# ***C***atheter ***A***blation Versus Thoracoscopic ***S***urgical ***A***blation in Long Standing Persistent ***A***trial ***Fi***brillation (CASA-AF)

## Statistical Analysis Plan

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**CHIEF INVESTIGATOR:**

**Dr Tom Wong**
Consultant Cardiologist and Electrophysiologist
Department of Cardiology
Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital (RBH)
Sydney Street
London SW3 6NP

**Phone: +**44 (0)207 352 8121 Ext: 8619
**Email:** t.wong2@rbht.nhs.uk

**STATISTICIAN**

**Prof Simon Jones**
Professor of Population Health (Research)
New York University School of Medicine
NYU Translational Research Building
227 East 30th Street
New York, NY 10016

**HEALTH ECONOMIST**

**Prof Joanne Lord**
Director Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House, Enterprise Road,
University of Southampton Science Park,
Southampton, SO16 7NS, United Kingdom

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# 1 Introduction

## 1.1 Preface

Atrial fibrillation (AF) is the commonest heart rhythm disturbance, affecting 1-2% of the population. Its prevalence increases with age, from 0.5% at 40-50 years to 5-15% at 80 years. With an ageing population, AF becomes increasingly larger problem for the health services [1]. In the UK alone, NHS admissions have risen 60% over 20 years, with total cost to the NHS of £2.2bn a year, and projected to double by 2050 [2,3].

Atrial fibrillation is a heterogenous condition and for clinical purposes usually categorised into three types: paroxysmal AF (recurrent fibrillation that terminates spontaneously within 7 days), persistent AF (lasting longer than 7 days or successfully terminated before with cardioversion) and longstanding persistent AF (arrhythmia persisting for more than a year) [4].

AF is characterised by an irregularly irregular pulse, loss of atrial contractile function and attendant loss of active ventricular filling, and risk of thromboembolic stroke. In addition to prevention of stroke with anticoagulants, there are two principal therapeutic strategies for treatment of AF: rhythm control (to restore sinus rhythm) and rate control (to accept AF and simply control the ventricular rate). Rhythm control is preferred in symptomatic, especially younger, more active patients with symptoms despite adequate rate control. Traditionally, rhythm control is attempted with antiarrhythmic drugs (AADs) and direct current (DC) cardioversion. Long-term efficacy of these treatments is poor, and they are associated with side-effects and risk of proarrhythmia. Consequently, there has been an increasing impetus particularly over the last two decades to advance non-pharmacological approaches to AF management.

Interventional treatments (surgical or catheter) have evolved over the years and nowadays allow reliable clinical success in treating paroxysmal AF, albeit with repeat procedures necessary in a proportion of patients.

CASA AF randomised clinical trial was designed to examine which of the two interventions will be most effective in patients with LSPAF, the most difficult to treat form of AF. The trial protocol with detailed description of the two treatments was published previously [5] and this manuscript is the proposed statistical analysis plan (SAP).

## 1.2 Purpose of the analyses

The main purpose of the analyses is to compare the efficacy and safety of catheter ablation and thoracoscopic surgical ablation in adults with LSPAF.

# 2 Study Objectives and Endpoints

The objectives of this study are in line with questions defined as important in the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF [4]:

- To identify the most effective ablation strategy in treating patients with LSPAF.
- To relate the effectiveness of the ablation techniques to quality of life using validated general and disease-specific tools.
- To assess the cost-effectiveness of interventional techniques by performing a comprehensive health economic assessment.

## 2.1 Primary Objective

1. The primary hypothesis is that thoracoscopic surgical ablation is more effective than percutaneous catheter ablation in establishing freedom from atrial arrhythmias (≥ 30 seconds atrial tachycardia/AF) within 12 months of follow-up after a single procedure without anti-arrhythmic drugs. The data will be evaluated from the end of the 3 month blanking period to the end of the follow up.

## 2.2 Secondary objectives

1. To evaluate and to compare the safety of the two interventions. The safety end-point is defined as the intervention-related major complication resulting in permanent injury or death, one that requires unplanned intervention for treatment, or prolongs or requires unplanned hospitalization for more than 48 hours.
2. To evaluate and to compare the clinical success of the arrhythmia interventions (distinct from arrhythmia-free survival) - defined as a 75% or greater reduction of AF burden assessed by implantable loop recorder during 12 months follow-up with or without AADs.
3. To evaluate freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up.
4. To identify changes in atrial anatomy and function following ablation as assessed by echocardiography and CMR imaging using tissue Doppler and strain.
5. To evaluate and to compare the effects of the arrhythmia interventions on the patients' symptoms and quality of life as assessed by change in AF symptom score (EHRA score) [6] and quality of life assessments (EQ5D, AFEQT) from baseline to follow-up [7,8].
6. To evaluate Quality Adjusted Life Years (QALYs) accrued during 12-month study period
7. To evaluate cost-effectiveness (Incremental Cost per QALY gained) for surgical ablation compared with catheter ablation estimated over the 12-month study period ('within trial' analysis) and over a lifetime horizon (estimated by modelling).

## 2.3 Endpoints

The primary outcome of the trial is the proportion of AF patients undergoing ablation that are free from atrial arrhythmias within 1 year after a single ablation procedure. The analyses will be performed on intention to treat principle. Sensitivity analysis will be used to explore the impact of missing data, non-compliers, protocol deviations, spurious data, deaths and withdrawals in analysis. Sub group analysis will be avoided.

## 2.4 Derived variables

The primary outcome measure (and all other ILR data) will be assessed by cardiac physiologist(s) based centrally at the Royal Brompton and Harefield Foundation NHS Trust (RB&HFT), which will act as the core lab. The cardiac physiologist(s) will be blinded to the patients' mode of intervention. The results of these assessments will be passed to the trial statistician for analysis.

A binary variable indicating if a patient **is atrial arrhythmias free** will be derived by combining atrial arrhythmias status from 4$^{th}$ to 12$^{th}$ month post ablation. This is to allow for a 3 month blanking period after treatment.

A binary variable indicating a **clinical success** is derived by combining data from the implantable loop recorder from 4-12 months post ablation. This is to allow for a 3 month blanking period after treatment.

A binary variable indicating a **freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up** is derived by combining ILR data with relevant medications and additional procedures data at 6, 9 and 12 months follow up visits, allowing for a 3 month blanking period after treatment.

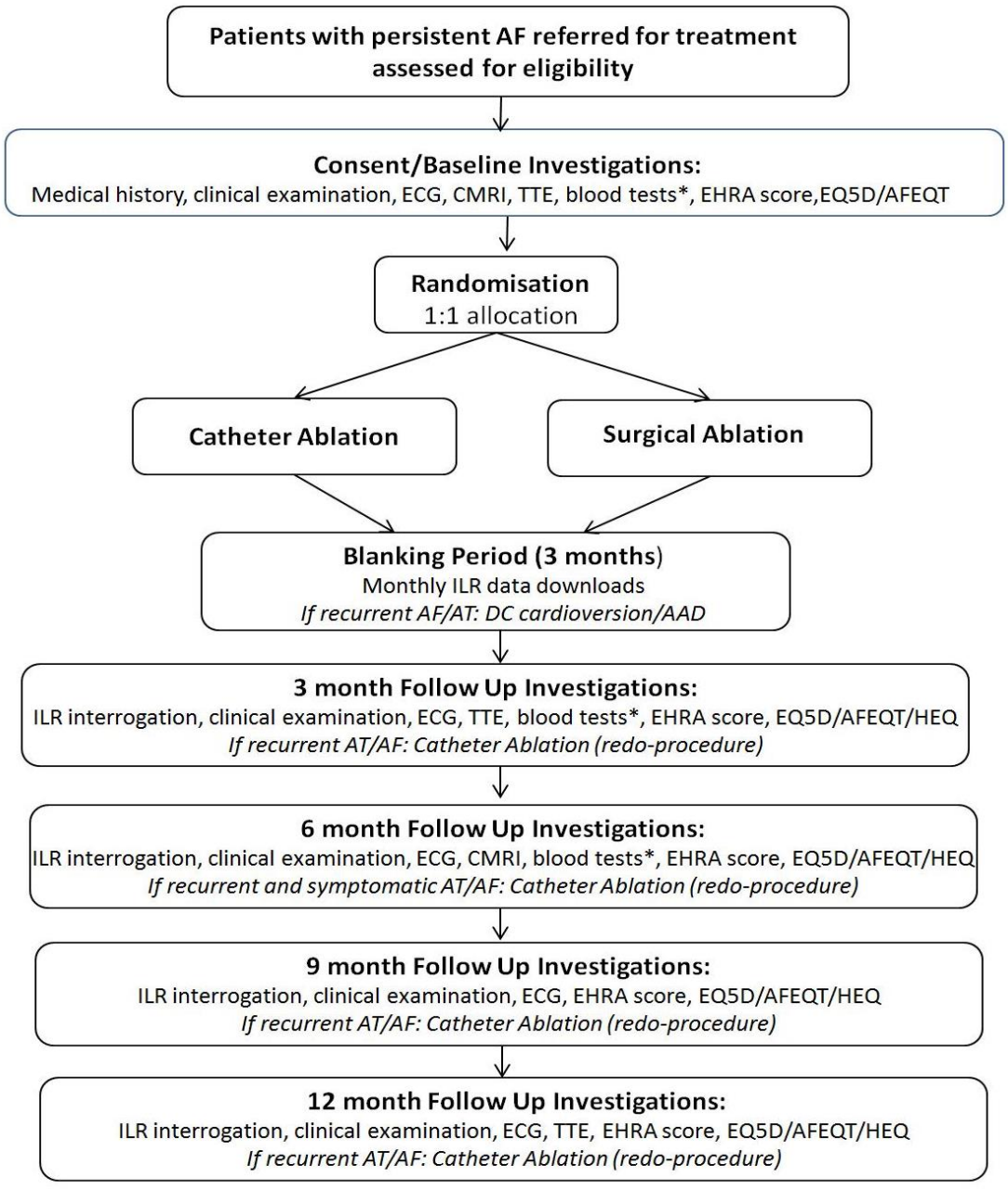
**Changes in scores from EHRA, EQ5D5L and AFEQT questionnaires** will be analysed at 3, 6, 9 and 12 months' follow up visits and compared to the baseline values.

# 3 Study Methods

## 3.1 General Study Design and Plan

Eligible participants will be invited to take part in the study, sign the consent form and complete baseline investigations to confirm eligibility.
Subsequent stages in their progress in the trial are summarised in the flowchart below.

**Figure 1**: CASA AF flowchart



## 3.2 Inclusion-Exclusion Criteria and General Study Population

### 3.2.1 Inclusion criteria

a. Age ≥ 18 years
b. Long-standing persistent AF (>12 months duration)
c. EHRA symptom score >2 (see Appendix A)
d. Left ventricular ejection fraction ≥ 40%
e. Suitable for either ablation procedure

### 3.2.2 Exclusion criteria

a. Valvular heart disease with severity greater than mild
b. Contraindication to anticoagulation
c. Thrombus in the left atrium despite anticoagulation in therapeutic range
d. Cerebrovascular accident within the previous 6 months
e. Previous thoracic or cardiac surgery (including surgical interventions for AF)
f. Prior left atrial catheter ablation for AF
g. Unable to provide informed written consent
h. Active malignancy, another severe concomitant condition or presence of implanted cardiac devices that would preclude patient undergoing study specific procedures
i. Pregnant or breast-feeding, or women of childbearing age not using a reliable contraceptive method.

## 3.3 Randomisation and Blinding

Randomisation will be via a 24 hour bespoke web based randomisation system hosted at the King's Clinical Trials Unit on a secure server. 120 adult patients with long-standing persistent atrial fibrillation will be randomised 1:1 at the level of the individual using the method of minimisation. Stratification variables will be gender (male or female), study site and left atrial diameter (< 50 mm and ≥ 50 mm). Treatment allocation will be concealed from the researchers randomising patients in the study.

### 3.3.1 Randomisation Procedure

A patient identification number (PIN) will be generated by registering the patient on the electronic case report form (eCRF, InferMed Macro), after consent has been signed. This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study.

Authorised site staff will be allocated a username and password for the randomization system. Once a patient is consented, all baseline data collected and eligibility confirmed (usually within a week from date of consent), the staff member will log into the randomization system (www.ctu.co.uk) to obtain treatment assignment.

Patients that withdraw will not be replaced; levels of attrition have formed part of the sample size calculation to accommodate this.

Patients will be randomised as close as possible to the time of the intervention (within four weeks), reducing the risk of post-randomisation or pre-intervention dropouts. Individual participants who are randomised into the trial will be followed up as per protocol.

### 3.3.2 Blinding

The cardiac physiologist reviewing heart rhythm data from the ILR will be blinded.
It is not possible to blind patients to the procedure as the mode of access will be obvious (incisions at the side of chest in thoracoscopic ablation *vs.* small punctures in the groin for percutaneous ablation).
The statistician will be blinded to treatment arms until after the analyses are complete.
Although it would be preferable that all members of the research team are blinded to the patients' intervention arm, in practice this is not achievable. It should be noted, however, that the primary endpoint is such that it cannot be altered by the researcher knowing which arm of the study the patient is in. In addition, a need for further intervention and/or anti-arrhythmic drug use outside of the 3 month blanking period will constitute a fail in the primary endpoint.

## 3.4 Study Variables

A full list of study variables can be found in the attached CASA-AF codebook (Appendix B).
A synopsis of data collection forms and study visits schedule is shown in Table 1 below but more comprehensive list can be found in Appendix C.

**Table 1:** Summary of the main data collection forms and study time points

| Data collection forms | Baseline | 3 months | 6 months | 9 months | 12 months |
|---|---|---|---|---|---|
| Medical history, concomitant medications and clinical examination | X | X | X | X | X |
| Questionnaires | X | X | X | X | X |
| Transthoracic echocardiogram | X | X | | | X |
| Cardiac MRI (or CT) | X | | X | | |
| Blood Tests | X | X | X | | X |
| Remote monthly ILR interrogation | | X | X | X | X |
| 12 lead ECG | X | X | X | X | X |

Measurements outside the specified time windows will not be used to assess outcomes.

## 3.5 Sample Size

The sample size calculation is based on data obtained from our pilot study. In the surgical ablation group 76% of patients (13/17) at 6 months were free of AF and AADs compared with 44% patients (8/18) in the catheter ablation group based on a serial 7-day continuous ambulatory ECG monitoring. Using these data, we calculated that a sample size of 48 per group is required to achieve this effect size at 90% power and 5% significance level.

The implantable loop recorder, used in this trial, has a tendency to detect a higher number of patients with AF recurrences (31 vs. 24%; P = 0.125) when compared to 7-day continuous ambulatory ECG monitoring [63]. This may affect the proportions of patients free from AT/AF and reduce the success rates which would also impact on the sample size requirements. We have therefore increased the sample size to a total of 120 patients (60 in each treatment arm) to maintain the power and significance levels.

# 4 General Considerations

## 4.1 Timing of Analyses

The final analyses will be performed once the last patient completes the last visit in the study and the data is transferred to the statistician, having been documented as meeting the cleaning and approval requirements of the protocol and after the finalisation and approval of this SAP document.

## 4.2 Analysis Population

All subjects who were consented and randomised in the trial.

## 4.3 Covariates and Subgroups

In addition to the Chi-squared test used to assess the primary outcome, a secondary analysis will be conducted to adjust for the variables used for stratification in the minimisation algorithm:

- gender,
- study site and
- left atrial diameter (< 50 mm and ≥ 50 mm).

Both the unadjusted and adjusted results will be included in any paper. The unadjusted analysis using the chi-squared test will be considered the primary analysis.

No subgroup analysis will be performed.

## 4.4 Missing Data and Dropouts

Every effort will be made to ensure a complete set of data. However, some missing values are inevitable. A complete case analysis will be presented as the primary analysis. The number, treatment arm and timing of dropouts will be reported in papers related to the study. We will use multiple imputation using the R statistical software MICE library as a sensitivity analysis. This will be presented in the supplementary tables of any published work from the trial.

## 4.5 Interim Analyses and Data Monitoring

There will be no formal interim analysis, but the trial statistician will verify that there are no significant problems with the data collection tools or other parts of the trial's methodology, prior to undertaking primary analysis.

The trial statistician will perform pre-analyses checks for the regular 6 monthly meetings of the independent Data Monitoring Committee. The committee will be provided with an open report for both arms combined showing:

- recruitment progress,
- baseline characteristics,
- compliance with randomization outcome,
- compliance with study visits and follow-up,
- details on all recorded adverse events and serious adverse events

For the closed section of the meeting, the Data Monitoring Committee will receive an unblinded version of the above information.

## 4.6 Multi-centre randomised clinical trial

The study will recruit patients from the following sites:

- Royal Brompton Hospital,
- Harefield Hospital,
- Heart and Chest Hospital Liverpool,
- Brigthon and Sussex University Hospital

Data from all sites will be combined and analysed together.

## 4.7 Multiple Testing

There are no plans to conduct or adjust for multiple testing.

# 5 Summary of Study Data

## 5.1 Subject Disposition

**Consented**

The number of people consented and eligible will be assessed by having a valid entry in the ELIG reporting form. To be included they must have a valid PIN number and valid date of consent.

**Randomized**

The number of people randomized will be assessed by having a valid entry of the RAN form. To be included they will have a valid PIN number, and RAN_01 (indicating the subject was randomized) must be set to 'yes' and a RAN_02 (date of randomization) date must contain a valid date.

There is also an extract from an independent randomisation system which contains information on stratification variables used at randomisation. This file will be provided to the statistician and will also contain flags for participants who crossed over to the alternative treatment arm. These data need to be cross checked with relevant variables in the relevant data collection forms during pre-analyses checks.

**Treated**

The number of people treated will be assessed by a specially contracted extract that will enable the trial statistician to be blinded. To be valid an entry must consist of a valid PIN number and treatment date.

**Follow up**

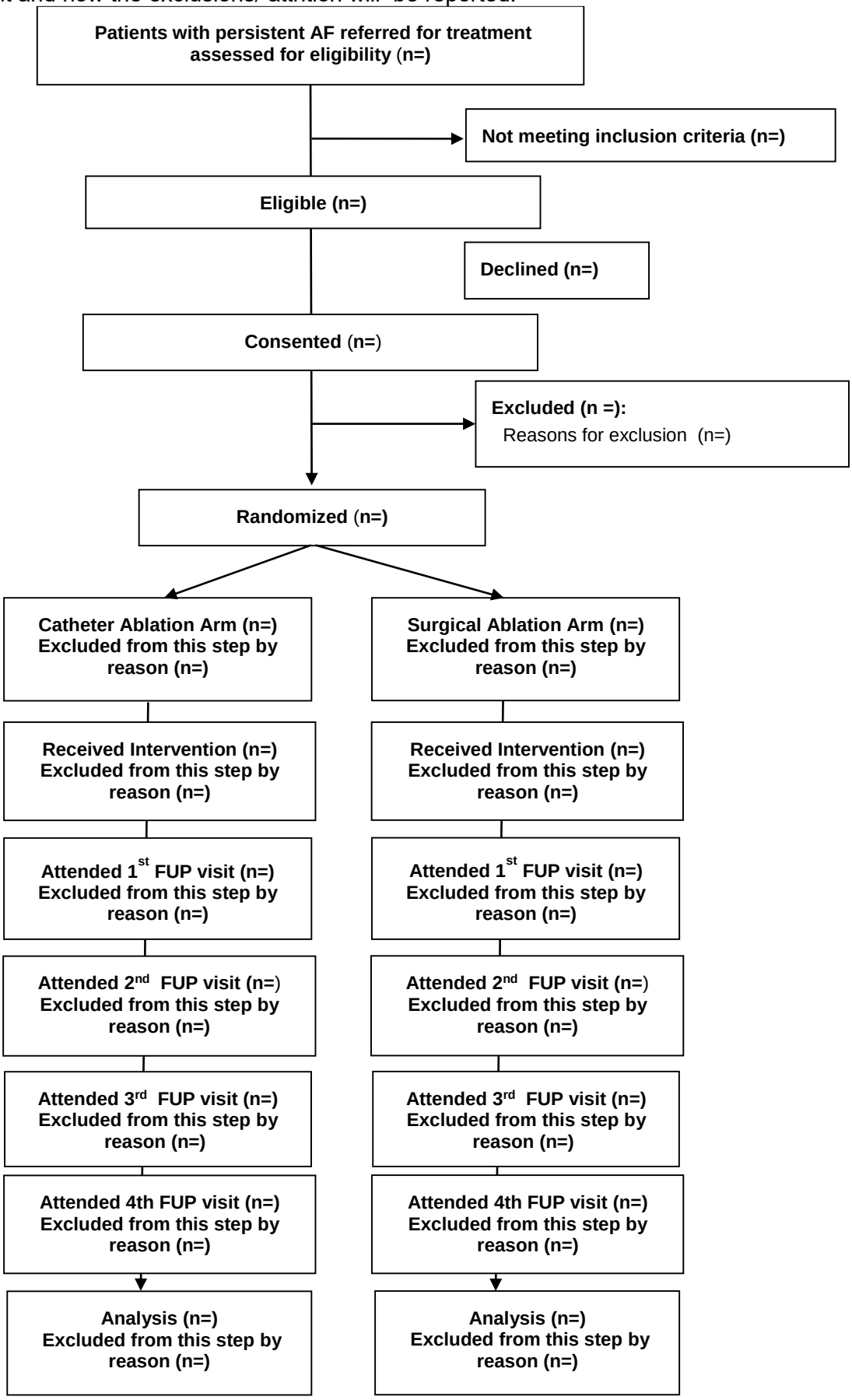
The number of people reaching each stage will be assessed as valid entry for that stage on the clinical examination (CE) form. To be valid the record must contain a valid PIN number, CE_01(date of clinical examination) a date of examination must be a valid date. Stage will be assessed by the Visit Cycle Flag.

**Adverse Events**

The number of people with an adverse event will be identified from the AE table. To be included a valid PIN number and AE_01 (description of the event) will be required.

The results of the analyses will be reported in line with CONSORT requirements, as shown in Figure 1 below.

**Figure 1**: A Schematic of the trial design (CONSORT) showing the number of participants reaching each study point and how the exclusions/ attrition will be reported.



## 5.2 Protocol Deviations

Analyses will remain on intention to treat principle but compliance with randomisation outcomes and study visits at all sites will be reported, as illustrated by the following tables.

**Table 3:** Compliance with randomization outcome for each study arm

| Treatment Arm | Randomised (n) | Underwent allocated treatment (n) | Had alternative treatment (n) | Withdrawn consent (n) |
|---|---|---|---|---|
| Catheter Ablation | | | | |
| Surgical Ablation | | | | |

**Table 4:** Compliance with study visits and follow-up for each study arm

| Study Intervals | Catheter ablation (n) | | Surgical ablation (n) | |
|---|---|---|---|---|
| | Mean (SD) | IQR (Min-Max) | Mean (SD) | IQR (Min-Max) |
| Consent to randomisation, days<br>Target = up to 12 weeks | | | | |
| Randomisation to treatment, days<br>Target = 4 weeks | | | | |
| Randomisation to 1st follow up visit,days<br>Target = 4 months | | | | |
| Randomisation to 2nd follow up visit, days<br>Target = 7 months | | | | |
| Randomisation to 3rd follow up visit, days<br>Target = 10 months | | | | |
| Randomisation to 4th follow up visit, days<br>Target = 13 months | | | | |
| Intervention to 1st follow up visit, days | | | | |
| Intervention to 2nd follow up visit, days | | | | |
| Intervention to 3rd follow up visit, days | | | | |
| Intervention to 4th follow up visit, days | | | | |

## 5.3 Demographic and Baseline Variables

Additional table with values for different classes of medications and anticoagulation therapy will be provided to the statistician.

**Table 5:** Baseline demographics and clinical data.

| | All | Catheter Ablation | Surgical Ablation |
|---|---|---|---|
| *Age, yr (median, IQR* | | | |
| *Male sex, no./total no. (%)* | | | |
| *BMI (median, IQR)* | | | |
| *Townsend Deprivation Index (median, IQR)* | | | |
| *Index of Multiple Deprivation score (median, IQR)* | | | |
| *Ethnicity, n(%)* | | | |
| **White** | | | |
| **Bangladeshi** | | | |
| **Other Asian** | | | |
| **Black** | | | |
| **Middle-eastern** | | | |
| **Afro-Caribbean** | | | |
| *Systolic Blood Pressure, mmHg (meanSD/medianIQR/range)* | | | |
| *Diastolic Blood Pressure, mmHg (meanSD/medianIQR/range)* | | | |
| *Heart rate, beats/min (meanSD/medianIQR/range)* | | | |
| *Ejection fraction, % (median, IQR)* | | | |
| *Left atrial diameter, mm (median, IQR)* | | | |
| *Time from first diagnosis of atrial fibrillation to randomisation, months(median, IQR)* | | | |
| *Time from first diagnosis of atrial fibrillation to procedure, mths (median, IQR)* | | | |
| *Time from first diagnosis of persistent atrial fibrillation to randomisation, mths (median, IQR)* | | | |
| *Time from first diagnosis of persistent atrial fibrillation to procedure, mths (mean,SD)* | | | |
| *Medical history, no. (%)* | | | |
| **Hypertension** | | | |
| **Diabetes** | | | |
| **Coronary artery disease** | | | |
| **Stroke or transient ischemic attack** | | | |
| | | | |
| *CHA2DS2VASc Score, no. (%)* | | | |
| **0** | | | |
| **1** | | | |
| **2** | | | |
| **3** | | | |
| **4** | | | |
| **5** | | | |
| *HASBLED Score, no. (%)* | | | |
| **0** | | | |
| **1** | | | |

| | | | |
|---|---|---|---|
| **2** | | | |
| **3** | | | |
| **4** | | | |
| **5** | | | |
| *Medications, no. (%)* | | | |
| **Anti-arrhythmic drugs** | | | |
| Amiodarone | | | |
| Dronedarone | | | |
| Flecanide | | | |
| Sotalol | | | |
| **Rate control** | | | |
| Beta-blocker (atenolol/bisoprolol) | | | |
| Calcium-channel blocker (Verapamil/diltiazem) | | | |
| Cardiac glycoside (Digoxin) | | | |
| **Others** | | | |
| ACEi/ARB | | | |
| Calcium-channel blocker (Amlodipine/Felodipine/Lercanidipine) | | | |
| Aldosterone antagonist | | | |
| Diuretics | | | |
| Other anti-hypertensives (Bendroflumethazine, Indapamide, alpha-blocker) | | | |
| Statins | | | |
| **Anti-coagulants** | | | |
| Vitamin K antagonist | | | |
| Oral direct thrombin inhibitor | | | |
| Dabigatran | | | |
| **Anti-platelets** | | | |
| Aspirin | | | |
| Clopidogrel | | | |

# 6 Efficacy Analyses

The primary analysis of proportions will be carried out using a Chi Squared test implemented with R's prop.test command. The primary analysis of continuous outcomes will be analysed by either t-test or Mann-Whitney test as appropriate. As a robustness check, binary outcomes will also be analysed using a logistic regression model that will control for the stratification variables used in the minimization algorithm, specially;

- gender (male or female),
- study site and
- left atrial diameter (< 50 mm and ≥ 50 mm).

Confidence intervals for proportions will be estimated using the exact method.

## 6.1 Primary Efficacy Analysis

**The primary efficacy end-point is freedom from atrial arrhythmias after a single procedure without anti-arrhythmic drugs (AADs) within 12 months (as assessed from the end of the 3 months blanking period to 12 months).**

**Test**: Chi Squared using the statistical package R's prop.test command
**Null Hypothesis**: The proportion of people achieving this outcome is the same in the catheter ablation arm and the surgical arm.
**Alternative Hypothesis**: The proportion of people achieving this outcome is not the same in the catheter ablation arm and the surgical arm.

**Test**: Logistic regression with outcome variable being atrial arrhythmias free with covariate treatment arm and the stratification variables listed above.
**Null Hypothesis**: The odds ratio achieving this outcome for catheter ablation arm over in the surgical arm is one
Alternative Hypothesis: The odds ratio achieving this outcome for catheter ablation arm over in the surgical arm is not one

**Table 6**: Primary outcome analysis

| | **Catheter ablation (n)** | **Thoracoscopic surgical ablation (n)** |
|---|---|---|
| **Freedom from atrial arrhythmias** | | |
| Number of people with freedom from atrial arrhythmias from 4-12 months | | |
| Number of people assessed for this outcome | | |
| Rate and 95% confidence interval | | |
| P value from Chi-squared test and from logistic regression model that adjusts for stratification variables. | | |

## 6.2 Secondary Efficacy Analyses

### 6.2.1 Clinical success - defined as a 75% or greater reduction of AF burden assessed by implantable loop recorder (ILR) during 12 months follow-up with or without AADs.

**Test**: Chi Squared using the statistical package R's prop.test command
**Null Hypothesis:** The proportions of people achieving this outcome is the same in the catheter ablation arm and the surgical arm.
**Alterative Hypothesis:** The proportions of people achieving this outcome is not the same in the catheter ablation arm and the surgical arm.

**Test**: Logistic regression outcome variable being clinical success with covariates treatment arm and the stratification variables listed above.
**Null Hypothesis**: The odds ratio achieving this outcome for catheter ablation arm over in the surgical arm is one
**Alternative Hypothesis**: The odds ratio achieving this outcome for catheter ablation arm over in the surgical arm is not one

**Table 7:** Clinical success analysis

| | Catheter ablation (n) | Thoracoscopic surgical ablation (n) |
|---|---|---|
| **AT/AF burden reduction ≥75%** | | |
| Number of people with ≥75% burden reduction from 4-12 months | | |
| Number of people assessed for this outcome | | |
| Rate and 95% confidence interval | | |
| P value from Chi-squared test and from logistic regression model that adjusts for stratification variables. | | |

### 6.2.2 Freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up.

**Test**: Chi Squared using the statistical package R's prop.test command
**Null Hypothesis**: The proportions of people achieving this outcome is the same in the catheter ablation arm and the surgical arm.
**Alterative Hypothesis:** The proportions of people achieving this outcome is not the same in the catheter ablation arm and the surgical arm.
.
**Test**: Logistic regression outcome variable being Freedom from atrial arrhythmia, after multiple procedures without AADs during 12 months follow-up with covariates treatment arm and the stratification variables listed above.
**Null Hypothesis**: The odds ratio achieving this outcome for catheter ablation arm over in the surgical arm is one
**Alternative Hypothesis:** The odds ratio achieving this outcome for catheter ablation arm over in the surgical arm is not one

**Table 8:** Freedom from AT/AF after multiple procedures with/without AADs

| | Catheter ablation (n) | Thoracoscopic surgical ablation (n) |
|---|---|---|
| **Freedom from AT/AF after multiple procedures with/without AADs** | | |
| Number of people with multiple procedures free from AT/AF 4-12 months post index procedure | | |
| Number of people assessed for this outcome | | |
| Rate and 95% confidence interval | | |
| P value from Chi-squared test and from logistic regression model that adjusts for stratification variables. | | |

### 6.3 Exploratory Efficacy Analyses

A General Estimating Equation (GEE) [10,11] will be used to explore the relationship between time and each outcome measure. It will be stressed in any publication that this was an exploratory analysis and the study has not been designed to be powered for this approach. The analyses will be performed using R's gee library.

# 7 Safety Analyses

Safety end-point is the intervention-related major complication (serious adverse event) defined as:

- permanent injury or death,
- the one that requires unplanned intervention for treatment,
- the one that prolongs or requires unplanned hospitalization for more than 48 hours.

### 7.1 Table of expected adverse events in the study

| Adverse Events | Serious Adverse Events |
|---|---|
| Bruising, hematoma, vascular injury not requiring intervention | Vascular complications requiring blood transfusion or intervention |
| Pericardial/pleural effusion (observation only) | Symptomatic pericardial/pleural effusion or requiring intervention |
| Broken rib | Stroke (TIA) |
| Pneumothorax requiring observation | Pneumothorax requiring chest drain |
| Infection (i.e. pneumonia) | Empyema |
| Pulmonary oedema | Myocardial infarction |
| Temporary phrenic nerve damage | Permanent phrenic nerve damage |
| Pain near surgical sites | Pulmonary vein stenosis (>50% reduction in diameter from baseline) |
| | Requirement to insert PPM (with or without prior conduction tissue damage) |
| | Cardiac trauma requiring surgical intervention |
| | Radiation induced skin damage |

| | |
|---|---|
| | Oesophageal atrial fistula |
| | Death |

### 7.2 Extent of Exposure

The summary statistics will be produced in accordance with section 6-8.

### 7.3 Adverse Events

The summary statistics will be produced in accordance with sections 7 & 8.

**Table 9a**: Adverse events in each arm

| Treatement Arm | AE, n people (events) | AEs within 30 days of treatment, n people (events) | SAE, n people (events) | AEs within 30 days of treatment, n people (events) |
|---|---|---|---|---|
| CA | | | | |
| TSA | | | | |

**Table 9b**: Description of adverse events in each arm

| Adverse events categories | CA (n) | TSA |
|---|---|---|
| | | |
| | | |
| | | |

### 7.4 Deaths, Serious Adverse Events and other Significant Adverse Events

The summary statistics will be produced in accordance with section 8.

### 7.5 Clinical Laboratory Evaluations

The summary statistics will be produced in accordance with section 8.

### 7.6 Other Safety Measures

The summary statistics will be produced in accordance with section 8.

# 8 Other Secondary Outcomes Analyses

### 8.1 Identify changes in atrial anatomy and function following ablation as assessed by echocardiography and CMR imaging using tissue Doppler and strain.

Each of these indictors will be assessed for normality inspecting their histogram and using the Kolmogorov–Smirnov test implemented with R's ks.test
If it is believed that they are normally distributed we will use the following:

**Test**: t-test implemented with R's t.test command
**Null Hypothesis:** The mean of this outcome is the same in the catheter ablation arm and the surgical arm.

**Alternative Hypothesis:** The mean of this outcome is not the same in the catheter ablation arm and the surgical arm.

If data shows extreme skewness, then we will use the following

**Test**: Mann Whitney test implemented with R's wilcox.test(…, paired=FALSE) command
**Null Hypothesis:** The distribution of scores for this outcome is the same between the catheter ablation arm and the surgical arm.
**Alternative Hypothesis:** The distribution of scores for this outcome is not same between the catheter ablation arm and the surgical arm.

## 8.2 Change in AF symptom score (EHRA score) and quality of life assessments (EQ5D5L, AFEQT)

Each of these indicators will be assed for normality inspecting their histogram and using the Kolmogorov–Smirnov test implemented with R's ks.test
If it is believed that they are normally distributed, then we will use the following

**Test**: t-test implemented with R's t.test command
**Null Hypothesis:** The mean of this outcome is the same in the catheter ablation arm and the surgical arm.
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If data shows extreme skewness, then we will use the following

**Test**: Mann Whitney test implemented with R's wilcox.test (…, paired=FALSE) command
**Null Hypothesis:** The distribution of scores for this outcome is the same between the catheter ablation arm and the surgical arm.
**Alternative Hypothesis:** The distribution of scores for this outcome is not same between the catheter ablation arm and the surgical arm.

## 8.3 Quality Adjusted Life Years (QALYs) accrued during 12-month study period

Each of these indictors will be assed for normality inspecting their histogram and using the Kolmogorov–Smirnov test implemented with R's ks.test
If it is believed that they are normally distributed, then we will use the following

**Test**: t-test implemented with R's t.test command
**Null Hypothesis:** The mean of this outcome is the same in the catheter ablation arm and the surgical arm.
**Alternative Hypothesis:** The mean of this outcome is not the same in the catheter ablation arm and the surgical arm.

If data shows extreme skewness, then we will use the following

**Test**: Mann Whitney test implemented with R's wilcox.test(…, paired=FALSE) command
**Null Hypothesis:** The distribution of scores for this outcome is the same between the catheter ablation arm and the surgical arm.
**Alternative Hypothesis:** The distribution of scores for this outcome is not the same between the catheter ablation arm and the surgical arm

## 8.4 Health economic analysis

Cost-effectiveness will be assessed using both trial-based and model-based health economic analyses. Both will follow international methodological guidelines [64, 65] and the 'reference case' recommended by NICE for use in its technology appraisals [66]: including the use of an NHS and personal social services perspective for costing; and discounting of costs and QALYs at an annual rate of 3.5%.

The trial-based analysis will use EQ-5D-5L and health and social care resource use data to estimate the costs and QALYs accrued over the 12-month follow-up period by trial participants. In our main analysis we will include costs for all health and social care recorded in the CRF and reported by patients in the health economic questionnaire at 3, 6, 9 and 12 month economic questionnaires. We will also conduct a sensitivity analysis including only costs judged by the research team to be potentially related to AF or to AF treatment. QALYs will be estimated from EQ-5D UK Social Tariff scores at 0, 3, 6, 9 and 12 months, using an 'area-under-the-curve' approach. Mean between-group differences in QALYs and costs will be estimated using a bivariate regression approach [12], taking account of correlations between costs and effects and adjusting for any baseline differences in EQ-5D scores or other key patient characteristics (such as age, $CHA_2DS_2VASc$ or HASBLED scores). Multiple imputations will be used to account for missing data if appropriate [13]. If the results indicate a trade-off between costs and health effects, an Incremental Cost Effectiveness Ratio (ICER) will be calculated – the 'cost per QALY'. The extent of uncertainty over the results will be estimated using bootstrap regression [14], and presented in the form of a Cost Effectiveness Acceptability Curve (CEAC).

A model-based economic analysis will also be conducted to estimate long-term benefits, harms and costs of surgical and catheter ablation compared with AAD therapy in patients with LSPAF. This will extrapolate costs and health outcomes observed in the trial, including freedom from arrhythmia, utility (EQ-5D-5L scores) and incidence of major side effects, over a long time horizon (up to lifetime). The model will also allow us to estimate costs and outcomes for the trial participants under medical management, which will provide further information about the comparative cost-effectiveness of treatment options for this patient group for healthcare commissioners and research funders. The model will be based on the MAPGuide AF model [15]. This is a Discrete Event Simulation (DES), which estimates lifetime costs, and QALYs for a heterogeneous population of individuals with AF treated according to a defined pathway of care, including anti-thrombotic and AAD therapy. The base case version of the model reflects the recommended care pathway in the NICE clinical guideline for AF. This care pathway can be changed to estimate costs and QALYs associated with different treatments (e.g. catheter ablation, thoracoscopic surgical ablation or AAD).

## 8.5 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

## 8.6 Technical Details

The main statistical analysis will take place on NYU secure data cluster using the R statistical software version 3.3.1. Integration of the multiple CRF will be carried out using PostgreSQL version 9.6.

# 9 List of Appendices

1) Appendix A
2) Appendix B
3) Appendix C

# 10 References


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# 11 SAP Approval and Agreement

**SAP version number being approved: V3.0, dated 13/11/2019**

**Trial Statistician**

Name **Prof. Simon Jones**

Signed Date/ electronic confirmation (email)

**Chief CASA AF Investigator**

Name **Dr Tom Wong**

Signed Date/ electronic confirmation

**DMC Statistician**

Name **Prof. Gareth Ambler**

Signed Date /electronic confirmation (email)

**Chair DMC**

Name **Dr Malcolm Walker**

Signed Date /electronic confirmation (email)

**Chair TSC**

Name **Prof William Toff**

Signed Date/electronic confirmation (email)