JRMO Research Protocol for Interventional Studies

Full Title	***Objective Randomised Blinded Investigation of Therapeutic Ablation versus cardioversion for persistent Atrial Fibrillation***
Short Title	***ORBITA-AF***
Version	1.0
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1. Contents

2. Glossary

AE	Adverse Event
AF	Atrial Fibrillation
AR	Adverse Reaction
ASR	Annual Safety Report
AV	Atrioventricular
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CA	Cryoballoon Ablation
CHADS VAR	Score for estimating risk of stroke
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CVCTU	Cardiovascular Clinical Trials Unit
DC	Direct Current
DCCV	Direct Current Cardioversion
DMC	Data Monitoring Committee
EC	European Commission
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
FU	Follow-up
GA	General Anaesthetic
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCS	Glasgow Coma Scale
HRA	Health Research Authority
ICD	Implantable cardioverter-defibrillator
ICF	Informed Consent Form
ILR	Implantable loop recorder
ISF	Investigator Site File
JRMO	Joint Research Management Office
LA	Left Atrial
LIPV	Left Inferior Pulmonary Vein
LSPV	Left Superior Pulmonary Vein
NICE	National Institute for Health and Care Excellence
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
pAF	Paroxysmal Atrial Fibrillation
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QUALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RAG	Red Amber Green
REC	Research Ethics Committee
RFV	Right Femoral Vein
RIPV	Right Inferior Pulmonary Vein
RSPV	Right Superior Pulmonary Vein
SAE	Serious Adverse Event
SDV	Source Document Verification

SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSP	Transeptal Puncture

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Richard Schilling**

Signature: 

Date: **12 February 2019**

Principal Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Malcolm Finlay**

Signature: 

Date: **12 February 2019**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: **Jackie Cooper**

Signature: 

Date: **12 February 2019**

4. Summary and synopsis

Short title	ORBITA-AF
Methodology	Internal Pilot as part of a future study, Randomised, blinded, controlled trial, 2 arms.
Research sites	1 Barts Health NHS Trust – 2 sites: Whipps Cross and Barts Heart Centre for the pilot study, with the potential to progress recruitment within 4-5 UK centres for larger
Objectives / aims	The main aim of the research is to investigate whether patients undergoing pulmonary vein isolation with cryoablation for atrial fibrillation (AF) will have lower rates of AF recurrence than those treated by DC cardioversion without an ablation procedure. The objectives of the Pilot Study are to trial the key study logistics with a view to optimising methods to be used in the main study.
Number of participants	20 patients (10 per group) for the pilot study 208 patients for the larger trial
Inclusion and exclusion criteria	Inclusion criteria : Persistent AF (atrial fibrillation lasting > 7days) of total continuous duration <2 years, Age 18-80, ability to give informed consent. Exclusion criteria : Creatinine clearance (eGFR) < 30mls/min, contraindication or unable to take anticoagulation, uncontrolled hypertension, contraindication or catheter ablation, BMI > 35. Contraindication or unable to tolerate amiodarone.
Statistical methodology and analysis (if applicable)	The sample size for a pilot study is based on 10% of the sample size of the full trial. The sample size for the full trial is calculated based on the comparison of recurrence free survival in the two groups using the logrank test. The expected percentage of patients with recurrence of AF within one year is 47% for the ablation group[1] (January et al., 2014) and 66% for DCCV[2,3,4] (Heeringa et al., 2006; Jones, Pollit, Fitzmaurice, Cowan, & Guideline Development, 2014; Wilber et al., 2010)based on published data. This is equivalent to a hazard ratio of 1.7.To detect an effect of this size with 80% power at the 5% significance level would require N=104 patients in each group. For secondary endpoints the sample size of 104 patients will give 80% power at the 5% significance level to detect an effect size of 0.4 standard deviations in any continuous variable. Secondary endpoints: Results will be presented as the mean (SD), median (IQR) or percentage (number) in each group. Continuous variables will be compared between the two groups using Student's T test for normally distributed variables and Mann-Whitney U test for those with non-normal distributions. Categorical variables will be compared with Chi-squared tests.
Study duration	The Pilot study will take place at Barts Health NHS Trust : 4

	months to set up, 3 months to recruit, treatment (1 day), 3 month follow up and 2 months study closure. For the larger trial in 4-5 UK centres: Set-up 6 months, 6 month recruitment, treatment (1 day), 12 month follow-up, 3 months study closure.

5. Introduction

Patients with persistent atrial fibrillation undergoing catheter ablation are reported to have fewer symptoms and better quality of life than those undergoing DC cardioversion (DCCV) or optimal medical therapy. However, as yet this has not been subjected to a randomised, prospective, blinded clinical trial (January et al., 2014).

Atrial fibrillation (AF) is the commonest cardiac arrhythmia, with a prevalence of 5.5% (Heeringa et al., 2006). A major cause of the life-changing complication of stroke, AF is associated with severe symptoms, such as palpitations, shortness of breath, lethargy and a reduced quality of life. AF can be classified into paroxysmal, persistent or long-standing persistent. Paroxysmal AF refers to when episodes last less than 7 days before spontaneously termination, persistent AF implies episodes lasting greater than 7 days or requiring either electrical or pharmacological cardioversion, and longstanding persistent AF describes AF episodes lasting more than one year in duration trial (January et al., 2014).

Patients differ widely in the diversity and severity of their AF symptoms. Some 15-30% of patients with AF are asymptomatic. Data from implantable cardioverter-defibrillators (ICDs) and pacemakers have demonstrated that up to 70% of paroxysms of AF are asymptomatic. There is a need to clarify the relationship between patient reported symptoms and the arrhythmia itself. It is likely that both somatic and psychological factors contribute to this relationship. Patient perception or awareness of symptoms is often not a good discriminator of the severity of the arrhythmia. In the present study we will also collect information from patients on reported symptoms and effects on quality of life (both physical and mental), functional status and treatment satisfaction. We will be able to look at these and assess the correlations between reported symptoms and arrhythmia as captured by the LINQ device.

5.1 Background

After adequate stroke prevention (e.g. anticoagulation) and rate control, the optimum strategy for patients who continue to be symptomatic with persistent atrial fibrillation has not been established for patients without heart failure (Jones et al., 2014). Cardioversion with antiarrhythmic medication is commonly used as a first-line rhythm control strategy despite very high recurrence rates of the index arrhythmia and high serious complications associated with this strategy. Further treatment options, such as catheter ablation or implantation of a pacemaker and ablation of the AV node, are considered once AF recurrs. The benefits of first-line ablation in patients presenting with persistent AF has not been tested. We seek to perform a blinded, randomised trial comparing an electrical cardioversion-led strategy with a pulmonary-vein isolation strategy for the treatment of persistent atrial fibrillation.

5.2 Preclinical data

Catheter ablation of AF has emerged as a highly effective treatment for symptomatic atrial fibrillation (AF), particularly in those cases refractory to antiarrhythmic treatment, (Calkins et al., 2009; January et al., 2014; Stabile et al., 2006; Wilber et

al., 2010) and has become an established treatment of paroxysmal AF (pAF). Registry and trial data suggest that pulmonary vein isolation, involving the electrical isolation of the pulmonary veins by endocardial ablation, can lead to a >80% maintenance of sinus rhythm in patients with pAF, even up to five years (Ouyang et al., 2010). Recent data have indicated that patients with persistent AF and heart failure have improved outcomes, including in all-cause mortality, over and above best conservative therapy with catheter ablation (Packer et al., 2018). Furthermore, on-treatment analysis of the CABANA trial (Packer et al., 2018), showed patients who underwent catheter ablation for AF had better survival and fewer unplanned hospital admissions than those treated with best medical therapy.

Electrical reconnection of the pulmonary veins after the initial ablation procedure has been held responsible for the majority of recurrences following ablation (Rajappan et al., 2008), and has driven technical and procedural efforts towards establishing durable electrical isolation of the pulmonary veins at the first procedure. Specifically, the cryoballoon (Artic Front, Medtronic) has emerged as a leader in enabling durable pulmonary vein isolation from predictable, safe and reproducible procedures (Aryana et al., 2016; Canpolat & Aytemir, 2016; Kojodjojo et al., 2010; Tzeis, Pastromas, Sikiotis, & Andrikopoulos, 2016). Point-by-point radiofrequency ablation procedures have also become more rapid, safe and reproducible with technology developments such as catheter contact force sensing, 3D mapping and better steerability of catheters (Finlay et al., 2012; Lee et al., 2016).

5.3 Clinical data

Catheter ablation of AF is less established in patients with persistent AF, but compelling evidence exists that AF recurrence is reduced in patients with persistent AF who undergo catheter ablation when compared to electrical cardioversion plus antiarrhythmic medication. The SARA study (Mont et al., 2014)randomised 146 patients with persistent AF to antiarrhythmic medication plus electrical cardioversion or to catheter ablation, with 60% vs 30% of patients having recurrence of their arrhythmia at one year. The recent STAR-AFII trial (Conti et al., 2017) confirmed pulmonary vein isolation as the cornerstone of catheter ablation in this patient group, with no difference in the recurrence rates of patients undergoing AF ablation with pulmonary vein isolation alone (41% recurrence) or those who had pulmonary vein isolation plus electrogram ablation (51%) or plus linear ablation (54%) (Verma et al., 2015). Similar or greater rates of freedom from AF after a single procedure have been seen in registry data, with up to around 80% long-term freedom from AF with multiple procedures (Hunter & Schilling, 2010; January et al., 2014).

These data imply that the newer one-shot technologies such as the cryoballoon which provide durable PVI from a single, rapid, safe procedure, and thus would be effective in the ablation of persistent atrial fibrillation. Registry data support this assumption, with between 55 and 70% of persistent AF patients maintaining long-term sinus rhythm following cryoablation PVI (Ciconte et al., 2015; Coutino et al., 2016). These assumptions are being tested in ongoing clinical trials, where the efficacy of cryoablation PVI is being tested against point-by-point radiofrequency ablation.

However, it is well established that the effectiveness of any therapy aiming for rhythm control is determined in part to the duration of AF (Kirchhof & Calkins, 2017; Voskoboinik et al., 2017). The mantra “AF begats AF” has repeatedly been shown to be relevant to catheter ablation of persistent AF (Wijffels, Kirchhof, Dorland, & Allessie, 1995). The enthusiasm for treating AF aggressively early in the course of

the disease is reflected in recent NICE guidelines (Jones et al., 2014). A treatment strategy where patients have a definitive PVI procedure early may be far more effective, and prevent multiple repeated hospital attendances. Side-effects of antiarrhythmic medications may be also be avoided.

But a major stumbling block in performing early AF ablation for such patients has been the length and complexity of the procedure, drawbacks which have now been overcome by refinement of the cryoballoon ablation technique (Kojodjojo et al., 2010). Indeed, an effective PVI procedure can now be performed routinely in under one hour, with complications only occurring rarely (Ang, Domenichini, Finlay, Schilling, & Hunter, 2015). Certainly, when compared to the effectiveness and risk of an electrical cardioversion, early PVI with a cryoballoon ablation for persistent AF appears a very attractive treatment proposition (Buch & Shivkumar, 2017).

5.4 Rationale

No blinded randomised controlled trial comparing early-ablation strategies to cardioversion-led strategies has been performed. The rationale for blinding where possible in clinical trials is well established (Brim & Miller, 2013; Miller & Kaptchuk, 2004; Redberg, 2014). The recently published ORBITA trial (Al-Lamee et al., 2018) performed a blinded, multicentre randomised trial of PCI in stable angina compared to a placebo procedure. This trial demonstrated that the efficacy of invasive procedures can be assessed with a placebo procedure and that this type of trial remains necessary. Knowledge of treatment assignment influences physician behaviour, drug recommendations and encourages bias in outcome reporting. The treatment effect size and the effects of confounding factors will be exaggerated and thus limit the interpretation of the true patient experienced outcomes either strategy. In a comparison of surgical procedures, a sham-control arm represents the gold standard of blinding. In a systematic review of placebo-controlled surgical trials (Wartolowska et al., 2014) found no evidence of harm to participants assigned to the placebo group. For a procedure whose primary purpose is to give sustained symptomatic relief, definitive quantification of the true placebo-controlled effect size of AF ablation is necessary. There is a need to clarify the relationship between patient reported symptoms and the arrhythmia itself. Patient reported symptoms may not always be related to the severity of the arrhythmia or quality of life. No bias-resistant blinded, randomised, trial has yet been performed seeking to measure the benefits of AF ablation.

5.5 Risks / benefits

The potential subjects for this study would be eligible to have either a DCCV or AF ablation as these are standard procedures for treatment of AF, and as such these interventions are performed as standard in the NHS care setting and have known risks and benefits. The risks of the ablation procedure also need to be balanced against the risks associated with the patient being maintained on medications to reduce their risk of arrhythmia.

The study procedures will be performed by an experienced clinical team, such that the risks associated with the interventions are low, and procedures are in place to minimise risks. A more detailed explanation of risks and mitigations for the study interventions are documented in Section 10.

5.5.1 Hypothesis

We hypotheses that AF ablation reduces recurrences of persistent AF and improves quality of life compared to acute treatment of heart rhythm by cardioversion and best medical therapy.

6. Study objectives

6.1 Primary objective

The primary hypothesis being tested is that 20 patients undergoing pulmonary vein isolation with cryoablation with DCCV for atrial fibrillation will have lower rates of AF recurrence than those treated by DC cardioversion without an ablation procedure.

Once funding is available and dependent on the results of the pilot, it is planned that the study will be extended to a larger trial following an amendment to the REC, to increase the recruitment target to 208 participants and involve 4-5 other UK centres.

6.2 Secondary objective

The secondary objective of the trial will be to determine whether an early-ablation strategy is superior in terms of patient's quality of life than a cardioversion strategy, and to compare medication burden, cost efficacy and secondary endpoints of cardiac function (change in ejection fraction) between these strategies. Finally, the safety of the approaches will be compared.

6.3 Primary endpoint

- Recurrence of Persistent AF (AF episode lasting > 7 days).

6.4 Secondary endpoints

- Death
- Hospital admission
- Procedural complications
- Bleeding events
- Requirement for repeat procedures
- Change in ejection fraction
- Cumulative treatment cost at 12 months
- Clinical success (as defined by 75% or greater reduction in the number of AF episodes – or percentage time the patient is in AF as measured by the LINQ device.)
- Change in quality of life, as measured by SF-12 and AF-PROMS questionnaires.
- AF symptom score
- AF burden as measured on continuous monitoring
- Antiarrhythmic drug use.

6.5 Long Term passive follow-up

Follow the completion of the active portion of the larger trial, patients will be followed up in a registry to track their long-term outcomes from routinely collected clinical data. During this period, patients may be contacted to ascertain their AF and medical status, but no investigations or interventions other than those in routine clinical care will be performed.

7. Study population

Patients referred for either cardioversion for persistent AF or catheter ablation of persistent AF will be approached.

7.1 Inclusion criteria

Patients who meet the following inclusion criteria will be eligible for the study;

- Ability to give informed consent
- Age 18-80 years
- Persistent AF (atrial fibrillation lasting > 7days) of total continuous duration <2 years as documented in medical notes.
- Patients being considered for cardioversion.

7.2 Exclusion criteria

Patients who meet the following exclusion criteria will be ineligible for study participation;

- Creatinine clearance (eGFR) < 30mls/min
- Contraindication or unable to take anticoagulation
- Contraindication or unable to tolerate amiodarone
- Uncontrolled hypertension
- Contraindication or catheter ablation
- BMI > 35

8. Study design

Bart's Health patients referred from other Barts Health NHS Trust Hospitals (Homerton, Chase Farm, Barnet) for either cardioversion for persistent AF or catheter ablation of persistent AF will be approached for recruitment.

- All patients:
    - Patient drug treatment will follow local clinical guidelines for AF ablation and be recorded in the CRF.
    - Patient baseline characteristics recorded at preadmission
        - Estimated AF duration
        - LA dimensions (Echocardiogram)
        - Ejection fraction
        - Routine Bloods

    - Creatinine & Electrolytes,
    - Full blood count,
    - Thyroid function
  - Quality of Life measures
  - BP
  - CHADS VASC score / assessment
  - Medical History and Comorbidities
  - Demographics (Age, sex , ethnicity)
  - Physical exam (BP, HR, Weight, Height, BMI)
  - Medications
- Day of Procedure – blinded randomisation to intervention (DCCV, or Pulmonary Vein Isolation plus DCCV). Reveal LINQ inserted during procedure.
- 6 weeks: QoL measures, telephone FU
- 3 months: Clinical follow up, 12 lead ECG, Repeat QOL measures
- 12 months: Clinical follow up, Endpoints measured. Once subject participation in the trial is complete, the patient and physician will be unblinded. If the patient is in AF, management of AF proceeds as clinically indicated.
- All patients who consent to have data capture continue in AF registry for 5 years.

The pilot study patients will be analysed at 3 months and 12 months to allow assessment of feasibility of a larger trial, and patients who complete the 12 month follow-up visit and consent will continue in registry follow-up for 5 years post procedure.

9. Study procedures

9.1 Recruitment

The usual clinical care provider will identify patients suitable for the study who will then be approached by the study team for consent. Patients referred for DC cardioversion or management of persistent AF will be screened for inclusion into the trial.

All potential participants will be given the Participant Information Sheet by a member of the study team, once identified as interested and eligible by their usual treating clinician, and be given sufficient time to consider study participation.

9.2 Informed Consent

The clinicians obtaining informed consent will have current GCP training. They will be familiar with the study, the clinical procedures and will use the current version of the Patient Information Sheet (PIS) and Informed Consent Form (ICF) which has been approved by the HRA/REC.

The clinicians obtaining consent at the pre-admission (screening) visit will ensure that the participant is able to understand the information given and will explain the nature, purpose, procedures, risks and benefits of the study to the participant. The clinician will answer any questions the patient may have to the patient's satisfaction. The patient will be given at least 24 hours to decide whether or not to take part in the study following being given the PIS. The date the PIS is given to the patient will be

documented in the hospital notes to ensure that sufficient time is given for consideration.

The clinician will explain the consent form and obtain the patient's initials and dated signature on the consent form. They will then countersign and date the consent form after the participant has signed it. The original signed consent and PIS will be kept in the Investigator Site File, a copy will be filed in the hospital notes, and a copy will be given to the patient.

Any delegation of responsibility by the PI for consent taking, or any other trial activity, should be documented on the Study Delegation Log.

Written informed consent from the participant must be obtained prior to his or her involvement in any aspect of the trial that requires consent. Any revised written ICF and other written information to be provided should receive favourable opinion by the REC in advance of use and distribution. The PIS and ICF will be identifiable by date, version number and be printed on local trust headed paper of the trial site at which the participant is to be consented.

9.3 Procedure protocol

9.3.1 All patients

Patient gives informed consent in pre-admission. Patients will be blinded to their ECG and rhythm. Admitted to day ward. Arrival in Lab and checked in as for Cryo PVI. Skin electrodes placed. Conscious sedation or GA administered and sterile field prepared. 8F and 7F sheaths placed in RFV under ultrasound guidance. Heparin given as per local AF ablation protocol.

Once sheaths in place and GCS < 10, randomisation will be performed via REDCap, a web-based, electronic database. Patients will be randomised in a 1:1 ratio to either DCCV+ PVI or DCCV alone.

9.3.2 DCCV + PVI group

Transeptal puncture done using standard techniques. Heparin given as per local protocol. Change TSP sheath over-the-wire to cryosheath. Cryoballoon to LA. Achieve wire through cryoballoon. Cryoablation to LSPV, RIPV, RSPV, LLPV, with phrenic pacing via quadripolar catheter via 7F sheath during right sided lesions. As is standard practice, the catheter will be placed in the superior vena cava and manipulated to allow consistent phrenic capture with pacing stimulation. Phrenic stimulation will be confirmed by diaphragmatic movement and recording of diaphragmatic surface electrograms. Pulmonary venous isolation will be confirmed with electrograms in veins. Veins considered isolated if sudden loss of electrogram signal, or if pacing through all poles of achieve catheter is able to produce electrical capture of vein but not of LA. Termination of freeze if loss of phrenic capture, vein temperature < -60°C, or operator decision for termination. Isolation was considered indeterminate if unable to confirm signal loss or electrical capture. At end of isolation, DCCV performed (if patient still in AF). Sheath withdrawal, Femostop haemostasis and protamine as per local protocol. An implantable loop recorder will be inserted in the prepectoral area with local anaesthetic at the end of the procedure. Confirmed electrical isolation of all 4 pulmonary veins will be classified as a procedural success. Confirmation of electrical recording by the implantable loop recorder will be considered implant procedural success.

9.3.3 DCCV group

Sedation maintained for 30 minutes. An electrophysiological catheter will be passed to the superior vena cava using fluoroscopic guidance and 6 minutes of phrenic pacing will be performed, starting at 20 minutes following first local anaesthetic. At 30 mins, sedation optimised and DCCV performed. Sheath withdrawal, Femostop haemostasis and protamine as per local protocol. An implantable loop recorder will be inserted in the prepectoral area with local anaesthetic at the end of the procedure.

9.3.4 All patients

Recovered to ward. 12 lead ECG performed but not shown to patient. Patient mobilised and discharged after 4 hours.

Blinding

There is a study specific Standard Operating Procedure on the blinding procedure used in this study. No information on the procedure given will be transferred from cath lab staff to the recovery ward staff.

Patients and other healthcare professionals will also be blinded to which treatment the patient received. The cath lab staff performing the procedure will have no further contact with the patient during the study. A 'chaperone' will be assigned for each patient, who will take over from the cath lab staff in caring for the patient post intervention.

A standard procedure report will be used for clinical records, with a procedure report entered into the study database. This will be transferred to the clinical database at the end of the study or at a patient unblinding event, whichever is earlier.

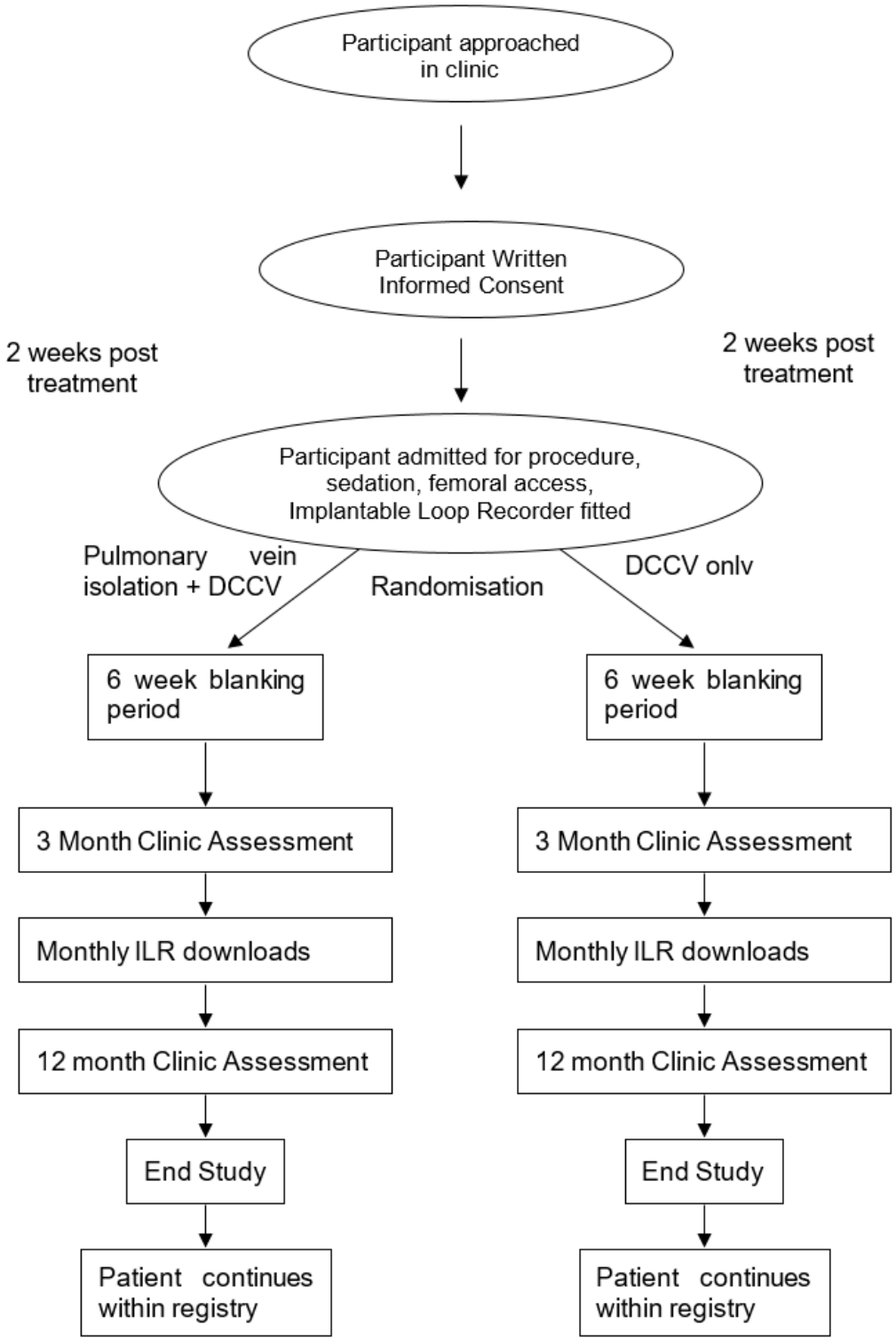
In the present study we will use a modification of the blinding procedure used in the ORBITA trial (Al-Lamee et al., 2018). A specific blinding questionnaire will be used at the end of the day of the intervention asking the patient and ward staff to guess the treatment allocation. As is typical of AF studies involving ablation, a blanking period will be observed. This accounts for the frequent recurrence of arrhythmia in the days following ablation, where healing atrial tissue can be vulnerable to arrhythmia which is not predictive of longer-term outcome. At the end of the blanking period (ie. 6 weeks) patients will be asked to complete the blinding questionnaire again. This blinding index will be reported on the day of the intervention and at 6 weeks and 3 months follow up to allow the degree of blinding to be assessed.

9.4 Schedule of Assessment

Assessment	Screening/ pre-admission	Randomisation	Treatment/ Procedure	Implant	Recovery	6 weeks (telephone)	3 month (clinic)	12 month /EOS (clinic)	Monthly downloads	Registry
Visit window							+/- 7 days	+/- 2 weeks		
Informed consent	X									
Patient baseline characteristics recorded: estimated AF duration, LA dimensions (echo), LVEF, Bloods, Medications, Age, Sex, BP, CHADS VASC score, co-morbidities, demographics, weight, height, BMI.	X									
Randomisation		X								
DCCV only			X							
DCCV plus Pulmonary Vein Isolation			X							
Telephone FU						X				
Quality of life measures	X					X	X			
Clinical FU						X	X	X		
Loop recorder inserted				X						
12 lead ECG					X		X	X		
Interrogation of loop recorder				X			X	X	X	
Symptom questionnaires	X					X	X	X		
Clinical status and mortality data										X

The long term passive follow up will track patient mortality and clinical status from routinely collected clinical data. No intervention or investigations will be performed as part of this long term follow up.

9.5 Study Scheme Diagram



9.6 Blinding procedures

The aim of blinding will be to prevent patients, their treating clinicians and their treatment choices being influenced by knowledge of the procedure being performed. The pilot study will establish the effectiveness and feasibility of blinding procedures. Patients will be admitted to the day ward for "Orbita AF DCCV±ablation". They will undergo confirmation of study and procedural consent by a senior cardiology fellow/registrar or consultant. Patients will be accompanied to the cath lab by a clinical fellow or research nurse (Chaperone), and at this point their care will be transferred to the cath lab team. The patient will enter the catheter lab and standard AF preprocedural checks will be performed. Patients will be offered to wear headphones playing relaxing music of their choice during the procedure. A groin access / draping pack will be opened for all patients and sedation given. After GCS < 10, the patient will be randomised to either DCCV and ablation, or DCCV alone using REDcap (mobile app). The procedure will be performed according to protocol. At the end of the procedure, a "sign out" will be performed, where the procedure performed is confirmed to the operating team. Here the randomised allocation will not be specified in keeping with the blinding SOP. If no complications occurred, the procedure performed will not be specified on sign-out, hand over to the ward staff will be as follows:

"A DC cardioversion plus or minus Cryoablation under the study protocol was performed with groin sheath access and no complications. The patient should be managed assuming they have undergone an ablation procedure".

Patients who are accidentally unblinded will be withdrawn from the trial.

Patients will complete a questionnaire immediately prior to discharge to establish their perception of which procedure was performed.

Randomisation will be performed in a 1:1 ratio, between 3 and 4 patients per day will have procedures performed as per this protocol. Individual randomisation will be performed after insertion of groin sheath and administration of sedation.

9.7 Follow up

Patients will be followed up for a total of 12 months regardless of the results of any interim analysis. Monthly remote interrogation of the loop recorder will measure the burden of AF (proportion of time in AF) and the duration of AF episodes. At follow up patients will undergo interrogation of their loop recorder, a 12 lead ECG and a symptom questionnaire. For patients travelling long distances for their treatment ECGs and device interrogations will be requested from their local device centre and questionnaires will be administered by telephone, mail and or email. Patients will remain within an observational registry for 5 years following the end of the trial.

9.8 End of Study Definition

The last patient attending for the 12 month clinic assessment will mark the end of the study. Patients who have consented to have their AF data collected will then go into the registry for 5 years. Once all the data has been collected from the last clinic assessments then final data analysis will be completed.

9.9 Entry into Registry

Following study completion, patients will be entered into a data registry which will gather standard clinical data from patient notes. This will follow patients up for 5 years.

9.10 Subject Withdrawal

Patients can withdraw from the trial at any time and without giving a reason. The Principal Investigator can also withdraw a patient from the study for any of the following reasons:

1. Any adverse event or serious adverse event
2. Any concurrent illness that prevents further treatment
3. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion
4. Withdrawal of consent for treatment by the patient
5. Any study device or procedural complications
6. Any reasons the subject cannot adhere to study visits or procedures

If a patient withdraws from the study, another patient will be randomised to replace them. Patients who are randomised but withdraw will not have their medical care affected and return to standard clinical care.

10. Assessment and management of risk

The risks of both DC cardioversion and of catheter ablation for AF are well established, as detailed below. However, the procedures will be performed by experienced clinicians who part of the research team for all study participants, which should minimise any known/expected risks.

10.1.1 DCCV risks:

- Sedation complications (<1%), chest discomfort, redness, irritation at site of skin pads (5%), failure of DCCV.

10.1.2 Catheter ablation of AF risks:

- Groin access complications (1% historically, <0.2% with ultrasound guidance)
- Minor (Total <6%)
  - Groin: Bleeding bruising at groin access site (5%)
  - Pericardial effusion not requiring drainage (1%)
  - Transient phrenic nerve palsy (3%)
- Major (Total <1%)
  - Groin complication or vascular damage requiring surgical or radiological intervention (0.5%)
  - Cardiac tamponade requiring percutaneous drainage (0.7%)
  - Stroke (<0.2%)
  - Oesophageal damage (<0.2%)
  - Death (<0.1%)
  - Pulmonary vein stenosis causing breathlessness (<0.1%)

10.1.3 Changes in risks c.f. standard cardioversion procedure in placebo group

- Groin access complications (<0.2% with ultrasound guidance)

- Electrophysiologist administering cardioversion in catheter lab environment (potentially better safety monitoring than in standard cardioversion environment)

11. Statistical considerations

11.1 Sample size

The sample size of 20 subjects for the pilot study has been chosen as an achievable recruitment target that would enable assessment of feasibility of the study, and to confirm whether a larger trial could be conducted.

The sample size for the larger trial is calculated based on the comparison of recurrence free survival in the two groups using the logrank test. The expected percentage of patients with recurrence of AF within one year is 47% for the ablation group[1] and 66% for DCCV[2,3,4] based on published data. This is equivalent to a hazard ratio of 1.7. To detect an effect of this size with 80% power at the 5% significance level would require N=104 patients in each group.

For secondary endpoints the sample size of 104 patients will give 80% power at the 5% significance level to detect an effect size of 0.4 standard deviations in any continuous variable.

11.2 Method of analysis

The statistical analysis plan (SAP) will describe the statistical methods which will be used in the analysis of data, including any interim analyses and the level of significance that is to be used.

Progression criteria

This study has been designed with an internal pilot phase aimed at assessing the feasibility and optimizing the methods to be used in the main study, piloting key study logistics, improving quality and efficient use of resources. Eldridge (Eldridge et al., 2016)have described a new framework where 'internal pilot' studies which have some feasibility objectives but focus on the processes to be used in the main study generating data which can contribute to the final analyses. They describe the use of operational 'progression criteria' which can be used to measure pre-identified targets at the end of the pilot phase which will determine whether or not to proceed to the main trial. This approach has been advocated by the members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research (Avery et al., 2017). Avery and colleagues describe some of the key issues to consider in development and review of these criteria.

In the current study the following progression criteria have been identified to assess operational aspects of the design and progression to the main trial:

- Protocol non-adherence – (a) cross-over from DCCV to AF ablation group. Estimate 25-30% as in CABANA trial (Packer et al., 2018). We will take this level of cross-over into account in our power calculations. (b) Measure the amount of off protocol intervention.

- Recruitment rate – we estimate being able to recruit 4 patients per month. If the number falls below this we will need to build this into timelines for the larger trial.
- Loss to follow-up. Estimate 2%.
- Key study logistics – especially around the delivery of the intervention, including the use of a 'chaperone' to maintain blinding.
- Identifying barriers and facilitators to implementation.
- Assessment of the success of the blinding procedure (ie. blinding index).
- Assessment of the feasibility of the blinding SOP.
- Assessment of the acceptability of the interventions
- Data collection – completeness and quality. How much missing data are we willing to tolerate?
- Assessment of outcome measures.

The TSC will discuss and evaluate the progression criteria at the end of the Pilot phase and use a Red Amber Green (RAG) system to decide which operational aspects of the design need to be changed before proceeding to the main trial.

12. Ethics

The Principal Investigator will ensure that the study will be carried out in accordance with the ethical principles in the UK Policy Framework for Health and Social Care Research (Nov 2017), and applicable legal and regulatory requirements. This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an independent NHS Research Ethics Committee (REC). Written Approval from the Committee must be obtained and subsequently submitted to the JRMO to obtain Final Sponsorship approval.

12.1 Risks of the procedures:

All patients having either a DCCV or AF ablation are given conscious sedation or general anaesthetic.

An AF ablation is performed using transeptal puncture using standard techniques. The risks associated with a transeptal puncture are very low. Groin access complications are around 1% and even less with ultrasound guidance (0.2%).

The DCCV only group would require the patients to have a line put in, which is not normally done. However, this venous access could be used for the administration of anaesthetic agents, sedation and fluids. The use of a femoral venous access will allow patients to be blinded to which procedure they have received and enable the specific effects of the AF ablation to be measured.

Any risks associated with femoral access will have been minimised by using ultrasound guidance for the venous access. The risks of the ablation procedure also need to be balanced against the risks associated with the patient being maintained on medications to reduce their risk of arrhythmia.

12.2 Informed consent:

The risks to the study participants will be adequately explained in the Patient Information Sheet and Informed Consent Form.

The patients will be considered suitable to have either a cardioversion of ablation procedure. So, they need to be willing to have the transeptal puncture for the AF ablation. The risks of this procedure are low (as detailed above). As the procedure is performed under anaesthetic it will be performed without the patient experiencing any pain.

There is a benefit to participants in the study in having the implantable cardiac device which will monitor their heart allowing immediate knowledge if their heart rhythm goes back into AF. Otherwise there are no further individual benefits in participating in the study.

12.3 Blinding considerations

No blinded randomized controlled trial comparing early-ablation strategies to cardioversion-led strategies has been performed. For a procedure whose primary purpose is to give sustained symptomatic relief, definitive quantification of the true placebo-controlled effect size of AF ablation is necessary. The present study was designed to address the lack of clinical research / lack of evidence-based practice in this area.

12.3.1 Rationale for blinding

The rationale for blinding where possible in clinical trials is well established, and discussed in Introduction (Section 5.4).

Placebo effects and distorted participant reporting appear to be greater in surgical trials than in drug trials. There are many factors involved in surgical procedures such as hospitalization, ancillary treatments, the surgical ritual itself or the technology used that can all heighten the placebo effect. Correcting for placebo effects is becoming more important as more subjective 'soft' outcome measures are used eg. Quality of Life (which are more prone to be influenced by placebos).

The magnitude of the placebo effect may be a critical factor in determining the outcome of a trial. A difference between two treatments such as DCCV and PVI might result from differences in their placebo effects so it is important to blind patients to the intervention they have received.

Specific emphasis will be placed on this being a blinded trial. Patients will be informed that they may receive an electrical cardioversion with or without pulmonary vein isolation procedure. The procedure performed will be determined at random following administration of sedation and insertion of groin sheaths under ultrasound guidance. Patients will not be informed which procedure they have undergone until the end of the trial period or the study end-point whichever is sooner. Patients who undergo a cardioversion only who revert to persistent AF will be offered a pulmonary vein isolation procedure if indicated as standard medical care under current guidelines.

12.4 Specific procedural considerations

All patients having either a DCCV or AF ablation are given conscious sedation or general anaesthetic.

An AF ablation is performed using transeptal puncture using standard techniques. The risks associated with a transeptal puncture are very low. Groin access complications are around 1% and even less with ultrasound guidance (0.2%).

The DCCV only group would require the patients to have a line put in, which is not normally done. However, this venous access could be used for the administration of anaesthetic and sedation agents, and for fluids if required. This will allow the patients to be effectively blinded to which procedure they have received and allow the specific effects of the AF ablation to be measured.

The risks and harms to the patient of a transeptal puncture are very low and patients who are suitable for an AF ablation (i.e. all patients eligible for the trial) would require this access for the procedure to be performed. The risks have been minimised by using ultrasound guidance for the venous access.

The risks of this procedure also need to be balanced against the risks associated with the patient being maintained on medications to reduce their risk of arrhythmia.

Subjects are free to withdraw from the study at any time, without providing a reason. If the subject asks the investigator to destroy all identifiable samples taken from the subject and/or not enter into the CRF results of the follow-up examination, the investigator will comply with the subject's requests.

The CI will ensure that the REC is informed promptly of any serious adverse event that occurs during this study and that is both related and unexpected (see section 13), in line with NRES SOPs, and will provide the REC with annual progress reports of the study, if it lasts longer than a year.

12.5 Annual Safety Reporting

The CI will send an Annual Progress Report to the REC and the sponsor using the HRA template on the anniversary of the REC "favourable opinion".

13. Public Involvement

We have obtained input from our patient volunteers at the William Harvey Heart Centre and from the Trials Connect patient group. They have reviewed our patient facing literature (PIS and ICF) and had input into our trial design. This has ensured that our proposal, particularly the lay summary, is understandable to our patient population. We have also had input from our AF patients treated at our Trust. We will also include a patient representative on our Trial Steering Committee.

14. Data handling and record keeping

14.1 Data management

A REDCap database will be designed by CVCTU to capture the study data. The eCRFs will have an audit trial, will have electronic signatures, users will have specific access

and user rights, and they will enable real-time data clarifications and cleaning, and data exports and analysis. All source documents will be kept securely in the participant study files or Investigator Site File (ISF) within locked cabinets in restricted access rooms within the Barts Health Centre. The CVCTU will maintain the Trial Master File (TMF), and provide trial management support and tracking for recruitment, data capture, monitoring and safety reporting.

14.2 Source data

Source data are the original forms of data used in the study. Some source data will be generated directly by the study (e.g. ablation reports, questionnaire responses) while others may need to be collected from other 'source documents' (e.g. a participant's medical history in their case notes for inclusion). All source data will be collected by the Investigator or delegated member of the research team, filed in a participant study file (which will include study documents such as the consent form, inclusion and exclusion criteria, cardioversion and ablation reports, AEs, medication records, EQ5D questionnaire etc), and source data will be captured in an electronic database (REDCap). A Source Data Agreement will be completed to determine what is considered as the 'source' data for the trial.

14.3 Confidentiality

The Principal Investigator has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, the General Data Protection Regulation (GDPR), NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research, and the conditions of Research Ethics Committee favourable opinion. All research team members have undergone GCP training. The Chief Investigator and the study team will adhere to these parameters to ensure that the Participant's identity is protected at every stage of their participation within the study.

Following consent and during the study, all participant study records and samples will be marked by a single, unique pseudoanonymised identifier. The code for the pseudoanonymised will be kept on a study ID log with the ISF, which will be kept within a locked filing cupboard within a locked room that only the researchers involved have access to. A paper record of any information will be coded and any patient identifiable information (PID) will be removed e.g. name, date of birth and NHS number.

Personal information will only be used on the consent form and the pseudoanonymisation code (screening log). Personal information will be used by the site study team to contact participants if needed and to remind participants of study dates. Fully anonymised data will be shared with fellow researchers via conference presentation and via publication of the results in scientific journals. Pseudoanonymised data will be shared between the research teams named in the application, and access will be granted to members of the Sponsor and Barts CVCTU teams for the purposes of data monitoring and audit.

Only the clinical care team will have access to clinical case notes, which have identifiable personal information for the purposes of identifying potential participants.

The research team will create a separate study file for each participant which will comprise of information given by the participant at the time of screening and during

visits. Routine biochemistry will be measured in Barts Health NHS Trust clinical laboratory by the laboratory biochemists.

The Investigator Site File (ISF) and subject study files will be kept in a locked cupboard in a locked room that only the researchers involved have access to. The Trial Master File (TMF) will be maintained and stored by the Barts CVCTU in the William Harvey Heart Centre, in a locked room with restricted access.

Under no circumstances will non-encrypted named data be placed on a laptop computer, portable storage device (memory stick or CD-ROM) or transferred by email.

14.4 Record Retention and Archiving

Data will be managed with reference to the Barts CTU SOP 'Data Management'. During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. The UK Policy Framework for Health and Social Care Research requires that research records are kept for 20 years after the project has completed. For studies involving Barts Health NHS Trust patients, undertaken by Barts Health NHS Trust staff, or sponsored by Barts Health NHS Trust or Queen Mary, University of London, the approved repository for long-term storage of local records is the Trust Corporate Records Centre. Both electronic and paper documentation will be retained in physical form for archiving. Sponsor approval will be requested prior to final destruction of the trial records.

15. Laboratories

15.1 Central and local laboratories

Biochemical and haematology assays will be performed in the pathology labs of the Barts Health NHS Trust. Blood samples will be taken at the screening visit, and these are standard blood tests to assess baseline characteristics of the participant and confirm eligibility.

15.2 Sample collection and preparation

Blood tubes will be labelled with the following information:

- Subject Number
- Date of Collection
- Sampling Time (nominal)
- Study Name

16. Interventions and tools

16.1 Devices

Loop recorder	• Manufacturer: MEDTRONIC LTD

	• Indication : Long-term monitoring of heart rhythm. Determination of duration of AF episodes and confirmation of primary endpoint • CE Mark : Yes • Source of Device : Medtronic Ltd In-kind research grant contribution • How device used : The Reveal device is inserted in the pre-pectoral position under the skin. This is performed with local anaesthetic in the preadmission clinic by a trained nurse or doctor. The device will provide a continuous recording of the heart rhythm and rate, and will be able to down load duration of AF episodes via a home monitoring system to establish the primary endpoint of the study.
Cryoballoon, Cryocath, Achieve wire, Console and related items	• Manufacturer: MEDTRONIC • Indication: AF ablation catheter and sheath • CE Mark: Yes • Source of Device: Clinical use for AF ablation • How device used: The cryoballoon is the key specified technique for performing pulmonary vein isolation in the ablation arm in this trial. This allows the physician electrophysiologist to perform a circumferential freeze around the pulmonary veins to electrically isolate the vein, thus preventing pulmonary vein ectopy from triggering arrhythmia.

16.2 Techniques and interventions

Conscious sedation or GA administered and sterile field prepared. 8F and 7F sheaths placed in RGV under ultrasound guidance.

16.2.1 PVI group

Transeptal puncture (TSP) done using standard techniques using operator preference equipment. Heparin given as per local protocol. Change TSP sheath over-the-wire to cryosheath. Achieve wire through cryoballoon and cryoballoon placed in LA through cryosheath. Cryoablation to LSPV, RIPV, RSPV, LLPV, with phrenic pacing via quadripolar catheter via 7F sheath during right sided lesions. Isolation confirmed with electrograms in veins. Veins considered isolated if sudden loss of electrogram signal, or if pacing through all poles of achieve catheter is able to produce electrical capture of vein but not of LA. Termination of freeze if loss of phrenic capture, vein temperature < -60ºC, or operator decision for termination. Isolation was considered indeterminate if unable to confirm signal loss or electrical capture. At end of isolation, DCCV performed (if patient still in AF). Sheath withdrawal, Femostop haemostasis and protamine as per local protocol.

REVEAL-LINQ insertion will be performed at the end of the case. Prepectoral area will be cleaned and any overlying ECG leads removed. 10mls of local anaesthetic will be infiltrated to the skin and the device injected under the skin in a sterile manner. The incision will be closed according to local practice.

16.2.2 DCCV group

Sedation maintained for 30 minutes. At 30 minutes, sedation optimised and DCCV performed. Sheath withdrawal, Femostop haemostasis and protamine as per local protocol.

REVEAL-LINQ insertion will be performed at the end of the case. Prepectoral area will be cleaned and any overlying ECG leads removed. 10mls of local anaesthetic will be infiltrated to the skin and the device injected under the skin in a sterile manner. The incision will be closed according to local practice.

16.2.3 All patients

Recovered to ward. 12 lead ECG performed but not shown to patient. Patient mobilised and discharged after 4 hours. The cardiac physiologist will register the patient for remote monitoring, a physiologist will show the patient how to use their monitoring station.

16.3 Tools

16.3.1 Questionnaires:

Short Form (SF 12) The short form health survey
This is a shorter version of the SF-36 and consists of 12 questions. It is comparable with the SF-36 especially for the physical component summary (PCS) and mental component summary (MCS). This test gives more precision than the EQ-5D and has been extensively validated in general and also in cardiac populations (De Smedt, Clays, Annemans, & De Bacquer, 2014).

Atrial Fibrillation Specific Patient Reported Outcome Measure (AF PROMS)
This 28 item inventory measures how AF has impacted the patient's quality of life. It assesses how much the patient has been concerned by specific symptoms and how AF has impacted their emotional state and daily activities. This inventory was developed at Barts and has been validated by Sarah Horan (unpublished PhD thesis).

16.4 Medicinal product

- Heparin given as per local AF ablation protocol

16.5 Antiarrhythmic drugs

Physicians will be encouraged to use anti-arrhythmic drugs in the periprocedural period, such as Amiodarone 200mg tds in a reducing dose commencing at least 2 weeks prior to index procedure. Choice of antiarrhythmic medication will be at the discretion of the patient's physician and will be recorded on the CRF. Participating centres will be encouraged to follow local centre periprocedural guidelines for antiarrhythmic medication for AF ablation for all patients

17. Safety reporting

17.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

17.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

17.3 Notification and reporting of Adverse Events and Reactions

If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants' source documents, the Case Report Form (CRF), and, where appropriate, medical records.

The following events will be considered and reported as Adverse Events, and not serious adverse events, as they are expected as known complications of procedures:

- Phrenic nerve damage
- Tampanade or pericardial effusion
- Haematoma
- Skin Burns
- Chest pain
- Groin vascular complications.

The period for adverse events reporting will be from the signing of consent until the end of study visit at 12 month follow-up.

17.4 Serious Adverse Events (SAEs) or reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

SARs will be reported to the REC where in the opinion of the Chief Investigator the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

17.5 Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

The treatment code for the participant will be broken when reporting an 'unexpected and related' SAE. The unblinding of individual participants by the PI / CI in the course of a clinical study will only be performed if necessary for the safety of the study participant.

17.6 Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However the CI will inform the sponsor and Research Ethics Committee (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

17.7 Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

17.8 Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

The CVCTU team will maintain safety reporting responsibilities on behalf of the Sponsor, following the JRMO SOP 26b – Safety reporting for non-CTIMPs and using the SAE template to capture SAEs electronically via REDCap, and the Investigator teams will report all SAEs to the CVCTU, and the CVCTU will ensure adherence to the Sponsor safety reporting requirements.

For the purposes of this protocol, a 'serious breach', is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the participants of the trials; or
- The scientific value of the trial.

The CI is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours**. The sponsor will notify and report to REC within 7 working days of becoming aware of the serious breach.

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The CVCTU will maintain a log of the non-compliances identified and reported to them, and these will be maintained on a site Deviation log. The CVCTU will action a timeframe in which they need to be dealt with, and each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, they will be escalated to the Sponsor, who will confirm an appropriate action, which may include an on-site audit.

18. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

The trial will be monitored with reference to the Barts CTU SOP Monitoring. A trial specific monitoring plan will be developed by the CVCTU and determined by a formal risk assessment. The Study team will be initiated and monitored in accordance with the sponsor SOPs led by the Barts CVCTU, who will provide overall study management. A CVCTU monitor will conduct on-site monitoring visits, and be the primary contact for the research team in relation to study queries, including those related to source data and data capture, safety reporting, and participant recruitment and follow-up activities.

The CVCTU Project Manager is responsible for creating the trial specific monitoring plan, to ensure adequate monitoring of the trial and that both on-site and central monitoring is conducted to verify that source data is accurate, reliable and complete.

The CVCTU will have its own audit schedule for trials on their portfolio. A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits may be conducted by a sponsor's or funder representative.

19. Trial committees

Trial Steering Committee

A Trial Steering Committee (TSC) will be established to review and monitor all aspects of the conduct and progress of the trial, ensuring that the protocol is adhered to, appropriate action is taken to safeguard the twenty participants and the quality of the

trial maintained. The TSC will be composed of two independent experts in the field of electrophysiology with experience in clinical trials along with the investigators and the trial manager. A medical statistician will join the TSC to provide expertise in clinical trials and one lay members of the committee will be appointed. This committee would meet before patient recruitment and then quarterly to assess safety, feasibility or any other arising problems (e.g. with recruitment) and their recommendations will be followed.

The TSC will meet on a monthly basis, and will include the following:

- An independent/external Chair
- One independent/external collaborator who will participate in the larger trial
- CI/PI
- Statistician
- Trial Manager
- Patient representative

Data Monitoring and Safety Committee

An independent Data and Safety and Monitoring Committee (DSMC) will be formed to monitor patient safety as the study progresses. The DSMC has been selected by and communicates directly to the study's TSC. There will be an independent chair of this committee, an independent member with clinical cardiovascular trials expertise, and other members of the trial management group, including the PI, statistician, and trial manager will attend open sessions. The DSMC will meet prior to initiation of the clinical study, after the recruitment of 4 patients and then at 3 monthly intervals. The DSMB will have access to unblinded patient data. If a serious concern with the safety of the patients in the trial would arise, the DSMC may recommend early termination of the study.

20. Finance and funding

Funding for the study has been provided by the Barts Charity and with support from Medtronic, who are providing the REVEAL devices for the trial.

21. Indemnity

The NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

22. Dissemination of research findings

All relevant data from this study will be submitted to peer review journals for publication following the termination of the study in line with sponsor and trust publication policy.

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