Statistical Analysis Plan

1 Title page

Full Title	***Objective Randomised Blinded Investigation of Therapeutic Ablation versus cardioversion for persistent Atrial Fibrillation***
Short Title/Acronym	***ORBITA-AF Pilot Trial***
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2 SAP revision history

Protocol Version	Updated SAP version No.	Section number changed	Description of and reason for change	Date changed
5.0	1.0	NA	NA	NA
8.0	2.0	11.1	Amendment to include an interim analysis, in line with the trial protocol.	10 June 2022

3 Table of contents

4 GLOSSARY of Terms and Abbreviations

AE	Adverse event
AF	Atrial Fibrillation
BMI	Body Mass Index
BP	Blood Pressure
CHADS	Score for estimating AF stroke risk
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DC	Direct Current
DCCV	Direct Current Cardioversion
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
FU	Follow-up
HR	Heart Rate
IQR	Interquartile Range
LA	Left Atrial
LINQ	Reveal LINQ cardiac monitoring system
LVEF	Left Ventricular Ejection Fraction
MCS	Mental Health Composite Scale (SF-12)
MI	Myocardial infarction
BI	Blinding Index
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PCS	Physical Health Composite Scale (SF-12)
PROMS	Patient Reported Outcome Measures
PVI	Pulmonary Vein Isolation
QoL	Quality of Life
R	"R" Statistical Programming Software
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-12	Twelve item short form survey
SBP	Systolic Blood Pressure
SD	Standard Deviation

5 Introduction

This SAP has been written based on information from the study protocol version 2.0, dated 25/06/2019.

5.1 Preface

Cardioversion with antiarrhythmic medication is commonly used as a first-line rhythm control strategy for patient with persistent atrial fibrillation (AF) despite having high recurrence and complication rates. Further options such as catheter ablation are considered once AF recurs. Patients with persistent AF 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 to measure the benefits of first-line AF ablation[1].

5.2 Purpose of the analyses

The aim of a future main clinical trial would be to investigate whether patients undergoing DC cardioversion (DCCV) with the addition of a pulmonary vein isolation (PVI) cardiac ablation procedure with cryoablation for atrial fibrillation (AF) will have lower rates of AF recurrence than those treated by DCCV without a cardiac ablation procedure. The trial will also assess symptoms, quality of life, functional status and treatment satisfaction. This pilot study aims to validate the key study logistics with a view to optimising the methods to be used in a future main trial and will also give an initial assessment of efficacy outcomes.

6 Study objectives and design

6.1 Design

ORBITA-AF feasibility study is an internal pilot study. It is a randomised blinded controlled trial at two sites. Patients will be randomised to receive DCCV+PVI or DCCV alone. No information about the procedure will be transferred from catheterisation laboratory (cath lab) staff to recovery staff and cath lab staff will have no further contact with the patient during the study. Patients and other healthcare professionals will remain blinded to treatment allocation. If a future trial is determined to be feasible and no major changes to the design have been made from this pilot study, then pilot study patients will be included in the future main trial. This pilot study aims to recruit 20 patients.

6.2 Study objectives

The main hypotheses to be tested in a full trial of this nature would be that AF ablation reduces the recurrence of persistent AF and improves quality of life compared to acute treatment of heart rhythm by cardioversion and best medical therapy. Through this pilot study, the main objective is to assess operational aspects of the trial in order to optimise methods for a future main trial. In addition, descriptive analyses of study outcome measures will also be undertaken.

6.3 Feasibility Endpoints

- Protocol non-adherence – (a) cross-over from one study group to the other, (b) do not receive randomised intervention.
- Recruitment rate (number recruited per month).
- Loss to follow-up at 12-months.
- Assessment of the success of the blinding procedure (i.e. blinding index).
- Data completeness.
- 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 feasibility of the blinding SOP.
- Assessment of the acceptability of the interventions.
- Descriptive assessment of outcome measures for main trial (as below).

6.4 Efficacy Endpoints

6.4.1 Primary endpoint

- Recurrence of Persistent AF (AF episode lasting > 7 days) within 12 months.

6.4.2 Secondary endpoints

- Death within 12 months.
- Hospital re-admission for any reason.
- Procedural-related complications.
- Bleeding events within 7 days of procedure.
- Requirement for repeat procedures within 12 months.
- Change in ejection fraction.
- Clinical success of procedure.
- Change in quality of life, as measured by SF-12 and AF-PROMS at 12 months.
- AF burden as measured on continuous monitoring.
- Antiarrhythmic drug use within 12 months.

6.4.3 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	-14 days	Day 0	Day 0	Day 0		42 days +/- 3 days	+/- 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	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

6.4.4 Assessment of feasibility endpoints

Protocol non-adherence is defined as the proportion of patients in each randomised group who undergo the treatment that they were not randomised to as part of the index procedure, i.e. those randomised to DCCV only undergoing DCCV plus PVI, and those randomised to the DCCV plus PVI group who only undergo DCCV as part of the index trial procedure.

Recruitment rate will be defined as the total number of patients recruited divided by the number of months during which recruitment takes place.

Loss to follow-up will be defined as a) the number lost to follow-up at 12 months as a proportion of the number randomised. b) the number who do not consent to the collection of 5-year registry data as a proportion of the number randomised.

Data completeness will be defined as the number of subjects completing each assessment as a proportion of the total randomised. For this pilot study, analyses will be conducted on a complete case basis, and the level of missing data will be assessed to help inform as to best methods to use to handle potential missing data within a larger future trial.

Blinding index will be assessed as described by Bang et al (BI)[2]. Patients and staff will be asked to guess the treatment allocation and will answer DCCV, DCCV+PCI, or don't know. The BI is scaled to an interval of -1 to 1 with 1 being complete lack of blinding, 0 being perfect blinding and -1 indicating opposite guessing.

Other feasibility endpoints including assessing study logistics, identifying barriers and facilitators to implementation, and assessing the acceptability of the interventions will be assessed qualitatively, and hence will not be described further in the SAP.

6.4.5 Assessment of primary and secondary efficacy endpoints

The primary endpoint is defined as the proportion of randomised patients with recurrent AF (AF episode lasting > 7 days) within 12 months, but outside of the initial 6-week blanking period (see section 8.1.2).

Secondary endpoints to be described are:

- Proportion dying within 12 months
- Proportion with hospital admission for any reason within 12 months
- Proportion with procedural-related complications defined as any AE that is deemed at least possibly related to intervention
- Proportion with bleeding events within 7 days of procedure
- Proportion with repeat procedures (any additional procedure for AF after the baseline index trial procedure(s)) within 12 months
- Change in ejection fraction from baseline at 12 months
- Proportion with clinical success of procedure
- Change in QoL at 12 months, as measured by SF-12 and AF-PROMS
- AF burden by 12 months
- Anti-arrhythmic drug use.

Clinical success will be defined as a 75% or greater reduction in the number of AF episodes as measured by the Reveal LINQ implant device within 12 months, but outside of the initial 6-week blanking period.

Change in QOL will be measured by the change in AF-PROMS summary scores and SF-12 PCS and MCS between screening and 12 months. SF-12 scores will be calculated as described in the appendix supplementary table 2[3].

AF burden will be defined as the proportion of time in AF over the 12 months but outside of the initial 6-week blanking period, as measured by the Reveal LINQ implant device.

6.5 Level of significance

No hypothesis testing will be done for this pilot study.

For efficacy outcome measures we will use 80% one-sided confidence intervals to give an indication of whether the endpoint is likely to be of interest, an approach described by Cocks et al. for pilot trials[4].

6.6 Sample size

The sample size of 20 subjects 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. At around 10% of a sample size required for a future main trial, this will also allow an initial assessment of the effectiveness of the intervention using a confidence interval approach[4].

7 General Analysis Definitions

7.1 Study period and visit definitions

7.1.1 Visits

Patients will be identified as suitable for the study by their usual clinical care provider. Patients referred for DC cardioversion or management of persistent AF will be screened for inclusion into the trial. Patients will give informed consent in pre-admission. Baseline characteristics, quality of life and symptom measures will be assessed at this point.

On the day of the procedure patients will be randomised to DCCV or Pulmonary Vein Isolation plus DCCV. LINQ will be inserted during the procedure. Patients will be followed up at 6 weeks by telephone for quality of life and symptom measures.

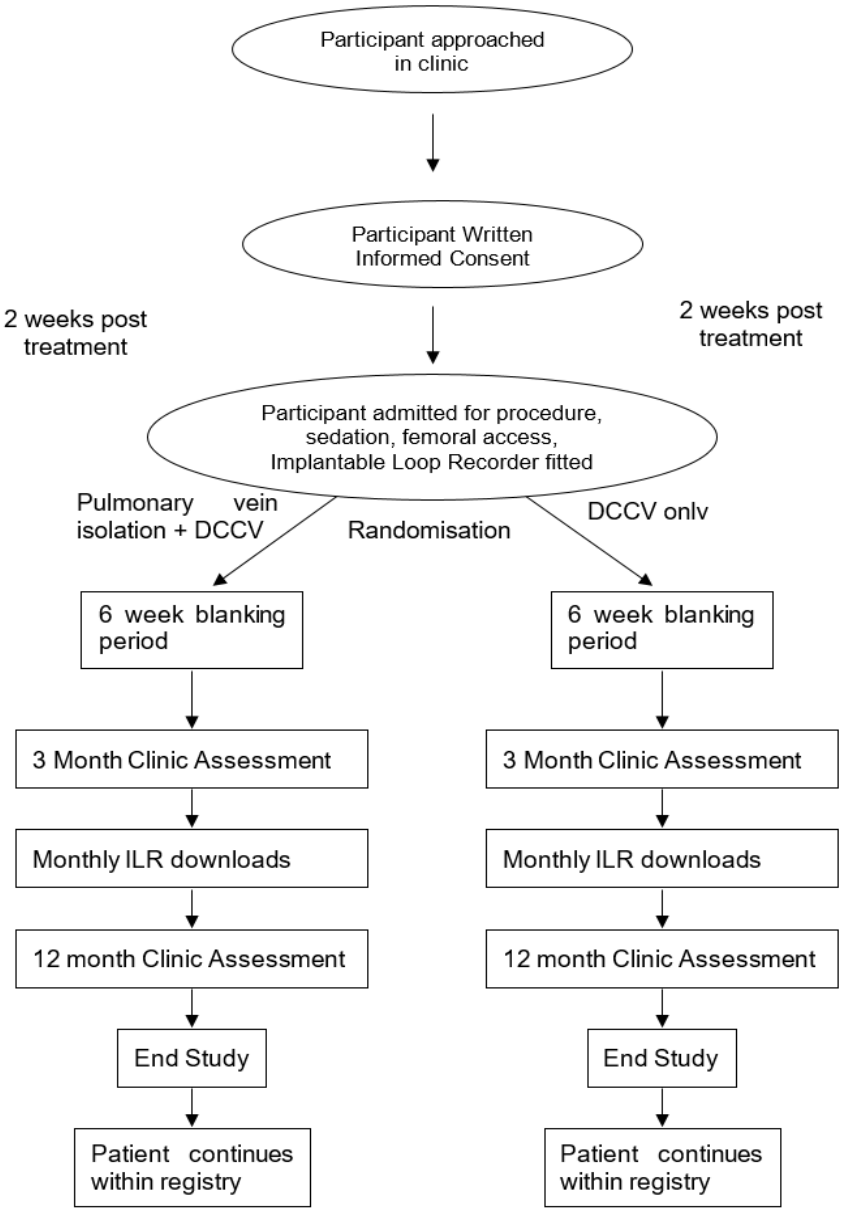
Patients will return to the clinic at 3 months (clinical follow-up, 12 lead ECG, repeat QOL and symptom measures) and at 12 months (clinical follow-up, 12 lead ECG and symptoms). Monthly remote interrogation of the loop recorder will measure burden of AF (time in AF) and duration of episodes.

Patients who consent will remain within an observational registry for 5 years following the end of the trial. This 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.

Data from this pilot study will be analysed at 12 months to allow assessment of feasibility for 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.

7.1.2 Study Scheme Diagram



7.2 Study Populations

7.2.1 Intention- to-treat population.

Results will be presented on an intention to treat basis with all randomised patients analysed according to the group they were assigned to, regardless of whether the treatment was received or whether the protocol was adhered to.

7.2.2 Safety population

The safety population will consist of all randomised patients who received the allocated treatment.

7.3 Subgroup definitions

No subgroup analysis will be undertaken.

7.4 Treatment assignment and treatment groups

Patients will be randomised on a 1:1 basis to either DCCV alone or DCCV + PVI. Block randomisation is used with randomly varying block sizes of length 2, 4, and 6. Randomisation will not be stratified by any factors. The allocation algorithm is written by the study statistician using R (randomizeR package). Details of the randomisation method and validation details are stored in a separate document which can be accessed by the trial statistician and the database manager.

The randomisation list will then be uploaded to the study database (REDCap). When a patient has been screened and has met all of the entry criteria in order to be eligible for trial participation, the unblinded investigator will go to the randomisation module on the database and complete the randomisation form. Once complete, the allocation (which is next in the sequence on the randomisation list) will be revealed to the unblinded investigator.

8 Patient Disposition

Participants will be those referred for either cardioversion for persistent AF (> 7 days) or catheter ablation of persistent AF. Inclusion/exclusion criteria are detailed in the protocol (section 7). Numbers of patients screened, excluded prior to randomisation by reason and overall, randomised and completing each phase of the study will be shown by treatment groups and overall following the Consort structure.

9 Demographics and Baseline characteristics

Demographic and baseline (screening data) will be:

1. Age
2. Sex
3. Ethnicity
4. BMI
5. SBP
6. DBP
7. HR
8. AF duration
9. LVEF
10. Diabetes
11. Current Smoking
12. Hypertension
13. Hypercholesterolaemia
14. Previous MI
15. Previous PCI

Demographic and baseline data will be summarised by randomisation group and overall. For continuous data the number of subjects, mean, SD, median and interquartile range will be shown. For categorical data number and percentage will be shown. No formal testing will be performed for the comparison of baseline characteristics.

10 Interim analysis and timing for analysis.

10.1 Interim analysis

On completion of the 6-week blinding period of the last patient to be enrolled into the pilot study, an interim analysis will be performed, including endpoints assessed from baseline to 6-weeks. No other interim analyses are panned prior to the completion of the study, unless specifically requested by the DSMC.

The main analysis will take place at the end of this pilot study and this information will be used to inform decisions regarding procedure to a main future trial. Patients will be followed up for 12 months regardless of interim analysis results.

10.2 Time points for analysis.

The DSMC will monitor patient safety and will meet prior to initiation of the study, after the recruitment of 4 patients and then at 3 monthly intervals. All other analysis described in this SAP will take place at the end of this pilot study.

11 Feasibility and Efficacy Analysis

11.1 Method for analysis of endpoints

11.1.1 Analysis of feasibility endpoints

Proportions will be shown along with the number with each binary endpoint and total number.

The recruitment rate will be shown overall as the total number of patients recruited divided by the number of months.

Data completeness will be assessed as the numbers with and without data recorded and the proportion with complete data for each treatment group and overall.

For the blinding index, the number and percentage with each response will be given for each treatment arm. The blinding index will be reported for each group.

Other feasibility endpoints, including assessment of key study logistics, and the feasibility of blinding SOP, acceptability of interventions, will be assessed more qualitatively, and hence will not be described further in this SAP.

11.1.2 Analysis of efficacy endpoints

Categorical variables will be shown as the number with each endpoint and total number in each group along with the proportion. Odds ratios and 80% one-sided exact confidence intervals will also be shown as an assessment of efficacy, an approach described by Cocks et al[4].

For continuous variables mean, SD, and number of patients with available data will be presented along with estimated mean difference between trial arms and 80% one-sided confidence intervals.

For AF burden (proportion of time in AF), median and IQR will also be reported.

11.1.3 Analysis of subgroups

There is no plan to conduct any subgroup analyses.

11.1.4 Covariate adjusted analysis

No covariate adjustment will take place.

11.2 Assumptions for analysis.

For continuous efficacy outcomes, confidence intervals for differences will be constructed assuming a normal distribution. Normality of distribution for continuous variables is hard to assess with such a small number of subjects in this pilot trial and so will not have much value.

11.3 Methods for handling of missing data and outliers

This pilot study will assess data completeness to inform decisions about missing data for a future main trial. Analysis will use all patients with available endpoint data. The level of missing data will be tabulated for each outcome, presenting the number of subjects with a data record and number with missing data, separately by trial arm.

11.4 Multiple comparisons

No adjustment for multiple comparisons will be made.

11.5 Multi-centre studies

No adjustment will be made for centre in this pilot study.

12 Safety analysis

12.1 Adverse events (AE)

AEs will be summarised using counts and percentages. The number of subjects having at least one AE will be presented overall and tabulated by treatment. The number of subjects with AEs of mild/moderate/severe intensity will be shown overall and by treatment using the maximum severity experienced for each patient. The total number of AEs for each treatment, allowing multiple events per patient, will also be presented.

12.2 Deaths or serious adverse events (SAE)

SAEs will be listed separately along with details of the treatment and whether the event is unexpected and whether it is thought to be related to the treatment.

13 Presentation of analysis

Results will be presented as follows.

Figure 1: Consort flow diagram

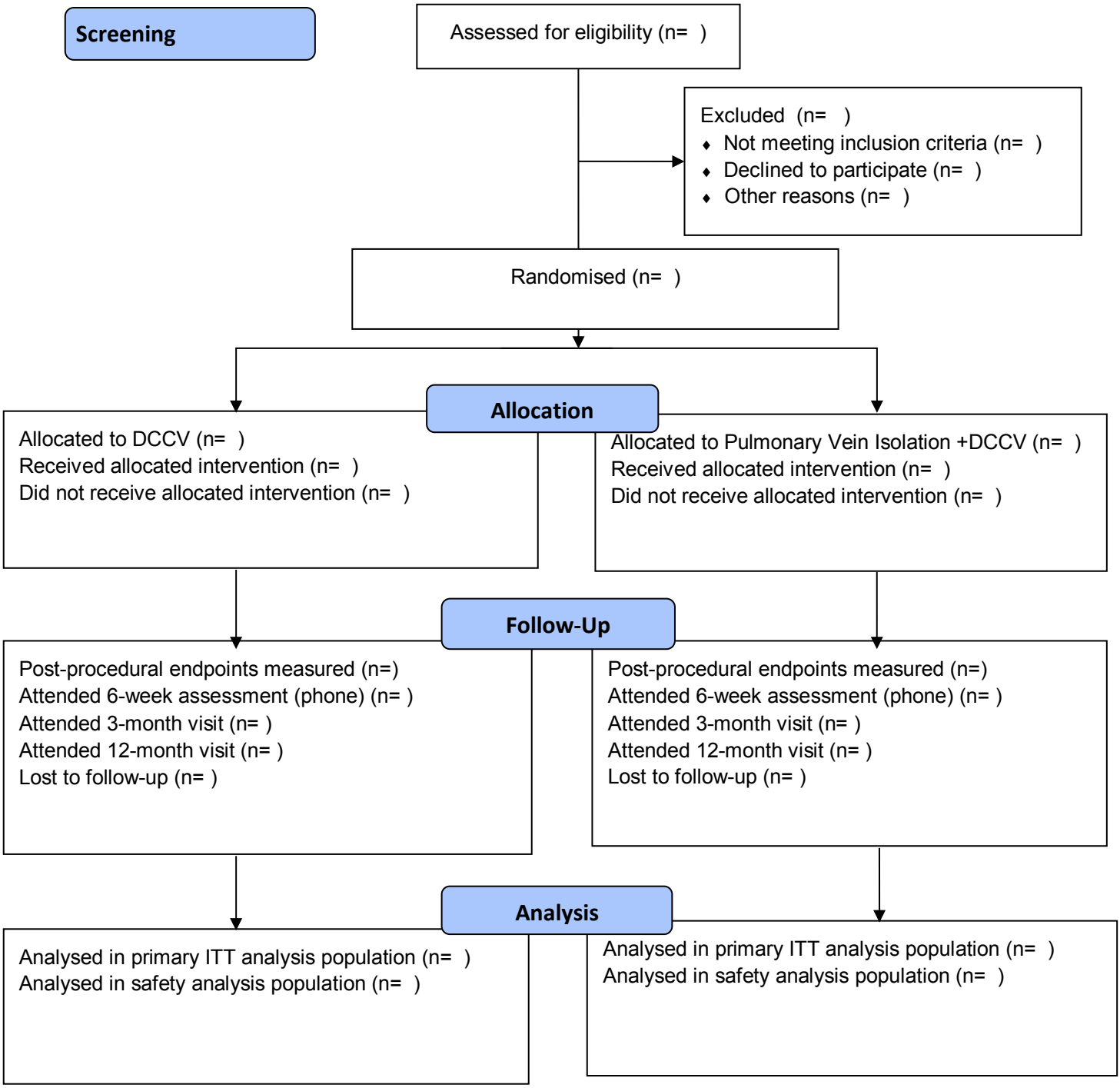


Table 1: Tables of demographic and baseline characteristics, overall and by treatment group

		Treatment group		
		DCCV (N=)	**DCCV +PVI (N=)**	**Combined (N=)**
Age (years)		Mean (SD)	Mean (SD)	Mean (SD)
Sex	Female	n/N (%)	n/N (%)	n/N (%)
	Male	n/N (%)	n/N (%)	n/N (%)
Ethnicity	Asian	n/N (%)	n/N (%)	n/N (%)
	Black	n/N (%)	n/N (%)	n/N (%)
	Mixed	n/N (%)	n/N (%)	n/N (%)
	Other	n/N (%)	n/N (%)	n/N (%)
	White	n/N (%)	n/N (%)	n/N (%)
BMI (kg/m^2)		Mean (SD)	Mean (SD)	Mean (SD)
SBP (mmHg)		Mean (SD)	Mean (SD)	Mean (SD)
DBP (mmHg)		Mean (SD)	Mean (SD)	Mean (SD)
HR (bpm)		Mean (SD)	Mean (SD)	Mean (SD)
AF duration (months)		Median [IQR] Mean (SD)	Median [IQR] Mean (SD)	Median [IQR] Mean (SD)
Left Ventricular Ejection Fraction (%)		Median [IQR] Mean (SD)	Median [IQR] Mean (SD)	Median [IQR] Mean (SD)
Current Smoking	**Non- smoker**	n/N (%)	n/N (%)	n/N (%)
	Previous smoker	n/N (%)	n/N (%)	n/N (%)
	Current smoker	n/N (%)	n/N (%)	n/N (%)
Diabetes		n/N (%)	n/N (%)	n/N (%)
Renal insufficiency		n/N (%)	n/N (%)	n/N (%)
Peripheral vascular disease		n/N (%)	n/N (%)	n/N (%)
Hypertension		n/N (%)	n/N (%)	n/N (%)
Hypercholesterolaemia		n/N (%)	n/N (%)	n/N (%)
Previous stroke		n/N (%)	n/N (%)	n/N (%)
Previous MI		n/N (%)	n/N (%)	n/N (%)
Previous PCI		n/N (%)	n/N (%)	n/N (%)

Table 2: Feasibility endpoints

	Treatment group		
	DCCV (N=)	**DCCV +PVI (N=)**	**Combined**
Proportion crossing over	n/N (%)	n/N (%)	-
Proportion with off-protocol deviation	n/N (%)	n/N (%)	n/N (%)
Recruitment rate (patients per month)	-	-	Rate
Loss to follow-up at 12 months	n/N (%)	n/N (%)	n/N (%)
Not consenting to 5-year registry data follow-up	n/N (%)	n/N (%)	n/N (%)
Blinding index			
Staff - post procedure			
DCCV	n11 (p11)	n21 (p21)	-
DCCV + PCI	n12 (p12)	n22 (p22)	-
Don't know	n13 (p13)	n23 (p23)	-
Total	N1	N2	-
Blinding index	BI	BI	-
Patients - post procedure			
DCCV	n11 (p11)	n21 (p21)	-
DCCV + PCI	n12 (p12)	n22 (p22)	-
Don't know	n13 (p13)	n23 (p23)	-
Total	N1	N2	-
Blinding index	BI	BI	-
Patients - 6 weeks			
DCCV	n11 (p11)	n21 (p21)	-
DCCV + PCI	n12 (p12)	n22 (p22)	-
Don't know	n13 (p13)	n23 (p23)	-
Total	N1	N2	-
Blinding index	BI	BI	-
Patients - 3 months			
DCCV	n11 (p11)	n21 (p21)	-
DCCV + PCI	n12 (p12)	n22 (p22)	-
Don't know	n13 (p13)	n23 (p23)	-
Total	N1	N2	-
Blinding index	BI	BI	-

Table 3: Data completeness

	Treatment group		
	DCCV (N=)	**DCCV +PVI (N=)**	**Total**
Primary Endpoint data (Persistent AF)	N1 N2 % with data	N1 N2 % with data	N1 N2 % with data
SF12 **3 months** **12 months**	 N1 N2 % with data N1 N2 % missing	 N1 N2 % with data N1 N2 % missing	 N1 N2 % with data N1 N2 % with data
AF-PROMS **3 months** **12 months**	 N1 N2 % with data N1 N2 % with data	 N1 N2 % with data N1 N2 % with data	 N1 N2 % with data N1 N2 % with data
Loop recorder interrogation performed **3 months** **12 Months**	 N1 N2 % with data N1 N2 % with data	 N1 N2 % with data N1 N2 % with data	 N1 N2 % with data N1 N2 % with data
Patients completing all study assessments	N1 N2 % with data	N1 N2 % with data	N1 N2 % with data

N1= Number with data recorded

N2=Number with missing data

Table 4: Primary and Secondary Efficacy Endpoint analysis (ITT population)

	Treatment group		
	Placebo N=	**Active N=**	**OR (80% CI)**
Recurrent AF within 12 months	n/N (%)	n/N (%)	
Death within 12 months	n/N (%)	n/N (%)	
Hospital admission within 12 months	n/N (%)	n/N (%)	
Procedural-related complications	n/N (%)	n/N (%)	
Bleeding events within 7 days	n/N (%)	n/N (%)	
Requirement for repeat procedures within 12 months	n/N (%)	n/N (%)	
Clinical success of procedure	n/N (%)	n/N (%)	
AF drug use within 12 months	n/N (%)	n/N (%)	
	Placebo N=	**Active N=**	b (80% CI)
Change in ejection fraction at 12 months	Mean (SD)	Mean (SD)	
AF-Burden	Median [IQR] N Mean (SD)	Median [IQR] N Mean (SD)	
Change in QoL score at 12 months: **SF-12 MCS** **SF-12 PCS** **AF-PROMS**	 Mean (SD) N Mean (SD) N Mean (SD) N	 Mean (SD) N Mean (SD) N Mean (SD) N	

Table 5: Safety analysis – adverse events (safety population)

		Treatment group	
		Placebo N=	**Active N=**
Number of patients experiencing an AE within a year		n/N (%)	n/N (%)
Maximum severity AE experienced	Mild	n/N (%)	n/N (%)
	Moderate	n/N (%)	n/N (%)
	Severe	n/N (%)	n/N (%)
Total number of AEs across patients		n	n

Table 6: SAE listing

SAE number	Patient ID	SAE term (MedDRA)	SAE severity	Expected/ unexpected	Treatment group	Details of treatment	Related to treatment?
1							
2							
3							
4							
…							

14 REFERENCES

1) January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland, J. C., Jr.American College of Cardiology/American Heart Association Task Force on Practice, G. (2014). 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol, 64*(21), e1-76.

2) Bang H, Ni L, Davis CE (2004). Assessment of blinding in clinical trials. Controlled Clinical Trials, 25(2): 143-156.

3) Gonzalez-Chica DA, Dal Grande E, Bowden J, Musker M, Hay P, Stocks N (2017). Are we reducing the risk of cardiovascular disease and improving the quality of life through preventive health care? Results of a population-based study in South Australia. Preventive medicine, 99,164-170.

4) Cocks K, Togerson DJ (2013), Sample size calculations for pilot randomized trials: a confidence interval approach. Journal of Clinical Epidemiology, 66:197-201.