Ablation Verses Anti-arrhythmic Therapy for Reducing All Hospital Episodes from Recurrent Atrial Fibrillation

AVATAR-AF

Version 6.1 (9th February 2018)

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Sponsor

Imperial College Academic Health Sciences Centre is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the AVATAR-AF study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections and amendments may be necessary. These will be circulated to the investigators in the study. Problems relating to this study should be referred, in the first instance to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd Edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

Glossary of Abbreviations

AE	:	Adverse Event
AF	:	Atrial fibrillation
BRC	:	Biomedical Research Centre
DSMB	:	Data & Safety Monitoring Board
ECAS		European Cardiac Arrhythmia Society
eCRF	:	Electronic Case Report Form
ECG	:	Electrocardiogram
EHRA	:	European Heart Rhythm Association
EP	:	Electrophysiology
GI	:	Gastro-Intestinal
GCP	:	Good Clinical Practice
GP	:	General Practitioner
HRS	:	Heart Rhythm Society
ICTU	:	Imperial College Trials Unit
L	:	Litre
LV	:	Left Ventricle
mg	:	Milligram
min	:	Minute
mmol	:	Millimole
NHS	:	National Health Service
NYHA	:	New York Heart Association
OPD	:	Outpatients Department
PV	:	Pulmonary Vein
PVI	:	Pulmonary Vein Isolation
R&D	:	Research and Development
SAE	:	Serious Adverse Event
s	:	Seconds
SSA	:	Site Specific Assessment
TOE	:	Trans-Oesophageal Echocardiogram
TSE		Trial Steering Committee
µmol	:	Micromole

AVATAR-AF Protocol Summary

SPONSOR	Imperial College London Academic Health Science Centre
PROTOCOL TITLE	**A**blation **V**erses **A**nti-arrhythmic **T**herapy for Reducing **A**ll Hospital Episodes from **R**ecurrent **A**trial **F**ibrillation (**AVATAR-AF**)
STUDY HYPOTHESIS	A streamlined AF ablation procedure done without PV mapping as a daycase is more effective than anti-arrhythmic drugs at reducing all hospital episodes for recurrent atrial fibrillation.
STUDY DESIGN	Multicentre, randomised clinical trial
TREATMENT REGIMEN	Arm 1-AVATAR-AF Ablation Protocol Arm 2-Anti-arrhythmic therapy Arm 3-Conventional AF Ablation
MAIN INCLUSION CRITERIA	1. Documented paroxysmal atrial fibrillation 2. Modification or initiation of anti-arrhythmic agent required for symptom control 3. Males or females eighteen (18) to eighty (80) years of age. 4. Suitable candidate for catheter ablation 5. Signed informed consent
MAIN EXCLUSION CRITERIA	1. Contraindication to catheter ablation 2. No carer to enable daycase discharge 3. Arrhythmias other than AF documented unless they have had curative ablation (eg. for atrial flutter)§ – Please see page 13 for more details. 4. No documentation of sinus rhythm within 3 months 5. Valvular or other heart disease needing regular follow up 6. EF <45% or moderate/severe LV dysfunction (determined by Echocardiogram in the last 6mths) 7. Active gastrointestinal disease precluding anticoagulation or trans-oesophageal echocardiogram 8. Renal failure with creatinine >200 µmol/L or on dialysis 9. Active fever or infection 10. Life expectancy shorter than the trial 11. Allergy to contrast 12. Severe cerebrovascular disease precluding daycase discharge 13. Bleeding or clotting disorders or inability to receive heparin 14. Uncontrolled diabetes (HbA1c ≥73 mmol/mol or HbA1c ≤64 mmol/mol and Fasting Blood Glucose ≥9.2 mmol/L) (shown in the last six months without evidence of being brought under control) 15. Serum Potassium [K^+] <3.5 mmol/L or >5.0 mmol/L (shown in the last six months without evidence of being brought under control) 16. Malignancy needing surgery, chemotherapy or radiotherapy 17. Pregnancy or women of child-bearing potential not using a highly effective method of contraception 18. Must not have previous (4 weeks prior to screening) or current participation in another clinical trial with an investigational drug or investigational device 19. Unable to give informed consent

	20. Uncontrolled thyroid disease defined as abnormal thyroid function tests causing cardiac manifestations within the last 6mths 21. Unable to attend follow-up visits
NUMBER OF PATIENTS	321 patients, 1:1:1 randomisation
DURATION OF STUDY	1 year recruitment period/1 year follow-up for each patient
NUMBER OF SITES	13 United Kingdom sites
PRIMARY ENDPOINT	Time to any hospital episodes (Emergency Room or outpatient) related to treatment for atrial arrhythmia
SECONDARY ENDPOINTS	1. Time to Death or Stroke from any cause 2. Any complications caused by the procedure (pericardial effusion, bleeding >2 units, phrenic nerve palsy and other) or the anti-arrhythmic drug (GI disturbance, skin irritation and other) 3. All hospital episodes which result in a change in therapy for atrial arrhythmia

1 INTRODUCTION

1.1 Background

Atrial fibrillation (AF) is the most common clinical cardiac arrhythmias and pulmonary vein isolation (PVI) has been shown to be more effective than anti-arrhythmic agents for maintaining sinus rhythm.[1-4] These comparative studies have used stringent methods for judging success. The current 2012 HRS/EHRA/ECAS guidelines recommend assessing outcome by 'any detectable AF' which is defined as 30seconds of sustained AF on a 24hour holter monitor or event recorder.[5] The previous 2007 guidelines, on which most current practice is based also indicated that Holter monitoring should be performed every 6months for 2years. These outcome measures are effective for determining the efficacy of a technology but have limited use for decision making in patients. A one minute episode on a 24hr tape at 12 months after an ablation in an asymptomatic patient may be deemed a 'failure' on scientific grounds but would not result in a repeat ablation or change in medication. There is a risk that trying to achieve 'perfect' outcomes may lead to procedures that are more complicated than is necessary to meet the patient's needs. Furthermore, patients with effective symptom control are expected to attend for hospital review and investigation, with the associated inconvenience and resource consumption without any prospect of a change in management strategy. There is some evidence that pursuing such a strategy may improve the stroke risk in an asymptomatic patient, but this has not been incorporated into any guidelines.[6,7] Multiple Holter recordings demonstrating sinus rhythm are reassuring but in patients with a high CHADSVASC score, the absolute reduction in risk and long term recurrence is not known. We would suggest that the main value of Holter recording is to diagnose the cause of ongoing palpitations following ablation as these may not be AF.

Therefore, we would propose that the definition of success in AF ablation and its implication needs re-evaluation. One level of success would be to eliminate stroke risk. This may need frequent monitoring and prevention of all episodes of AF both symptomatic and asymptomatic. Such an approach may need aggressive ablation endpoints with increased procedural and long term follow-up costs.[8] This may be justified by the number of strokes prevented. Studies addressing such endpoints would need several thousand patients, similar to RELY, ROCKET-AF and ARISTOTLE, which is probably beyond the scope of interventional studies at present.[9] Another level of defining success would be according to symptom control, but due to the lack of objectivity in symptom status, it has not been a popular endpoint for studies. Quality of life questionnaires have been used but most clinicians find these cumbersome to use and the data analysis difficult to understand.[10] As an alternative we would propose that attending hospital appointments and investigations both electively or as an emergency are objective and measurable events. Hospitalisation for inpatient treatment is a well-established endpoint and adding routine outpatient appointments is a minimal change but is more relevant to this type of symptom monitoring. Following post-operative checks after an AF ablation, symptom control that is good enough to not need regular review could be used a 'success' measure. 'If successful, you will not need to attend hospital' is also a tangible outcome measure for the patient unlike the current outcome target of 'any detectable AF which requires the physician to clarify and then add the caveat of the limitations of the detection method and that stroke risk remains unknown despite this seemingly conclusive outcome. Furthermore, using hospital episodes aligns the results of the procedure with those used by healthcare commissioners.

This re-evaluation of the objectives of AF ablation, also raises the question of which components of an AF ablation procedure are needed to deliver the effective symptom control rather than prevent any detectable AF. Originally, pulmonary vein (PV) ectopic foci were shown to trigger AF and a technique for identifying and ablating these ectopic foci was proposed as a potential treatment for AF. The unpredictability of ectopy and the high incidence of PV stenosis, led to this approach being abandoned in favour of ostial segmental pulmonary vein isolation (PVI) guided by circular PV mapping catheter on the basis that >90% of ectopy originated from the PV. Subsequently it was shown that circumferential antral ablation (CPVA) with acute isolation proven by PV mapping and entrance block was superior to segmental ostial ablation or ablation without PV mapping. Most current approaches are based on this data and produces a consistent and reproducible success rate of around 50-70% for paroxysmal AF.[5] However,

the mechanism for success is uncertain as a significant proportion of ablated veins will electrically reconnect even in patients without AF recurrence.[11] It has been assumed that improving the durability of PV isolation by altering energy type and reducing the need for operator skill would be the path to better results and has included balloon ablation catheters such as the cryoballoon and laser balloon, robotic technologies and multipolar circumferential catheters that can map and ablate. However, there has been no discernible improvement with any of these approaches (though the cost per procedure has increased). We believe that this is because all these technologies use PV isolation as an endpoint and this is the outcome that can be expected using this endpoint.[12-14] The attempts to demonstrate the benefits of these new technologies revealed some intriguing data, particularly the finding that ablation 'quality' in the antral region (by using steerable sheaths or simply additional lesions) has a better association with clinical outcomes than pulmonary vein isolation in multivariate analysis.[15,16] This may be related to effect on the local autonomic innervation, but raises the question of the necessity of demonstrating pulmonary vein isolation during ablations using current ablation modalities.[17] The need for an aggressive approach with electrical isolation of all veins has not been tested against symptom-based outcome measures such as the requirement for further hospital intervention.

Such a proposal may be controversial but its justification rests on whether symptom control or stroke prevention is the goal of AF ablation. Currently all guidelines indicate that symptoms are the only indication and yet 'any detectable AF' is used to assess procedures and it has become a 'sacred cow' that is rarely challenged. [3,4,12-14] Cost-effectiveness studies on paroxysmal AF ablation, which have excluded any putative stroke or mortality benefits suggest incremental cost-effectiveness ratio of ablation versus medical therapy was $51 431 per quality-adjusted life-year.[18] This is still a considerable increase particularly as population studies suggest that the burden of AF is increasing with the aging population. Changing the definition of a successful ablation to the prospect of avoiding hospital episodes may enable the reduction of absolute costs of the procedure which would have a significantly beneficial effect on the cost effectiveness calculations. Review of our internal data suggests using the Advance™ Cryoballoon (Medtronic,Minneapolis) produces PV isolation >80% of veins without the need for additional ablation which requires PV mapping catheters. If the procedure is done without PV mapping, there are multiple cost savings PV mapping catheter, EP recording equipment and specialist staff. This would also shorten the procedure and may enable most patients to be completed as a day case which would be a cost saving through reduced bed occupancy. One series has suggested that nearly 90% of patient can already be discharged safely as a daycase.[19] Our annual audits would support this view in that most complications (pericardial effusion, femoral bleeding, urinary retention, phrenic nerve injury) occur within three hours of the end of the procedure. The rest do not present during the overnight stay (atrio-oesophageal fistula, pulmonary vein stenosis, delayed tamponade). Simply changing the definition of success may enable all of these cost-savings to be made without compromising outcome to the patient.

In summary, developments in paroxsymal AF ablation have been monitored against the definition of any detected 30seconds of AF, which is not necessarily measure of symptom control. Hospital episodes are an objective and well established endpoint throughout the healthcare system and are more reflective of the patient's expectations. The increasing population burden of AF will need more cost effective approaches to treatment of symptoms. It is not known whether current approaches to antral pulmonary vein ablation still necessitates pulmonary vein mapping, which is a major source of to cost and complexity.

The proposed study is based on the following observations:

i) AF ablation is well established as the most effective method for preventing recurrence.

ii) Current methods for AF ablation are costly and complex with only a small minority of the AF population having access to such procedure.

iii) The Advance Cryoballoon is effective at producing antral PV ablation mapping.

iv) AF ablation has not been compared against anti-arrhythmic agents with the primary goal of controlling symptoms.

1.2 Research Hypothesis

A streamlined AF ablation procedure done without PV mapping as a daycase is more effective than anti-arrhythmic drugs at reducing all hospital episodes for recurrent AF.

2 STUDY OBJECTIVES

2.1 Primary Objective

To determine if antral AF ablation without electrophysiological confirmation of PV isolation is more effective than anti-arrhythmic agents at achieving freedom from hospital based treatment.

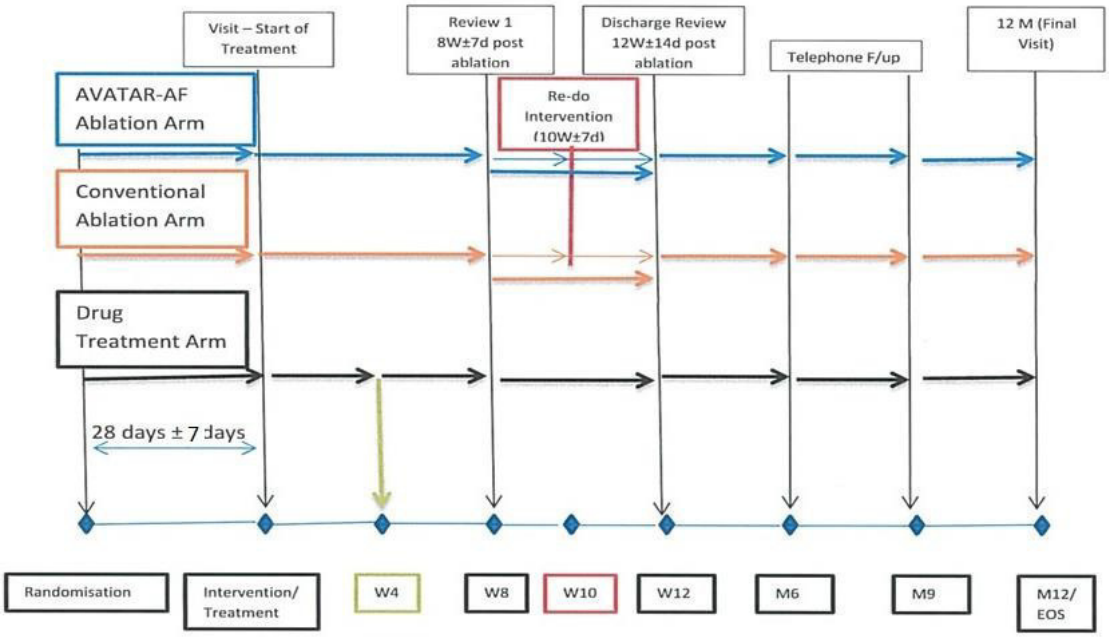
2.2 Secondary Objectives

To determine if antral AF ablation without electrophysiological confirmation of PV isolation performed as a daycase is less effective than the conventional approach.

3 STUDY DESIGN

AVATAR-AF is a multicentre, randomised controlled study comparing a streamlined AVATAR-protocol ablation procedure to anti-arrhythmic therapy in patients with documented paroxysmal AF who are considered to be failing current strategy for AF. A secondary control arm will also compare the AVATAR-protocol to conventional AF ablation. 321 patients who are on no prior anti-arrhythmic, 'pill-in-pocket' or taking regular anti-arrhythmics will be randomised in a 1:1:1 manner to a treatment strategy of either AVATAR-protocol ablation, anti-arrhythmic therapy or conventional AF ablation and followed-up for 1 year.

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and all applicable regulatory requirements.



4 Endpoints

4.1 Primary Endpoint

Time to all hospital episodes (Emergency Room or patient request for OPD) related to treatment for atrial arrhythmia.

4.2 Secondary Endpoints*:*

1. Time to death or stroke from any cause.

2. Any complications caused by the procedure (pericardial effusion, bleeding >2 units, phrenic nerve palsy and other) or the anti-arrhythmic drug (GI disturbance, skin irritation and other).

3. All hospital episodes which result in a change in therapy for atrial arrhythmia.

5 PATIENT RECRUITMENT

5.1 Patient Selection Procedures

Research staff will identify potential study patients against inclusion and exclusion criteria, before the Investigator determines their eligibility for participation. The Investigator will discuss the rationale for the study, study procedures, risks and benefits and all other issues mandated by the consent process. The potential participant will be offered an opportunity to participate in the study and written informed consent will be obtained if they agree. Study procedures and assessments will only be performed after written informed consent has been obtained.

At the screening visit, the patients general health will be assessed in a physical examination and recording of vital signs. The patient's medical and medication history will also be recorded.

A fasting blood sample will also be taken to exclude patients with uncontrolled diabetes or [K^+] and serum creatinine outside acceptable safety ranges and the patient will be asked to complete a Quality of Life questionnaire (EQ5D) and an Atrial Fibrillation Effect on QualiTy of life (AFEQT) questionnaire. . A blood test result within 6 months is acceptable. Any blood test result taken more than 6 months prior to randomisation will need to be repeated. A copy of the blood results must be filed in the patient notes. Any other routine clinical tests should be performed as per local practice.

Both the AVATAR protocol and conventional ablation procedures will be discussed with the patient and the anti-arrhythmic agent or the change in dose that would be selected as the next line of treatment would be agreed at this stage in preparation for potential anti-arrhythmic arm.

The informed consent process and all study assessments will be documented in the patient's medical notes and study case report forms.

5.2 Inclusion Criteria

To be eligible for the trial, subjects must meet all of the following criteria:

1. Documented paroxysmal atrial fibrillation
2. Modification or initiation of anti-arrhythmic agent required for symptom control
3. Males or females eighteen (18) to eighty (80) years of age
4. Suitable candidate for catheter ablation
5. Signed informed consent

5.3 Exclusion Criteria

Subjects with any of the following will be excluded from the study:

1. Contraindication to catheter ablation
2. No carer to enable daycase discharge
3. Documented Arrhythmias other than AF unless they have had curative ablation (eg. for atrial flutter)§ .
4. No documentation of sinus rhythm within 3 months
5. Valvular or coronary heart disease needing regular follow up
6. EF <45% or moderate/severe LV dysfunction(determined by Echocardiogram in the last 6 months)

7. Active gastrointestinal disease precluding anticoagulation or trans-oesophageal echocardiogram
8. Renal failure with creatinine >200 µmol/L or on dialysis
9. Active fever or infection
10 Life expectancy shorter than the trial
11. Allergy to contrast
12 Severe cerebrovascular disease
13. Bleeding or clotting disorders or inability to receive heparin
14. Uncontrolled diabetes (HbA1c ≥73 mmol/mol or HbA1c ≤64 mmol/mol and Fasting Blood Glucose ≥9.2 mmol/L) (shown in the last six months without evidence of being brought under control)*
15. Serum Potassium [K^+] <3.5 mmol/L or >5.0 mmol/L (shown in the last six months without evidence of being brought under control)
16. Malignancy needing surgery, chemotherapy or radiotherapy
17. Pregnancy or women of child-bearing potential not using a highly effective method of contraception **
18. Must not have previous (4 weeks prior to screening) or current participation in another clinical trial with an investigational drug or investigational device
19. Unable to give informed consent
20. Uncontrolled thyroid disease defined as abnormal thyroid function tests causing cardiac manifestations within the last 6mths21. Unable to attend follow up visits

§ **AVATAR-AF Guidance on Atrial Flutter**

(I) 12 lead ECG documentation of typical atrial flutter during screening

- *Patient should not be recruited to the AVATAR study and should undergo Cavo-Tricuspid Isthmus line(CTI)ablation.*
- *If symptomatic atrial fibrillation is still present then the patient can be considered for AVATAR recruitment.*

(II) **12 lead ECG documentation of typical atrial flutter after randomisation**.

- *Patient should be suspended from the AVATAR study intervention and should undergo CTI ablation.*
- *If symptomatic atrial fibrillation still present then the patient can be considered for AVATAR intervention.*

(III) Holter monitor – Atrial fibrillation + organised atrial activity suggestive of paroxsysmal atrial flutter.

- *Can be recruited to AVATAR study, but cannot have CTI at first ablation.*

(IV) CTI dependent flutter (or any other arrhythmia) occurs during AF ablation procedure.

- *These patients should not be ablated during the first ablation procedure*

***(V)* Symptomatic atrial flutter picked up as an endpoint.**

Can progress to ablation as per physician discretion

* A fasting blood glucose must have been done within the last 6mths confirming that blood glucose under control. If no blood test result available,a new fasting blood glucose sample will be taken from all consented potential participants at screening to exclude uncontrolled diabetes, defined as:

- HbA1c ≥73 mmol/mol or
- HbA1c ≤64 mmol/mol and Fasting Blood Glucose ≥9.2 mmol/L

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** Women of child-bearing potential not using a highly effective method of contraception must undergo a pregnancy test. Acceptable methods of contraception include the following:

- Barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used ONLY in combination with a spermicide.
- Intra-uterine devices.
- Oral contraceptive agents started at least 90 days before start of study.
- Depo-Provera (medroxyprogesterone acetate).
- Levonorgestrel implants.
- Naturally or surgically sterile (amenorrheic for at least 1 year and no record of child birth for naturally sterile persons).
- Male partner is sterile and is the only sexual partner

Women not of child-bearing potential and eligible for the trial will have been hysterectomised, sterilised or be post-menopausal (ie. at least one year since their last period).

5.4 Randomisation Procedures

Eligible patients who have given written, informed consent and who meet all the inclusion criteria and no exclusion criteria will undergo 1:1:1 randomisation to an un-blinded treatment of either AVATAR-protocol AF Ablation, medical anti-arrhythmic therapy or conventional AF ablation. Randomisation will be performed electronically using the InForm electronic data capture system and will be stratified by site.

From the date of randomisation, the 1st Intervention date (ablation or anti-arrhythmic medication change) must occur 28 days ± 7days after this, therefore an ablation procedure date will be identified according to local EP catheter lab availability for each consenting, eligible patient and randomisation of the patient will then be scheduled for 28 days ± 7days from this available date.

The patient may be withdrawn from any AF ablation treatment by the Investigator if any safety concerns arise during the period between randomisation and the ablation which make the patient an unsuitable candidate for the procedure. The patient will then be withdrawn from the study.

6 TREATMENT ARMS

In the 4 week period (28 days ± 7days) between Randomisation and 1st Intervention, there will be no change to the patient's arrhythmia treatment: the treatment which the patient has been randomised to will only occur on the date of 1st Intervention. All three treatment arms will follow the same scheduling protocol regardless of intervention.

6.1 AVATAR-AF Ablation Protocol

Anticoagulation regime will be at physician's discretion according to established HRS/ESC guidelines guided by CHADSVASC scoring system. Patients on anticoagulation may follow a continuous, bridging or without anticoagulation as per local protocol.

The procedure is performed under sedation or general anaesthetic according to local preference. TOE is performed according to local protocols. Femoral sheaths placed in the right femoral vein (ultrasound guidance allowed). A single transeptal puncture is performed under TOE, ICE, CS catheter or aortic pigtail guidance. If coronary sinus catheter is used, this should be performed without electrograms if possible.

Pulmonary venography taken. The sheath is exchanged for a Cryosheath or other suitable large sheath and an Arctic Front Advance balloon is used to occlude the PV to Grade 3/4 and deliver

2 x 3min cryoablations to each vein. Phrenic nerve monitoring will be done with a temporary transvenous pacing wire and box. No specialist EP catheters are deployed and no formal assessment of PVI is done. ACT kept above 300s. Reversal of heparin with Protamine is allowed.

Transthoracic Echo (hand-held echo with documentation sufficient), Hb check and groin survey at 6 hours post-procedure. If all are stable, the patient is discharged as a daycase procedure and given appropriate instructions and advice on potential concerns and process for seeking advice

Patient is given a date for possible 'redo' procedure at 10wks ± 7 days post ablation.

All medication is continued for 4 weeks post-ablation and then all agents being used for anti-arrhythmic effect are stopped.

6.1.1 Review 1 (8 weeks ± 7 days post-ablation)

The patient is first reviewed 8 weeks ± 7 days post ablation. If asymptomatic for palpitations, weekly improvement or not possible to assess in time scale then the patient is entered into discharge protocol at 12 weeks ± 14days.

If there are ongoing symptoms then the redo procedure (as scheduled post 1st Intervention ablation) will be performed which will be a conventional PVI using radiofrequency thermocool catheter and PV mapping catheter or according to local practice. A daycase approach is taken again as per first procedure and the patient is reviewed at 12 weeks ± 7days and if stable enters Discharge protocol at 12 weeks ± 14days.

6.2 Anti-arrhythmic therapy

The anti-arrhythmic agent or the change in dose that was discussed with the patient selected as the next line of treatment at the initial screening visit is initiated at the 1st Intervention date. The anti-arrhythmic treatment is chosen should be done in accordance with local practice and guidelines.

The patient will undergo 2 reviews prior to entering the Discharge protocol.

- ***Review 1 (4 weeks post-1st Intervention)***
- ***Review 2 (8 weeks post-1st Intervention)***

At each review, the patient can be left unchanged, have an increase in drug dose or change of agent as required. Review 1 at 4 weeks post 1st intervention can take place as a telephone follow up followed by a clinic visit if required. Following the 2 reviews, the patient enters the Discharge protocol at 12 weeks ± 14days.

6.3 Conventional AF Ablation

Patients randomised to the conventional AF Ablation arm will undergo the conventional Cryoablation procedure. This arm will be used as a second control arm to compare the differences in impact on healthcare resources, complication rates and clinical outcomes between conventional ablation and AVATAR-protocol ablation.

Anticoagulation regime will be physician discretion according to established HRS/ESC guidelines guided by CHADSVASC scoring system. Patients on anticoagulation may follow a continuous, bridging or without anticoagulation as per local protocol.

The procedure is performed under sedation or general anaesthetic according to local preference. TOE is performed according to local protocols. Femoral sheaths placed in the right

femoral vein (ultrasound guidance allowed). A single or double transeptal puncture may be done guided by TOE, aortic pigtail, ICE or CS catheter guidance. Pulmonary venography taken. The sheath is exchanged for a Cryosheath or other suitable large sheath and an Arctic Front Advance balloon is used to occlude the PV to Grade 3/4 and deliver 2 x 3min cryoablations to each vein. Phrenic nerve monitoring can be according to local protocol.

The PV will be mapped using a circular mapping catheter of the operators choice and the number of veins isolated with this approach documented. PV isolation is completed with either repeat cryoballoon, deflectable cryotherapy catheter or radiofrequency catheter. The catheters used and outcomes documented.

The patient is monitored overnight and should have an Hb, groin and echo (handheld with documentation sufficient) check prior to discharge.

All medication is continued for 4 weeks post-ablation and then all agents being used for anti-arrhythmic effect are stopped.

6.3.1 Review 1 (8 weeks ± 7 days post-ablation)

The patient undergoing conventional AF ablation is also first reviewed 8 weeks ± 7 days post ablation. If asymptomatic for palpitations, weekly improvement or not possible to assess in time scale then the patient is entered into discharge protocol at 12 weeks ± 14days.

If there are ongoing symptoms then the redo procedure (as scheduled post 1st Intervention ablation) will be performed at 10wks

6.4 Redo Ablation (10 weeks*± 7 days*)

Anticoagulation regime will be physician discretion according to established HRS/ESC guidelines guided by CHADSVASC scoring system. Patients on anticoagulation may follow a continuous, bridging or without anticoagulation as per local protocol.

The procedure is performed under sedation or general anaesthetic according to local preference. TOE is performed according to local protocols. Femoral sheaths placed in the right femoral vein (ultrasound guidance allowed). A single or double transeptal puncture is performed under TOE, ICE, aortic pigtail or CS catheter guidance.

Pulmonary venography taken and PV mapping performed. Further ablation can be performed according to operator preference by radiofrequency ablation, Cryoballoon or cryocatheter.

Transthoracic Echo (hand-held echo with documentation sufficient), Hb check and groin survey at 6 hours post-procedure.

Patients in AVATAR-AF protocol arm are discharged as a daycase procedure and given appropriate instructions and advice on potential concerns and process for seeking advice.

Patients in conventional ablation arm are kept overnight.

All medication being used for anti-arrhythmic effect are stopped.

6.5 Discharge Review (Week 12*± 14 days*)

Patient will be assessed at week 12 for evidence of Primary and secondary endpoints. Patients will also be reviewed for suitability for entering discharge protocol.

7 ASSESSMENT AND FOLLOW-UP

7.1 Discharge Protocol

Patients from the all therapy arms will enter the Discharge protocol 12 weeks ± 14days post-1st Intervention providing no ongoing symptoms are presented before this.

Patients will be given the centre's Research Nurse contact details and are able to request an unscheduled visit if they experience recurrent symptoms and need hospital review. A blinded research Nurse or designee will contact the patient by telephone every 3 months to ensure that no endpoints have occurred.

The patient will be advised that the blinded research Nurse or designee making the phone call will not know which treatment they have received and the patient will be given a copy of the questions that they will be asked.

7.1.1 Patients unable to enter the Discharge Protocol

Patients not able to enter the discharge protocol at 12 weeks will have necessary advice (further OPD, procedure) which will be a primary endpoint. The date of the endpoint will be the date of the subsequent event. These patients will be followed up at their usual study visits at M6, M9 and Final visit.

7.2 Telephone Follow-up (All patients)

All patients who have been randomised to the trial will be followed up by telephone every three months (6/9/12mths) after week 12 visit. Questions asked during this follow-up will cover hospital attendance (reason/outcome/medication changes/investigations), any symptoms experienced and whether the patient needs to see the research team for an unscheduled visit. The Month 12 questions can be done by either telephone or face to face as a part of the End of Study Visit.

7.2.1 Telephone questions;

The staff making the telephone query will be blinded to the treatment arm and may be from a different site. At the beginning of the conversation the caller will explain that they do not know which treatment arm they are in and that they should try to avoid any references to the treatment and just try and answer the question directly. Please see the Appendix 1 for the details of the telephone questions.

7.3 1-Year Follow-up (All patients)

1st Intervention will be considered baseline, all patient returning for follow-up 1 year ± 14days after this date. At this visit, all patients will undergo the following assessments:

- Physical Examination
- Vital signs
- Concomitant medications
- ECG
- 24 hour holter monitor tape
- EQ5D quality of life questionnaire
- Adverse Events
- Study Endpoints
- Atrial Fibrillation Effect on QualiTy of life (AFEQT) patient questionnaire

All data will be recorded on the InForm eCRF.

8 Endpoints

8.1 Primary Endpoint:

1. Time to any hospital episode (Emergency Room or patient request for OPD) related to treatment for atrial arrhythmia.

8.2 Secondary Endpoints:

1. Time to death or stroke from any cause.

2. Any complications caused by the procedure (pericardial effusion, bleeding >2 units, phrenic nerve palsy and other) or the anti-arrhythmic drug (GI disturbance, skin irritation and other).

3. All hospital episodes which result in a change in therapy for atrial arrhythmia

All study endpoints will be reported from the date of 1st intervention.

8.3 Crossover between therapies

Following the week 12 visit, a patient from any group, the Investigator may initiate further drug therapy or schedule a standard ablation procedure for the patient. However, the following are required;

i) *Ablation Arms (Conventional and AVATAR-AF):* Can start anti-arrhythmic drugs or further redo-ablation if there is ECG/Holter documentation of recurrent AF/AT

ii) *Drug Therapy Arm:* May receive ablation therapy if failed one anti-arrhythmic at maximum standard dose or two anti-arrhythmic agents at sub-maximal dose or due to side effects.

iii) *New tachycardia documented that needs treatment (VT/AVNRT/AVRT).* The patient is withdrawn from the study

8.4 Endpoint Adjudication

The endpoint adjudication will be done by an independent Endpoint Adjudication Committee (EAC). The EAC will centrally review and classify suspected outcome events, verifying whether they meet protocol definitions. Any hospital episodes (Emergency Room or outpatient) related to treatment for atrial arrhythmia, Stroke or Death from any cause, Any complications caused by the procedure (pericardial effusion, bleeding >2 units, phrenic nerve palsy and other) or the anti-arrhythmic drug (GI disturbance, skin irritation and other), All hospital episodes which result in a change in therapy for atrial arrhythmia.

Any attendance to hospital or specialist cardiac clinic will require the documentation of a discharge letter or clinic letter for primary endpoint adjudication.

Definitions of study endpoints: see Appendix 2

9 Patient visit schedule

	VISIT (Month)					
PROCEDURE	SCREENING (M-0.5 ± 14d)	1ST INTERVENTION (M0 +7 d)	WK4 REVIEW (M1 ± 7d)	WK8 REVIEW (M2 ± 7d)	WK12 REVIEW (M3 ± 14d)	EOS (M12 ± 14d)
Obtain Informed Consent	X					
Eligibility Criteria	X					
Vital Signs	X				X	X
Physical Examination	X				X	X
Medical History Assessment	X				X	X
Concomitant Medications	X				X	X
Fasting Blood Sample	X					
Quality of Life Questionnaire	X					X
Allocate 1st Intervention date	X					
Randomisation *	X					
Initiate 1st Intervention		X				
Allocate possible ablation 're-do' date **/^		X				
Review anti-arrhythmic medication †			X	X		
Post-ablation symptoms review **/^				X	X	
Enter Discharge Protocol					X	
Electrocardiogram						X
24-Hour Holter monitor tape						X
Echocardiogram	X					
Adverse Events		X	X	X	X	X
Study Endpoints			X	X	X	X
AFEQT patient questionnaire	X					X

* = Randomisation date to be scheduled 28d ±7 d from allocation of 1st Intervention date

** = AVATAR-protocol ablation arm patients only

† = Anti-arrhythmic therapy arm patients only

^ = Conventional ablation arm patients

10 Safety Reporting

Information about trial adverse events will be collected from randomisation until the end of the trial

10.1 Adverse Event Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the even; it does not refer to an event which hypothetically might have caused death if more severe.
  Requires hospitalisation (>24 hrs), or prolongation of existing inpatient hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

Any Adverse Events that are <u>related</u> to atrial arrhythmia will be reported as endpoints rather than Adverse Events. Serious Adverse Events that are related to atrial arrhythmia must be reported as SAEs.

Any planned hospitalisations such a for a redo ablation procedure prior to entry into the Discharge protocol or planned surgery will not be reported as Serious Adverse Events as these are expected.

10.2 Expected Serious Adverse Events

- Symptoms of atrial fibrillation/tachycardia
- Pericardial Effusion
- Vascular Bleeding
- Phrenic Nerve Palsy
- PV stenosis
- Shortness of Breath more than 1 week from the procedure
- Chest pain more than 1 week from the procedure

10.3 Adverse Event Intensity or Severity

The intensity or severity of each adverse event should be classified by the investigator according to the following guidelines:

Intensity	Description
Mild	Any event that results in minimal transient impairment of a body function and does not threaten damage to a body structure, and/or does not require intervention other than monitoring.

Moderate	Any event which results in moderate transient impairment of a body function or damage to a body structure, or which requires intervention.
Severe	Any event which is life threatening, results or could result in significant permanent impairment of a body function or damage to a body structure, requires significant and timely intervention to prevent permanent impairment of a body function or damage to a body structure, or which is intolerable or places the subject at immediate risk of harm.

10.4 Adverse Event Causality

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

Relationship	Description
Unrelated	There is no evidence of a causal relationship with the anti-arrhythmic therapy or ablative therapy.
Unlikely	There is little evidence to suggest a causal relationship with the anti-arrhythmic or ablative therapy (e.g the event did not occur within a reasonable time after study treatment). There is another reasonable explanation for the event (e.g the participants clinical condition, other concomitant treatments).
Possible	There is some evidence to suggest a causal relationship with the anti-arrhythmic or ablative therapy (because the event occurs within a reasonable time after the study therapy). However, the influence of other factors may have contributed to the event (e.g the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship with the anti-arrhythmic or ablative therapy and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship with the anti-arrhythmic or ablative therapy and other contributing factors can be ruled out.
Not Assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

10.5 Reporting Procedures

All adverse events should be reported via the eCRF within 24 hours of awareness of the event. All adverse events occurring between randomisation and the patient's last study follow-up visit will be reported. All adverse events will be followed up until resolution or until the end of trial..

Adverse events for any patients who withdraw from the study prematurely should be collected and followed up through at least the time of discontinuation.
Depending on the nature of the event, the reporting procedures should be followed. All questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Non-Serious AEs
All such events, whether expected or not, should be recorded on the eCRF.

Serious AEs
An SAE form should be completed via the eCRF within 24 hours of awareness of the event. The Chief Investigator or designee will review each SAE via the eCRF,

Please refer to section 7.1 Adverse Event Definitions for further clarification on definitions of AEs and SAEs and how to report in relation to study endpoints.

Related and Unexpected SAEs
All SAEs should be reported to the NRES Committee London - Brent (United Kingdom) where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Local Investigators should report any SAEs as required by the Sponsor, Research & Development office and other appropriate authorities/committees.

11 STATISTICAL ANALYSIS

11.1 Sample Size Calculation

In this time-to-event study of hospital episodes, required sample numbers have been estimated using the log-rank test under the Freedman method based on the occurrence of first event during the 12-month follow-up period. The null hypothesis is that there is no difference in the distributions. Adopting a conservative approach, an initial two-sided alpha of 0.05 is chosen, given the need to allow for the inherent multiple testing between the three arms of the study, the conservative Bonferroni correction is applied and the alpha value used in the power calculations is reduced to 0.025.

Estimating the proportion experiencing a hospital episode in the follow-up period in the anti-arrhythmic arm as 0.63 and the corresponding proportion in the AVATAR ablation arm as 0.40, assuming the occurrence of 103 events, with 100 evaluable patients in each of the two treatment arms yields a power of 0.8. A similar power is obtained for the comparison of the AVATAR ablation arm (0.40) and the conventional AF ablation arm (0.20).

A sensitivity analysis indicates that these sample size estimates are reasonable. It is anticipated that the loss to follow-up will be small, approximately 7%. Consequently, 321 patients will be randomised in a 1:1:1 manner to a treatment strategy of either AVATAR-protocol ablation, anti-arrhythmic therapy or conventional AF ablation and followed-up for 1 year.

11.2 Data Analysis

Primary outcome: Failure is counted when a patient experiences any hospital episode related to treatment for atrial arrhythmia. Patients are censored from their treatment group when they switch to a treatment other than that to which they were originally assigned or when they leave their treatment group without having experienced a hospital episode.

Data will be analyzed using the intention-to-treat principle and a p value of 0.05 or less will be considered significant. Primary outcome will be analysed using Kaplan-Meier statistics and differences will be tested using log-rank test and proportional hazards models. Other outcomes will be compared using t-test for continuous and Chi-square test or Fisher exact test for categorical variables and the appropriate generalized linear model will be used.

12 DATA MANAGEMENT AND QUALITY CONTROL

The complete dataset will be collected for all patients who are randomised into the trial. If consent to participate is withdrawn then any data collected will be retained and used in the study, with no further data collected or study procedures carried out on the patient. The electronic data capture system, InForm will be used to document clinical data.

The signed, original informed consent forms and the documentation of all study procedures and assessments will be kept in the patients' study notes. All data to be transferred to the study co-ordination centre with all appropriate supporting documentation will be done as required such as hospital reports or imaging reports with all patient identifiers removed. Patients study documents will be identified by their study-specific patient number allocated at randomisation.

12.1 Electronic Recording of data

(Electronic CRF): The principal means of data collection from patient visits will be Electronic Data Capture (EDC) via the internet (InForm). Data is entered into the EDC system via site personnel. All data recorded in the CRF will be signed by the Investigator or his/her appropriate designee. All changes made following the electronic signing will have an electronic audit trail with a signature and date. Specific instructions and further details will be outlined in SOPs and/or manuals.

12.2 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

12.3 Monitoring

The trial conduct will be monitored and by Imperial Clinical Trials Unit (ICTU), in accordance with the trial risk assessment and monitoring plan. Further details of level of monitoring to be performed will be provided to study sites in the Investigator Site File. The monitor will assess compliance with the protocol, GCP and regulatory requirements. They will also review the patient consenting process, essential study documents, AE and SAE reporting as well as verifying source data to ensure the quality, accuracy and validity of the data at each investigational site.

12.4 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

12.5 Archiving

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, defined as the last patient's last visit. Local investigator sites will be responsible for making arrangements for the secure archiving of study documents locally.

13 ETHICAL and LEGAL ISSUES

13.1 Ethics Approval

Ethics approval has been granted by the NRES Committee London - Brent to conduct the study in the United Kingdom. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. ICTU will require a copy of the Trust R&D approval letter before participants can be entered into the study.
The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later versions.

13.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information sheet offered and time allowed for consideration. Signed participant consent must be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so must be recorded. In these cases, the participants remain in the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

13.3 Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and RECs

13.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

13.5 Sponsor

Imperial College Academic Health Science Centre will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the Investigational Centres taking part in the study.

13.6 Funding

Medtronic and British Heart Foundation (BHF) are providing the funding for this study in the form of a grant.

14 STUDY MANAGEMENT STRUCTURE

14.1 Trial Steering Committee (TSC)

A Trial Steering Committee consisting of an Independent Chair (i.e. an individual with experience in clinical research who is not part of the trial team), Chief Investigator, Independent Experts, Operations Manager, Trial Manager and representatives of the funders is convened. The TSC will be responsible for the scientific and ethical conduct of the study and will supervise progress of the trial. The trial protocol and subsequent amendments will be approved by the TSC. The TSC members will be required to attend TSC meetings which will be held prior to the start of the trial and as required throughout the trial.

14.2 Data & Safety Monitoring Board (DSMB)

An independent Data & Safety Monitoring Board (DSMB) will be convened and meet to provide independent advice on study conduct and safety issues. The DSMB will meet at the start of the trial and as required thereafter based on planned interim analyses. Meetings will be held approximately annually or as required throughout the duration of the trial. Safety data will be studied after 75 and 150 patients have received treatment, or one year after the first patient is randomised, whichever occurs sooner. Meetings will also be held as necessary should any urgent issues occur. The DSMB will develop a charter which describes the framework within which it will operate.

14.3 Early Discontinuation of the Study or Individual Subjects

14.3.1 Early Discontinuation of the Study by Data Safety Monitoring Board (DSMB)

If, in the opinion of the DSMB the clinical observations in the study suggest that it might not be justifiable to continue, the study may be terminated following consultation with the Sponsor and the TSC. Alternatively, the Sponsor may give written notification to the investigator, Ethics Committee of the early discontinuation of the study, including reasons.

In case of early discontinuation of the study, the next Follow-up Visit assessment should be performed for each subject, as far as possible. The patient will then be returned to the treating secondary care team.

14.3.2 Early Discontinuation of Individual Subjects

The reason for a patient discontinuing study will be recorded in the case record form. A discontinuation occurs when an enrolled patient permanently and totally withdrew the study consent regardless of the circumstances, prior to completion of the protocol. A discontinuation must be reported immediately to the co-ordinating centre. It may not be necessary for a patient to stop follow-up after an endpoint. The investigator will provide or arrange for appropriate follow-up for such patients, and document the course of the patient's

condition. The patients should, if at all possible, be followed to the end of the study despite reaching the study endpoint as the intention-to-treat analysis includes all patients.

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. In case of early discontinuation of a subject, the Follow-up assessments should be performed, as far as possible.

14.4 Trial Management Group (TMG)

The Trial Management Group (TMG) consisting of the Chief Investigator, Operations Manager, Trial Manager, Trial Monitor and additional members as appropriate, will meet fortnightly to ensure that the study runs smoothly and according to the pre-agreed timetable

14.5 End of trial

The trial will end when all patients have completed month 12 follow-up visit.

15 PUBLICATION POLICY

Trial results will be released in several manuscripts providing outcomes of the trial as a whole. All publications and presentations relating to the trial will be authorised by the Trial Steering Committee. Named authors will include the Investigators from all participating investigational centres.

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: AVATAR-AF

Protocol Number: Protocol Version 6.1

Signed: _____

Prapa Kanagaratnam
Dr.

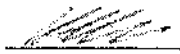
Date: 6/3/2018

16 SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: AVATAR-AF

Protocol Number: Protocol Version 6.1

Signed: 

Name of Sponsor's Representative Ruth Nicholson
Title Research Governance Manager
Sponsor name Imperial College London

Date: 06/03/18

17 SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: AVATAR-AF

Protocol Number: Protocol Version 6.1

Signed: _____

Name of Statistician Emanuela Falasheti
Title Senior Statistician
Organisation/Company ICTU

Date: 6/3/2018

18 **SIGNATURE PAGE 4 (Principal INVESTIGATOR)**

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

STUDY TITLE: AVATAR-AF

PROTOCOL NUMBER: PROTOCOL VERSION 6.1

ADDRESS OF INSTITUTION:

_____

_____

_____

SIGNED: _____

PRINT NAME AND TITLE:

_____

DATE: _____

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20 Appendix 1: Telephone Questions

i) Have you attended hospital for any reason other than for routine blood tests (yes/no)
If yes –
a) Was the problem related to your atrial fibrillation? (yes/no)
b) What were you suffering from? (palpitations/breathlessness/fainting/ bleeding/weakness/ confusion)
c) What was the outcome? (Reassured (no further appointments or tests needed)/Asked to see your Cardiologist/Asked to see another hospital specialist/Asked to see GP)

d)) Did you had any of the following investigations done in hospital? (ECG,Non-invasive ambulatory cardiac monitoring (including holter/memo etc)/Echo/Exercise test/Coronary angiogram/MRI/CT/Ultrasound/endoscopy/CXR)
e) Were you given any drugs for you heart?
If yes – which ones
f) Were you advised to change any of your medications?
If yes – which one
g) Did you have any procedures whilst you were in hospital
If yes- what was it

ii) Have you had any of the following symptoms;
a) racing heart beat lasting more than half an hour
if yes – <1/week or >1/week
b) racing heart beat more than 5mins but less than half an hour
if yes – <1/week or >1/week
c) Have you had any unexplained breathlessness, dizzy spells, chest pain, fainting attacks/weakness/confusion
if yes which-

iii) Do you think you the situation is bad enough that you need to change medication or have another procedure to help make you better? (yes/no)

iv) Do you think you are having side effects or complications from your treatment? (yes/no)

v) If you have answered yes to any of the questions we recommend that you see your GP and discuss whether you need another appointment with you heart specialist. We will pass on the information from the phone call to you heart specialist and they may contact you directly if they are concerned about any of the answers you have given.

21 Appendix 2: AVATAR-AF Endpoint definitions

Symptoms of atrial fibrillation/tachycardia:	palpitations lasting >5min, transient dizziness or fainting, lethargy, shortness of breath on exertion, chest discomfort
• ECG documentation:	• irregularly narrow QRS without p-waves lasting >30secs narrow QRS with A>V evident or 1:1 at >100bpm with sudden onset lasting >30sec or incessant at constant rate
Pericardial Effusion:	global echo-lucent space around myocardium >0.5cm maximally in diastole • SEVERE: pericardial drain inserted, sternotomy, • MODERATE: delayed discharge
Vascular Bleeding:	Bleeding visualised by haematoma or imaging associated with Hb drop of >2g/dl • SEVERE: Surgical intervention, transfusion required
Phrenic Nerve Palsy:	Reduced excursion of hemi-diaphragm on chest x-ray in inspiration and expiration more than 1day after procedure • SEVERE: exertional symptoms with CXR changes at >3mth • MODERATE: asymptomatic with CXR changes at >3mth
PV stenosis:	Evidence of >50 reduction in ostial PV diameter by any form of imaging. • SEVERE: exertional symptoms at >3mth • MODERATE: asymptomatic at >3mth
Drug Side Effect:	Symptoms that are well recognised with drug or stop after ceasing drug
Stroke:	logical symptoms/signs associated with MRI or CT evidence of neurological bleeding/ischaemia