Papworth Hospital

Study Protocol

The Amaze trial: a randomised controlled trial to investigate the clinical and cost-effectiveness of adding an ablation device-based maze procedure as a routine adjunct to elective cardiac surgery for patients with pre-existing atrial fibrillation (AF)
ISRCTN82731440; UKCRN ID 5245

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Study Identification Numbers: R&D ref: P01181
HTA ref no: 07/01/34
ISRCTN82731440

Date of Protocol: 11/05/2015

Protocol Version Number 4

Trial Sponsor: Papworth Hospital

Trial Funder: NIHR Health Technology Assessment Programme (ref: 07/01/34)

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Signature Page for the Trial Sponsor

Sponsor: Papworth Hospital NHS Foundation Trust

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Study Identification Number: R&D ref: P01181
HTA ref: 07/01/34
ISRCTN82731440

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Signature page for Investigators

Insert Title of Study and Study Identification Number

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the EU Directive for Clinical Trials 2004.

Investigator Name:

Signature:

Date:

The Amaze trial. A randomised controlled trial to investigate the clinical and cost-effectiveness of adding an ablation device-based maze procedure as a routine adjunct to elective cardiac surgery for patients with pre-existing atrial fibrillation (AF). ISRCTN82731440; UKCRN ID 5245

1. INTRODUCTION

AF is the most common disturbance of heart rhythm. With a UK prevalence of 7.2% in patients aged 65 and over and 10.3% in patients aged 75 and over [1] AF has considerable impact on quality of life and NHS resources [2,3]. Treatment of AF and its consequences (anti-arrhythmic and anti-coagulant drugs, hospital monitoring & stroke treatment) is expensive for the NHS. Implementation of the recent NICE guidelines (June 2006) [2] on management of AF is estimated to cost £21.86m per year. [3] The NHS devotes 5% of its budget to strokes and 15% of these are associated with AF.[1] Routine anticoagulation is used to reduce the risk of stroke, however this incurs an increased risk of bleeding and the burden of monitoring treatment falls on general practice, anticoagulant clinics and haematology laboratories.

AF ablation devices are a new and costly technology being marketed to treat this condition. The use of this technology is increasing in NHS practice despite the lack of good research evidence to support adoption.

The study will test the hypothesis that treating AF by incorporating a modified maze procedure (using an ablation device) into elective cardiac surgery will promote a return to SR and improve quality of life as well as being cost-effective from an NHS perspective.

Elective cardiac surgical patients with pre-existing AF will be randomly allocated to receive, or not receive, a device-based maze procedure as an adjunct to their operation (' adjunct maze '). As this is a pragmatic, ' real-life ', trial the ablation devices will be those in routine use in the participating centres. The trial is not designed or powered to distinguish between different types of device.

AF occurs in around 30% of patients after cardiac surgery. It has a multifactorial aetiology, arises out of micro-re-entry circuits and is usually self-terminating. The management of this complication has been extensively studied [4] and is outside the scope of this trial.

1.1 Existing research

The current basis for treatment and management of AF is dealt with in a UK NICE Guideline (2006) [2] a Cochrane review [5] and European Guidelines [4]. International recommendations on surgical and catheter ablation of AF were published in 2007 jointly by the Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society in their Expert Consensus statement [6].

A number of studies (cited in ref.6) suggest that AF not only marks out a prospective cardiac surgery patient as high risk but that AF is also an independent risk factor for operative morbidity and mortality. This leads to the (unproven) hypothesis that efforts to eliminate pre-existing AF during cardiac surgery may improve survival and reduce adverse cardiac events after surgery.

The maze procedure can be performed in two ways:
1. The traditional cut-and-sew technique, known as the Cox-maze with its many modifications, is reliable in restoring sinus rhythm in the majority of patients (references cited in 6). Despite being available since 1987, this procedure has signally failed to achieve widespread use. The main reason for this is that it is technically demanding and adds substantially to the operative burden of a heart operation. It is currently in very limited use by a few surgeons in a few centres and tends to be reserved for otherwise fit patients with

severely symptomatic AF who are prepared to take the risk of a major intervention to relieve their symptoms.

2. The ablation device maze procedure uses an energy source (heat, cold, radiofrequency or microwave) to replicate the lesion set of the Cox-maze. As a rule, the procedure is safe, well tolerated and adds little to the length and burden of the operation.

There has been no direct comparison between traditional Cox-maze and ablation maze, presumably due to the problems of incorporating such technically demanding surgery into an adequately powered randomised controlled design. However a propensity analysis which matched patients who underwent ablation maze with those having Cox-maze showed no differences in freedom from AF at 3, 6 and 12 months afterwards [(7)].

Common sense suggests that treating AF at the time of cardiac surgery is advantageous to the patient. However the only evidence supporting this comes from 5 small randomised controlled trials of ablation devices as adjuncts to surgery [(8 - 12)]. These trials found that SR was restored in 44 – 94% of treated patients compared to 5 - 33% of controls. The trials were small and follow-up was short. Success was mostly defined on the basis of single ECG recordings. No trial looked at patient-centred outcomes or cost effectiveness. Despite this lack of robust evidence, an increasing number of patients with AF having open heart surgery are now being offered concomitant ablation maze procedures (' adjunct maze ') (cited in ref. 6).

We therefore have a situation where there is no rigorous evidence that attempting to restore SR by treating AF with an ablation device during cardiac surgery is of benefit to the patient. Nevertheless these devices are being incorporated into routine practice nationally and internationally. The recent Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation [(6)] developed by Heart Rhythm Society in partnership with European Heart Rhythm Association and European Cardiac Arrhythmia Society has launched a call for high quality prospective multi-centre trials to adopt consistent definitions of procedural success in long term assessments of the safety and efficacy of ablation maze.

The proposed trial will respond to this call and inform patients, clinicians and the NHS about the routine adoption of this technology.

2. STUDY OBJECTIVES

The primary objective of assessing patient benefit will be achieved by comparing the two groups for the rate of return to stable SR at 12 months as well as quality-adjusted survival over 2 years. 4-day ECG monitors will be used to assess the predominant rhythm (SR or AF) and the AF load ie the percentage of time that the patient is in AF if the predominant rhythm is SR.

The secondary objective of assessing cost-effectiveness for the NHS will be achieved by collecting resource use data and costs incurred by both groups and comparing their costs per quality-adjusted life year (QALY). Further longer term economic modelling will also be undertaken.

Other secondary objectives will be to determine whether the adjunct maze procedure

- improves the rate of return to stable SR at 24 months after surgery,
- decreases thromboembolic neurological complications (eg stroke),
- enables anticoagulant treatment to be withdrawn safely,
- enables safe reduction or withdrawal of antiarrhythmic medication.

3. INVESTIGATIONAL PLAN

3.1 Design:

The proposed study will be a multi-centre, prospective, double blind, randomised controlled trial to compare clinical, patient-based and cost outcomes for patients with pre-existing AF who undergo routine cardiac surgery either with or without an adjunct device-based ablation procedure (' adjunct maze ').

The trial will be double blind to the extent that neither the patient nor the cardiologist who analyses the 4-day ECG, nor the quality of life assessor will be aware which group the patient has been allocated to. Where possible the standards of design and reporting of this trial will adhere to the guidelines of the CONSORT statement [13] and incorporate recommendations of the Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation [6].

3.2. Setting and Investigators

Eight acute NHS cardiac surgical centres (Papworth, Brompton, Brighton, Coventry, Leicester, Manchester, Sheffield, St Thomas's) will participate with Papworth Hospital as the lead centre. Each centre already has one or more surgeons experienced in the use of ablation devices and further training will be incorporated into the study. They are all members of the UK AF Study Group with interest in surgical treatment of AF and one member (Prof Spyt) has published on this topic. [10]

3.3 Study population

Eligible patients will be consecutive elective cardiac surgical patients undergoing major cardiac surgery (such as coronary, valve or combined operations) with a history of paroxysmal, persistent or chronic AF beginning more than 3 months before the date of the operation.

- Paroxysmal AF is defined as recurrent AF ($\geq$ 2 episodes) that terminates spontaneously within 4 days (Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation). [6]
- Persistent AF is defined as AF which continues beyond 4 days.
- Chronic or longstanding AF is persistent AF beyond 1 year.

Inclusion criteria:

- age over 18
- elective cardiac surgery planned
  (coronary surgery, valve surgery, combined coronary and valve surgery, any other cardiac surgery requiring cardiopulmonary bypass.)
- history of documented atrial fibrillation (chronic, persistent or paroxysmal) beginning more than 3 months before entry into the study
- written informed consent to participation

Exclusion criteria:

- previous cardiac operations
- emergency or salvage cardiac operations
- surgery without cardiopulmonary bypass
- unlikely to be available for follow-up over a two-year period
- deemed not competent to provide consent

3.4 Devices

This is a pragmatic clinical trial to assess outcomes in a 'real world' context. Furthermore, there is no evidence whatsoever for the superiority of one device or one energy source over another. We will therefore include any AF ablation device that is routinely used within the NHS by the investigators. This will allow surgeons to use the devices with which they are most familiar and comfortable. However, the trial will record which device and which

energy source were used for individual patients and some subgroup analysis will be undertaken.

3.5 Recruitment

3.5.1 Sample size

The primary outcome includes a purely clinical end point as well as an outcome of importance to patients.
It consists of: 1) return to sinus rhythm (SR) at 12 months and 2) clinical effectiveness measured as quality-adjusted survival over 2 years. Sample size calculations are based on both these primary endpoints.

1) Return to SR at 12 months.
Published RCTs of ablation as an addition to cardiac surgery have reported rates of return to SR at 12 months [8-12] ranging from 44% to 87% in the trial arms and 5% to 33% in the control arms. If we take a conservative estimate of the difference between the groups (45% vs. 30%) then we would have 80% power to detect this difference with a sample size of 176 in each group, total 352 (2-sided significance 5%). With recruitment of 400 patients this would allow for deaths or loss to follow up at 12 months of approximately 15%.

2) Clinical effectiveness measured as quality-adjusted survival over 2 years.
The emphasis in cost-effectiveness studies is on estimation rather than hypothesis testing so that formal sample size calculations are less important. However, we provide a power calculation based on the effectiveness measure QALY. We could find no studies reporting comparative QALYs in similar patients undergoing ablation and cardiac surgery. From previous studies of patients undergoing angiography for suspected ischaemic heart disease [16] and patients with refractory angina [17] the standard deviation of QALYs over 12 and 18 months is at most 0.3. Over follow up of 2 years the minimum clinically important improvement is considered to be one extra month of quality-adjusted life, or 0.083 QALYs. With a sample of 200 patients per group, total 400, we would have approximately 80% power to detect a difference of 0.083 QALYs, (2-sided significance 5%).
If the accepted threshold for cost effectiveness were in the range £20-30,000 per QALY and we could demonstrate a significant increase in QALYs of 0.0833, then the procedure would be cost-effective for an incremental cost of at most £2,500.

3.5.2 Feasibility of proposed recruitment:

Our proposed sample size is 400 recruited over 18 months from a minimum of 6 centres. A survey of the centres interested in participating shows that they conduct an average of approximately 800 cardiac surgical procedures per year per centre. More than 10% of these patients will be in AF giving an average eligible population of at least 80 patients per year per centre. We propose to recruit 400 patients over 18 months, so the rate of recruitment will average 43 patients per year per centre. This means that we only need to recruit half the eligible patients to achieve our proposed recruitment rate. Previous experience shows that patients are generally very willing to consent to this adjunct surgical procedure as it presents very little additional risk and could possibly relieve them of their debilitating AF symptoms.
The proposed recruitment rate translates to 3 to 4 procedures per month which is considered to be well within the capability of the participating centres (see Appendix 2 Recruitment Schedule).

3.5.3 Identifying, informing and consenting patients

The procedure for informing and consenting patients will be the same in all centres and devised to accommodate local variations in the patient pathway. (See Appendix 1 for arrangements at Papworth.) The local investigator will make the initial approach to the patient. The Trial Coordinator or local research nurse will provide any further information subsequently and take written consent.

The following scenario will be adopted at Papworth: the surgeon will outline the study to eligible patients at a routine surgical clinic and provide them with a simple summary to take home. The trial coordinator (or research nurse) will contact patients at home to ask whether they would be interested in participating. If patients agree, the trial coordinator/research nurse will post further information and the patient information sheet and consent form to their home.

When patients attend the pre-admission clinic (approximately 1 month before their surgery) the trial coordinator/research nurse will go through the trial in detail and answer any questions. The surgeon will also be available to provide further information if necessary. If patients are still willing to participate the trial coordinator/research nurse will confirm eligibility and obtain written informed consent.

Once consent has been obtained patients will be trained in the use of the 4-day ECG recording device and will use it at home to monitor their heart rate for 4 days.

3.5.4 Blinding

Patients themselves, any researchers collecting Health-related Quality of Life data and cardiologists assessing the 4-day ECG results will be unaware of the group to which the patient has been allocated.

The Patient Information Sheet (PIS) will state clearly that the patient will not know whether or not they have had the adjunct maze procedure. However the PIS will also explain that the patient can be un-blinded for medical reasons but that they will still be followed up and remain part of the trial.

Blinding of the patient is essential because the primary outcome is patient benefit. However this is unlikely to be successful if details of the patient's operation are fully accessible in their notes. On the other hand this information must not be held too securely because the patient could be at risk if details are not immediately available if required for medical reasons.

The following strategy will be adopted to accommodate these requirements:
Patients' medical notes will be labelled to indicate that they are participating in the Amaze trial. Routine reports will provide details of their elective surgery but will only state that the patient was randomised within the Amaze trial. Notes describing the research intervention (ie the adjunct maze procedure or no trial-related surgery) will be placed in a sealed envelope entitled ' The Amaze Trial ' and kept in the patient's notes. Clinicians will be able to access this information should a medical need arise. The Trial Management Protocol will include details of this ' unblinding protocol '.

4. INTERVENTION

4.1 Randomisation

Eligible patients who fulfil the inclusion criteria, have provided full written consent and have had sufficient time for discussion and consideration, will be randomised (in a 1:1 ratio) to one of two groups. They will receive either their routine cardiac surgery with no additional procedure or their routine cardiac surgery with an adjunct maze procedure.

Patient allocations will be computer generated by the trial statistician and will be in random permuted blocks of variable lengths, stratified by surgeon and by planned cardiac procedure (CABG, aortic valve, mitral valve, combined procedure).

On the day of surgery, when the patient is in the anaesthetic room, the local centre will register the participating patient with Papworth Hospital R&D Unit by telephone or fax.

Patient details, surgeon and planned cardiac procedure will be recorded by R&D unit staff not otherwise directly involved with the trial. Once registration is complete the group allocation will be released to the surgical team who will also be responsible for completing the surgical data forms. The group allocation will not be made available to any other staff who are directly involved with the trial.

4.2 Control intervention

Patients randomised to the control arm will receive their pre-operative management, elective cardiac surgery (without an adjunct maze procedure) and post-operative management according to standardised hospital protocols. All subsequent management, follow up and data collection will be identical to the experimental intervention group.

4.3 Experimental intervention

Patients randomised to the experimental arm will receive their pre-operative management and elective cardiac surgery as described in the protocols. During the operation, the surgeon will also conduct the adjunct maze procedure using the agreed standardised protocol. Investigators will use the ablation device in routine use at their institution. The procedure will be fully defined in the Trial Management Protocol. Post-operative management and subsequent follow-up and data collection will be identical to the control group.

4.4 Standardisation between centres:

In order to minimise potential confounding by other components of the patient's care the following aspects of the trial will be standardised at all the collaborating centres. The agreed protocols will form part of the Trial Management Protocol for this study.

4.4.1 Management of patients before, during and after surgery

This will be undertaken according to the local site's normal practice irrespective of randomisation. The only exceptions will be processes required to maintain blinding of the patient, cardiologist and quality of life interviewer, which will be described in the Trial Management Protocol.

4.4.2 Conducting and reporting on the adjunct maze procedure [14] and defining the prescribed lesion set [6]

Clinicians are free to carry out the lesions that they would perform in normal practice. Details of the ablation procedure and all lesions will be documented. The full lesion set is illustrated in Figure 1.

Recently published guidelines for reporting data and outcomes for surgical treatment of atrial fibrillation [14] will be followed.

4.4.3 Post-operative drugs

i. Amiodarone – unless contraindicated 200mg tds reducing over 3 weeks to 200 mg per day for 6 weeks. The drug will be stopped if stable sinus rhythm (SR) is established at 6 weeks. Further prescription after this period will be based on individual clinical judgement. Details will be fully documented.

ii. Warfarin – will be prescribed until the patient is in stable SR. After this, centres will adopt their normal practice. Details will be fully documented.

iii. β Blockers – will be prescribed according to individual clinician's judgement. Details will be fully documented.

iv. Other drugs – will be prescribed according to individual clinician's judgement. Cardiac drugs with anti-arrhythmic, anti-hypertensive and anti-coagulant actions, including aspirin and warfarin, will be documented.

4.4.4 Indications for cardioversion, timing and number of attempts

The protocol does not require cardioversion to be carried out at discharge but if it is performed for clinical reasons the details must be recorded. If the patient is in AF at the time of the first follow-up appointment cardioversion must be attempted no later than 3

months after surgery. If cardioversion is unsuccessful it should be attempted again at about 6 months after surgery.

5. OUTCOME MEASURES

5.1 Primary outcomes:

i) Return to SR at 12 months

The number of patients in SR at 12 months after surgery will be determined by 4-day ECG monitors that will be provided for patients to wear continuously for 4 days at 12 months after their operation.

ii) Clinical effectiveness - quality-adjusted survival over 2 years

Clinical effectiveness will be measured by QALYs, which will be calculated by combining length of survival and the EQ-5D (administered at randomisation, on discharge and at 6 weeks and 6, 12 and 24 months after the procedure).

5.2. Secondary outcomes:

(i) Clinical endpoints of SR at 24 months after surgery, overall survival and stroke-free survival, incidence of anticoagulant-related haemorrhage.
(ii) Health-related quality of life measured by the EuroQoL, SF-36 & NYHA (for breathlessness)
(iii) Resource use and cost-effectiveness of the adjunct maze procedure.
(iv) Anticoagulant and antiarrhythmic drug usage.

6. DATA COLLECTION

6.1 Methods

The data will be collected on to a web-based system designed and coordinated by the Data Scan and Quality Officer at Papworth Hospital. He will be responsible for training researchers to use the system and will conduct initiation visits. The Clinical Research Nurse (CRN) at each centre will enter the data directly on to the database or enter the data manually on to the printed form until such time as it can be entered directly. Surgical data will be recorded by a designated member of the surgical team either directly or via a paper form. All paper data collection forms will be returned to the R&D Unit at Papworth. The Trial Coordinator (TC) will be responsible for training the CRNs and other data collection staff in each hospital, and for data monitoring and quality control. Data audits (to be designed) will be carried out by the Trial Coordinator at 3-6 month intervals depending on the recruitment and activity rates. The whole process will be overseen by the Trial Manager situated in the co-ordinating centre at Papworth Hospital.

6.2 Baseline data collection

We will adhere to the ACC/AHA/ECS 2006 Guidelines [15] which recommend that the initial patient description includes demographics, type and duration of AF and the planned cardiac procedure.

The first 4-day ECG recording will start after the patient attends the preadmission clinic and has consented to participate. All other baseline measurements will be recorded on the day of admission for surgery. Once these measurements have been taken the participating patient with be registered with the co-ordinating centre's R&D unit and then randomised as described in 4.1.

6.3 Data collection during and after surgery

(See Appendix 3 for the Schedule of Events and Appendix 4 for the full list of data to be collected.)

Data collection will be based on the recommendations of Shemin et al [14] and include procedural details – including the lesion set in the experimental group.

Data to be collected after surgery will include: mortality, stroke/thromboembolic events, medications, EuroQoL, health-related quality of life, cardioversion plan if appropriate, 4-day ECG recordings, resource use, adverse events.

Data will be collected during surgery, at discharge, 6 weeks after surgery (at a routine service visit), at 6, 12 and 24 months after surgery during out-patient research visits and thereafter by telephone follow-up Patients will be invited to participate in the Amaze five year follow up which will involve recording mortality, stroke/thromboembolic events, medications, EuroQoL, health-related quality of life and have a stand alone ECG either at their GP or Papworth whichever is the most convenient.

6.4 Analysis of ECG recordings

All 4 day continuous ECG recordings will be analysed centrally at Papworth Hospital. Participating centres will be requested to forward the SD cards from the ECG recorders to Papworth Hospital. Analysis of this data using the proprietary automated software package, together with manual checking of the recording in its entirety, will be done. Total time spent in sinus rhythm and in AF (AF burden) during the 4 day recording will be calculated, with only those episodes of AF lasting greater than 60 seconds duration included in the analysis. Episodes of atrial flutter will be noted and included in the AF burden.

6.5 ONS tracking

All patients enrolled in this trial (with their consent) will be registered with the Office of National Statistics (ONS) Tracking System to allow long term follow up of survival.

7. STATISTICAL & ECONOMIC ANALYSES

7.1 Statistical analysis

All statistical analyses and reporting will comply with CONSORT guidelines [13] where possible. For the intermediate primary outcome, return to SR at 12 months, all patients with 4-day ECG results at 12 months will be included in the analysis according to the group to which they were randomised. Secondary analyses will consider a Complier Average Causal Effect analysis [18] and assessment of sensitivity of results to a range of assumptions regarding missing data. Results will be summarised as the number and percentage in SR and compared using Likelihood Ratio Tests. QALYs will be estimated from serial measurements of the EQ-5D for each patient up to 2 years using interpolation (see economic analysis below).

Secondary outcome measurements will be analysed in a similar way to the above, but will include only those patients for whom measurements were available. Time to all cause death will be explored using Kaplan-Meier curves. Health related quality of life scores and the EQ-5D utility score will be compared using Likelihood Ratio Tests from linear regression models including baseline levels and treatment group.

7.1.1 Sub-group analyses

Sub-group analyses will investigate the variation in treatment effects between:
i. patients with paroxysmal and non-paroxysmal AF,
ii. individual centres,
iii. different ablation devices,
iv. complete and incomplete lesion sets,
v. different cardiac surgical procedures.

7.2 Economic analysis

An NHS perspective will be adopted for the economic analysis. For both groups patient-specific resource use data will be collected until all patients have completed at least 12-

months post-randomisation (mean 2 years, maximum 3 years). According to current Department of Health guidelines [19] an annual discount rate of 3.5% will be applied to all costs incurred between 12 and 24 months post-randomisation. The following resource areas will be measured and valued.

i. Costs of Surgery

The average cost of the initial cardiac surgery will be based on the capital cost of the equipment, variable costs, staff and overhead costs involved. The extra capital cost of the RF ablation device will be annualised and apportioned, where relevant, on a per patient basis. Staff and overhead costs will be allocated according to theatre time and annual patient throughput. The use of variable consumable costs (e.g. blood products, IV heparin) will also be recorded prospectively on a per patient basis.

ii. Costs after surgery

Resource use will be monitored from surgery through to at least 12 months post-randomisation. Information will be collected on hospital admissions due to adverse events including readmissions to hospital, any further cardiac procedures and pacing, GP and outpatient visits and cardiac-related medication. Patients will be asked to record medications taken, inpatient and outpatient visits and any procedures in a purpose-designed questionnaire to be administered alongside the quality of life measures. Patient responses will be validated against hospital and primary care records. Unit costs will be taken from the hospital accounting system for each participating centre and nationally published estimates. [20, 21]

iii. Economic outcome measurement

At baseline, on discharge and at 6 weeks, 6 months, 12 months and 24 months post surgery all patients will be asked to complete the EuroQoL questionnaire, including the EQ-5D. The social tariff for the EQ-5D, as estimated by Dolan *et al* will be applied to each patient's self-reported classification in order to calculate utility values.[22] Using actual rather than nominal times of assessment, and assuming a linear change in values between time points, patient-specific utility curves up to 24-months post randomisation will be calculated. A value of zero will be applied at the date of death for those patients who died.

iv. Economic Analysis

The QALYs experienced by each patient to 24-months post randomisation will be calculated as the area under their utility curve to 24-months or time of death, whichever occurs first. In order to adjust for differences in baseline utilities a linear regression will be fitted to the utilities post treatment, with baseline utility and treatment group as explanatory variables. Treatment effects will be taken from the treatment group coefficient of this regression. For patients who do not complete all EuroQoL/resource use measurements and are censored the methods of Willan and Lin [23] will be used to estimate mean QALYs and costs.

The incremental cost-effectiveness ratio (ICER), calculated as the ratio of the difference in costs and QALYs, will be estimated using the sample means. In order to generate confidence intervals without assuming any parametric form for the distribution of the costs, bootstrapping will be used to resample patients and repeat the calculations described above 1000 times. [24] Measurements will be summarised as the mean and 95% confidence interval, estimated using bootstrapping. The bootstrap samples for the treatment comparison will also be plotted on the cost-effectiveness plane. In addition, cost-effectiveness acceptability curves (CEAC) for these comparisons will be plotted. The CEAC plots the probability that a functional test is cost-effective if we are willing to pay at most £*X* per QALY on the vertical axis, against *X* on the horizontal axis. Sensitivity analysis will be used to explore the impact of the deterministic variables within the economic analysis (e.g. unit cost estimates discount rate).

8. MANAGEMENT & GOVERNANCE

The Trial Manager (TM) and Trial Coordinator (TC) (who are based at Papworth) will work directly with the other centres to coordinate these aspects and ensure that the study is conducted according to ICH-GCP standards. They will be responsible for any necessary training.

8.1 Sponsorship

Papworth Hospital NHS Foundation Trust is an experienced sponsor of HTA Clinical Trials and has agreed to assume the responsibilities of sponsor. The respective responsibilities of the sponsor, investigator and Trial Manager will be identified and delegated at the start of the trial (see Appendix 5 Allocation of Research Governance Responsibilities).

8.2 Study project team:

The study project team will include the chief investigator, cardiologist, statistician, health economist, theatre manager, trial manager and trial coordinator. This group will provide daily oversight of the initiation and subsequent progress of the trial. Meetings will be at Papworth and will be frequent (monthly) during the start-up and early recruitment phases and less frequent (3-6 monthly) subsequently. E mail or teleconferencing will be used for input from collaborators at other centres. This group will be responsible for the 6 monthly reports to the HTA.

8.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), consisting of an independent chair, at least two independent members, the patient representative and the Chief Investigator, Mr Sam Nashef, will be convened and meet two to three times a year. This committee will monitor the progress of the trial in relation to the stated milestones and the interim and overall objectives and instigate any remedial actions. It will also review any relevant information from other sources and implement recommendations from the Data Monitoring and Ethics Committee (DMEC). Observers from the HTA will be invited to attend these meetings.

8.4 Data Monitoring and Ethics Committee (DMEC)

A separate Data Monitoring and Ethics Committee (DMEC) will also be convened as nominated by the TSC at their first meeting. The DMEC will meet annually but will be in regular contact to view the data and the results of any interim analysis and to instruct un-blinding if necessary. The DMEC membership will include a clinician, a statistician and a health economist independent of the TSC, the study and the Chief Investigator.

8.5 Monitoring & audit

Recruitment of patients and collection of data will be monitored by the Papworth Trial Coordinator on a regular basis and according to a defined protocol (see Appendix 6).

8.6 Ethical Arrangements

Ethical approval for this multi-centre study will be obtained from a National Research Ethics Service Multi-centre Research Ethics Committee (MREC) and site-specific approval for all participating investigators' NHS hospitals will be obtained from their local RECs.

The main ethical issue associated with this project is the need to blind patients, the cardiologist analysing the ECG recordings and the quality of life interviewer. This blinding is necessary due to the potentially subjective nature of the primary outcome (quality-adjusted survival). For this blinding to be effective, it is essential that the patient's allocation and details of their surgical procedure are not freely accessible from their medical notes. However there could be occasions when the patient would be at risk if their operative details were not available immediately.

The following strategy has been devised to circumvent this problem. All participants' notes will be labelled to indicate that they are part of The Amaze trial. Routine operation notes will contain full details of the elective surgery but will only state that the Amaze trial procedure was carried out. Notes describing the research intervention (ie the adjunct maze procedure or no trial-related surgery) will be kept in a sealed envelope entitled The Amaze trial which will be kept in the patient's notes. Clinicians will be able to access this information should a medical need arise. The Trial Management Protocol will contain details of this ' unblinding ' procedure. The patient information sheet will state clearly that the patient will not know whether or not they have had the adjunct maze procedure.

There is also a very small risk associated with extending the routine cardiac surgery by up to 20 minutes and patients will be informed of this.

Another issue is the future treatment of control patients who are still in AF after the trial has ended. If the adjunct maze procedure is found to be superior it will not be offered automatically to patients in the control group. This is because they would need to be offered a stand alone ablation maze procedure and this has not been evaluated in this trial. Decisions on future treatment will be made on a case by case basis and will need to be based on the severity of the patients' symptoms, their wishes and the surgeon's recommendations. Redo surgery for a stand alone ablation maze can only be justified for the severest symptoms as the risks are high.

8.6.1 Risks and anticipated benefits for trial participants

The extension of routine cardiac surgery by up to 20 minutes to accommodate the additional device-based ablation procedure presents negligible risk to the patient. Most patients when presented with this information are likely to consider that the benefits of living without AF (and its debilitating palpitations, breathlessness, risk of stroke and necessary medications) outweigh the risks of extended surgery. However they are free to make their own judgements based on information provided by study investigators and other sources, as participation is entirely voluntary.

8.6.2 Informing potential trial participants of possible benefits and known risks.

Individual investigators will discuss the proposed study with potential participants when they attend for assessment prior to proposed cardiac surgery. Possible benefits and known risks will be included in this discussion and will be described in detail in the patient information sheet which the patient will be given time to read and discuss.

8.6.3 Obtaining informed consent from participants

When patients have had sufficient time to consider and discuss the study the investigator will ask them to provide written consent. This is likely to be about two weeks before admission for elective cardiac surgery.

8.6.4 Proposed time period for retention of relevant trial documentation

Documentation will be retained for 15 years in line with recommendations of the local research ethics committee whose approval will be sought for this study.

8.6.5 Proposed action to comply with Medicines for Human Use (Clinical Trials Regulations 2004)

This is not a trial of a medicinal product and therefore these regulations do not apply.

8.7 Adverse and Serious Adverse Events

An Adverse Event is defined as ' any untoward medical occurrence in a patient which does not necessarily have a causal relationship with this treatment' and includes any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study intervention.

A Serious Adverse Event is one that fulfils at least one of the following criteria:

- results in death
- is life threatening
- requires in-patient hospitalization or extends hospital stay
- results in persistent or significant disability/incapacity

or

- is a congenital anomaly or birth defect.

HRS/EHRA/ECAS Expert Consensus on Catheter and Surgical Ablation of Atrial Fibrillation [6] recommend standardised reporting of all complications (ie resulting in permanent injury, death, requires intervention for treatment, or prolongs or requires hospitalisation) and these will be incorporated into the Trial Management Protocol and monitored regularly by the Trial Coordinator.

The reporting and recording of adverse and serious adverse events will be described in the Trial Management Protocol.

9. FINANCE & INSURANCE

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA). Clinical Trial Agreements will be agreed with all participating sites.
Normal NHS indemnity will provide indemnity and/or compensation for negligent harm. NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm. However the normal National Health Service complaints mechanisms will still be available to participants.

10. PUBLICATION POLICY

The HTA requires a study report every 6 months and the final report must be submitted within 3 months of completion of the trial.
A formal publication policy will be devised.

11. AMENDMENTS

All substantial amendments must be approved the MREC and the individual Trusts (via their R&D departments) before being implemented in the individual centres.

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APPENDICES

1. Pathway for informing and recruiting patients (Papworth model)

2. Recruitment schedule

3. Schedule of Events

4. Data collection

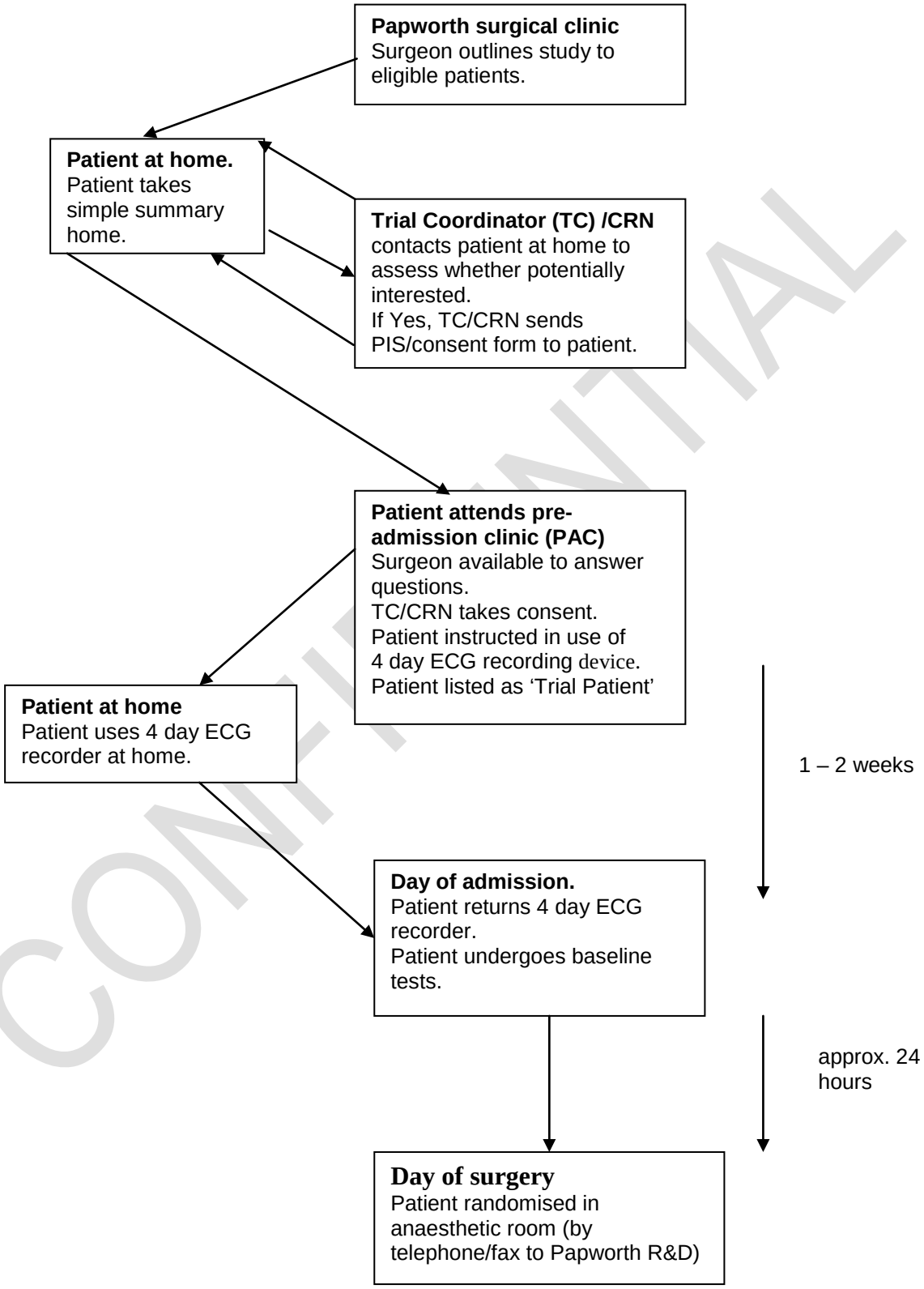
5. Responsibilities for Research Governance

6. Patient diary

FIGURES

1. Maze lesion set

Appendix 1. **Recruitment and randomisation (at Papworth)**



Appendix 2. 07/01/34 **The clinical and cost effectiveness of adding an ablation device-based maze procedure as an adjunct to elective cardiac surgery for patients with pre-existing atrial fibrillation. The Amaze trial** (n = 400)

Month	Baseline clinic	Surgery	6 week visit (routine)	6 month visit	12 months visit	24 months visit	Total - new patients	Total follow-ups	Total episodes
1	TRIAL START UP: Appoint staff, local project teams, TSC, DMEC. Oversee regulatory approvals all sites.								
2									
3	Agree protocols. Surgical & research staff training. Establish reporting & monitoring strategy. Initiate sites.								
4	15						15		15
5	16	15					16		16
6	16	16	13				16	13	29
7	20	16	15				20	15	35
8	25	20	15				25	15	40
9	25	25	19				25	19	44
10	25	25	23				25	23	48
11	25	25	24	13			25	37	62
12	18	25	24	15			18	39	57
13	20	18	23	15			20	38	58
14	24	20	19	19			24	38	62
15	24	24	18	23			24	41	65
16	25	24	24	24			25	48	73
17	24	25	23	24	12		24	59	83
18	25	24	24	23	14		25	61	86
19	24	25	23	19	14		24	56	80
20	24	24	24	18	18		24	60	84
21	25	24	22	24	22		25	68	93
22		25	23	23	23		0	69	69
23			24	24	22		0	70	70
24				23	22		0	45	45
25				24	18		0	42	42
26				22	17		0	39	39
27				23	23		0	46	46
28				24	22			46	46
29					22	12		34	34
30					22	14		36	36
31					23	14		37	37
32					21	18		39	39
33					22	22		44	44
34					23	23		46	46
35						22		22	22
36						22		22	22
37						18		18	18
38						17		17	17
39						23		23	23
40	Primary & secondary outcome analysis & reporting FINAL REPORT TO HTA					22		22	22
41						22		22	22
42						22		22	22
43						23		23	23
44						21		21	21
45						22		22	22
46						23		23	23
47	Long term analysis and reporting (not funded by HTA)								
48									
49									
Totals	400	400	380	380	360	360	400	1480	1880

NOTE:

352 patients are required for analysis of return to sinus rhythm at 12 months after surgery. 15% drop out is anticipated - this consists of 5% post surgical mortality and an additional 10% failure to provide primary outcome data. To accommodate this attrition we will recruit 400 patients.

Appendix 3 **Summary schedule of events**

Data collected	Baseline	Procedure	Discharge	6 weeks (routine)	6 mos	12 mos	24 mos	5 Year
HRQoL (SF-36, NYHA)	X				X	X	X	X
EQ-5D	X		X	X	X	X	X	X
Angina class (CCS score)	X							
Procedural data		X						
Stroke diagnosis & stroke-specific quest.				X	X	X	X	X
Mortality		X		X	X	X	X	X
Medication	X		X	X	X	X	X	X
4-day ECG	X					X	X	
Resource use		X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	

Appendix 4: **Data to be collected**

Stage of trial	Data to be collected
i. Baseline screening prior to consent	• Confirmation of eligibility and adherence to inclusion/exclusion criteria
ii. Baseline post consent	• Basic demographics • Symptoms & severity, including angina class, NYHA class and palpitations • Type and duration of AF • Current medication • Details of previous attempts at cardioversion (consistent with ACC/AHA/ECS 2006 Guidelines) • EuroSCORE • Underlying cardiac disease including coronary lesions, valve lesions and ventricular function • Details of planned operation • Baseline HRQoL (EuroQoL, SF-36 & NYHA) • 4-day ECG
iii. Peri-procedural	• Detailed operative data • Ablation device used (in intervention group) • Details of lesions used (in intervention group) • Immediate post-operative electrocardiogram (ECG) • Mortality, morbidity, length of stay • Resources (theatre time, device costs, consumables, length of stay in ICU and cardiac ward)
iv. At discharge	• ECG • Cardiac medication, including anticoagulants and antiarrhythmics • Any pacemaker implant • EuroQoL • Resource use • Adverse events
v. 6 weeks post-surgery (routine clinic visit)	• Stroke diagnosis and stroke specific/thromboembolic event questionnaire • Mortality • Details of medication (anticoagulant,antiarrhythmic) • Cardioversion plan if appropriate • EuroQoL • Resource use • Adverse events
vi. 6 months post-surgery	• Details of medication (anticoagulant, antiarrhythmic) • Stroke diagnosis and stroke specific questionnaire/thromboembolic event • Mortality • HRQoL (EuroQoL, SF-36 & NYHA questionnaires) • Details of any cardioversion and outcome • Details of any pacemaker insertion • Resource use • Adverse events
vii. 12 & 24 months post-surgery	• Details of medication (anticoagulant, antiarrhythmic) • Stroke diagnosis and stroke specific and thromboembolic event questionnaire. • Mortality • HRQoL (EuroQoL, SF-36 & NYHA questionnaires) • Details of any cardioversion and outcome • Details of any pacemaker implant • 4-day ECG monitoring • Resource use

	• Adverse events
iix. Five year follow up	• Details of medication (anticoagulant, antiarrhythmic) • Stroke diagnosis and stroke specific questionnaire/thromboembolic event • Mortality • HRQoL (EuroQoL, SF-36 & NYHA questionnaires) • Details of any cardioversion and outcome • Details of any pacemaker insertion • ECG monitoring •

Appendix 5: **Responsibilities for Research Governance**

Research Governance function	Sponsor (Papworth) responsibility	Investigator responsibility	Trial Manager responsibility
Ethics approval	X	X	X
R&D, Trust Approval	X		X
Financial administration	X		X
Employment of TC	X		X
Training of research nurses: ICH-GCP & study-specific training	X	X	X
Data collection		X	
Monitoring of study data	X		X
Serious adverse event reporting to sponsor		X	X
Serious adverse event reporting to ethics, R&D	X		X
Trial management: start up meeting	X	X	X
Production of site file and Trial Management Protocol	X		X
Maintenance of site file	X	X	X
Maintenance of responsibility log	X	X	X
Establish TSC, DMEC, arrange meetings	X		X
Liaise with TSC, DMEC			X
Organise project team meetings		X	X
Liaise with other centres			X
Conduct monitoring visits to other centres			X
Report writing		X	X

Patient Diary

For 4 Day ECG Recording

Patient Details

Patient Hospital No.

Name

Address

Date recording began

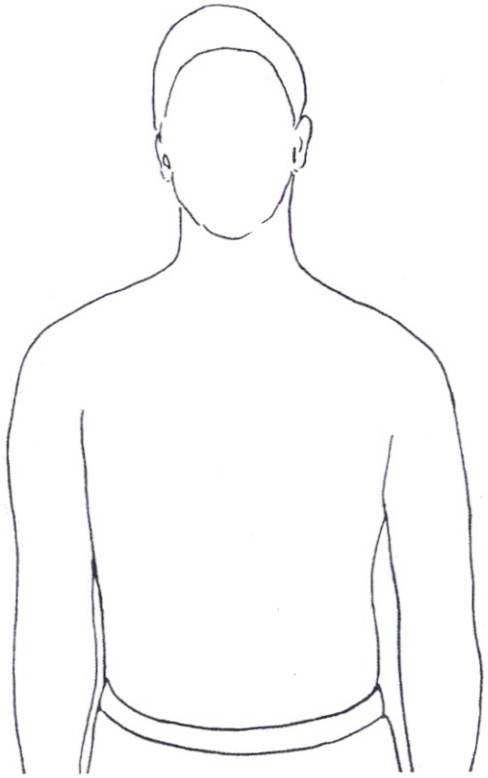
Recorder serial no.

To the Patient
Your doctor requires a continuous recording of your electrocardiogram, the action of your heart, as you go about your normal daily routine. The special digital recorder with which you have been fitted has been designed to interfere with your activities as little as possible: you should be able to ignore its presence.

Please use this diary to note important activities and any symptoms that you may feel. Write down the time against each entry in the diary.

Important
The recorder stops automatically and needs no attention.

Hook Up Positions



Re-apply electrodes/patient leads as drawn above by your Cardiac Technician

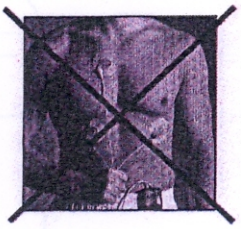
<u>Note to Technician:</u> show the patient how to apply new electrodes, if used. Mark the colour of each connector against the electrode positions.

3

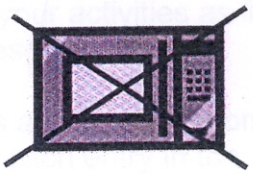
Instructions for Use

- Carry out your normal daily routine. Do not open the recorder.

- Do not tug on the electrodes or leads. Avoid scratching the electrodes.



- Avoid electric blankets, microwave ovens, industrial machinery. Place mobile phones as far away from the recorder as possible.

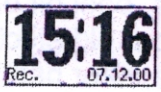


4

Instructions for Use

- Remove the recorder **before** bathing or showering (see page 6 onwards for instructions).

- Use the Lifecard clock time to record your activity/sympton diary.

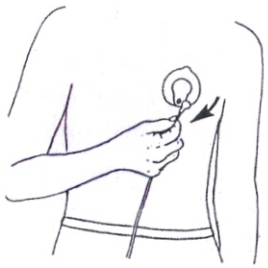


- If you have been asked to do so, press the **green** Patient Event button which is on the front right of the recorder if you experience symptoms, and make a note in your patient diary.

5

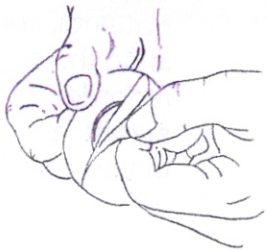
How to remove the recorder and change the electrodes

1 Disconnect the 'Patient Leads' from the electrodes and remove the recorder. The recorder will beep after the electrodes have been disconnected.

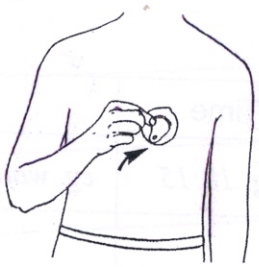


2 If you have been given new electrodes, peel off and discard your old electrodes. Otherwise, after bathing, go to Step 6.

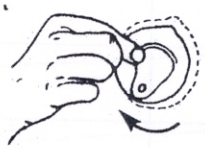
3 After bathing, dry yourself well and peel off the backing from the new electrodes.



4 Place the new electrodes onto the original positions

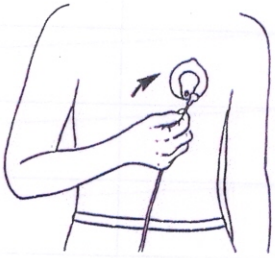


If you have experienced any irritation from the electrode, you can place it slightly to one side of the original position, but not on body hair.



5 Apply the electrodes as you were shown by the Cardiac Technician. (See page 3).

6 Snap on the poppers of the patient cable, ensuring you have the appropriate leads in the correct positions (see page 3). Reattach the recorder.



7

Diary of Events

Day 1

Date _____

Time recording started _____

Time	Activity	Symptoms
eg. 18:15	*eg. walked upstairs*	*eg. dizziness, palpitations, shortness of breath, sickness*

8

Day 2

Time	Activity	Symptoms

9

Day 3

Time	Activity	Symptoms

10

Day 4

Time	Activity	Symptoms

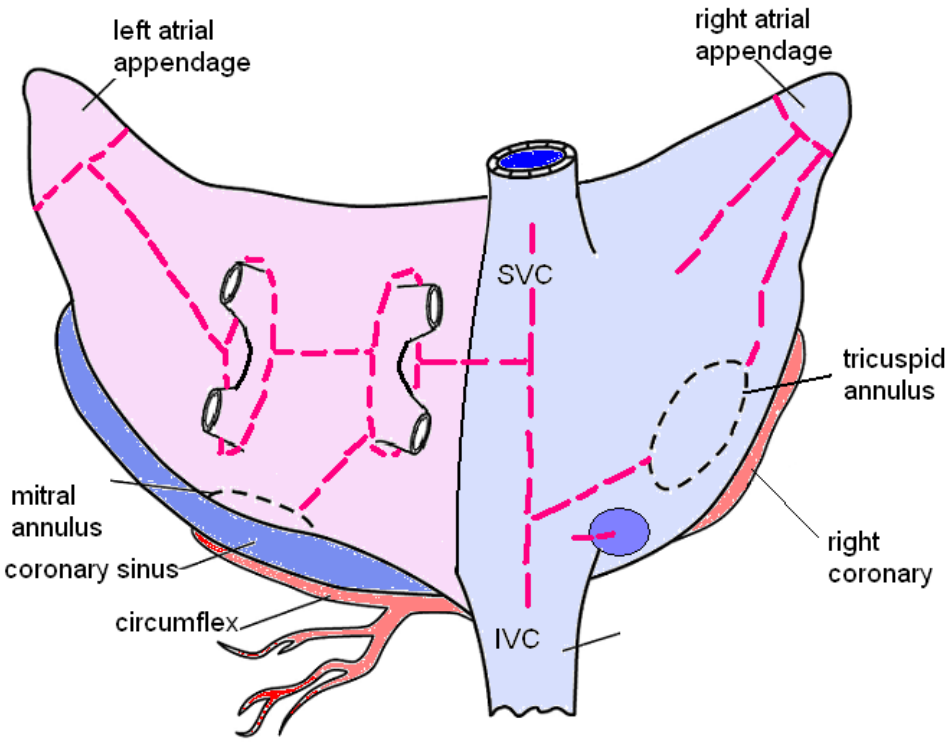
11

Notes

15

Figure 1 **Maze lesion set**

The drawing below illustrates the complete modified Cox-maze III lesion set. It is accepted that not all lesions will be carried out in all patients, but it is important that what is carried out is documented.



Lesions

Left-sided

1. around right pulmonary veins (RPV)
2. around left pulmonary veins (LPV)
3. connecting RPV to LPV lesions
4. connecting RPV lesion to mitral annulus
5. left atrial appendage
6. left atrial appendage lesion to LPV

Right-sided

1. SVC to IVC
2. SVC-IVC lesion to tricuspid annulus
3. trans-septal SVC-IVC lesion to RPV lesion
4. right atrial appendage
5. right atrial appendage to RA body
6. right atrial appendage to tricuspid annulus
7. coronary sinus ostium