Study Title: Radiofrequency **P**ower, **L**esion size Index and **O**esophageal **T**emperature alerts during **A**trial **F**ibrillation ablation: a pilot study

Internal Reference Number / Short title: PiLOT-AF study

Ethics Ref:

Date and Version No: 10th March 2016, version 1.2

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Funder:	St Jude Medical, Dot Medical Ltd, Oxfordshire Health Services Research Committee (OHSRC)

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Potential conflicts of interest to declare: none.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	Radiofrequency **P**ower, **L**esion Size Index and **O**esophageal **T**emperature alerts during **A**trial **F**ibrillation ablation: a pilot study	
Internal ref. no. / short title	PiLOT-AF study	
Study Design	Prospective, randomized, single centre observational clinical investigation	
Study Participants	Patients admitted for elective radiofrequency (RF) ablation for paroxysmal or persistent atrial fibrillation (AF)	
Planned Sample Size	80 patients (pilot study)	
Planned Follow-up duration	6 months	
Planned Study Period	15 months	
	Objectives	**Outcome Measures**
Primary	Assessment of the risk of oesophageal damage associated with radiofrequency (RF) ablation on the left atrial (LA) posterior wall when using different power settings	Luminal oesophageal temperature rises > 39°C during RF application on the LA posterior wall as recorded by an oesophageal temperature probe
Secondary	Comparison of oesophageal complications with the different RF settings on LA posterior wall Comparison of acute and short-term procedure success using different RF settings on LA posterior wall as marker of lesion transmurality and durability	Symptoms of oesophageal injury during 6 months follow-up Rate of first-pass pulmonary vein isolation (PVI), rate of acute pulmonary vein reconnection (PVR), total procedure time and RF time of the index ablation procedure AF-free survival during 6 months follow-up
Tertiary	Comparison of rate of procedural complications using the different RF settings	pericardial effusion, TIA/stroke, phrenic nerve injury, pulmonary vein stenosis, open-heart surgery, death

2. ABBREVIATIONS

ACT	Activated Clotting Time
AF	Atrial fibrillation
CF	Contact Force
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
FTI	Force Time Integral
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
LA	Left atrium
LSI	Lesion Size Index
NHS	National Health Service
NRES	National Research Ethics Service
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PVs	Pulmonary Veins
PVI	Pulmonary Vein Isolation
PVR	Pulmonary Vein Reconnection
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RF	Radiofrequency
SOP	Standard Operating Procedure
TOE	Trans-Oesophageal Echocardiogram

3. BACKGROUND AND RATIONALE

3.1 Pulmonary Vein Isolation (PVI): rationale and pitfalls

Catheter ablation is a well-recognized treatment, with a class I indication, for symptomatic and drug-refractory atrial fibrillation (AF) (1-3). The current technique focuses on the elimination of mechanisms involved in the initiation and maintenance of AF. In this scenario, the pulmonary veins (PVs) are considered

to play a major role as the site of origin of ectopic atrial activity initiating and maintaining AF. Therefore, ablation of myocardium at the junction between the PVs and the left atrium (LA), leading to electrical isolation of the PVs, is currently the cornerstone of the treatment of both paroxysmal and persistent AF (4, 5). Unfortunately, although pulmonary vein isolation (PVI) can be achieved acutely in up to 100% of cases, recovery of electrical conduction of one or more arrhythmogenic PVs is quite common, both acutely and chronically. Acute pulmonary vein reconnection (PVR) is observed before the end of the ablation procedure in up to 50% of cases (6). Even if PVI is reached and maintained until the end of the procedure, chronic PVR is found in up to 80% of redo procedures performed for arrhythmia recurrence (7). As a consequence of reconnection rate, AF or associated atypical flutter recurrences lead to repeat AF ablation procedures in 30-50% of patients (8).

Although the pathological basis of PV reconnection is not yet known, it is suspected to result from deficiencies of the index ablation procedure, specifically gaps in the initial line of ablation, and/or failure of initial lesions to deliver permanent, transmural necrosis and permanent scar. Of note, recent histological data have correlated partial thickness ablation lesions with chronic and persistent PV conduction (9).

3.2 Radiofrequency (RF) ablation: principles and determinants of lesion formation

For radiofrequency (RF) energy delivered through an irrigated-tip ablation catheter, the reasons for lesion failure are multifactorial.

RF energy generates an ablation lesion through tissue heating. The transformation of electromagnetic energy into thermal energy, as electrical current passes through a resistive medium, is responsible for direct resistive heating in the narrow rim of tissue in close contact with the catheter electrode (2 to 3 mm). However, because direct resistive heating of the tissue decreases proportionally with the distance from the electrode to the fourth power, heating of deeper tissue layers occurs passively through heat conduction. While resistive heating is a fast process, taking place in a few seconds, conductive heating is a much slower process, requiring up to 30 sec (10, 11). In this process, delivered power, application time and catheter tip-tissue contact pressure all play a role (12, 13). Higher power delivery increases the source temperature and the radius of the heat source (although it hardly exceeds 2-3 mm regardless of the delivered power), thereby increasing lesion size in two ways. Time is required for thermal conduction to deeper tissue layers. Greater electrode-tissue contact pressure increases lesion size by improving electrical coupling with the tissue, increasing the electrode surface area in contact with the tissue, and reducing the shunting of current to the blood pool.

It has been demonstrated that the maximum lesion size is achieved after 40 to 60 seconds of RF delivery and longer RF deliveries increase the risk of complications without a substantial benefit in terms of lesion formation (36).

Contact force (CF)-sensing ablation catheters, able to monitor constant, real-time contact force during mapping and ablation, are now available for clinical use (14-16). Moreover, formulas combining contact force, RF power and application time such as Force Time Integral (FTI) (17) or Lesion Size Index (LSI) have been developed in order to predict the lesion size and depth and to guide the RF ablation. In particular, LSI is a non-linear function that combines power, CF and ablation duration; it has been found to be especially effective in calculating gap formation and estimating lesion quality (18).

Based on clinical studies (19-24), the current CF recommendations to achieve transmural lesions and durable PVI are: minimum CF > 10 g with target CF of 20 g, target FTI > 400 gs, suggested LSI ≥ 6 on the LA anterior wall, ≥ 5 on the LA posterior wall and ≥ 5.5 on the LA roof and floor.

Among the different parameters (RF power, CF, FTI, LSI), LSI seems to be the best predictor of lesion size and gap formation at 3 months post-PVI (23).

3.3 Oesophageal damage and atrio-oesophageal fistula after AF ablation

Unfortunately, deeper lesions mean a higher risk of overheating and damage of extra-cardiac structures close to the LA, in particular the oesophagus when ablating on the LA posterior wall. Heating of the connective tissue layer between the LA and oesophagus, containing oesophageal vascular structures, and of the oesophageal wall itself, are thought to contribute to the genesis of atrio-oesophageal fistulae, a rare but fatal complication of AF ablation (25).

In view of the variable position of the oesophagus relative to LA posterior wall, its positional changes over time and of the variable thickness of the posterior LA wall, fat pad and connective tissue layer between the LA and oesophagus, the prevention of oesophageal damage during AF ablation is quite challenging (26-29).

Lower RF powers and shorter application times are usually used on the LA posterior wall but this is a completely empirical approach which has not been proved to be effective in preventing oesophageal damage. Continuous luminal oesophageal temperature monitoring during the AF procedure is a suggested strategy to prevent oesophageal damage related to AF ablation. The rationale behind this strategy is that luminal oesophageal temperature is a surrogate marker of the mural temperature and therefore it can predict and avoid tissue damage. Observational studies employing real-time luminal oesophageal temperature measurements during LA catheter ablation have shown that lower oesophageal luminal temperatures are associated with lower rates of oesophageal ulcerations detected by endoscopy after ablation (30-33). To this aim, a temperature probe is inserted nasally or orally and advanced to the level of the posterior LA under fluoroscopic guidance where it permits real-time intraluminal oesophageal temperature monitoring during the ablation. Moreover, it marks the location of the oesophageal lumen that can also be visualized in the electro-anatomical map to evaluate the distance of the ablation catheter tip from it. Different oesophageal temperature probes are currently available: single-sensor ones, linear multi-sensor and 2-dimensional sinusoidal multi-sensor ones. The advantage of the multi-sensor probes, and especially of the sinusoidal one, is that their design allows for a greater area of temperature monitoring and their position does not require adjustments to be in close vicinity of the ablation catheter tip during RF delivery (34).

When using an oesophageal temperature probe-guided ablation strategy, RF delivery on the LA posterior wall is promptly terminated in case of any oesophageal temperature rises >39°C and power is reduced in contiguous sites. However, the big challenge of this approach is in not knowing how much delivered RF energy is both simultaneously “safe” and “effective”.

In our experience, oesophageal temperature alerts are very common during PV encirclement on LA posterior wall, occurring in the majority of procedures and, regardless of the power used, they tend to occur before the achievement of the suggested LSI of 5. Moreover, lower RF powers are generally used on LA posterior wall but, in view of the strict relation between power and application time in determination of

lesion size, the adoption of lower RF powers usually implies longer RF applications in order to reach the suggested LSI and maximize the chance to achieve a durable PVI.

Interestingly, the relationship between RF energy settings and oesophageal temperature alerts is anything but clearly defined (35). Of note, the oesophageal injury during LA ablation is attributed to conductive heat transfer from the ablation site, a time-dependant process.

3.4 Research questions

On these premises, our research questions are:

- is it better to use higher RF powers for shorter times, than lower RF powers for longer times, to reduce the risk of oesophagus overheating and oesophageal temperature alerts?

- is the suggested LSI value of 5 on the LA posterior wall feasible or thwarted by frequent occurrence of temperature alerts leading to premature termination of RF delivery, regardless of maximum power?

- what is the impact of the different RF energy settings on PVI, acute pulmonary vein reconnection (PVR) and short-term clinical success of the AF procedure?

- which LSI value and RF power should be used during RF ablation on the LA posterior wall in order to achieve the best compromise between safety from oesophageal damage and lesion transmurality and durability?

To these aims, the PiLOT-AF study aims to test different combinations of RF power and LSI during PV encirclement on LA posterior wall.

The rate of oesophageal alerts will be collected and compared for each procedure modality. The rate of first pass PVI and acute PVR (related to breakthrough signals on LA posterior wall), the procedure duration and RF ablation time will be also collected as clinical indicators of lesion transmurality and acute procedure success. The freedom from AF at 6 months follow-up will be used as clinical indicators of lesion durability and short-term procedure success. The occurrence of any oesophageal symptoms at follow-up will be recorded as surrogate clinical indicators of oesophageal damage. All other procedural complications will be also recorded as safety outcomes.

No data are currently available on this topic. Therefore, this study has been designed as pilot study for power analysis and sample size calculation of a further main study.

This pilot study will hopefully give us some insights about the best combination of RF power, application time and target LSI to use during AF ablation on the LA posterior wall in order to achieve durable PVI with minimal risks of oesophageal damage.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the risk of oesophageal damage associated with different RF settings during AF ablation on the LA posterior wall	Rate of oesophageal temperature alerts (defined as oesophageal temperature rise > 39°C) during RF ablation on the LA posterior wall	Index procedure
Secondary Objectives **1.** To compare the acute success of the index AF ablation using different RF settings on the LA posterior wall	**1.** Rate of first-pass PVI, rate of acute PVR related to breakthrough signals on the LA posterior wall, total procedure time and RF ablation time	**1.** Index procedure
2. To compare the short-term success of the index AF ablation using different RF settings on the LA posterior wall	**2.** Freedom from atrial fibrillation	**2.** During the follow-up period (6 months)
3. To compare the rate of oesophageal injury related to different RF settings on the LA posterior wall during the index AF ablation	**3.** Rate of oesophageal symptoms (difficult or painful swallowing, heartburn, acid reflux, sore throat, hoarseness, cough, nausea, vomiting, non-cardiac chest pain)	**3.** During the follow-up period (6 months)
Tertiary objectives To evaluate the rate of complications associated with the different RF settings	Pericardial effusion, TIA/stroke, phrenic nerve injury, pulmonary vein stenosis, open-heart surgery, death	Index procedure

5. STUDY DESIGN

The PiLOT-AF study is a prospective single-centre randomized observational study aiming at comparing different RF settings during AF ablation on the LA posterior wall, in terms of oesophageal heating, acute and long-term procedure success and procedural complications.

Patients, age 18-80, scheduled for their first RF ablation because of a history of symptomatic and drug-refractory paroxysmal or persistent atrial fibrillation, will be considered for inclusion in the study.

Potential subjects will initially be approached 4-6 weeks before their ablation procedure, in order to give the patients enough time to consider the information, to ask questions to the Investigator, their GP or other independent parties to decide whether they wish to participate in the study or not.

For those interested in participation, a baseline assessment will be arranged to coincide with their standard pre-admission visit, for informed consent, screening and eligibility assessment and randomization.

All AF ablation procedures will be performed in a standard fashion, under general anaesthesia and with continuous oesophageal temperature monitoring using a sinusoidal multi-sensor oesophageal temperature probe (CIRCAtemp). After LA geometry reconstruction using 3-dimensional electroanatomical mapping EnSite Velocity and a multipolar circular mapping catheter St Jude Medical Optima, a CF ablation catheter Endosense Tacticath through a deflectable sheath St Jude Medical Agilis will be used for PVI. Standardized RF settings will be used during ablation on the LA anterior wall as current practice in our centre. Different RF settings will be used on the LA posterior wall, according to randomization group. Duration of RF delivery on the LA posterior wall will be dictated by achievement of target LSI or oesophageal temperature rise > 39°C during ablation. PVI will be achieved and confirmed after 30 minutes waiting time. In case of acute PV reconnection, ablation at sites of breakthrough signals will be performed in order to achieve durable PVI. The occurrence of acute PV reconnection with sites of breakthrough signals on the LA posterior wall will be recorded for each procedure. The total procedure and RF ablation times will be also collected.

After the ablation, before discharge the symptoms status and heart rhythm will be assessed and the patient will be instructed to commence a symptoms diary. Telephone follow-ups will be then performed at 3 and 6 months to assess current symptom status. Standard care follow-up Arrhythmia Clinic visits will be also performed 3-4 months after the ablation procedure. Ad hoc visits and/or additional investigations as prolonged ECG monitoring will also take place, dictated by arrhythmia symptoms and assessment for potential adverse events related to the procedure, in accordance with standard practice.

The end of the study for each patient will be the date of the 6 months telephone follow-up.

A flowchart of the study design, indicating the time points and procedures, is shown in Appendix 1.

6. STUDY RISKS AND BENEFITS

6.1. Study risks

The patients taking part will be undergoing a standard AF ablation on the basis of clinical reasons (symptoms and no response to medical therapy). When compared with the ablation protocol currently used in our centre, the study ablation protocol differs only for the use of predefined RF powers and target LSI values during PV encirclement on LA posterior wall. All proposed values of RF power and LSI have been already tested and approved in preclinical and clinical studies. Therefore no additional risks are expected from the study procedure.

Standard risks associated with an AF ablation procedure in our centre:

- bruising in the groin, mild chest discomfort, a sore throat and palpitations, which are usually self-limiting, occur in 1 in 10-20 people

- femoral vascular injury requiring a minor surgical repair occurs in 1 in 200 people;

- cardiac perforation requiring a drain at the time of the operation occurs in 1 in 50-100 people;

- pulmonary vein stenosis requiring treatment is 1 in 500;

- TIA or stroke is approximately 1 in 200 people;

- needing urgent open-heart surgery is 1 in 500 people;

- fatal complication is estimated to be 1 in 1000 people;

- cancer secondary to fluoroscopy exposure during the AF ablation is negligible considering the average low radiation dose and the short fluoroscopy time used.

6.2. Study benefits

The patient could get direct benefit from the study participation in terms of reduction of oesophageal temperature alerts during the procedure and more durable PVI, translating into freedom from AF and no need for redo procedure.

The main benefits will be for future patients if the best combination of RF power and LSI is found for ablation on LA posterior wall.

7. PARTICIPANT IDENTIFICATION

7.1. Study Participants

Patients aged 18-80 years old, scheduled for elective AF ablation in view of a history of symptomatic and drug-refractory AF.

7.2. Inclusion Criteria

The participant must satisfy the following conditions:

- male or female, aged 18 to 80 years;
- willing and able to give informed consent for participation in the study;
- history of symptomatic and drug-refractory atrial fibrillation;
- planned AF ablation on a clinical basis.

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- previous AF ablation;
- pregnancy, trying for a baby or breast feeding;
- oesophageal obstruction (mass, stricture), diverticulum or varices, tracheo-oesophageal fistula or any other oesophageal conditions prohibiting the use of oesophageal temperature probe for continuous luminal temperature monitoring;
- any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

8. STUDY PROCEDURES

8.1. Recruitment

Potential participants will first be approached 4-6 weeks before the AF procedure. Outpatient clinic letters of patients placed on the waiting list for catheter ablation of AF by the OUH NHS Trust Cardiac Rhythm Management team will be screened by a member of the research team to assess suitability for inclusion in the study. A letter of invitation, a patient information leaflet and a consent form will be given to potential participants at their routine clinic visits or sent by post at the time their procedure date is determined (usually 6 weeks in advance). The letter will contain a reply slip which patients can use to express their interest in the study and request more information if they wish. The participant will be allowed time to consider the information, and the opportunity to ask questions to the Investigator, their GP or other independent parties to decide whether they will participate in the study.

Once patients have had time to consider the information (and discuss with relatives, friends and their GP if they wish), they will be contacted by an investigator who will ask if they wish to discuss the study further. If they wish to take part, they will be approached at their pre-admission visit before the procedure (1-2 weeks before the AF ablation) for a baseline visit including informed consent, screening and eligibility assessment and randomization.

8.2. Baseline visit

8.2.1. Informed Consent

Informed consent will be obtained by a qualified and experienced investigator who is familiar with the study protocol and procedures. This may be the chief investigator, a principal investigator, the research fellow or a research nurse. The list of eligible individuals will be specified in the delegation log.

Written versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the study and the benefits and risks involved in taking part. It will be clearly stated that

the participant is free to withdraw from the study at any time without giving a reason or any prejudice to future care and rights.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. A copy of the signed consent form will be given to the participants. The original signed form will be retained at the study site. The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

8.2.2. Screening and Eligibility Assessment

It will include:

a. demographics;
b. exclusion of pregnancy or breast feeding in case of child-bearing age female;
c. detailed collection of any relevant medical history, but especially concerning AF, heart (including left atrial size and left ventricular function on most recent echocardiogram if any) or oesophageal diseases;
d. list of current medications and antiarrhythmic drugs previously taken;
e. current heart rhythm on 12-lead ECG.

8.2.3. Randomisation

A block randomization, with blocks of size four, type 1234, will be used to assign each patient to one of the following four treatment arms:

- ✓ Group 1: 20 W RF power and target LSI = 4 on LA posterior wall;
- ✓ Group 2: 40 W RF power and target LSI = 4 on LA posterior wall;
- ✓ Group 3: 20 W RF power and target LSI = 5 on LA posterior wall;
- ✓ Group 4: 40 W RF power and target LSI = 5 on LA posterior wall.

Briefly, the study population will be divided into 4 blocks of 20 patients. Within each block, every patient will be randomly assigned to 1 of the 4 treatment arms by using sealed envelopes. At the end of each block of 20 patients, there will be 5 patients enrolled in each of the 4 treatment arms. At the baseline visit, following consent, the study nurse or doctor will telephone the Research Office and ask the administrator to open a sealed envelope from the current block of 20 and reveal the allocated treatment arm. The treatment will be unblinded to the investigator and blinded to the patient.

8.3. AF ablation

The patient will be admitted to hospital on the morning of the procedure or on the night before the procedure, as per local SOP's. Apart from the RF settings on the LA posterior wall that will be dictated by the study randomization group, the AF ablation will be conducted in a completely standard fashion. After the procedure, the patient will be kept in hospital overnight and monitored.

The procedure details are described in the intervention section.

8.4. Pre-discharge review

As part of standard care, each patient will be reviewed the day after the ablation procedure, before discharge. The current symptoms status and occurrence of any procedural complications will be investigated and an ECG will be performed to check the heart rhythm. As part of the research study, the patient will be advised to commence a symptom diary where to record occurrence of palpitations and/or any other cardiovascular symptoms as well as oesophageal symptoms (difficult or painful swallowing, heartburn, acid reflux, sore throat, hoarseness, cough, nausea, vomiting, non-cardiac chest pain).

8.5. Arrhythmia Clinic visit at 3-4 months

As part of standard care, each patient will be reviewed in the Arrhythmia Clinic 3-4 months after the ablation to assess the current symptoms status and check the heart rhythm on ECG. In the case of recurrence of AF, the decision to restart an antiarrhythmic drug and/or to plan a redo procedure will be left to the clinician involved in the care of the patient. Moreover, in accordance with usual practice, additional investigations as prolonged ECG monitoring will also take place dictated by arrhythmia symptoms and assessment for potential adverse events related to the procedure.

8.6. Telephone follow-ups 1 (at 3 months) and 2 (at 6 months)

As part of the research study, telephone follow-ups will be performed 3 and 6 months after the procedure to assess the current symptoms status and collect information about symptoms recorded in the diary. The patient's existing clinical care team will be informed about occurrence of palpitations and any other cardiovascular or oesophageal symptoms and the decision to carry any additional investigations to investigate will be left to them.

8.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of Consent
- Loss to follow up

No specific procedures or observations will be required in case of discontinuation/withdrawal of participants from study rather than standard medical care.

The reason for withdrawal will be recorded in the CRF.

In case of withdrawal from the study in an early stage (before the intervention), the patient data will be excluded from the analysis and a new participant will be enrolled.

In case of withdrawal from the study during the follow-up period, neither exclusion of the data of that participant from analysis nor replacement with a new participant will be required.

8.8. Definition of End of Study

The end of study will be the date of the last 6-month telephone follow-up.

9. INTERVENTION: AF ablation

As current practice in our centre, all AF ablations will be performed under general anaesthesia and on uninterrupted therapeutic anticoagulation with warfarin (target INR 2-3 in the last 3 weeks at least) or one of the new non-Vitamin K anticoagulant drugs. A heparin infusion will also be administered during the procedure, with target Activated Clotting Time (ACT) values of 300-350 sec. Fluoroscopy and tri-dimensional electroanatomical mapping will be used by the operator, as usual, as anatomical guide during the procedure.

The procedure critical steps can be detailed as follow:

- *General anaesthesia and TOE.* After general anaesthesia and oro-tracheal intubation, a trans-oesophageal echocardiogram (TOE) will be performed to rule out the presence of thrombus in the LA appendage.

- *Vascular access, coronary sinus catheter placement and LA access.* Venous femoral access will be achieved and a deflectable decapolar diagnostic catheter placed to the coronary sinus. One or two atrial trans-septal punctures will be performed under TOE-guidance. The choice of the trans-septal kit (needle and sheath) and of the number of performed trans-septal punctures will be left to the operator.

- *Luminal oesophageal temperature monitoring.* After the trans-septal puncture(s), the TOE probe will be taken out. A two-plane sinusoidal oesophageal temperature probe, CIRCA's S-Cath (CIRCA, Englewood, CO) will be placed orally to the oesophagus and advanced to the level of the LA. It will be connected to a dedicated CIRCA Temperature Monitor (CIRCA, Englewood, CO), displaying graphically and numerically temperature data from all 12 sensors, updated 20 times per second. Any luminal oesophageal temperature rise ≥ 39◦C will result in a temperature alert and cessation of RF delivery at that site.

- *LA geometry.* The LA geometry will be reconstructed using the EnSite Velocity mapping system (SJ Medical, St Paul, MN, USA) and an Optima mapping catheter (SJ Medical, St Paul, MN, USA).

- *LA ablation strategy and technique.* The PVs will be encircled in pairs to isolation using an irrigated-tip ablation catheter Tacticath Quartz (SJ Medical, St Paul, MN, USA) via an Agilis deflectable sheath. A point-by-point ablation technique will be used, with a minimum CF of 10 g and a target CF of 20 g for each RF lesion. As current practice, the circumferential ablation line around the PV pairs will be predefined on the electroanatomical LA map, at 1-2 cm from PV ostia with individual adjustments in order to avoid RF delivery in close proximity of the oesophageal probe.

- *RF settings on the LA anterior wall, roof and floor.* As current practice in our centre, an RF power of 40 W will be used on LA anterior wall, roof and floor. The RF application time will be dictated by the achievement of the target FTI and LSI (FTI ≥ 400 gs; LSI ≥ 6 on LA anterior wall and LSI ≥ 5.5 on LA roof and floor).

- *RF settings on the LA posterior wall.* Different RF settings will be used during RF ablation on LA posterior wall, according to randomization group:

- ✓ *Group 1:* 20 W RF power, with target LSI = 4;
- ✓ *Group 2:* 40 W RF power, with target LSI = 4;
- ✓ *Group 3:* 20 W RF power, with and target LSI = 5;
- ✓ *Group 4:* 40 W RF power, with target LSI = 5.

Regardless of the LSI achieved, RF delivery on the LA posterior wall will be promptly terminated in case of any oesophageal temperature rise ≥ 39◦C or after 60 seconds of continuous RF delivery. The ablation catheter will be then moved to a contiguous lower or higher site on the predefined circumferential ablation line.

- *PVI confirmation.* Disappearance of PV potentials or dissociated PV potentials in the vein and inability to capture the LA during PV pacing will confirm bidirectional block across the PV circumferential ablation line and PVI.

- *Waiting time.* After a waiting time of 30 min, the PVs will be rechecked in order to confirm the persistence of PVI.

- *Acute PVR.* In case of acute PVR, additional RF ablation will be performed in correspondence of breakthrough signals. The same RF settings of the first PV encirclement will be used.

- *Procedure completion.* The procedure will be terminated after achievement of electrical isolation of all PVs. A trans-thoracic echocardiogram will be performed at the end of the procedure to rule out the presence of pericardial effusion. Protamine will be administered to reverse heparin.

Apart from the RF settings on LA posterior wall (RF power and target LSI) that will be dictated by the study randomization, every other procedure step will be performed according to standard clinical practice. Of note, no particular equipment will be used for the research study rather standard clinical equipment. No additional fluoroscopy time or procedure time will be added to the standard procedure.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- congenital anomaly/birth defect
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. The Number of Participants

The PiLOT-AF study aims to give some insights about the relation among RF power, LSI and incidence of oesophageal temperature alerts during AF ablation on the LA posterior wall. In view of the absence of data on this topic, it has been designed as pilot study for power analysis and sample size calculation of a further main study.

As suggested before for pilot studies (38), we aim to a final sample size of 12 patients with primary outcome data per each treatment group. We know from previous studies that oesophageal temperature alerts occur in 55-75% of AF ablations. Therefore, if taking into account also participants who do not experience oesophageal temperature alerts during AF ablation, we plan to recruit a total of 80 patients in order to achieve primary outcome data in 12 patients per group.

11.2. Description of Statistical Methods

Comparison of primary, secondary and tertiary outcome measures among different treatment groups will be performed at each time point using appropriate statistical testing. In particular, ANOVA tests will be used to compare numerical variables and chi-square tests will be used to compare categorical values.

11.3. Analysis of Outcome Measures

Summary statistics, including means, medians, and variances, will be calculated at each time point and for each type of data (e.g. parameters derived from index AF procedure and follow-up visits).

If patients withdraw from the study we will analyse data already collected, unless the patients request otherwise.

12. DATA MANAGEMENT

12.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.2. Data Recording and Record Keeping

- The study staff will ensure that the participants' anonymity is maintained.
- NHS code of confidentiality will be followed.
- All electronic records will be stored on a NHS server within password-protected user accounts.
- Personal data will be anonymised with the use of a study participant number. The study number will be correlated with personal data about the patient in one electronic file, which will be individually password protected and secured as above.
- Paper records will be stored in a locked filing cabinet to which only the research team have access.
- The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.
- Data analysis will be performed by Dr Leo and Dr Betts in the JR hospital. No further data transfer will be performed.
- After the end of the trial period, participant's personal data will be stored and accessible for 5 years.
- Similarly, remaining patient data, labelled only with study participant number, will be kept for a further period of up to 5 years to allow for full analysis and results publication, as per Trust Policy, before being deleted.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

We intend that the majority of study visits will be performed at the time of routine clinical visits to hospital so would not expect that patients will have to make many extra visits to hospital.

Light refreshments will also be available.

14. FINANCE AND INSURANCE

14.1. Funding

The study will be supported by the Cardiac Rhythm Management Unit, which research funds will be used to cover additional expenses apart from standard medical care.

14.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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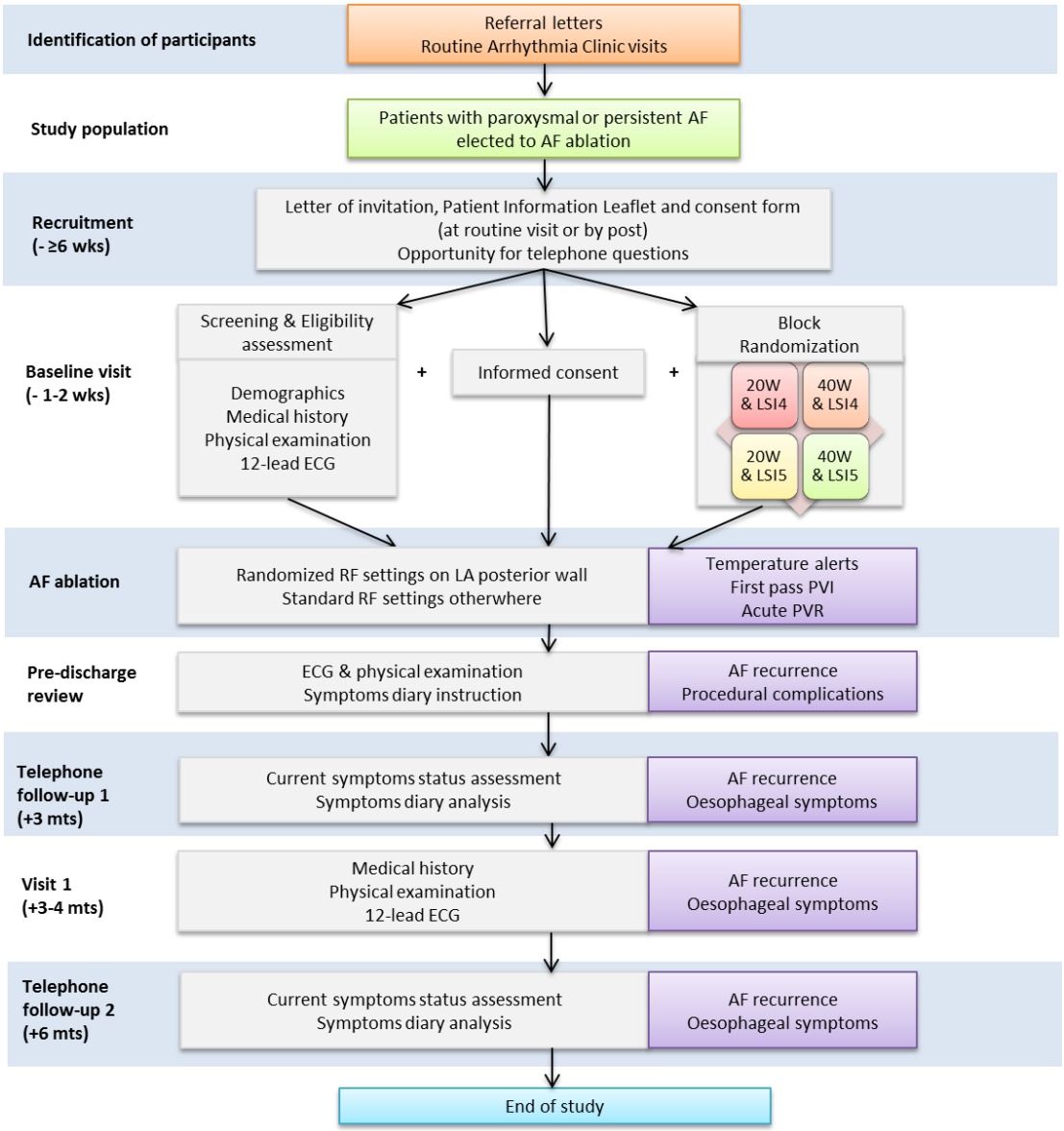
APPENDIX A: STUDY FLOW CHART



APPENDIX B: SCHEDULE OF TIMING OF STUDY APPOINTMENTS AND STUDY PROCEDURES

	Recruit-ment	Baseline visit	Study intervention	Pre-discharge review	Telephone f-up 1	Arrhythmia Clinic visit	Telephone f-up 2
Time since AF ablation	≥ 6 wks	- 1-2 wks	0	+ 1 d	+ 3 mts	3-4 mts	+ 6 mts
Study procedures							
Eligibility assessment	X	X					
Patient's information	X						
Informed consent		X					
Randomisation		X					
Demographics		X					
Medical history		X		X	X	X	X
ECG		X	X	X		X	
AF ablation			X				
Symptom diary instruction				X			
Symptom diary collection					X	X	X

d = day; f-up = follow-up; mts = months; wks = weeks.

17. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	11/11/2015	Dr M Leo/ Dr T Betts	Method of randomization clarified in detail (paragraph 8.2.3, page 14) As requested by Ethic Committee, period of time during which the patients' personal data will be stored and accessed after the study prolonged to 5 years (paragraph 12.2, page 2)
2	1.2	10/03/2016	Dr M Leo/Dr T Betts	On the basis of observations during the first 10 research cases, study intervention protocol modified as follow: - FTI removed from the target parameters for termination of RF delivery on the LA posterior wall; - maximal duration cut-off of 60 sec added for RF delivery on the LA posterior wall.