Statistical Analysis Plan (SAP)

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

AVATAR-AF

13SM1798

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1.0	28/06/2016	Nicholas Johnson
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2. Updates to SAP

Version	Date	Summary of Updates
v1.1	24MAR2018	Section 3.2 – Secondary Objective: Text changed from "…performed as a daycase has a comparable safety and efficacy profile to the conventional approach." to "…performed as a daycase is less effective than the conventional approach." to reflect update to Protocol v6.1 Section 5.5 – Sample Size: The alpha value assigned due to the Bonferroni Correction has been updated from 0.017 to 0.025 to as the trial is only analysing two pairs of treatments. Section 5.5 – Sample Size: Number of events corrected from 97 to 103 (calculation not affected).Section 5.6 – Time and Events: Updated to reflect protocol update (±3 days changed to ±7) Section 5.7 - Randomisation: Updated to reflect protocol update (±3 days changed to ±7) Section 6 – Analysis Set: Additional text added to include for proposed per-protocol analyses. Section 8.2 – Primary Analysis: The alpha has been updated to 0.025 due to the Bonferroni Correction alteration as above. Section 8.2 – Primary Analysis: Additional text added to clarify analysis is to be carried out as per primary (AVATAR vs Anti-Arrhythmics) and secondary (AVATAR vs Conventional) objectives. Section 8.2 – Primary Analysis: Additional text added to allow for per protocol analyses. Section 8.3 – Secondary Analyses: see above edits for Primary Analysis Section 8.4 – Safety Analyses: see above edits for Primary Analysis

3. Study Objectives

3.1. Primary Objectives

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.

3.2. 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.

4. Study 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. Background/Introduction

5.1. Introduction

Developments in paroxysmal 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 minority of the AF population having access to such procedure.

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

iv) AF ablation has not been compared against anti-arrhythmic agents with the primary goal of reducing hospital episodes.

5.2. 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 need an escalation of therapy. 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.

5.3. Treatment Groups

Arm 1: AVATAR-AF Ablation Protocol

Arm 2: Conventional AF Ablation

Arm 3: Anti-arrhythmic therapy

5.4. Study Population

The AVATAR-AF study is recruiting patients between the ages of 18 and 80 with documented paroxysmal atrial fibrillation including modification or initiation of anti-arrhythmic agent required for symptom control.

In order to be eligible for the study the patient must not have any of the following:

- Contraindication to catheter ablation
- No carer to enable daycase discharge
- Documented Arrhythmias other than AF unless they have had curative ablation (e.g. for atrial flutter)
- No documentation of sinus rhythm within 3 months
- Valvular or coronary heart disease needing regular follow up
- EF <45% or moderate/severe LV dysfunction(determined by Echocardiogram in the last 6 months)
- Active gastrointestinal disease precluding anticoagulation or trans-oesophageal echocardiogram

- Renal failure with creatinine >200 μmol/L or on dialysis
- Active fever or infection
- Life expectancy shorter than the trial
- Allergy to contrast
- Severe cerebrovascular disease
- Bleeding or clotting disorders or inability to receive heparin
- 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)*
- 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)
- Malignancy needing surgery, chemotherapy or radiotherapy
- Pregnancy or women of child-bearing potential not using a highly effective method of contraception **
- Must not have previous (4 weeks prior to screening) or current participation in another clinical trial with an investigational drug or investigational device
- Unable to give informed consent
- Uncontrolled thyroid disease defined as abnormal thyroid function tests causing cardiac manifestations within the last 6mths
- Unable to attend follow up visits

* 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

** 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

At the screening visit, the patient will be examined to ensure that none of the exclusion criteria are met. Their 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. 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.

If the patient does not meet any of the exclusion criteria and no additional complications are encountered during the screening process then once written, informed consent has been received the patient is eligible for randomisation.

5.5. Sample Size

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 0.80. 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.

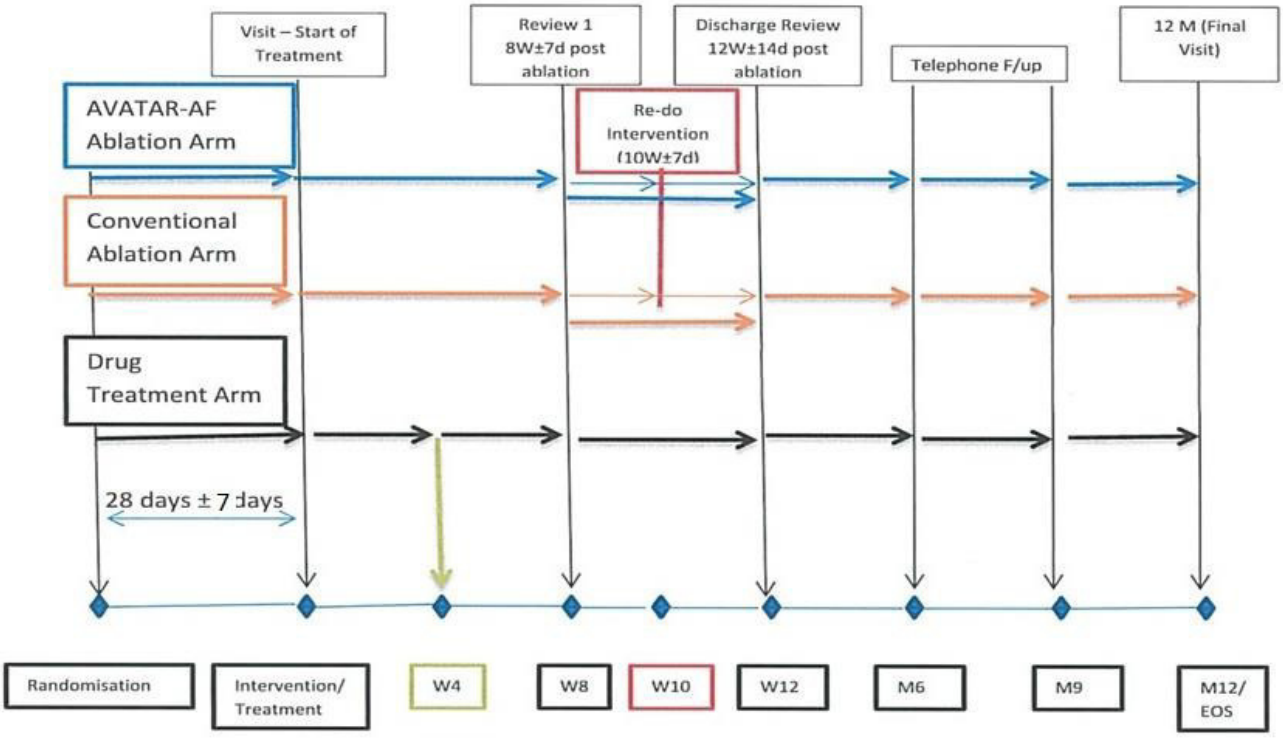
5.6. Schedule of Time and Events

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.

1st Intervention will be considered baseline, all patient returning for follow-up 1 year ± 14 days 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



	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

5.7. Randomisation

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. Analysis Set

All treatment evaluation will be performed on the principle of intention to treat (ITT) with additional per-protocol analyses ran alongside if defined (see Section 8). The per-protocol analysis set will consist of patients who received treatment originally allocated.

A sensitivity analysis will also be performed excluding patients who are withdrawn from the study between randomisation and start of treatment / 1st intervention. Any subjects that have withdrawn during this period will still be required to attend the end-of-study follow-up visit.

7. Variables of Analysis

7.1. Primary Endpoint Variable

Time from 1st intervention to any hospital episodes (Emergency Room or patient request for OPD) related to treatment for atrial arrhythmia that has been formally adjudicated by an independent committee as a primary endpoint. Failure to enter discharge protocol at the Week 12 Review will also result in the primary endpoint being met.

7.2. Secondary Endpoint Variables

1. Time from 1st intervention to death or stroke from any cause.

2. Number of and time from 1st intervention to any of the following complications caused by:

- Pericardial Effusion
- Vascular Bleeding (>2 units)
- Phrenic Nerve Palsy
- PV Stenosis
- Drug side-effects (including GI disturbance, skin irritation and other)
- Other

3. Number of and time from 1st intervention to any hospital episodes which result in a change in therapy for atrial arrhythmia.

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

7.3. Safety and Efficacy Variables

The following information will be recorded and reported to demonstrate treatment safety and efficacy:

- Vital Signs (variables including; weight, blood pressure, pulse, body temp)
- Physical Examination
- Patient Health Questionnaires
    - Quality of Life (QoL)
    - Atrial Fibrillation Effect on QualiTy-of-life (AFEQT)
    - Telephone Follow-up
- CHADSVASC score
- ECG (variables including; ventricular rate, PR & QRS interval)
- Concomitant Medications
- Pulmonary Vein Isolation Measurements of Ablation Treatments (variables including; total duration of freeze, number of applications, Grade 4 occlusions, lowest temperature)
- Protocol Deviations and Violations
- Adverse and Serious Adverse Events

7.4. Baseline and Demographic Variables

The following additional information will be recorded and reported:

- Baseline Demographics (variables including; age, gender, ethnicity, height, weight).
- Medical History (including past cardiovascular medication)
- Echocardiogram Results

8. Statistical Methodology

8.1. Baseline Demographics

Baseline demographic variables and other relevant clinical baseline characteristics (including, but not limited to, medical history, pulse rate, blood pressure, QoL/AFEQT questionnaire results, CHADSVASC score, echo-cardiology readings, ECG and 24hr holter monitor results) will be summarised for each treatment group.

Summaries of continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data, whilst categorical variables will be presented as frequencies and percentages.

8.2. Primary Endpoint Analysis

Failure is counted when a patient experiences any hospital episode related to treatment for atrial arrhythmia. Time to failure will be taken as the time from 1st Intervention to the time of event.

Data will be analysed using the intention-to-treat principle and a p-value of 0.025 or less will be considered significant. Primary outcome will be analysed using Kaplan-Meier statistics and differences between treatment arms will be assessed using log-rank testing and proportional hazards models. Models containing one or more of the following covariates may also be assessed if deemed necessary; site, weight, hypertension, number of anti-arrhythmic taken by patient prior to 1st intervention.

Primary endpoint analysis will be carried out between AVATAR-AF Ablation and the Anti-Arrhythmic drug treatment arm in order to investigate the primary objective. The secondary objective will be assessed by testing AVATAR-AF Ablation against the Conventional Ablation arm.

An additional per-protocol analysis will be carried out in conjunction with the above.

8.3. Secondary Endpoint Analysis

Time to death or stroke; time to procedural/drug-based complication and time to hospital episode resulting in change in therapy will be analysed using Kaplan-Meier statistics. Differences between treatment arms will be assessed using log-rank testing and proportional hazards models. Models containing one or more of the following co-variates may also be assessed if deemed necessary; site, weight, hypertension, number of anti-arrhythmic taken by patient prior to 1st intervention.

Secondary endpoint analysis will be carried out between AVATAR-AF Ablation and the Anti-Arrhythmic drug treatment arm in order to investigate the primary objective. The secondary objective will be assessed by testing AVATAR-AF Ablation against the Conventional Ablation arm.

Additional per-protocol analyses will be carried out in conjunction with the above.

8.4. Safety Variable Analysis

Adverse events will be summarised by treatment and severity. A separate table summarising adverse events and their relationship to study treatment will also be produced.

Serious adverse events will be listed and summarised by site, category and treatment. A separate table summarising serious adverse events and their relationship to study treatment will also be produced.

All safety variables will be summarized in the form of frequency tables for categorical variables or descriptive statistics for continuous variables. Quality-of-Life (QoL) questionnaire results will be summarised by Health State Score. Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire results will be summarised by both overall AFEQT score and subscale score derived using the formulae stated within the AFEQT Questionnaire Instruction and Scoring ManualREFERENCES

If it is deemed appropriate, treatment effect will be assessed via t-test for continuous variables and Chi-square test or Fisher exact test for categorical variables (with the appropriate generalized linear model being used). Models containing one or more of the following co-variates may also be assessed if deemed necessary: site, weight, hypertension, number of anti-arrhythmics taken by patient prior to 1st intervention. A p-value of 0.025 or less will be considered significant. Any testing for treatment effect will be carried out between AVATAR-AF Ablation and the Anti-Arrhythmic drug treatment arm in order to investigate the primary objective. The secondary objective will be assessed by testing AVATAR-AF Ablation against the Conventional Ablation arm.

8.5. Health Economic Analysis

A health economist is to analyse selected data to determine the overall economic benefits of antral AF ablation without electrophysiological confirmation of PV isolation. Details of this analysis will be covered in a separate document, external from the SAP.

8.6. Interim Analysis

Interim reports detailing baseline demographics, safety endpoints and primary endpoints (if requested) will be produced for assessment and discussion at DSMB meetings, the framework of which will be provided within the DSMB charter.

8.7. Tables to Present

Table 1.1: Subject Disposition

	Site A	Site B	…	Total
Screened				
Randomised				
Treatment A				
Treatment B				
Treatment C				
Withdrawn				
Reason for Withdrawal				
Completed				

Table 2.1: Listing of protocol deviations

Treatment	Subject	Site	Type	Start Date	End Date

Table 2.2: Number of protocol deviations by centre and category

Type of Deviation	Site A	Site B	…	Total
Patient was incorrectly included in the trial (did not meet all the inclusion and exclusion criteria				
⋮				
Patient pregnancy				
Other				
Total				

Table 3.1: Baseline characteristics

Variable	Statistics	AVATAR-AF Ablation	Anti-arrhythmic therapy	Conventional AF Ablation
Age (y)	N			
	Mean			
	SD			
	Min			
	Median			
	Max			
Race (n (%))	xxxxxx			
	xxxxxx			
Ethnicity (n (%))	xxxxxx			
	xxxxxx			
Gender (n (%))	Female			
	Male			
Height (cm)	N			
	Mean			
	SD			
	Min			
	Median			
	Max			
Weight (kg)	N			
	Mean			
	SD			
	Min			
	Median			
	Max			
Pulse (bpm)	N			
	Mean			
	SD			
	Min			
	Median			
	Max			
Systolic BP	N			
	Mean			

	SD
	Min
	Median
	Max
Diastolic BP	N
	Mean
	SD
	Min
	Median
	Max
QoL Score	N
	Mean
	SD
	Min
	Median
	Max
QoL Score (n (%))	<40
	…
	90-99
	100+
Chadsvasc Score (n (%))	0
	1
	..
	6
AFEQT Score	N
	Mean
	SD
	Min
	Median
	Max
AFEQT Score (n (%))	0-19
	…
	80-100

Anti-Arrhythmics Taken (n (%))	Amiodarone	
	…	
	Propafenone	
Beta Blockers Taken (n (%))	xxxxx	
Calc. Ch. Blocker Taken (n (%))	xxxxx	
Record of Anti-Coag Pre-Procedure (n (%))	Yes – Bridging	
	Yes – Continuous	
	No	
Expectation of Anti-Coag Post-Procedure (n (%))	Yes	
	No	
Subjects displaying evidence of Paroxysmal Atrial Fibrillation (n (%))	Yes	
	No	
ECG Rhythm (n (%))	Sinus	
	SVT	
	…	
	Q-Waves	
Ejection Fraction (%)	N	
	Mean	
	SD	
	Min	
	Median	
	Max	
Pericardial Effusion (n (%))	Yes	
	No	
Presence of Thrombus (n (%))	Yes	
	No	

Table Note: To include the following variables - *Age, race, ethnicity, gender, height, weight, pulse rate, Systolic BP, Diastolic BP, QoL Score, AFEQT Score, CHADSVASC Score, Heart Medications Taken, Record of Anti-Coagulation pre-procedure, Anti-Coagulation requirements post-procedure 24hr Holter, ECG, Echocardiology.

PRIMARY ENDPOINT

Table 4.1: Listing of all hospital episodes (Emergency Room or patient request for OPD) related to treatment for atrial arrhythmia.

Treatment	Subj.	Date of Visit	Discharge Protocol?	Reason for Adjudication	Outcome	Endpoint?	Time to Event

Table 4.2: Log-rank test investigating occurrence of AF related hospital visits*

Treatment Arm	Events Observed	Events Expected
Total		

Chi2(1) = x.xxx

Pr>chi2 = 0.xxx

*4.2.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*4.2.2 – Comparison between AVATAR-AF and Conventional Ablation

Table 4.3: Cox proportional hazards model investigating occurrence of AF related hospital visits*

Variable	Obvs	Mean	SD	Min	Max
Time to Endpoint	xxx	xx.x	xx.xx	xx	xx
Endpoint Occurred	xxx				
Treatment	xxx				
_st	xxx				
_d	xxx				
_t	xxx				
_t0	xxx				

_t	Haz. Ratio	SE	z	P>|z|	95% CI	
Treatment	x.xxx	x.xxx	x.xx	0.xxx	x.xxx	x.xxx

*4.3.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*4.3.2 – Comparison between AVATAR-AF and Conventional Ablation

SECONDARY ENDPOINTS

Table 5.1: Listing of deaths or strokes from any cause.

Treatment Arm	Subject Number	Type of Event	Date/Time of Event	Time to Event	Cause of Event	Relation to Treatment	Comments

Table 5.2: Log-rank test investigating occurrence of deaths and strokes*

Treatment Arm	Events Observed	Events Expected
Total		

Chi2(1) = x.xxx

Pr>chi2 = 0.xxx

*5.2.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*5.2.2 – Comparison between AVATAR-AF and Conventional Ablation

Table 5.3: Cox proportional hazards model investigating occurrence of deaths and strokes*

Variable	Obvs	Mean	SD	Min	Max
Time to Endpoint	xxx	xx.x	xx.xx	xx	xx
Endpoint Occurred	xxx				
Treatment	xxx				
_st	xxx				
_d	xxx				
_t	xxx				
_t0	xxx				

_t	Haz. Ratio	SE	z	P>|z|	95% CI	
Treatment	x.xxx	x.xxx	x.xx	0.xxx	x.xxx	x.xxx

*5.3.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*5.3.2 – Comparison between AVATAR-AF and Conventional Ablation

Table 5.4: Listing of complications arising from therapy.

Treatment Arm	Subject Number	Type of Event	Date/Time of Event	Time to Event	Cause of Event	Relation to Treatment	Comments

Table 5.5: Log-rank test investigating occurrence of complications*

Treatment Arm	Events Observed	Events Expected
Total		

Chi2(1) = x.xxx

Pr>chi2 = 0.xxx

*5.5.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*5.5.2 – Comparison between AVATAR-AF and Conventional Ablation

Table 5.6: Cox proportional hazards model investigating occurrence of complications*

Variable	Obvs	Mean	SD	Min	Max
Time to Endpoint	xxx	xx.x	xx.xx	xx	xx
Endpoint Occured	xxx				
Treatment	xxx				
_st	xxx				
_d	xxx				
_t	xxx				
_t0	xxx				

_t	Haz. Ratio	SE	z	P>|z|	95% CI	
Treatment	x.xxx	x.xxx	x.xx	0.xxx	x.xxx	x.xxx

*5.6.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*5.6.2 – Comparison between AVATAR-AF and Conventional Ablation

Table 5.7: Listing of hospital episodes resulting in a change in therapy for atrial arrhythmia

Treatment Arm	Subject Number	Type of Event	Date/Time of Event	Time to Event	Cause of Event	Relation to Treatment	Comments

Table 5.8: Log-rank test investigating occurrence of hospital episodes resulting in a change in therapy for atrial arrhythmia*

Treatment Arm	Events Observed	Events Expected
Total		

Chi2(1) = x.xxx

Pr>chi2 = 0.xxx

*5.8.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*5.8.2 – Comparison between AVATAR-AF and Conventional Ablation

Table 5.9: Cox proportional hazards model investigating occurrence of hospital episodes resulting in a change in therapy for atrial arrhythmia*

Variable	Obvs	Mean	SD	Min	Max
Time to Endpoint	xxx	xx.x	xx.xx	xx	xx
Endpoint Occured	xxx				
Treatment	xxx				
_st	xxx				
_d	xxx				
_t	xxx				
_t0	xxx				

_t	Haz. Ratio	SE	z	P>|z|	95% CI	
Treatment	x.xxx	x.xxx	x.xx	0.xxx	x.xxx	x.xxx

*5.9.1 – Comparison between AVATAR-AF and Anti- Arrthymnics

*5.9.2 – Comparison between AVATAR-AF and Conventional Ablation

SAFETY AND EFFICACY – TREATMENT PROCEDURE

Table 6.1: Summary of 1st Intervention (Both Ablation Arms)

Variable	Statistics	AVATAR-AF Ablation	Conventional AF Ablation
CHADSVASC Score	N		
	Mean		
	SD		
	Min		
	Median		
	Max		
No. Subjects Anti-Coagulated pre-procedure	Yes – Bridging Protocol		
	Yes – Cont. Protocol		
	No		
No. Subjects Anti-Coagulated post-procedure	Yes		
	No		
Was TOE performed	Yes		
	No		
Sedation Type	GA		
	Sedation +/- Local		
	Local Only		
Transseptal Puncture Method	Transoesophageal Echo		
	Aortic pigtail		
	Coronary Sinus Catheter		
	Intracardiac Echo		
Diaphragmatic Monitoring Method	Visual Only		
	Phrenic Nerve Pacing w/ Temp Box		
	Phrenic Nerve Pacing w/ EP Stimulator		
	Other Phrenic Nerve Monitoring		
RLPV Lowest Temperature Recorded	N		
	Mean		
	SD		
	Min		
	Median		
	Max		
RUPV Lowest Temperature Recorded	N		
	Mean		
	SD		

	Min	
	Median	
	Max	
LUPV Lowest Temperature Recorded	N	
	Mean	
	SD	
	Min	
	Median	
	Max	
LLPV Lowest Temperature Recorded	N	
	Mean	
	SD	
	Min	
	Median	
	Max	
RLPV PV Isolation after Adv. Balloon Alone?	Yes	
	No	
RUPV PV Isolation after Adv. Balloon Alone?	Yes	
	No	
LUPV PV Isolation after Adv. Balloon Alone?	Yes	
	No	
LLPV PV Isolation after Adv. Balloon Alone?	Yes	
	No	
RLPV Complete (Grade 4) Occlusion Achieved?	Yes	
	No	
RUPV Complete (Grade 4) Occlusion Achieved?	Yes	
	No	
LUPV Complete (Grade 4) Occlusion Achieved?	Yes	
	No	
LLPV Complete (Grade 4) Occlusion Achieved?	Yes	
	No	
All Veins Isolated at end of procedure?	Yes	
	No	
Diaphragmatic Motion Normal at end of procedure?	Yes	
	No	
Patient Fully Anti-Coagulated on Discharge?	Yes	
	No	
Daycase Discharge?	Yes	
	No	

Table 6.2: Summary of Week 8 Review (Both Ablation Arms)

Variable	Statistics	AVATAR-AF Ablation	Conventional AF Ablation
Status of Patient at Review	Asymptomatic for palpitations		
	Showing weekly improvement		
	Not possible to assess in time scale		
	Experiencing ongoing symptoms		
No. Patients referred for Re-Do Procedure	Yes		
	No		

Table 6.3: Summary of 2nd Intervention (Both Ablation Arms)

Variable	Statistics	AVATAR-AF Ablation	Conventional AF Ablation
CHADSVASC Score	N		
	Mean		
	SD		
	Min		
	Median		
	Max		
No. Subjects Anti-Coagulated pre-procedure	Yes – Bridging Protocol		
	Yes – Cont. Protocol		
	No		
No. Subjects Anti-Coagulated post-procedure	Yes		
	No		
Was TOE performed	Yes		
	No		
⋮			
LUPV Isolation at Start?	Yes		
	No		
LLPV Isolation at Start?	Yes		
	No		
RUPV Isolation at Start?	Yes		
	No		
RLPV Isolation at Start?	Yes		
	No		

Table 6.4: Summary of 1st Intervention (Anti-Arrhythmic Arm)

Variable	Statistics	Anti-arrhythmic therapy
Number of Subjects	N	
Anti-Arrhythmic Assigned (%)	Amiodarone	
	Dronedarone	
	Sotalol	
	Digoxin	
	Flecainide	
	⋮	
Beta-Blocker Assigned (%)	Atenalol	
	Bisoprolol	
	Metoprolol	
	Propanolol	
	⋮	

***Table Note: To include for all Anti-Arrhythmics and Beta-Blockers**

Table 6.5: Review of Intervention (Anti-Arrhythmic Arm)

Variable	Statistics	Week 4 Review	Week 8 Review
Number of Subjects	N		
Was treatment changed at review? (%)	No		
	Increased		
	Decreased		
	Change of Agent		

SAFETY AND EFFICACY – ADVERSE EVENTS

Table 7.1: Summary of Adverse Events by Treatment and Severity

		Events				Patients			
		AVATAR-AF Ablation	Anti-arrhythmic therapy	Conventional AF Ablation	Total	AVATAR-AF Ablation	Anti-arrhythmic therapy	Conventional AF Ablation	Total
Severity	**Number of Adverse events**								
	Mild								
	Moderate								
	Severe								
Reason for SAE	**Number of SAEs**								
	Missing								
	Death								
	Hospitalisation required								
	Life threatening								
	Other medical important events								
	Total								

Table 7.2: Number of Adverse Events by Treatment and causality relationship

	Subjects with AEs*						
Treatment	**No Relationship**	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
AVATAR-AF protocol ablation							
Anti-arrhythmic therapy							
Conventional AF ablation							
All subjects							

	All AEs						
Treatment	**No Relationship**	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
AVATAR-AF protocol ablation							
Anti-arrhythmic therapy							
Conventional AF ablation							
All subjects							

***Table Note: Where subjects have more than one AE the highest relationship has been used.**

Table 7.3: Listing of Serious Adverse Events

Treatment	Subject	AE Diagnosis	Details	Relation to Treatment	Surgery Required?

Table 7.3: Listing of Serious Adverse Events (Continued)

Treatment	Subject	Start Date	Recovery Date	Expected-ness	Event Frequency	Comments

Table 7.4: Number of Serious Adverse Events by Treatment and causality relationship

	Subjects with SAEs*						
Treatment	**No Relationship**	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
AVATAR-AF protocol ablation							
Anti-arrhythmic therapy							
Conventional AF ablation							
All subjects							

	All SAEs						
Treatment	**No Relationship**	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
AVATAR-AF protocol ablation							
Anti-arrhythmic therapy							
Conventional AF ablation							
All subjects							

***Table Note: Where subjects have more than one AE the highest relationship has been used.**

SAFETY AND EFFICACY – CONCOMITANT MEDICATIONS

Table 8.1: Concomitant Medications: Anti-coagulants

Medication	**Statistics**	**AVATAR-AF Ablation**	**Anti-arrhythmic therapy**	**Conventional AF Ablation**
xxxx	Yes			
	No			
	Unavailable			
xxxxx	Yes			
	No			
	Unavailable			

SAFETY AND EFFICACY – ECG & HOLTER

Table 9.1: ECG Results for Subjects with Evidence of Atrial Fibrillation

			Treatment			
Test	**Visit**	**Statistics**	**AVATAR -AF Ablation**	**Anti-arrhythmic therapy**	**Conventional AF Ablation**	**TOTAL**
Rhythm	**BL**	**Atr. Fibril.**				
	M12	**Atr. Fibril.**				
Ventricular Rate (bpm)	**BL**	**n**				
		Mean				
	M12	**⋮**				
PR Interval (ms)	**⋮**	**⋮**				
QRS Interval (ms)	**BL**	**n**				
		Mean				
	M12	**⋮**				

***Table Note: To include the following variables – *Rhythm*, *Ventricular Rate, PR Interval, QRS Interval.* To include the following summary statistics – n, mean, SD, median, min, max.**

Table 9.2: Holter Monitoring Results

		Treatment			
	Visit	**AVATAR-AF Ablation**	**Anti-arrhythmic therapy**	**Convent-ional AF Ablation**	**TOTAL**
No. Subjects displaying evidence of Paroxysmal Atrial Fibrillation (n(%))	**BL**				
	M12				

SAFETY AND EFFICACY– QUESTIONNAIRES

Table 10.1: Quality of Life Questionnaire Results

		AVATAR-AF Ablation		Anti-arrhythmic therapy		Conventional AF Ablation	
		BL	M12	BL	M12	BL	M12
Heath State Score - Categorical	0-20						
	21-40						
	41-60						
	61-80						
	81-100						
	Unavailable						
Heath State Score - Summary	N						
	Mean						
	SD						
	Median						
	Min						
	Max						

Table 10.2: Atrial Fibrillation Effect on QualiTy of life (AFEQT) questionnaire Results

		AVATAR-AF Ablation		Anti-arrhythmic therapy		Conventional AF Ablation	
		BL	M12	BL	M12	BL	M12
AFEQT Score	N						
	Mean						
	SD						
	Median						
	Min						
	Max						
Symptoms Subscale Score	N						
	Mean						
	SD						
	Median						
	Min						
	Max						
Daily Activities Subscale Score	N						
	Mean						
	SD						
	Median						
	Min						

	Max	
Treatment Concern Subscale Score	N Mean SD Median Min Max	
Treatment Satisfaction Subscale Score	N Mean SD Median Min Max	

8.8. Figures to Present

- Kaplan-Meyer Plot showing incidence of Primary Outcome per treatment arm
- Kaplan-Meyer Plot showing incidence of Secondary Outcome - Time to death or stroke from any cause per treatment arm
- Kaplan-Meyer Plot showing incidence of Secondary Outcome - Complications caused by procedure per treatment arm
- Kaplan-Meyer Plot showing incidence of Secondary Outcome - Hospital Episodes which result in a change in therapy per treatment arm

REFERENCES

[1] – Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire Instruction and Scoring Manual, Version 1.0 May 19 2010;
http://www.afeqt.org/files/Instruction_Guide_for_AFEQT_Questionnaire-5-18-10.pdf