ETTAA:

Effective Treatments for Thoracic Aortic Aneurysms: A prospective cohort study

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Amendments

The following amendments and / or administrative changes have been made to this protocol since the date of preparation.

Amendment No	Date of Amendment	Version No.	Type of Amendment? (e.g. substantial / non-substantial / administrative change)
1			Minor – number of administrative amendments 1. Clarifying the end date of the study between different documents 2. Amending the protocol in line with final changes with the grant body and end date of study. 3. Use of EQ-5D 5 level rather than 3 level questionnaire
2	10th June 2014	3.0	
Minor Amendment 2	17th October 2014	3.1	One minor change to clarify the inclusion criteria. The inclusion criteria will read greater or equal (≥) to 4 cm rather than greater than (>) 4cm.
3	19th May 2015	4.0	The PIS has been changed to reflect the relocation of the database server to the UK from the US. Clarification to the exclusion criteria and definition of the arch and descending aorta included. Addition of a Glossary defining CRF clinical terms.
Minor Amendment 3	10th July 2015	4.1	Changing terminology of the Best Medical Therapy (BMT) group to Conservative Management (CM)

1 STUDY SYNOPSIS

Title of Study	Effective Treatments for Thoracic Aortic Aneurysms (ETTAA Study): A prospective cohort study
Protocol Number	V 4.1
Number of Study Sites	20 (approx)
Number of Patients	2200
Study Design	A prospective, multi-centre, observational, cohort study
Patient Population	Patients with a chronic thoracic aortic aneurysm (CTAA) of the aortic arch or descending aorta 4cm or over.
Objectives	1. To follow patients with CTAA referred to each collaborating multidisciplinary team (MDT), prospectively recording management, medical events, quality of life (QoL) and use of health and social services throughout the duration of the study. 2. To quantify clinical outcomes in each treatment cohort (watchful waiting WW, conservative management CM, endovascular stent grafting ESG and open surgical repair OSR) in terms of survival and quality of life. 3. To identify patient-specific or aneurysm-specific features that might predict poor outcome in each treatment group by risk-modelling methods. 4. To estimate the clinical- and cost-effectiveness of competing treatments to define optimal management strategies for patients in whom more than one treatment is considered appropriate.
Main Criteria for Inclusion	• Chronic arch or descending aortic aneurysm ≥4cm • Age ≥ 18 years • Ability to provide informed consent
Outcomes	• Aneurysm growth • Quality of life (QoL) • Freedom from reintervention; • Freedom from death or permanent neurological injury • Costs to the NHS • Incremental cost per quality adjusted life year (QALY) gained
Study Duration	6 year project (4 years recruitment and maximum 5 years follow-up).
Study Period	6 years from December 2013, Recruitment beginning February 2014

2 ABBREVIATIONS

CM	Conservative Management
CTAA	Chronic Thoracic Aortic Aneurysm
CRA	Clinical Research Assistant
CRF	Case Report Form
CT	Computed Tomography
CTC	Clinical Trial Coordiantor
EQ-5D-5L	EuroQol-5D-5L
ESG	Endovascular Stent Grafting
ETTAA	Effective Treatments for Thoracic Aortic Aneurysms
HES	Hospital Episode Statistics
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
iDMC	Independent Data Monitoring Committee
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OSR	Open Surgical Repair
PI	Principal Investigator
PPI	Patient and Public Involvement
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
R&D	Research & Development
REC	Research Ethics Committee
RF	Research Fellow
SAE	Serious Adverse Event
TSC	Trial Steering Committee
WW	Watchful Waiting

3 BACKGROUND INFORMATION

The incidence of chronic thoracic aortic aneurysm (CTAA) is rising as the UK population ages and will therefore pose an increasing challenge to health care providers and policy-makers. Based on an estimated incidence of 6-16/100,000/ year, there are 3000 – 8000 new cases per year. These patients are at risk of both fatal and non-fatal complications of the condition and the subsequent treatment costs for these patients are high. There are limited data describing the natural history of CTAA because it is often asymptomatic until presentation with rupture or dissection. Patients referred for elective intervention were usually diagnosed coincidentally during investigations for other conditions. The risk of rupture or dissection is related to size and rate of growth of the aneurysm, but these two factors alone are not sufficient to predict risk of rupture, dissection or death, since fatal complications occur even while the aneurysm is small. Control of blood pressure and smoking cessation help to reduce the risk of rupture or dissection but there is a greater risk reduction after endovascular stent grafting (ESG) or open surgical repair (OSR). Both ESG and OSR are known to be effective but each has limitations and cannot always be offered to all patients. OSR is a durable intervention but is more invasive with higher early mortality and morbidity than ESG. ESG is, however, only applicable when arterial morphology is suitable and is known to be less durable. Therefore, both patient and aneurysm factors must be considered while deciding upon a treatment.

There have been no prospective randomised controlled trials in this area. In published cohort studies, patients selected for ESG are usually older and have more comorbidity than patients selected for OSR. It is likely that these groups overlap but in the presence of current referral and selection biases, it is not clear how ESG and OSR truly compare in terms of quality of life outcomes, clinical endpoints and cost-effectiveness. Nonetheless, the studies have demonstrated less in-hospital morbidity and mortality after ESG when compared against OSR controls. In the mid-term, the re-intervention rate is higher after ESG. Each re-intervention incurs a risk of complication, as well as cost, to the patient, personal social services and the NHS. In-hospital costs of ESG are higher than OSR due to equipment costs. There are no formal economic comparisons, however, of the two techniques.

Our study is designed to overcome existing deficiencies in the body of evidence. In the UK in general and specifically in the centres collaborating on this project, specialist MDTs have become integrated into aortic practice in the last 5 years to reduce the impact of referral and selection biases. Furthermore, the ETTAA study will achieve a far-reaching and full economic evaluation of conservative management (CM), ESG and OSR to a maximum follow-up of 5 years (median follow-up of 3 years). Furthermore our planned risk modelling will assist in selecting patients for the three treatment strategies available.

4 STUDY AIMS & OBJECTIVES

This is a prospective observational cohort study that will collect data from the point of referral through to secondary care, aiming for 3 years median follow-up (range 1-5

years). The data collected will allow estimation of the success of any intervention (in terms of reducing rate of aneurysm growth, rupture or dissection) as well as estimation of the risks associated with the three procedures. Clinical outcomes in the treatment groups will be described.

Aims

We aim to answer the following questions:
1. Without procedural intervention for chronic thoracic aortic aneurysm (CTAA), what is the risk of aneurysm growth, dissection, rupture, permanent neurological injury or death? What is the effect on quality of life (QoL)?

2. If a patient has endovascular stent grafting (ESG) or open surgical repair (OSR), what is the risk of growth, dissection, rupture, permanent neurological injury or death?

3. How does QoL change from pre- to post intervention?

4. Can aneurysm or patient related predictors of good/poor treatment outcomes be determined?

5. What is the most cost-effective strategy in:
   a. Patients eligible for either ESG or OSR?
   b. Patients eligible for either ESG or conservative management (CM)
   c. Patients eligible for either watchful waiting (WW) or intervention (ESG/ OSR)?

6. What further research is required? What would be the most important research to pursue?

Objectives

The objectives are:

1. To follow patients with CTAA referred to each collaborating multidisciplinary team (MDT), prospectively recording management, medical events, QoL and use of health and social services throughout the duration of the study.

2. To quantify clinical outcomes in each cohort (WW, CM, ESG, OSR) in terms of survival and quality of life.

3. To identify patient -specific or aneurysm-specific features that might predict poor outcome in each treatment group by risk-modelling methods.

4. To estimate the clinical- and cost-effectiveness of competing treatments to define optimal management strategies for patients in whom more than one treatment is considered appropriate.

Health Technologies being assessed

ESG: Endovascular repair of the aneurysm via transluminal introduction of a stent-graft under X-ray guidance. Hybrid procedures that comprise a combination of a conventional surgical component and a transluminal repair are to be included in this group.

OSR: Replacement of the aneurysmal aorta with prosthetic conduit via a surgical incision with circulatory support.

CM: These patients have aneurysms that merit procedural intervention, however this is not planned either due to patient choice, co-morbidities or risk assessment. This refers to lifestyle modification (smoking cessation and dietary management) as well as medical management of hypercholesterolaemia and hypertension for patients who are considered unsuitable for, or who refuse, OSR / ESG.

WW: Patients with small aneurysms considered to be at low risk of rupture will remain under surveillance with annual CT / MRI scans and MDT review (as per local practice). These patients' data will contribute to the natural history component of the study.

5 STUDY DESIGN AND OUTCOME MEASURES

The ETTAA project is a prospective, multi-centre, observational, cohort study with statistical and economic modelling of patients with CTAA of the thoracic aortic arch or descending thoracic aorta.

Patients will be recruited and data collected for 5 years. There will be a four year recruitment phase with patients followed up for a minimum of 1 year and a maximum of 5 years.

5.1 Outcome Measures

Primary outcome measures are:
- Aneurysm growth;
- Quality of life (QoL);
- Freedom from reintervention;
- Freedom from death or permanent neurological injury;
- Costs to the NHS
- Incremental cost per quality adjusted life year gained.

5.2 Participating Centres & Participants

Patients will be enrolled from UK NHS centres with expertise in managing CTAA. Management options will be unchanged from routine clinical care and are watchful

waiting [WW] if the risk of aneurysm rupture is low and, ESG or OSR when the risk of aneurysm rupture is deemed higher than the risk of intervention. Patients will be allocated to CM when risk of ESG/OSR is considered prohibitive, the general health of the patient precludes ESG/OSR, or the patient refuses ESG/OSR. Treatment options will be discussed in the MDT, then agreed with the patient but will not be influenced by participation in this observational study.

Study personnel from participating centres will invite consecutive patients into the study. Patients enrolled in the study will be observed from referral for a minimum of 1 year until the study concludes allowing a median of 3 years follow-up.

Participants may move between groups during the course of the ETTAA study, but data will continue to be collected on these patients until the study concludes.

5.3 Recruitment

Eligibility for the study will be determined when the patient is reviewed either in an MDT setting or in a specialist clinic at any of the participating centres. Eligible patients will be invited to join the study and consent will be sought to collect and retain the patient's data.

5.4 Inclusion/ Exclusion Criteria

Inclusion criteria
• Chronic arch or descending aortic aneurysm ≥4cm*
• Age ≥18 years
• Able to give informed consent

*Patients with a long standing arch or descending aneurysm may still be included as long as they have not had intervention for this particular aneurysm. If a patient has already received treatment for an aneurysm on a different part of the aorta (e.g. ascending / abdominal) then the patient is still eligible. The arch is defined as between the brachiocephalic artery and the left subclavian artery. The descending aorta is defined as between the left subclavian artery and the coeliac axis.

Exclusion criteria
• Acute dissection or malperfusion syndromes (such as myocardial infarction,acute stroke or limb ischaemia)

5.5 Informed Consent

Participants will be given sufficient time to consider and discuss participation in the study, they must have a minimum of 1 hour. A member of the research team will explain the study to the patient and give them the opportunity to ask any questions. Participants will be advised that they are able to withdraw from the study at any point without any impact on their routine NHS care. The Principal Investigator or delegated research team member will confirm eligibility and obtain written informed consent before any patient data is collected. Consent may be obtained face to face or over the telephone with the Consent form posted back to the research team.

Participants will be given one copy of the signed consent form to keep and another copy will be filed in the patient's notes. The original signed consent form will be filed in the Investigator site file.

5.6 Study Assessments

Visits should be scheduled and performed according to Table 1 below.

Table 1. Assessment Schedule
☐ **= If clinically indicated**
    V=visit
*For OSR / ESG patients, complete a 3 month and 6 month post consent follow up if surgery has not yet been performed
** Number of months post procedure date for OSR / ESG patients or months post consent for WW/ CM patients
$ At 1 month post procedure if the patients has not been discharged complete the EQ-ED-5L only

Study Phase	Screen/ Baseline	Procedure Visits (if applicable)			Follow-up period								
ESG & OSR Visit/ phone/ post	V1	V2 (pre-op)	V3 (op)	V4 (post-op)	V5	V6	V7	V8	V9	V10	V11	V12	V13
WW & CM Visit/ phone/ post	V1					V2	V3	V4	V5	V6	V7	V8	V9
Month	M1	*			M1**	M3**	M6**	M12**	M18**	M24**	M36**	M48**	M60**
Inclusion/ exclusion criteria	☐												
Written informed consent	☐												
Basic demographics	☐												
Medical history	☐												
CT/MR scan	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
EQ-5D-5L	☐	☐			☐	☐	☐	☐	☐	☐	☐	☐	☐
Procedure related complications	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Clinical outcome data		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Screening/Baseline: A medical history will be undertaken to identify any contra-indications to participation. Participants will complete the EuroQol-5D-5L (EQ-5D-5L) quality of life questionnaire.

Follow-up visits: Subsequent visits to the hospital will be determined by the clinical team according to the investigations required or treatment chosen. Procedure-related complications, clinical outcome data and EQ-5D-5L QoL scores will be collected prospectively. Irrespective of treatment, clinical outcomes and EQ-5D-5L scores will be recorded at initial review, 3, 6, 12, 18, 24 months, then annually until the follow-up concludes. Clinical outcomes and EQ-5D-5L QoL scores will also be collected at 1 month for patients undergoing a OSR / ESG. It is anticipated that these time points for data-collection may overlap with but not always coincide with hospital attendances. Data will be collected at hospital attendances as well as by means of postal/ telephone questionnaires and review of primary and secondary healthcare databases (such as hospital episode statistics - HES). With the consent of patients, data will also be collected from National Databases (e.g. Health and Social Care Information Centre, Office for National Statistics).

For patients that move from WW or CM into ESG or OSR, a reassignment form should be completed at the time the clinical decision was made. Following reassignment the assessments should restart at V2 in Table 1 and subsequent visits

are based from the reassignment date. For patients waiting over 3 months for their surgery 3 and 6 months pre-procedure follow up should be carried out as required. For patients undergoing a staged procedure, the standard follow up schedule should be followed as appropriate depending on the time between procedures.

Follow up visits should be conducted within the following windows:
- 1 and 3 months follow up: ±1 week
- 6,12, 18 and 24 month follow up: ±2 weeks
- 36, 48 and 60 month follow up: ±4 weeks

5.7 Participant Withdrawal

Participants can withdraw from the trial at any time without having to give a reason and this will not affect their future care. A participant can be withdrawn from the trial under the guidance of the PI if clinically necessary or if the participant is considered lost to follow-up. All details will be recorded on the relevant CRF.

5.8 Participant Trial Completion

A participant will be considered to have completed the trial:
- when the trial closes at the end of 2019;
- if they are withdrawn for any reason;
- if they are lost to follow-up;
- if they die during the study period

Any outstanding data queries at trial completion will be followed up as thoroughly as possible.

5.9 Trial End

End of trial is defined as 31st December 2019. The TSC can end the trial prior to this date acting on the recommendation of the iDMC.

Stopping rules:

Sufficiency clause:
The iDMC will be convened quarterly to review recruitment and data quality. Annually the project team will produce an interim report for the iDMC reviewing the ability of the data to quantify the characteristics of each type of procedure and assessing the precision in the comparison between OSR and ESG. The clinical event rates and other outcomes for each of the cohorts within the study will be detailed in the report to the iDMC. We aim to register the first patients in our database in February 2014. Therefore the first iDMC meeting will be in June 2014, with subsequent meetings every 3 months (to allow 4 weeks for the Project team to prepare a report and circulate to the iDMC for review).

With our target population we will be able to estimate characteristics of each procedure, such as clinical event rates, with a standard error of at most 3-4% and the difference between the procedures with a standard error of at most 5%.

For this observational study, in which emphasis is on precise estimation of procedural characteristics, comparison of procedures and longer-term assessment of treatment outcome, we are hesitant to place a strong upper bound on recruitment. It will be suggested to the iDMC that they place a bound on precision of the clinical event rates in a single group of standard error <= 2.5% which would require a sample size of at most 400 per group or 133 per year. The iDMC will consider stopping recruitment to any of the procedure groups if the total number in that group has exceeded 400, or the precision in estimation of the main clinical events is <= 2.5%.

Futility clause
We estimate that a sample size of 16 patients per group per year would result in standard error of the estimated clinical event rates in a single group of at most 7%, and standard error of the comparison of clinical rates of at most 10%. We consider this to be the limit of what is acceptable precision for the study-based outcomes. Thus the iDMC will consider stopping recruitment to any of the procedure groups if expected total recruitment in that group falls below 4 patients recruited into each group per quarter.

Recruitment to a particular group may also be stopped if the event rate is more than 50% lower than that given in the grant application. If the recruitment falls below the thresholds estimated above but the event rate is higher than expected (or vice versa) the iDMC will be able to request a further analysis of the data for the following quarterly meeting to allow for a final decision to be made.

Under-recruitment in any single quarter will trigger a series of measures designed to ensure the targets are met. These measures will take place over a total of 3 subsequent quarters and therefore a total window of one year has been planned to achieve recruitment targets into any one group.

6 DATA COLLECTION AND RECORD KEEPING

6.1 Source Documentation

Data will be collected by a Consultant and a Research Nurse / Clinical Trial Coordinator (CTC) who will record the data on electronic case report forms (CRFs). All data will be anonymised with participants assigned a participation number at entry into the trial.

The investigator/CTC will maintain source documents (patient's hospital case notes) for each patient in the study, consisting of all demographic and medical information. A copy of the consent form and patient information sheet will also be filed in the patient's case notes. All information in the CRFs, apart from the questionnaires, will

be traceable to and consistent with the source documents in the patient's hospital case notes (Ref. ICH/GCP 4.9.2).

6.2 Labelling of Source Documentation

A copy of the signed consent form and the patient information sheet should be filed in the patients' hospital case notes to highlight they are taking part in the study. When a patient completes or if they are withdrawn from the study the patient notes will be updated.

6.3 Data Collection

Data will be recorded on the ETTAA electronic database. Instructions on the use of the database will be given separately.

Entries on paper versions of the CRF should be made in ballpoint pen and must be legible. Any entries must be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change. Paper copies should be stored in a safe location within the research site (e.g. locked research team office) and these will be used for source data verification.

Ensure that all sections of the forms are completed or that an explanatory comment is added if the data is not available.

It is the responsibility of the Principal Investigator to ensure the CRF has been completed correctly and that the data are accurate.

7 ETHICAL APPROVAL, TRUST APPROVAL AND AMENDMENTS

The study protocol and associated documentation will undergo ethical review. Once Ethical Approval has been obtained Trust Approval will be sought at each of the participating centres. Data collection will not begin at a centre until Trust Approval has been obtained.

All amendments will be discussed and approved by the Trial Management Group (TMG) before submission to the REC and R&D. No changes will be implemented before approval is given.

8 STATISTICAL ANALYSIS

We will also use the collected data to create a risk model to predict poor outcomes in CTAA patients in each treatment group (ESG, OSR or CM). Briefly, aneurysm growth and survival will be modelled jointly in a multi-state model that combines US (Yale University) and UK data. Comparisons of clinical outcomes will be based on regression models (logistic, linear and time-to-event models) which include

propensity matching of patients and their attendant risk factors. The statistical methods have been designed to allow us to detect differences in both common and uncommon complications in the study cohorts, with 80% power. If the initial data collection is successful, then we will review the potential research benefit of extending the study period to allow for longer follow up and make a submission as appropriate to the iDMC and HTA board.

i.Aneurysm growth and survival will be modelled jointly in a longitudinal model that combines the repeated measurements of aneurysm morphology from the Yale database with UK data from the WW and CM study groups. Using Bayesian modelling we will combine the information above in an attempt to jointly estimate aneurysm growth and clinical outcomes of rupture and death. The association between risk factors (e.g. aneurysm morphology at presentation and patient characteristics) and outcomes (growth and clinical events) will be determined from these models. To minimise bias in estimation of these parameters evidence from CM patients may be down-weighted according to the relevance of the population to the questions of interest. This analysis will draw on methods developed for aortic aneurysm screening.

ii.Assessment of predictors for clinical outcomes after an intervention will be based on regression models (logistic, linear and time-to-event models), with separate analyses for ESG and OSR. The type of models to be used will depend on the specific outcome but will be either generalised linear regression models or survival regression models. Since the actual numbers of adverse outcomes for any intervention may be small the models will be developed and validated using sampling-based techniques such as cross-validation or bootstrapping, the final methodology to be determined prior to the start of the study. Since this is a prospective cohort study we expect data to be reasonably complete, with few missing values. If there are substantial levels of missing data for important variables then appropriate missing data methods will be used to attempt to address any bias introduced. This may include multiple imputation or inverse-probability of censoring weighting and will depend on the cause and nature of missing values.

iii.Some patients will be suitable for more than one management option and for these patients' outcomes for the competing treatments will be compared. In order to minimise the bias in these comparisons, which is inherent in all observational studies, we will use two methods. First we will combine the analyses described in (ii) above to include all patients who undergo ESG or OSR during the study, including important predictors that are identified, and then incorporating treatment group. Second we will develop a propensity score for treatment received based on patient characteristics, co-morbidities and aneurysm morphology at the initial screen. This propensity score will then be used to match patients and comparisons will be undertaken to estimate the impact of treatment on clinical and cost-effectiveness.

Sample Size
From UK registry data, 360 elective operations and stents are performed each year in the UK for arch and descending aneurysms. Clinical collaborators estimate that 3 patients undergo WW and 1 patient is given CM for every 1 that undergoes ESG / OSR. According to these estimates, there are 1800 patients per year potentially

eligible for the study. Of these we hope to capture 40% in this study and we will recruit patients for 4 years

Our target sample size is 440 ESG/OSR cases over 4 years, with similar numbers of cases assigned to CM, and at least this number assumed to be untreated, making up the watchful waiting group. As clinical studies are expected to have slower recruitment in the first year we aim to recruit the following numbers over 4-years:

Table 2 Target sample size

Group	Year 1	Year 2	Year 3	Year 4	Total
OSR	27	40	40	40	147
ESG	53	80	80	80	293
CM	80	120	120	120	440
WW	>80	>120	>120	>120	>440

These numbers allow comparison between the OSR and ESG treatment groups based on a total of 440 patients, and comparison between OSR/ESG and CM based on 880 patients. We previously provided examples of sample size calculations based on the OSR and ESG comparisons, the most comparable groups. Briefly, using log-rank tests and assuming that approximately 25-35% of cases have a clinical event over the average 2 year follow-up, we will be able to detect moderate hazard ratios of 0.5-0.6 with 65-96% power[1].

Setting a minimum acceptable sample size of 300 (100 OSR and 200 ESG) would give reasonable precision of estimates for incidence of clinical events (and also continuous outcome measures) and would provide at least 50% power to detect hazard ratios of 0.5-0.6, resulting in the recruitment patterns tabulated below[2].

Table 3 Minimum sample size

Group	Year 1	Year 2	Year 3	Year 4	Total
OSR	19	27	27	27	100
ESG	38	54	54	54	200
CM	57	81	81	81	300
WW	>57	>81	>81	>81	>300

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[1] Assumes 440 cases in total, 1 OSR to 2 ESG patients, 2-sided significance of 5%. Power estimates 87% for 25% control incidence and HR =0.5, power 96% for 35% control incidence and HR =0.5, power 65% for 25% control incidence and HR =0.6, power 80% for 35% control incidence and HR =0.6.

[2] Assumes 50% power, 1 OSR to 2 ESG patients, 2-sided significance of 5%. Total sample size estimates n=179 for 25% control incidence and HR =0.5, n=126 for 35% control incidence and HR =0.5, n=309 for 25% control incidence and HR =0.6, n=218 for 35% control incidence and HR =0.6.

9 ECONOMIC EVALUATION

Cost-utility analysis will consider costs to the NHS and personal social services (PSS) in a 'within study analysis' and will estimate lifetime modelled using a state transition model. The outcomes of both analyses will be presented as incremental cost per QALY gained. In the base case analysis all costs and QALYs will be discounted at 3.5%.

Estimation of costs:

Data on resource use will be captured on case report forms (use of secondary care services, incidence and frequency of cost generating events) and participant completed questionnaires at 1, 3, 6, 12, 18, 24, 36, 48, 60 months for use of primary care and personal social services. Centres will be contacted for further details of resource use (e.g. for a description of the materials required for ESG and OSR). Costs for healthcare services will be cited from standard sources such as NHS reference costs, Healthcare Resource Group (HRG) tariffs, manufacturer/supplier costs and from the centres themselves. For each participant measures of resource use will be combined with unit costs to provide an estimate of cost for that participant.

Estimation of QALYs – Each participant will complete the EQ-5D-5L according to the sequence in Table 1. The responses for each participant will be converted into health state utilities using UK population tariffs and used to estimate QALYS using the area under the curve approach.

Data analysis

As described in above some patients will be suitable for more than one management and similar methods as described above to compare costs and QALYs will be used to estimate incremental cost per QALY gained. Bootstrapping methods will be used to estimate the imprecision around estimates of incremental costs, QALYs and incremental cost per QALY. Data on costs and QALYs will be presented as point estimates. Plots of incremental cost and QALY and incremental cost per QALY will be presented as cost-effectiveness acceptability curves (CEAC). Where data are missing we will investigate the nature and pattern of missingness and as outlined in the section of statistical analysis above we will choose appropriate methods to impute missing data if necessary. Deterministic sensitivity analysis will be used to explore key uncertainties e.g. use of different unit costs, discount rates, methods of imputation, etc. These deterministic analyses will be combined with stochastic analyses and presented as CEACs.

Model based analysis

The primary source of evidence to populate the economic model will be the observational study. The data on initial treatment cost (the operative, peri-operative and costs up to six months) will be based on the data derived from the study. The cost estimates and relative cost differences will be derived using the same methods as described above. The costs following the initial six month period will depend upon on-going surveillance costs and the incidence of clinical events requiring further health care. Where there are sufficient data we will explore using appropriate regression methods whether the cost of a clinical event varies according to the characteristics of the individuals who suffer that event. Where there are insufficient

data within the observational dataset we will assume that the cost for an event does not vary according to the characteristics of the individual. Where data on costs of an event cannot be obtained from the observational dataset we will create study specific estimates based upon data from the literature and advice from the clinical experts involved in the study. Data on utility weights for the model will be derived using similar methods to those used to derive costs. Further data required to populate the model will relate to the probability of clinical events. These will be derived from the statistical analyses described above. Where necessary e.g. for events that occur in the longer term and not captured by the observational study, focused searches of the literature will be used to identify relevant data.

Estimates of costs, utilities and probabilities will be defined in the model as distributions. The nature and type of distribution chosen for each parameter will be informed by the data available and recommendations for good practice in modelling. This will facilitate the use of probabilistic sensitivity analysis methods to provide estimates of variability around costs, QALYs and cost-effectiveness. The results of the model will be presented in terms of point estimates of costs, QALYs for each treatment and as incremental cost per QALY. The same methods used in the within trial study will be used to present the variability around these estimates. Deterministic sensitivity analysis, combined where appropriate with probabilistic sensitivity analysis, will be used to explore uncertainties. An extension of probabilistic sensitivity analysis and value of information analysis will be used to understand which information needs might have the greatest impact on the outcome of the model with a view to determining where research resources should be focused. The results will be presented as expected value of perfect information and as expected value of partial perfect information for specific groups of parameters e.g. parameter values used to estimate long-term effects, utilities, etc.

10 MONITORING

The study will be monitored and audited by a representative from the Papworth Hospital Research & Development Department who are independent of the trial.

A Trial Steering Committee (TSC) will be convened to monitor the progress of the trial, ensure all objectives are met, review all relevant information or amendments, and investigate any recommendations to the protocol. The TSC will consist of at least two external experts and a patient representative.

A Data Monitoring and Ethics Committee will meet quarterly a year to review recruitment rates and data quality. An independent chair and clinician will attend the meetings.

11 FINANCING AND PUBLICATION POLICY

This project is funded by the NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series. Visit the HTA programme website for more details www.hta.ac.uk/link to project page. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Authorship will be determined by mutual agreement. All publications will acknowledge the funding body of the study. The data will be analysed, as stipulated in the protocol, by the Trust statisticians.

12 APPENDICES

ETTAA Patient Flow

Assessed for eligibility = n

Total excluded = **n**
Not meeting inclusion/exclusion criteria = n
Refusal to participate = n

Informed consent = **n**
V.1- Initial data collection = **n**

Total excluded = **n**
Not meeting inclusion/exclusion criteria = n
Refusal to participate = n

Endovascular Stent Grafting (ESG) = n	**Open Surgical Repair (OSR)** = n	**Conservative Management (CMCM) = n**	**Watchful Waiting (WW)** = n

Endovascular Stent Grafting column:

V.2- Pre procedure*
Completed = n
Lost to follow-up = **n**
Died = **n**
Received ESG = n
OSR = **n**;   CM = **n**;   WW = **n**

V.3- Procedure
Completed = **n**
Lost to follow-up = **n**
Died = **n**
OSR = **n**;   CM = **n**;   WW = **n**

V.4- Post procedure
Completed = **n**
Lost to follow-up = **n**
Died = **n**
OSR = **n**;   CM = **n**;   WW = **n**

V.5- 1 month post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
OSR = **n**;   CM= **n**;   WW = **n**

V.6- 3 months post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
OSR = **n**;   CM = **n**;   WW = **n**

V.7- 6 months post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
OSR = **n**;   CM = **n**;   WW = **n**

V.8-13 12, 18, 24, 36, 48 and 60 months post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
OSR = **n**;   CM = **n**;   WW = **n**

Open Surgical Repair column:

V.2- Pre procedure*
Completed = **n**
Lost to follow-up = **n**
Died = **n**
Received OSR = n
ESG = **n**;   CM = **n**;   WW = **n**

V.3- Procedure
Completed = **n**
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   CM = **n**;   WW = **n**

V.4- Post procedure
Completed = **n**
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   CM = **n**;   WW = **n**

V.5- 1 month post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   CM = **n**;   WW = **n**

V.6- 3 months post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   CM = **n**;   WW = **n**

V.7- 6 months post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   CM = **n**;   WW = **n**

V.8-13 12, 18, 24, 36, 48 and 60 months post op
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   CM = **n**;   WW = **n**

Conservative Management column:

V.2- 3 months post P.1
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
Received CM = n
ESG = n;   OSR = n;   WW = **n**

V.3- 6 months post P.1
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   OSR = n;   WW = **n**

V.4-9 12, 18, 24, 36, 48, and60 months post P.1
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   OSR = n;   WW = **n**

Watchful Waiting column:

V.2- 3 months post P.1
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
Received WW = n
ESG = n;   OSR = n;   CM = **n**

V.3- 6 months post P.1
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   OSR = n;   CM = **n**

V.4-9 12, 18, 24, 36, 48 and 60 months post P.1
Completed = **n**   *In clinic* = n
                              By telephone = n
Lost to follow-up = **n**
Died = **n**
ESG = **n**;   OSR = n;   CM = **n**

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*Only complete a 3 and 6 month post consent follow up if the patient is still waiting for surgery

At any point during follow up - patients may change from any treatment arm to another, in which case their pathway in that treatment arm stops and begins again at V.2 in the new treatment arm

OBSERVED CLINICAL EVENTS DURING HOSPITAL ADMISSION

Death
Recorded death

Myocardial infarction
The clinical suspicion of myocardial infarction together with elevated CK-MB or Troponin, and/or ECG/echo findings consistent with acute myocardial infarction.

Cardiac support
Support of myocardial pump function either by the use of intravenous/ inhaled inotropic agents (e.g. adrenaline, noradrenaline, enoximone, dopamine, nitric oxide etc.) or the use of an intra-aortic balloon pump.

Prolonged ventilation >48hrs
Support of respiratory or ventilatory function by means of a mechanical ventilator for more than 48 hours after a) admission (for conservatively managed WW or CM patients) or b) procedural intervention by means of endovascular stent grafting or surgery.

Renal Support
    a) <u>Temporary</u>
- *Treatment of acute renal failure* by means of a period of haemofiltration that is confined within the hospital admission and not required after discharge.*
  - o **Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to intervention; or a rise in serum creatinine of 26 µmol/l or greater within 48 hours; or a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days*

    b) <u>Permanent</u>
    Renal dysfunction persisting more than 90 days and graded according to estimated GFR, or requirement for hemodialysis sustained for at least 90 days.

GI complications
A new diagnosis of any of the following conditions as determined by the clinical history and standard investigations, interpreted and documented by a qualified physician: upper/lower gastrointestinal bleeding, intestinal ischemia (small or large bowel), stoma formation, or others including (but not confined to) oesophagitis, duodenal ulcer (perforated or bleeding), erosive gastritis, pancreatitis, liver failure/necrosis, cholecystitis.

Neurological injury
Central Nervous System - Brain:
Any new, temporary or permanent, focal or global neurologic dysfunction ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician; or an abnormality identified by surveillance neuroimaging.

    a) Transient ischemic attack (TIA), defined as an acute transient neurological deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed

>24 hours after symptom onset; or MRI*).
    b) *Cerebrovascular accident (CVA), defined as a new acute neurological deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit, or attributable to intracranial hemorrhage.*

Central Nervous System - spinal cord:
    a) *Paraplegia: new onset of impairment in motor and sensory function of the lower extremities after aortic intervention*
    b) *Paraparesis: new onset partial impairment in motor or sensory function of the lower extremities after aortic intervention*

Thromboembolic event (DVT/PE)
Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Infection
Infection pertaining to the operated segment of aorta (including peri-prosthetic abcess), vascular access site, surgical incision, lungs, pleural/ peritoneal cavity or urinary tract; as diagnosed by an appropriately qualified physician according to standard clinical investigations.

Return to theatre
A secondary visit the operating/ hybrid theatre for treatment or examination of suspected complications following but during the same admission as the index intervention by ESG or OSR.

Access Vessel Injury
New onset intramural haematoma, pseudo-aneurysm, dissection, avulsion, disruption, rupture or occlusion of any vessel used to provide vascular access for the delivery of an endovascular stent graft.

Endoleak
- *Type I:*
  - a) *Leak at the proximal graft attachment site*
  - b) *Leak at the distal graft attachment site*
  - c) *Leak around a fenestration, branch end point, or branch occluding plug (eg, plug occluding a subclavian artery or iliac artery to prevent flow into an aneurysm sac2)*
- *Type II: Retrograde flow from branch arteries arising from the excluded segment*
- *Type III:*
  - a) *Modular disconnect or apposition failure (including branch junctions)*
  - b) *Fabric tear*
- *Type IV: Flow through porous fabric (generally resolves within a short time period, typically less than 24 hours)*
- *Type V: No detected endoleak, but aneurysm expansion (thus presumed failure to detect the endoleak or presumed pressure transmission through thrombus without blood flow).*

OTHER OBSERVED CLINICAL EVENTS

Aneurysm complication
Any direct complication localized to the operated segment of aorta, including (but not necessarily confined to) localized rupture, dissection, or pseudoaneurysm formation. This must be diagnosed and documented by an appropriately qualified physician (e.g. vascular/cardiothoracic surgeon or interventional radiologist) according to standard clinical and radiological investigations.

Fistula formation
Defined as an abnormal connection between the operated/ stent-grafted segment of

aorta and another epithelialized surface, and diagnosed according to standard clinical and radiological investigations.
Reintervention   *Any intervention undertaken in order to preserve or restore the function of an endovascular stent graft (e.g. re-ballooning/ additional stent/ surgery) or surgically implanted aortic graft*
Aneurysm growth rate   *Measured on orthogonal maximum diameter of the aneurysm on multiplanar reconstruction, from serial CT/ MR scans.*