Study Title: INtra-procedural ultraSound Imaging for DEtermination of atrial wall thickness and acute tissue changes during isolation of the Pulmonary Veins

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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	**Intra-procedural ultraSound Imaging for DEtermination of atrial wall thickness and acute tissue changes after isolation of the Pulmonary Veins**	
Internal ref. no. / short title	**INSIDE PVs**	
Study Design	Pilot study	
Study Participants	Patients admitted for elective catheter ablation for paroxysmal atrial fibrillation (AF)	
Planned Sample Size	12 patients (4 elected to radiofrequency, 4 to cryo-balloon and 4 to laser balloon ablation for atrial fibrillation)	
Planned Follow-up duration	1 week	
Planned Study Period	12 months	
	Objectives	**Outcome Measures**
Primary	Evaluation of the accuracy of intra-procedural intracardiac echocardiography (ICE) and intravascular ultrasound (IVUS) for real time imaging of the LA wall thickness and PV ostial diameters during AF ablation	ICE/IVUS measurements of LA wall thickness and PV ostial diameters in comparison with the corresponding cardiac computed tomography (CT) measurements
Secondary	1. Evaluation of the feasibility of ICE/IVUS for real time imaging of the LA wall thickness and PV ostial diameters during AF ablation	1a. Additional procedural time 1b. Image quality
	2. Comparison between acute tissue changes produced by radiofrequency (RF), cryo and laser energy	2. Percentage change of LA wall thickness with each ablation modality (RF, cryo and laser energy)
	3. Standardization of CT for LA wall thickness imaging with identification of a minimum dataset of acquisitions and reduction of radiation exposure	3. CT acquisitions associated to reproducible measurement of LA wall thickness with the lowest radiation exposure

2. ABBREVIATIONS

ACT	Activated Clotting Time
AF	Atrial fibrillation
CF	Contact Force
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
ICE	IntraCardiac Echocardiography
ICF	Informed Consent Form
IVUS	IntraVascular UltraSound
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
3D	Three-dimensional

3. KEY CONTACTS SECTION

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4. BACKGROUND AND RATIONALE

4.1 Rationale for real-time imaging of the left atrial (LA) wall during atrial fibrillation ablation

Catheter ablation is a well-recognized treatment, with a class I indication, for symptomatic, drug-refractory atrial fibrillation (AF) (1, 2). The current technique focuses on the elimination of mechanisms involved in the initiation and maintenance of AF. The pulmonary veins (PVs) play a major role as the site of origin of ectopic atrial activity initiating and maintaining AF (3, 4) .Radiofrequency (RF) catheter ablation is a long-standing method for burning heart muscle to create scars that prevent the conduction of the electrical impulse through heart muscle. Catheter ablation of the 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 (5) .

Despite widespread adoption of this approach over the last decade (with over 10,000 cases per annum in the UK), the long-term success rate, particularly single-procedure success rate, is still suboptimal and the associated risk of heart perforation and collateral damage is small but not negligible.

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 veins (6), although if seen during the operation energy can be reapplied until the vein is re-isolated. Late PVR, in the weeks or months following the procedure, is a common cause of recurrent arrhythmias leading to procedure failure and a need for repeat ablation in 30-50% of patients (7).

The pathological basis of PVR is not completely known, but 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 lead to permanent, transmural necrosis and permanent scar. Recent histological data have correlated partial thickness ablation lesions with chronic and persistent PV conduction (8).

The acute development of tissue oedema has been advocated as one of the possible factors responsible for lesion failure when using RF energy delivered through an ablation catheter. Trans-oesophageal (TOE) echocardiographic evidence of acute oedema, causing immediate tissue swelling and thickening of the atrial myocardium, narrowing the pulmonary vein ostia and increasing the thickness of the ridge between the left PVs and left atrial appendage in response to RF ablation, has been reported (9). Immediate expansion of the myocardium between the coronary sinus and the left atrium has also been demonstrated on intra-cardiac echocardiography (ICE) during mitral isthmus ablation (10). The hypothesis is that sudden increases in wall thickness may prevent subsequent lesion delivery achieving the depth required for transmural necrosis and permanent conduction block.

PV reconnection may also be found following cryo-balloon ablation and laser-balloon ablation, which have similar long-term results to RF energy. With cryo-ablation, recovery is thought to be due to temporary injury at the freezing border zone, where temperatures don't drop below -40°C, with only a transient effect on conduction and absence of tissue necrosis (11). Tissue oedema does occur after surgical cryo-ablation, but only once the tissue has thawed and become hyperaemic and it gradually progresses over the next 24

hours (12). Cryo-ablation preserves tissue architecture and whether local oedema leading to immediate atrial wall thickening, inhibiting subsequent attempts at ablation, is not known (13). Even less is known about the acute tissue changes produced by endoscopic laser balloon ablation. Although laser energy causes focal myocardial tissue ablation through tissue heating (similar to RF), gross pathological examination performed in animals acutely after delivery of laser energy has showed homogeneous lesions, with well-demarcated borders, no evidence of endocardial destruction such as surface pitting or granulation and no evidence of oedema (14).

At the other end of the spectrum, deep lesions can potentially result in perforation and collateral damage. Cadaveric anatomical studies show that the LA wall thickness is extremely variable from subject to subject, from less than 1 to more than 7 mm. Even within individual patient, significant differences in the mean and maximum LA wall thickness exist among different areas that are often targeted during catheter ablation (15). This inter- and intra-patient regional variability has significant implications in determining the appropriate duration and intensity of energy delivered during catheter-based ablation procedures.

For these reasons, real-time information about LA wall thickness and morphological changes of the LA wall during energy delivery for ablation would be extremely useful to predict the achievement of permanent trans-mural lesions, to identify the possible causes of ablation failure and to avoid the occurrence of perforation and/or other collateral damage (16) .

4.2 Techniques for LA wall thickness imaging

Cardiac computed tomography (CT), routinely used for the characterization of LA and PV anatomy and coronary arteries imaging before an AF ablation, has been recently tested to measure the mean LA wall thickness in patients with and without AF and to evaluate regional differences in patients with persistent AF. Of note, serial CT scans, performed before, immediately after and 1 month after the AF ablation, have documented the transient LA wall thickening suggestive of oedematous changes immediately after PVI by using RF ablation (17).Different CT study protocols have been successfully described for LA wall imaging (17-21) .

Preliminary data on animal studies also support the accuracy of real-time ultrasound imaging modalities such as intracardiac echocardiography (ICE) or IntraVascular Ultrasound (IVUS) imaging (22, 23). Compared with cardiac CT, they have the advantage of not requiring ionizing radiation and allow a real-time imaging of the LA wall, with measurement of wall thickness and monitoring of acute tissue changes related to AF catheter ablation, during the ablation procedure.

Both ultrasound techniques use miniaturized versions of traditional ultrasound transducers attached to a catheter tip. The catheter is introduced into a vessel via an arterial or venous puncture, advanced to the area of interest and pulled back through the vessel (or chamber of interest) to obtain a series of tomographic images. Most probes image in the axial plane, providing cross-sectional images of the vessel (or chamber of interest) and surrounding tissues. The close proximity of the catheter to the intervening tissue between the transducer and the object of interest improves the quality of the image by increasing

spatial resolution (the ability to discriminate between adjacent small objects) and contrast resolution (the ability to distinguish between differences in image intensity, i.e. the spectrum of gray scale of an ultrasound image). Moreover, higher ultrasound frequencies can be used to increase spatial and contrast resolution, although at the price of reduced image penetration (24, 25).

Ultrasound imaging with ICE has been used for years during ablation procedures to monitor the catheter position, to guide the trans-septal puncture and to help the electro-anatomical reconstruction of the left atrium. Radial ICE (e.g., Ultra ICE™ catheter, Boston Scientific) uses a mechanical, 9 Fr, 9 MHz catheter, with 360° radial image. The ultrasound transducer rotates every 1.4° and, with full mechanical rotation of the transducer, a panoramic 360° image is created that is perpendicular to the catheter shaft at the tip. The 360° scan with radial ICE allows for a comprehensive depiction of both atrial chambers and atrioventricular valves, and it also can be used as intravascular ultrasound for big vessels. Its placement in the LA through a deflectable trans-septal sheath and advancement into the PVs allows a detailed anatomic reconstruction of LA and PVs and close proximity of the catheter to the LA wall at the ablation sites, with higher image resolution(26). In a previous animal study ICE was successfully used to evaluate the changes in LA wall thickness and echo density at the ablation sites following RF delivery.

Since the development of IVUS in the late 1980s, this modality has been used both to image the vascular system and to direct interventions in target vessels. It was initially used to image atherosclerosis and aid in its treatment, but it has more recently been employed within the venous system (including the PVs through an intracardiac trans-septal approach), allowing for both intravenous and transvenous image-guided interventions (25, 27). A range of IVUS catheters are currently available, mainly differing in the ultrasound frequency used (from 10 to 45 MHz) that impacts on the maximum imaging diameter (from 60 to 14 mm respectively). Of note, a 40 MHz IVUS probe coupled to an RF catheter has been recently used to measure the LA wall thickness and image the acute LA wall changes associated with RF ablation in a porcine model (23).

Data about real-time imaging of LA wall thickness and ablation lesions in humans are lacking to date. Although both ICE and IVUS are routinely used in clinical practice in the cardio-vascular system (27, 28), their use for LA wall imaging in this setting has never been reported.

4.3 Research questions

- Intra-procedural ultrasound techniques (ICE and IVUS) have not previously been evaluated for LA wall imaging (thickness and acute changes in response to ablation) during PV isolation ablation. **How feasible is it to use these technologies for this purpose and do they provide accurate and reliable measurements compared to the gold standard of cardiac CT?**
- **Are there any differences in terms of acute tissue changes produced by the different energy modalities for AF ablation?**
- **What is the minimum dataset of CT acquisitions for a reproducible measurement of LA wall thickness with the lowest radiation exposure?**

We plan to address these questions in order to build a user-friendly, reliable and safe model to image the LA wall and to measure the acute tissue changes occurring during catheter ablation for AF.

5. STUDY DESIGN

Patients scheduled for their first pulmonary vein isolation ablation for symptomatic, drug-refractory paroxysmal AF, will be considered for inclusion in the study.

Potential subjects will initially be approached some weeks before their ablation procedure, in order to give the patients enough time to consider the information, to ask questions to the Investigator, their general practitioner (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. Moreover, a pre-operative imaging assessment with a cardiac CT scan will be performed to define the LA and PV anatomy and to measure the baseline LA wall thickness and PVs ostial diameters.

All AF ablation procedures will be performed in a standard fashion by using RF energy, cryo-balloon or laser balloon ablation under general anaesthesia (5) and with continuous oesophageal temperature monitoring. Ultrasound imaging by IVUS or ICE will be performed at sites corresponding with the PV/LA junction at the beginning and the end of the procedure in order to measure acute changes in LA wall thickness and PV ostial diameters.

The cardiac CT will be repeated within 24 hours post-procedure.

After the procedure, a pre-discharge review and a telephone follow-up at 1 week will be performed to identify any early and late complications related to the procedure.

A total of 12 patients will finally be enrolled in the study, 4 for each energy modality (RF, cryo and laser).

The end of the study for each patient will be the date of the telephone follow-up 1 week after the procedure.

For each patient the pre-procedural and post-procedural CT measurements of LA wall thickness and PVs ostial diameters will be compared with the corresponding IVUS or ICE measurements. Moreover, the acute tissue changes produced by the different energy modalities will be compared. Table 1 shows the main differences between the standard NHS process for AF ablation and the INSIDE PVs study appointments.

Standard NHS process for AF ablations	**INSIDE PVs study appointments**
Referral for procedure	Identification of participants

Patient sent booking letter	Patient sent Information Leaflet Opportunity for telephone questions
Pre-assessment clinic visit 1-2 weeks pre-procedure	Baseline assessment Recruitment and consent
Pre-ablation cardiac CT	Pre-ablation cardiac CT
AF ablation with PVI	AF ablation with PVI Intra-procedural ICE/IVUS imaging
Pre-discharge review	Pre-discharge review
---	Post-ablation Cardiac CT (12-24 h after ablation)
---	Telephone follow-ups at 1 week

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

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective **1.**Evaluation of the accuracy of intra-procedural intracardiac echocardiography (ICE) and intravascular ultrasound (IVUS) for real time imaging of the LA wall thickness and PV ostial diameters during AF ablation	**Primary Outcome Measure** **1.** ICE/IVUS measurements of LA wall thickness and PV ostial diameters before and after pulmonary vein isolation (PVI) in comparison with the corresponding cardiac CT measurements (before and the day following the AF procedure)	**1.**Day of and day after AF ablation procedure

Secondary Objectives	**Secondary Outcome Measure**	
1. Feasibility of ICE/IVUS for real time imaging of the LA thickness and PV ostial diameters during AF ablation	1a. Additional procedural time 1b. Image quality	Day of AF ablation procedure
2. Comparison between acute tissue changes produced by RF, cryo and laser energy	2. Percentage change of LA wall thickness with each ablation modality (RF, cryo and laser energy)	Day of AF ablation procedure
3. Standardization of CT for LA wall thickness imaging with identification of a minimum dataset of acquisitions and reduction of radiation exposure	3. CT acquisitions associated to reproducible measurement of LA wall thickness with the lowest radiation exposure	Some days before and day after AF ablation procedure

7. STUDY RISKS AND BENEFITS

7.1. Study risks

6.1.1 CT scans

Pre-procedure cardiac CT imaging is common practice for patients undergoing pulmonary vein isolation ablation for atrial fibrillation. The scans provide information on the presence or absence of coronary artery disease (which may have a role in antiarrhythmic and anticoagulant drug prescription) and pulmonary vein anatomy to aid procedure planning. The CT images can also be incorporated into the ablation guidance system for more precise delineation of the anatomy of interest, with reduced X-ray and left atrial access times (5, 29).

The post-operative CT scan to look for acute changes is an additional scan that would not take place as part of standard care. The mean radiation dose associated with the investigation has been previously estimated to 9-12mSv (30-32), which is approximately equivalent to 40-53 months exposure to UK background radiation (average UK natural background radiation dose 2.7mSv). This may be theoretically associated with an increased lifetime risk of developing a cancer of0.7%-0.07%, according to age and sex (32), over a latency period of 10-40 years. However, given this risk is age-dependent, it becomes 0.35% or less for ages above 40. The lifetime risk of developing a cancer in the general population is around 30 to 40%, so overall the risk

of cancer associated to an additional CT represents a very small addition to the underlying cancer risk from all causes.

We expect a mean effective dose equivalent of 9mSv for each research CT scan due to the need of multiple acquisitions for optimal standardization of the measurements. However, we are confident that at the end of this pilot study we will be able to restrict the number of CT acquisitions needed for optimal LA wall thickness imaging to a limited series, with a significant reduction of the radiation exposure to CT.

Of note, sophisticated CT imaging protocols have become widely available that can reduce the effective dose estimated to 2-4 mSv, nearly corresponding to the average annual UK natural background radiation dose (33).

6.1.2 AF ablation procedure

The patients taking part to the study will be undergoing a completely standard AF ablation on the basis of clinical reasons (symptoms and no response to medical therapy). No changes will be made to the standard ablation protocol in case of participation to the study; therefore no additional risks are expected (34). When compared with the standard AF ablation procedure, the study ablation procedure differs only with the additional use of ICE or IVUS for LA and PVs imaging during the procedure.

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

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

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

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

- TIA or stroke is approximately 1 in 200 people;

- pulmonary vein stenosis requiring treatment is 1 in 500;

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

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

6.1.3 Intra-procedural ultrasound imaging

Both rotational ICE and IVUS are approved for cardiac use. Possible complications are access site complications, benign and self-limiting catheter-induced atrial tachy-arrhythmias, LA perforation with pericardial effusion, LA thrombosis. Previous studies have documented no additional stroke events related to the use of ICE during AF ablation, and even a reduction of LA perforations and pericardial effusions, due to ICE guidance during trans-septal puncture, LA reconstruction and ablation (26).

We plan to introduce the ICE/IVUS catheter by exchange with the PV mapping catheter, without needing an additional venous puncture; therefore we do not expect additional access site complications. Similarly, we do not expect an increased stroke risk associated with ICE/IVUS because the catheter will be left in the LA only for the minimum time needed for imaging. The risk of perforation cannot be denied but we expect it to be negligible due to ultrasound-guidance.

6.2. Study benefits

Enormous benefits could come from this study if a user-friendly, reliable and not harmful technique for real-time imaging of the LA is developed. The real-time delineation of LA and PVs anatomy and measurement of the LA wall thickness could guide the catheter ablation, avoiding the occurrence of perforation and/or other collateral damage and predicting the achievement of trans-mural lesions. The monitoring of acute tissue thickness changes due to catheter ablation could help to identify the possible causes of ablation failure and develop new strategies to improve the procedure success. Ultimately the aim is to facilitate a safer procedure with increased single procedure success rates. Finally, the study could give us some insights regarding possible different mechanisms of lesion formation with the different energy modalities, to be investigated further in a bigger research study.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients scheduled for elective AF ablation in view of a history of symptomatic and drug-refractory paroxysmal AF.

8.2. Inclusion Criteria

The participant must satisfy the following conditions:

- Males older than 40 years or females older than 40 and sterile or in post-menopausal age;
- willing and able to give informed consent for participation in the study;
- history of symptomatic and drug-refractory paroxysmal atrial fibrillation;
- planned AF ablation on a clinical basis.

8.3. Exclusion Criteria

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

- age less than 40 years and more than 80 years;

- pregnancy, trying for a baby or breast feeding;
- 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;
- documented allergy to iodinated contrast medium; ;
- renal insufficiency (eGFR<30);
- weight exceeding the maximum load of the scanner (250kg).

9. STUDY PROCEDURES

9.1. Recruitment

Potential participants will first be approached some 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 a few weeks in advance). 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 invited to contact a member of the study team who can 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, eligibility assessment and pre-procedural cardiac CT imaging.

9.2. Baseline visit

9.2.1. 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.

9.2.2. 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;
d. list of current medications and antiarrhythmic drugs previously taken.

9.2.3. Pre-procedural CT imaging

As current practice, a pre-procedural cardiac CT scan will be performed to define the LA and PV anatomy and to measure the baseline LA wall thickness and PVs ostial diameters. The technical aspects of CT imaging are described in the intervention section.

9.3. AF ablation

The patient will be admitted to the hospital on the morning of the procedure or on the night before the procedure, as per local SOP's. Apart from intra-procedural ICE/IVUS imaging, the AF ablations will be conducted in a completely standard fashion.

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. Three-dimensional (3D) electro-anatomical mapping and/or fluoroscopy will be used by the operator, as usual, as anatomical guide during the procedure.

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.

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.

After the trans-septal puncture(s), pulmonary vein isolation (PVI) will be performed by using RF, cryo or laser energy as per operator's preference.

When using RF energy, the LA geometry will be reconstructed by using a 3-dimensional (3D) electro-anatomical mapping (EnSite Velocity or CARTO mapping system) and a multipolar circular mapping catheter (St Jude Medical Optima or Biosense Webster Lasso). Then a contact force ablation catheter (St Jude Medical EndosenseTacticath or Biosense Webster SmartTouch) through a deflectable sheath St Jude Medical Agilis will be used for PVI. The ablation sites will be annotated on the 3D electro-anatomical map. The choice of RF power, application time and mean contact force will be also left to operator preference.

When using cryo energy, LA and PV angiography will be performed in order to delineate their anatomy. A 11F FlexCath sheath (Medtronic, CA, USA) will be advanced to the LA and used to deliver either a 28 mm cryoablation balloon (Arctic Front Advance, Medtronic, CA, USA).). The balloon will be inflated at the ostium of each PV. After retrograde PV angiography, used to demonstrate PV occlusion, one or two 180-seconds freezes will be performed in each PV until PV isolation is confirmed using PV mapping with an Achieve guidewire and exit block confirmed with pacing.

When using laser energy, a laser balloon system (HeartLight, CardioFocus) will be delivered to the LA through a 12-F deflectable sheath and inflated at the ostium of each PV. Ablation lesions will be delivered in a circumferential, contiguous, and overlapping manner around the PV using 5–12 W power. Pulmonary vein isolation will be confirmed using PV mapping with an Achieve guidewire (Medtronic, CA, USA) and exit block confirmed with pacing (5)Before and after PVs encirclement, ultrasound imaging of the PVs-LA junctions with ICE or IVUS will be performed as described in the intervention section.

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.

9.4. Pre-discharge review

As part of standard care, each patient will be reviewed the day after the ablation procedure, before discharge. The occurrence of any procedural complications will be investigated.

9.5. Post-procedural CT imaging

A post-procedural cardiac CT will be performed within 24h of the AF ablation to look at acute changes in LA wall thickness and PVs ostial diameters. The technical aspects of CT imaging are described in the intervention section.

9.6. Telephone follow-up at 1 week

As part of the research study, a telephone follow-up will be performed 1 week after the procedure to assess late-presentation procedural complications (i.e. acute cerebrovascular events as TIA or stroke, pericardial

effusion, etc.). The patient's existing clinical care team will be informed about any symptoms and the decision to carry any additional investigations to investigate will be left to them.

The 1-week telephone follow-up will be the end of the study for each patient.

9.7. Image integration and data analysis

The pre-procedural CT images and the post-procedural CT images will be compared for each patient.

Moreover, the pre and post-procedural CT images will be compared with the corresponding IVUS or ICE images. The plane of the circumferential ablation line will be identified by using PV branching as reference anatomical markers and it will be divided into 12 segments by using a clock-face model. The LA wall thickness will be measured at each segment and comparisons will be made between pre and post-ablation and between IVUS/ICE and CT at each timepoint.

The percentage changes in LA wall thickness after AF ablation will be compared between the three energy modalities (RF, cryo and laser).

9.8. 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:

- 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 study interventions), 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.

9.9. Definition of End of Study

The end of study will be the date of last data analysis that will approximately be 3-5 days after the AF ablation of the last patient.

10. INTERVENTIONS

10.1. CT imaging

All cardiac computed tomographic (CT) studies will be performed using an Aquilion One scanner (Toshiba Medical Systems, Otawara, Japan), with 320 detector rows (each 0.5mm wide) and a gantry rotation time of 350ms. This allows the entire heart to be imaged in a single heartbeat, from carina to diaphragm, with a maximum of 16cm cranio-caudal coverage. The electrocardiogram (ECG) will be monitored to allow prospective gating of image acquisition, with a phase window set to 30-80% of the R-R interval to allow assessment of left atrial wall thickness in both atrial diastole and systole. If necessary, metoprolol will be administered intravenously in a series of doses (to a maximum of 80mg) to achieve a heart rate of 60bpm. The lowest tube voltage (100kVp or 120kVp) will be used that delivers a small focal spot based on scout image attenuation, with automatic selection of tube current (200-500mA).

A power injection of intravenous iodinated contast (Niopam 370, or equivalent) will be given via an intravenous cannula sited in an antecubital vein. A volume of 40-80ml will be used at an infusion rate of 4-6ml/s, depending on patient morphology. This will be followed by 50ml of normal saline given at a similar rate. A region of interest will be positioned within the descending aorta on a test slice, and when the Hounsfield units exceed 180 a breath-hold and image acquisition after a 3s delay will be triggered. Given uncertainty about the optimal way to image and measure the left atrial myocardium, after a delay of 40s, a second ("venous phase") acquisition will be performed using the same parameters as the first.

Images will be reconstructed iteratively with soft and sharp kernels, with a slice thickness of 0.5mm and an increment of 0.25mm. Analysis will be performed on a dedicated post-processing workstation (Terarecon). The thickness of the left atrial wall will be measured at a number of locations and especially in correspondence of the circumferential ablation line, identified retrospectively by using PV branching as anatomical markers. Of note, measurements will be optimally standardized according to position, phase of the R-R interval and arterial versus venous acquisition as this is another important aim of this pilot study.

Based on previous experience with an Aquilion One scanner (ADK), a prospectively gated scan covering 30-80% of the R-R interval (9 patients, range of kVp) delivers a dose-length-product of 165±100 mGy.cm. Therefore, the total DLP for study patients having two acquisitions (arterial and venous) before ablation and two afterwards will be 660 mGy.cm. Using a conversion factor of 0.014 mSv/mGy.cm, this equates to a mean effective dose equivalent of 9mSv.

10.2. Intra-procedural ultrasound imaging (ICE/IVUS)

Ultrasound imaging via ICE or IVUS will be performed in each patient during the AF ablation procedure. IVUS catheters Visions PV .018 (20 MHz digital probe, maximum imaging diameter 24 mm, Volcano Corp) or

ICE catheters Ultra ICE (9 MHz rotational transducer, maximal radial depth 50 mm, Boston Scientific) will be alternatively used. Before RF/cryo/laser delivery for PVI, the imaging catheter will be introduced in the LA. It will be sequentially placed in each PV, 1-2 cm distal to the ostium. Images will be recorded during slow retraction of the probe with a motorized linear pullback system from each vein to the trans-septal access.The same process will be repeated after PVI.

Reproducibility will be assessed by repeating the image acquisition via motorized linear pullback at least twice before and twice after PVI in two randomly chosen veins per patient.

11. SAFETY REPORTING

11.1. 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.

11.2. 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).

12. STATISTICS AND ANALYSIS

12.1. The Number of Participants

This investigational study aims at building a model for real-time imaging of LA wall thickness and acute changes produced by catheter ablation for AF. As pilot study, it will enrol 12 patients elected to AF ablation with radiofrequency energy (4 patients), cryo-balloon (4 patients) or laser balloon (4 patients).

As each patient will undergo two cardiac CT scans (one before and after AF ablation), with LA wall thickness measurements in different locations, and repeated intra-procedural ultrasound imaging, with 1-2 acquisitions before and 1-2 acquisitions shortly after RF delivery for PVI in each PV, we expect that at the end of the study we will have enough information to confirm if intra-procedural ICE and/or IVUS are feasible for real-time imaging of the LA wall thickness during AF ablation and to streamline the CT protocol to a minimum dataset of acquisitions, with reduced radiation exposure. The study could also give us some insights about different mechanisms of lesion formation and different acute tissue changes caused by the different energy modalities, to be investigated further in a bigger randomized study.

12.2. 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.

12.3. 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. For every participant who withdraws, another participant will be sought in order to have a total of 12 full datasets for 12 participants.

13. DATA MANAGEMENT

13.1. 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.

13.2. 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 Kelion, Dr Leo and Dr Betts in the JR hospital. No further data transfer will be performed.
- As per Trust Policy, after the end of the trial period, all study data will be kept for a further period of years before being deleted, to allow for full analysis and results publication.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

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

14.2. Guidelines for Good Clinical Practice

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

14.3. 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.

14.4. 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.

14.5. 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.

14.6. 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.

15. FINANCE AND INSURANCE

15.1. Funding

This research study was selected for the NIHR Oxford Biomedical Research Centre (BRC) Young investigator Award in 2014 and will be supported by the corresponding research grant awarded. The study cost centre A20328 Cardiac Rhythm Management Research (CRM) Hub will cover any shortfalls.

15.2. 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 Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

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

16. 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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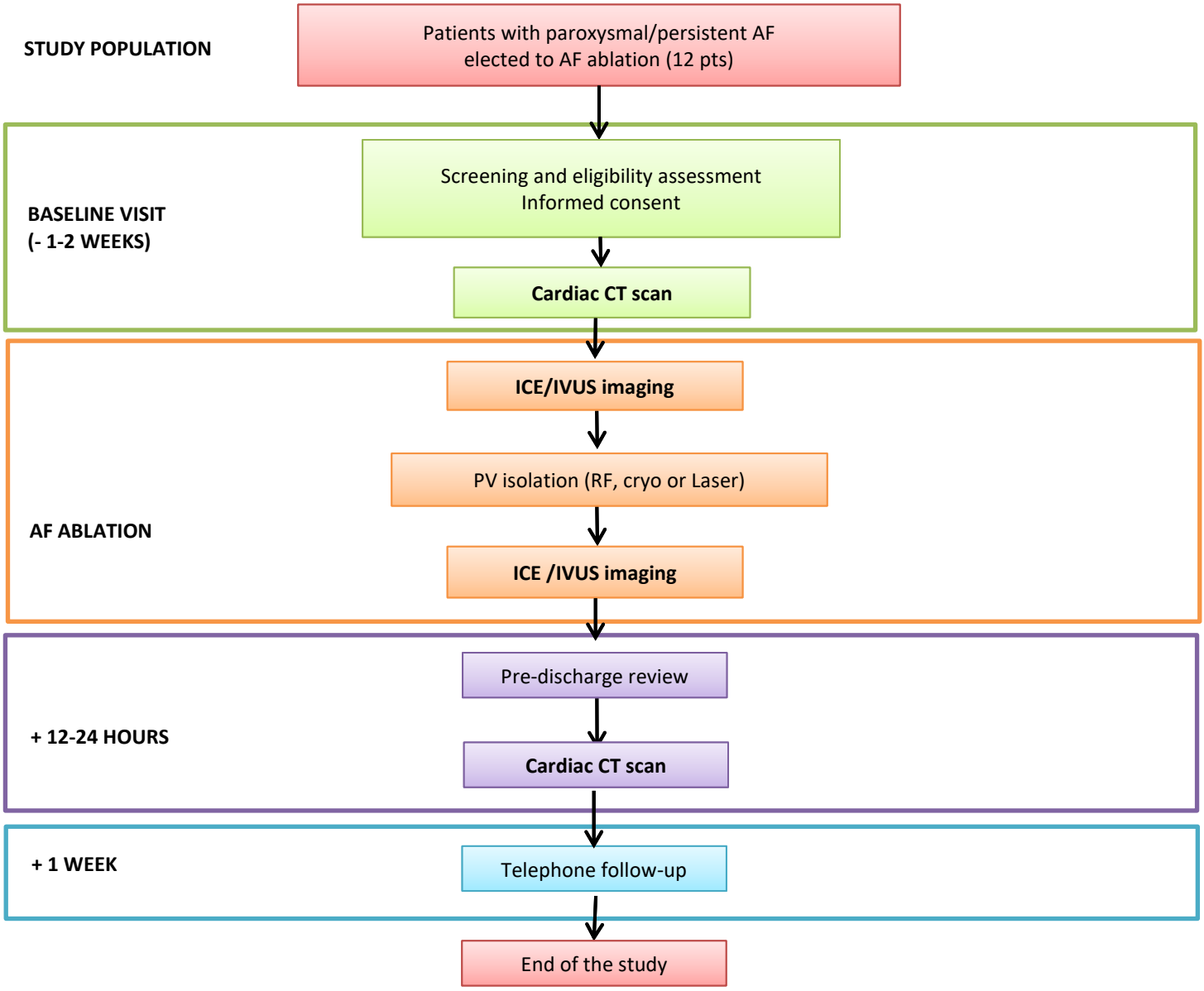
STUDY POPULATION
Patients with paroxysmal/persistent AF elected to AF ablation (12 pts)
BASELINE VISIT (- 1-2 WEEKS)
Screening and eligibility assessment Informed consent
Cardiac CT scan
AF ABLATION
ICE/IVUS imaging
PV isolation (RF, cryo or Laser)
ICE /IVUS imaging
+ 12-24 HOURS
Pre-discharge review
Cardiac CT scan
+ 1 WEEK
Telephone follow-up
End of the study

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

	Recruitment	Baseline visit	AF ablation	Pre-discharge review	Telephone f-up
Time since AF ablation	≥ 6 wks	- 1-2 wks	0	+ 1 d	+ 1 wk
Study procedures					
Eligibility assessment	X	X			
Patient's information	X				
Informed consent		X			
Demographics		X			
Medical history		X		X	X
Cardiac CT		X		X	
PVI			X		
ICE/IVUS imaging			X		

AF= atrial fibrillation; ICE= IntraCardiac Echoardiography; IVUS= IntraVascular UltraSound; PVI= Pulmonary Vein Isolation; d = day; f-up = follow-up; wks = weeks.

18. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made