremental Cost per QALY gained) for surgical ablation compared with CA estimated over the 12-month study period ('within trial' analysis) and over a lifetime horizon ≥ (estimated by modelling).

See health economic analysis below.

14.3.3 Health economic analysis

Cost-effectiveness will be assessed using both trial-based and model-based health economic analyses. Both will follow international methodological guidelines [64, 65] and the 'reference case' recommended by NICE for use in its technology appraisals [66]: including the use of an NHS and personal social services perspective for costing; and discounting of costs and QALYs at an annual rate of 3.5%.

The trial-based analysis will use EQ-5D-5L and health and social care resource use data to estimate the costs and QALYs accrued over the 12-month follow-up period by trial participants.

In our main analysis we will include costs for all health and social care recorded in the CRF and reported by patients in the health economic questionnaire at 3, 6, 9 and 12 month economic questionnaires. We will also conduct a sensitivity analysis including only costs judged by the research team to be potentially related to AF or to AF treatment. QALYs will be estimated from EQ-5D UK Social Tariff scores at 0, 3, 6, 9 and 12 months, using an 'area-under-the-curve' approach. Mean between-group differences in QALYs and costs will be estimated using a bivariate regression approach [67], taking account of correlations between costs and effects and adjusting for any baseline differences in EQ-5D scores or other key patient characteristics (such as age, CHA_2DS_2VASc or HASBLED scores). Multiple imputations will be used to account for missing data if appropriate [68]. If the results indicate a trade-off between costs and health effects, an Incremental Cost Effectiveness Ratio (ICER) will be calculated – the 'cost per QALY'. The extent of uncertainty over the results will be estimated using bootstrap regression [65], and presented in the form of a Cost Effectiveness Acceptability Curve (CEAC).

A model-based economic analysis will also be conducted to estimate long-term benefits, harms and costs of surgical and catheter ablation compared with AAD therapy in patients with LSPAF. This will extrapolate costs and health outcomes observed in the trial, including freedom from arrhythmia, utility (EQ-5D-5L scores) and incidence of major side effects, over a long time horizon (up to lifetime). The model will also allow us to estimate costs and outcomes for the trial participants under medical management, which will provide further information about the comparative cost-effectiveness of treatment options for this patient group for healthcare commissioners and research funders. The model will be based on the MAPGuide AF model [69]. This is a Discrete Event Simulation (DES), which estimates lifetime costs, and QALYs for a heterogeneous population of individuals with AF treated according to a defined pathway of care, including anti-thrombotic and AAD therapy. The base case version of the model reflects the recommended care pathway in the NICE clinical guideline for AF. This care pathway can be changed to estimate costs and QALYs associated with different treatments (e.g. catheter ablation, thoracoscopic surgical ablation or AAD).

14.4 RANDOMISATION

Randomisation will be via a 24 hour bespoke web based randomisation system hosted at the KCTU on a secure server. 120 adult patients with long-standing persistent atrial fibrillation will be randomised 1:1 at the level of the individual using the method of minimisation, stratified by

gender (male or female), study site and left atrial diameter (< 50 mm and ≥ 50 mm). Randomisation will protect pre-randomisation allocation concealment.

14.5 INTERIM ANALYSIS

There will be no formal interim analysis but the trial statistician will verify that there are no significant problems with the data collection tools or other parts of the trial's methodology, prior to undertaking primary analysis. .

15. COMMITTEES INVOLVED IN THE STUDY

1. Trial Management Group (TMG) - will include those individuals responsible for the day-to-day management of the trial, i.e., the CI, statistician, trial manager, research nurse, key grant co-applicants. The role of the group is to manage all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG is an operational committee.

2. Trial Steering Committee (TSC) - The Trial Steering Committee members will be invited by NIHR EME and will agree terms of reference at their first meeting. The TSC is an executive committee. Sponsor representation may be invited to observe these committees' meetings.

3. Data Monitoring Committee (DMC) – The independent Data Monitoring Committee members will be invited by NIHR EME and will agree a DMC Charter at their first meeting. The DMC is an advisory committee to the TSC and subsequent to each meeting; a recommendation will be passed from the DMC chair to the TSC chair advising whether the study should continue.

16. MONITORING AND AUDITING

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

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

The Sponsor delegated the responsibility for study monitoring to the CASA-AF trial manager. Trial Manager will undertake monitoring visits to study sites to verify adherence to protocol and study related SOPs. The monitoring plan will be developed in consultation with the CI, trial statistician and King's Clinical Trials Unit (KCTU) using the KCTU monitoring plan template.

The Trial Manager will send copies of all monitoring reports to the Research Office for information on the study progress, management and conduct and to ensure Sponsor oversight.

16.1 DIRECT ACCESS TO SOURCE DATA

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. The Trial Manager will undertake study site monitoring. The main areas of focus will include consent, serious adverse events, and essential documents in study site files.

16.1.1 Site monitoring will include:

- Reviewing all consent forms within the site file and medical notes.
- Source data verifying serious adverse events against medical records and a proportion of the primary outcome measure.
- Checking essential documents in the investigator site file and study files.

16.1.2 Central reviews will include:

- Ensuring accuracy and completeness of all applications for study authorisations and submissions of progress/safety reports, prior to submission
- Ensuring all documentation essential for study initiation are in place prior to site authorisation
- Reporting and following up all monitoring findings with the appropriate persons in a timely manner.

17. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the trial protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the

main Research Ethics Committee (REC), prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical approval prior to implementation.

Before site(s) can enrol patients into the trial, the PI must apply for Site Specific Assessment from the Trust Research & Development (R&D) department and be granted written NHS R&D approval. It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.
Within 90 days after the end of the trial, the CI and Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

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

18. FINANCE

The NIHR EME funding body funds this study. EME Project Ref No.12/127/127

19. INSURANCE AND INDEMNITY

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

20. PUBLICATION POLICY

Data ownership rights will lie with the institution sponsoring the trial.

The data will be the property of the Chief Investigator. Publication will be the responsibility of the Chief Investigator. It is planned to publish this study in peer review journals and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder. The Trial Steering Committee and Funder will review all manuscripts, abstracts or other modes of presentation of primary trial results prior to submission. Individuals

will not be identified from any study report.

21. STATEMENT OF COMPLIANCE

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

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

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

22. LIST OF PROTOCOL APPENDICES

Appendix 1 EHRA Score

Classification of AF-related symptoms (EHRA score)	
EHRA class	**Explanation**
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

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