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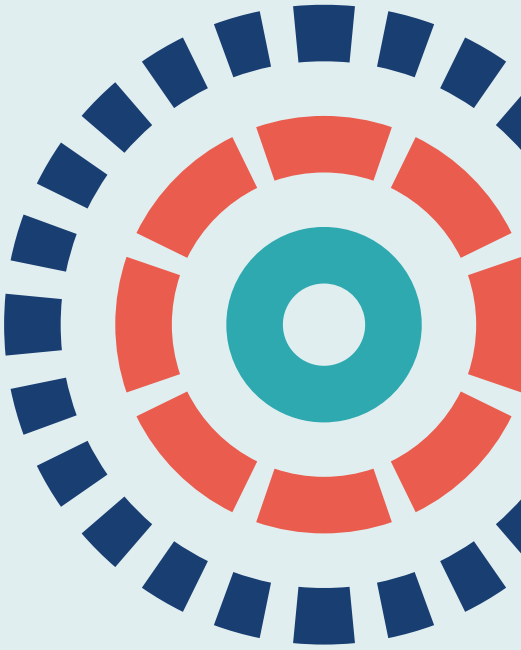
Linda Sharples, Priya Sastry, Carol Freeman, Joanne Gray, Andrew McCarthy, Yi-Da Chiu, Colin Bicknell, Peter McMeekin, S Rao Vallabhaneni, Andrew Cook, Luke Vale and Stephen Large on behalf of the ETTAA Collaborative Group



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Endovascular stent grafting and open surgical replacement for chronic thoracic aortic aneurysms: a systematic review and prospective cohort study

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Abstract

Endovascular stent grafting and open surgical replacement for chronic thoracic aortic aneurysms: a systematic review and prospective cohort study

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Background: The management of chronic thoracic aortic aneurysms includes conservative management, watchful waiting, endovascular stent grafting and open surgical replacement. The Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study investigates timing and intervention choice.

Objective: To describe pre- and post-intervention management of and outcomes for chronic thoracic aortic aneurysms.

Design: A systematic review of intervention effects; a Delphi study of 360 case scenarios based on aneurysm size, location, age, operative risk and connective tissue disorders; and a prospective cohort study of growth, clinical outcomes, costs and quality of life.

Setting: Thirty NHS vascular/cardiothoracic units.

Participants: Patients aged > 17 years who had existing or new aneurysms of ≥ 4 cm in diameter in the arch, descending or thoracoabdominal aorta.

Interventions: Endovascular stent grafting and open surgical replacement.

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Main outcomes: Pre-intervention aneurysm growth, pre-/post-intervention survival, clinical events, readmissions and quality of life; and descriptive statistics for costs and quality-adjusted life-years over 12 months and value of information using a propensity score-matched subsample.

Results: The review identified five comparative cohort studies (endovascular stent grafting patients, $n = 3955$; open surgical replacement patients, $n = 21{,}197$). Pooled short-term all-cause mortality favoured endovascular stent grafting (odds ratio 0.71, 95% confidence interval 0.51 to 0.98; no heterogeneity). Data on survival beyond 30 days were mixed. Fewer short-term complications were reported with endovascular stent grafting. The Delphi study included 20 experts (13 centres). For patients with aneurysms of ≤ 6.0 cm in diameter, watchful waiting was preferred. For patients with aneurysms of > 6.0 cm, open surgical replacement was preferred in the arch, except for elderly or high-risk patients, and in the descending aorta if patients had connective tissue disorders. Otherwise endovascular stent grafting was preferred. Between 2014 and 2018, 886 patients were recruited (watchful waiting, $n = 489$; conservative management, $n = 112$; endovascular stent grafting, $n = 150$; open surgical replacement, $n = 135$). Pre-intervention death rate was 8.6% per patient-year; 49.6% of deaths were aneurysm related. Death rates were higher for women (hazard ratio 1.79, 95% confidence interval 1.25 to 2.57; $p = 0.001$) and older patients (age 61–70 years: hazard ratio 2.50, 95% confidence interval 0.76 to 5.43; age 71–80 years: hazard ratio 3.49, 95% confidence interval 1.26 to 9.66; age > 80 years: hazard ratio 7.01, 95% confidence interval 2.50 to 19.62; all compared with age < 60 years, $p < 0.001$) and per 1-cm increase in diameter (hazard ratio 1.90, 95% confidence interval 1.65 to 2.18; $p = 0.001$). The results were similar for aneurysm-related deaths. Decline per year in quality of life was greater for older patients (additional change −0.013 per decade increase in age, 95% confidence interval −0.019 to −0.007; $p < 0.001$) and smokers (additional change for ex-smokers compared with non-smokers 0.003, 95% confidence interval −0.026 to 0.032; additional change for current smokers compared with non-smokers −0.034, 95% confidence interval −0.057 to −0.01; $p = 0.004$). At the time of intervention, endovascular stent grafting patients were older (age difference 7.1 years; 95% confidence interval 4.7 to 9.5 years; $p < 0.001$) and more likely to be smokers (75.8% vs. 66.4%; $p = 0.080$), have valve disease (89.9% vs. 71.6%; $p < 0.0001$), have chronic obstructive pulmonary disease (21.3% vs. 13.3%; $p = 0.087$), be at New York Heart Association stage III/IV (22.3% vs. 16.0%; $p = 0.217$), have lower levels of haemoglobin (difference −6.8 g/l, 95% confidence interval −11.2 to −2.4 g/l; $p = 0.003$) and take statins (69.3% vs. 42.2%; $p < 0.0001$). Ten (6.7%) endovascular stent grafting and 15 (11.1%) open surgical replacement patients died within 30 days of the procedure ($p = 0.2107$). One-year overall survival was 82.5% (95% confidence interval 75.2% to 87.8%) after endovascular stent grafting and 79.3% (95% confidence interval 71.1% to 85.4%) after open surgical replacement. Variables affecting survival were aneurysm site, age, New York Heart Association stage and time waiting for procedure. For endovascular stent grafting, utility decreased slightly, by −0.017 (95% confidence interval −0.062 to 0.027), in the first 6 weeks. For open surgical replacement, there was a substantial decrease of −0.160 (95% confidence interval −0.199 to −0.121; $p < 0.001$) up to 6 weeks after the procedure. Over 12 months endovascular stent grafting was less costly, with higher quality-adjusted life-years. Formal economic analysis was unfeasible.

Limitations: The study was limited by small numbers of patients receiving interventions and because only 53% of patients were suitable for both interventions.

Conclusions: Small (4–6 cm) aneurysms require close observation. Larger (> 6 cm) aneurysms require intervention without delay. Endovascular stent grafting and open surgical replacement were successful for carefully selected patients, but cost comparisons were unfeasible. The choice of intervention is well established, but the timing of intervention remains challenging.

Future work: Further research should include an analysis of the risk factors for growth/rupture and long-term outcomes.

Trial registration: Current Controlled Trials ISRCTN04044627 and NCT02010892.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/ABUT7744).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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Glossary

Conservative management Management that excludes open surgical or endovascular interventions.

EuroQol-5 Dimensions, five-level version A questionnaire with five dimensions and five levels for each dimension.

EuroSCORE An assessment of cardiac surgical risk developed using logistic regression.

Hazard ratio The ratio of the instantaneous probabilities of an event in two levels of an independent variable.

Hybrid procedure A procedure that involves both open and endovascular surgery in a single admission.

Index procedure In the current study, the first procedure (endovascular stent grafting or open surgical replacement). If more than one procedure was planned, the first stage of that procedure.

Interquartile range The distance between the first and third quartiles of a measurement.

Missing at random The fact that a measurement is missing does not depend on its value, conditional on (adjustment for) observed data.

Missing completely at random The fact that a measurement is missing does not depend on its value.

Missing not at random The fact that a measurement is missing depends on its value.

Multiple imputation using chained equations A method for imputing missing data when missing at random can be assumed.

Proportional hazard An assumption in survival models that the ratio of hazards in different groups is constant through time.

Quartile The values of a variable such that 25% of measurements lie below (Q1) or above (Q3) the value.

Staged procedure A procedure that is planned to take place in more than one theatre session.

Watchful waiting Management during the study that could, but did not, include open surgical or endovascular interventions.

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List of abbreviations

A&E	accident and emergency
AAA	abdominal aortic aneurysm
ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
BMI	body mass index
CABG	coronary artery bypass grafting
CI	confidence interval
CM	conservative management
COPD	chronic obstructive pulmonary disease
CRF	case report form
CT	computerised tomography
CTAA	chronic thoracic aortic aneurysm
CTD	connective tissue disorder
DTA	descending thoracic aorta
EQ-5D-5L	EuroQoL-5 Dimensions, five-level version
ESG	endovascular stent grafting
ETTAA	Effective Treatments for Thoracic Aortic Aneurysms
EVAR	endovascular aneurysm repair
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
GERAADA	German Registry for Acute Aortic Dissection Type A
GP	general practitioner
HDU	high-dependency unit
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICU	intensive care unit
IPR	interpercentile range
IPRAS	asymmetry-adjusted interpercentile range
IPTW	inverse probability of treatment weighting
IQR	interquartile range
IRAD	International Registry of Acute Aortic Dissections
LV	left ventricular
MAR	missing at random
MCAR	missing completely at random
MCID	minimum clinically important difference
MDT	multidisciplinary team
MICE	multiple imputation using chained equations
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NYHA	New York Heart Association
OSR	open surgical repair
PCI	percutaneous coronary intervention
PI	principal investigator
PSS	Personal Social Services
QALY	quality-adjusted life-year
RAND	Research ANd Development
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
VoI	value of information
WW	watchful waiting

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Plain English summary

The aorta is the main artery that carries oxygen-rich blood from the heart to the body. An aneurysm is a swelling or bulging in a blood vessel, which usually occurs where the wall has become weak and has lost its elastic properties, which means that it does not return to its normal shape after the blood has passed through. A thoracic aortic aneurysm, or TAA for short, is an aneurysm in the section of the aorta in the chest (www.bhf.org.uk/informationsupport/conditions/thoracic-aortic-aneurysms).

The Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study aimed to investigate aneurysm growth rates, patient outcomes, quality of life and costs, including those from surgery. Surgical treatments include open heart surgery, in which the section of the aorta that contains the aneurysm is removed and replaced by a new aorta made from a synthetic material, and stent grafting, in which tubes are inserted into arteries to allow blood to flow freely, using less invasive 'keyhole' surgery. The existing research evidence was reviewed, but data comparing the effectiveness of these two approaches were sparse or of limited quality, and outdated.

Between 2014 and 2018, clinical experts were surveyed and 886 NHS patients with chronic thoracic aortic aneurysms ($\geq$ 4 cm in diameter) were observed to monitor aneurysm growth and patient outcomes.

If patients were unfit or unwilling to have surgery, they had conservative management with medication and lifestyle changes. For small aneurysms, experts recommended watchful waiting, with regular monitoring, until the aneurysm grew to about 6 cm in diameter. Open surgery was preferred for larger arch aneurysms and for descending aneurysms in patients with genetic disorders. Otherwise, stent grafting was preferred.

The observational study recruited 321 women and 565 men with an average age of 71 years from 30 English hospitals. A total of 489 patients underwent watchful waiting and 112 received conservative management. Without surgery, death rates were higher for women and older patients, while the risk of dying doubled for each centimetre of aneurysm diameter at baseline. Of the remaining patients, 150 underwent stent grafting and 135 had open surgery. One-year overall survival was 83% after stent grafting and 79% after open surgery but the difference could be due to chance. The factors affecting survival after stent grafting or open surgery were aneurysm location, age, breathlessness and time waiting for a procedure.

Small aneurysms are low risk, so blood pressure management and smoking cessation are recommended. For larger aneurysms, it is important that surgery is not delayed, as a longer waiting time to surgery means that outcomes are poorer.

Only about half of patients who had surgery were considered suitable for both stent grafting and open surgery, which limited the ability to determine the best use of NHS resources. No comparative cost-effectiveness analysis was feasible. The main cost in a stent grafting procedure was the stent graft, and the main cost in an open surgery procedure was days in an intensive care unit.

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Scientific summary

Background

Chronic thoracic aortic aneurysm (CTAA) is a long-term condition in which the aorta dilates beyond 50% of its normal diameter. If untreated, aneurysms expand, stretching vessel walls until the aorta tears (dissection) or ruptures. Both are life-threatening events.

The management of smaller aneurysms comprises watchful waiting (WW) if future intervention is envisaged and conservative management (CM) if patients are unfit for or refuse surgery. With larger aneurysms, intervention involves either endovascular stent grafting (ESG), in which stent(s) are placed into the aorta, or open surgical repair (OSR), where the chest is opened and the diseased segment is replaced. Both interventions are effective in some patients, but both are associated with significant postoperative recovery period, complications and cost.

Objectives

- To review the literature comparing ESG and OSR.
- To explore clinicians' views on optimal patient management.
- To prospectively record management and outcomes (aneurysm growth, survival, clinical events and quality of life).
- To identify the features predicting poor outcome.
- To estimate the clinical effectiveness and cost-effectiveness of competing treatments for patients suitable for more than one treatment.

Methods

Systematic review

Electronic databases were searched for studies between January 1994 and March 2020 to identify randomised controlled trials and non-randomised controlled trial comparative studies comparing ESG and OSR for the elective treatment of arch/descending aortic aneurysm. Studies that included other aortic conditions such as dissection were excluded if elective aneurysm treatment was not reported separately. The ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool was used to assess risk of bias, with results reported narratively and meta-analysis used where appropriate.

Delphi study methods

Based on five key criteria [connective tissue disorder (CTD), age, aneurysm size, aneurysm location and operative risk], 360 hypothetical case scenarios were defined. Expert panels (including an anaesthetist, an interventional radiologist, and cardiac and vascular surgeons) assessed each scenario for appropriate patient management to provide consensus, equipoise between two options or no consensus.

Observational study design

Inclusion

Patients aged $\geq$ 18 years presenting to NHS hospitals with existing or new aneurysms of $\geq$ 4 cm in diameter in the arch, descending or thoracoabdominal aorta (including aneurysms secondary to atherosclerotic degeneration, after acute dissection and secondary to aortopathy).

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Exclusion
Patients suffering from acute dissection with or without malperfusion syndromes or who had previous intervention for the same aneurysm.

Study groups
The study groups were WW, CM, ESG and OSR.

Data collection
Patient characteristics, medical history, health-related quality of life and NHS resource use were recorded at consent and at 3, 6, 12, 18, 24, 36 and 48 months (plus 1 month post intervention). Aneurysm growth was monitored using thoracic computerised tomography (CT) or magnetic resonance images in accordance with local protocols.

Outcomes
Aneurysm diameter growth, pre-/post-intervention survival, clinical events, hospital admissions and quality of life. An estimation of incremental cost per quality-adjusted life-years (QALYs) gained was planned.

Statistical methods
The sample size of 170 ESG and 112 OSR patients was based on identifying moderate to large effects on survival [hazard ratio (HR) > 0.5)], with 5% significance and 80% power. This allowed an estimation of EuroQoL-5 Dimensions, five-level version (EQ-5D-5L) utility differences of 0.1, with 90% power.

Main data analysis methods
Analysis included Cox regression for predictors of survival, negative binomial regression to compare event rates and longitudinal mixed effects for aneurysm growth and quality-of-life trajectories. Sensitivity to assumptions about missing covariates was assessed using multiple imputation. In sensitivity analyses, patients with a contraindication to either intervention were excluded and the analyses were repeated based on propensity scores.

Health economic analysis
Within-study and model-based analyses were planned but were revised to a description of quality-adjusted life-years and costs from an NHS and Personal Social Services (PSS) perspective. Further analysis involved the exploration of the drivers of costs and the prediction of the value of information (VoI) of future research. Costs were reported in 2018 Great British pounds and QALYs were estimated from responses to the EQ-5D-5L.

Results

Systematic review
The review identified five comparative cohort studies (ESG patients, $n = 3955$; OSR patients, $n = 21{,}197$). Risk of bias was rated as being moderate to severe across all studies. Pooled short-term all-cause mortality favoured ESG [odds ratio 0.71, 95% confidence interval (CI) 0.51 to 0.98; no heterogeneity]. Data on survival beyond 30 days were mixed. Fewer short-term complications were reported with ESG.

Delphi study
Twenty experts from 13 centres took part. Among 360 scenarios, consensus was reached in 247 (69%) and equipoise in 34 (9%), leaving neither consensus nor equipoise in 79 (22%).

For patients with smaller aneurysms, of ≤ 6.0 cm in diameter (110/144, 76% scenarios), WW was generally the preferred management; the main exceptions were older or high-risk patients (CM) and

patients with CTDs (OSR). Equipoise between WW and OSR was evident for a small number of scenarios. There was no consensus for low-/medium-risk patients aged > 85 years or for patients aged < 65 years with CTDs.

For patients with aneurysms of > 6.0 cm in diameter, experts generally favoured OSR in the arch, except in older/high-risk patients, and in the descending thoracic aorta if patients had CTDs. Otherwise ESG was preferred. Experts expressed equipoise between OSR and ESG for medium-risk patients aged 65–75 years with aneurysms in the arch of > 6.0 cm in diameter and for patients with CTDs at low/medium surgical risk and aged 75–85 years.

Effective Treatments for Thoracic Aortic Aneurysms patient cohort

Between March 2014 and July 2018, 886 patients were recruited from 30 English centres [WW, $n = 489$ (55.2%); CM, $n = 112$ (12.6%); ESG, $n = 150$ (16.9%); OSR, $n = 135$ (15.2%)]. The mean time between diagnosis and recruitment was 2 (range 0–22) years.

Baseline predictors

A total of 321 (36.2%) patients were women and 565 were men; patients' mean age was 70.9 [standard deviation (SD) 10.9] years, and 86–96% had treated hypertension. Patients receiving CM were significantly older and more likely to have comorbidities. OSR patients were significantly younger. There were significant differences between the groups in the prevalence of some comorbidities, biomarkers and cardiac medication.

Details of procedures

A total of 150 patients underwent ESG and 135 underwent OSR. Thirty-seven OSR patients had concomitant cardiac procedures that could have been completed only during open surgery. Aneurysms were more likely to be treated with OSR if they were in the arch (103/139) and less likely to be treated with OSR if they were in the descending aorta (82/221). Aneurysms involving the ascending aorta were always treated with OSR. Twelve ESG patients and 25 OSR patients had a second procedure; three progressed to a third.

Pre-procedure survival, clinical events, readmissions, aneurysm growth and quality of life

Aneurysm growth

Analysis included 1767 scans that allowed for 6433 aneurysm diameter measurements to be taken in 886 patients. The mean baseline aneurysm diameters (cm) in patients with repeated measurements were 4.11 (SD 0.87) in the ascending aorta, 3.98 (SD 0.85) in the arch of the aorta, 5.26 (SD 1.09) in the descending aorta and 3.48 (SD 0.81) in the thoracoabdominal aorta. Baseline aneurysm diameter was higher in older patients, current smokers and patients with CTDs, chronic obstructive pulmonary disease (COPD) or valve disease. On average each year, aneurysms grew by 0.04 cm in the arch, 0.07 cm in the descending aorta and 0.10 cm in the thoracoabdominal aorta.

Survival

Pre intervention, 129 patients died during 1498.2 patient-years of follow-up (8.6% per patient-year); 64 (49.6%) deaths were aneurysm related. In unadjusted Cox regression for overall survival, the hazard ratio (HR) for CM was 3.05 (95% CI 2.12 to 4.37; $p < 0.001$). In multivariable analysis, the hazard of death from any cause was higher for women (HR 1.79, 95% CI 1.25 to 2.57; $p = 0.001$) and older patients (HR 2.50, 95% CI 0.76 to 5.43, age 61–70 years; HR 3.49, 95% CI 1.26 to 9.66, age 71–80 years; HR 7.01, 95% CI 2.50 to 19.62, age > 80 years; $p < 0.001$) and per 1-cm increase in aneurysm diameter (HR 1.90, 95% CI 1.65 to 2.18; $p = 0.001$). Weak evidence suggested that New York Heart Association (NYHA) class was associated with increasing risk of all-cause death (HR 1.23 per class, 95% CI 1.00 to 1.52 per class; $p = 0.052$). Similar results were found for aneurysm-related deaths. Predictions from this analysis suggest that intervention should be discussed once aneurysms exceed 6 cm in diameter if the operative risk is low/moderate.

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Hospital admissions

Pre procedure, 363 admissions were reported for 222 patients; 52 admissions for 39 patients were aneurysm related. Adjusting for age and sex, and taking WW as the reference group, the relative admission rate was 1.31 (95% CI 0.89 to 1.92) for CM patients, 2.10 (95% CI 1.30 to 3.42) for ESG recipients and 0.90 (95% CI 0.46 to 1.76) for OSR recipients ($p = 0.016$). Two non-fatal ruptures and seven dissections were reported. Combining fatal and non-fatal events, there were 69 ruptures/dissections in 1489 years of patient follow-up: 4.6% per patient-year. Eight non-fatal neurological events were reported.

Quality of life pre intervention

The analysis included 3492 EQ-5D-5L utilities from 855 patients. The mean utility at baseline was 0.73 (SD 0.23) for WW patients, 0.68 (SD 0.25) for CM patients, 0.77 (SD 0.24) for ESG patients and 0.76 (SD 0.18) for OSR patients. For patients who had average covariates at baseline, the mean utility was 0.85 (95% CI 0.82 to 0.88), decreasing for patients who required formal/informal care (decrement −0.206, 95% CI −0.255 to −0.156; $p < 0.001$) and with each increase in NYHA class (decrement −0.089, 95% CI −0.108 to −0.069; $p < 0.001$). There was little change in quality of life pre intervention (decrement −0.010 per year, 95% CI −0.022 to 0.003 per year; $p = 0.128$) for average patients. The decline per year in quality of life was greater for older patients (additional change −0.013 per decade increase in age, −0.019 to −0.007; $p < 0.001$) and smokers (additional change compared with non-smokers: 0.003, 95% CI −0.026 to 0.032, for ex-smokers, and −0.034, 95% CI −0.057 to −0.01, for current smokers; $p = 0.004$).

Post-intervention survival, clinical outcomes and quality of life

Baseline predictors

The key differences between the ESG and OSR patients at the time of the procedure were that ESG patients were older (mean age difference 7.1 years, 95% CI 4.7 to 9.5 years; $p < 0.001$) and more likely to be current smokers or ex-smokers (75.8% vs. 66.4%; $p = 0.080$), have valve disease (89.9% vs. 71.6%; $p < 0.0001$), have COPD (21.3% vs. 13.3%; $p = 0.087$), be at NYHA class III/IV (22.3% vs. 16.0%; $p = 0.217$), have lower average levels of haemoglobin (mean difference −6.8 g/l, 95% CI −11.2 to −2.4 g/l; $p = 0.003$) and take statins (69.3% vs. 42.2%; $p < 0.0001$). Patients with CTDs primarily underwent OSR (14.8% vs. 1.3%; $p < 0.001$).

Outcomes after procedure

Ten (6.7%) ESG and 15 (11.1%) OSR patients died within 30 days of the procedure ($p = 0.2107$). OSR patients required a significantly longer stay in the intensive care unit (median 5 vs. 0.5 days; $p < 0.0001$) and a longer stay in hospital (median 16 vs. 7 days; $p < 0.0001$) than ESG patients. OSR patients also had more complications (240 vs. 98; relative rate 2.72, 95% CI 2.04 to 3.68; $p < 0.001$). Overall, 58 (38.7%) ESG and 103 (76.3%) OSR patients experienced adverse events during the index procedure admission ($p < 0.001$).

Survival post procedure

During follow-up, 40 ESG and 36 OSR patients died, 17 and 25, respectively, from aneurysm-related causes. One-year overall survival rate was 82.5% (95% CI 75.2% to 87.8%) after ESG and 79.3% (95% CI 71.1% to 85.4%) after OSR (log-rank $p = 0.9918$). One-year aneurysm-related survival rate was 89.8% (95% CI 83.4% to 93.8%) after ESG and 87.7% (95% CI 75.9% to 89.1%) after OSR (log-rank $p = 0.1107$). There was a non-significant higher hazard of all-cause and aneurysm-related deaths for OSR patients (HR 1.27, 95% CI 0.78 to 2.09; $p = 0.332$; and HR 1.59, 95% CI 0.86 to 2.96; $p = 0.140$). The variables affecting survival were aneurysm location, age, NYHA class and time waiting for procedure.

Readmissions after discharge from index procedure

In the first 3 months after discharge, ESG patients were more likely to be readmitted; thereafter, readmission rates in both groups were similar. During follow-up, 40.7% of ESG and 31.9% of OSR patients

were readmitted ($p = 0.1398$). A similar pattern was observed for aneurysm-related readmissions. No readmissions were reported for rupture and one readmission was reported for dissection.

Post-procedure quality of life

For ESG, utility did not change over time, apart from a small decrease of −0.017 (95% CI −0.062 to 0.027) in weeks 0–6. For OSR patients, there was a substantial decrease in utility of −0.160 (95% CI −0.199 to −0.121; $p < 0.001$) up to 6 weeks. Otherwise, the difference in utility between the two procedures during follow-up for survivors was not significant. Women had a small increase in quality of life over time ($p = 0.029$), whereas men's quality of life did not change after 6 weeks. Current smokers and patients in higher NYHA classes had significantly lower quality of life throughout.

Direct comparison between groups suitable for both interventions

In total, 115 ESG and 35 OSR patients were considered suitable for both procedures. Despite the exclusion of patients who had contraindications to either treatment, important differences in baseline variables remained between the groups. Importantly, the age difference between the groups increased, with ESG patients a mean of 10.5 years older (95% CI 6.9 to 14.1 years older).

Survival and hospital readmissions

Eight (7.0%) ESG and three (8.6%) OSR patients died within 30 days of the procedure. The HR for OSR ranged from 0.87 to 1.43 for all-cause deaths and from 1.20 to 1.59 for aneurysm-related deaths; none was statistically significant. Hospital admission rates showed similar patterns to the full post-procedure cohort.

Post-procedure quality of life

Quality of life was available for 129 out of 150 patients, who completed a total of 548 questionnaires. The results of refitting quality-of-life models showed a larger decrease in quality of life for OSR patients throughout, which was significant across most models, but is likely to have been exaggerated by small-sample bias.

Health economic analysis

No formal comparative economic analysis was possible. However, an analysis of patients by arm showed that, on average, ESG procedures were more costly than OSR (£26,536, SD £9877, vs. £17,239, SD £8043) but incurred lower hospital costs (£7484, SD £7848, vs. £28,636, SD £23,083) and follow-up costs to 12 months (£6642, SD £11,927, vs. £15,989, SD £38,247). The main drivers of costs were the stents for ESG and hospital stays for OSR. The EQ-5D-5L scores in the OSR group were generally lower. At 12 months, the mean number of QALYs gained was, on average, 0.62 (SD 0.32) for ESG and 0.46 (SD 0.35) for OSR. VoI was, at most, £500,000.

Conclusions

The current literature comparing ESG and OSR is dated and of limited quality. The incidence of diagnosed CTAAs is low but may rise as the UK population ages, comorbidities become more prevalent and CT scanning becomes more prevalent. Patients have a high risk of death compared with the age-matched population, and have a range of comorbidities. With small aneurysms, the risk of rupture is low and monitoring with detailed cross-sectional imaging is appropriate, in addition to risk factor modification. Interventions often involve more than one aortic segment; 11.2% also require concomitant cardiac procedures and 4.6% require hybrid procedures. Recommending the type and the timing of intervention is challenging, but strong expert consensus is evident. The timing of intervention is driven primarily by aneurysm size and location, and intervention type is driven primarily by age, operative risk and presence of CTDs. Both ESG and OSR are successful in the medium term for carefully selected patients. Both interventions are expensive, but no cost-effectiveness comparison could be completed. The results indicate that a randomised trial is not feasible, and nor would such a study be of sufficient value in the UK.

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Strengths and weaknesses

The main strength of the Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study was the engagement of 30 centres that had specialist aortic aneurysm provision and rigorously applied research methods. The biggest limitations were the relatively small number of patients and, thus, the low power to detect differences in outcomes and limited adjustment for confounding.

Implications for service

1. The complex needs and relative rarity of CTAAs suggest that care may be best delivered by specialist centres with multidisciplinary teams.
2. For small aneurysms (4–5.5 cm in diameter) current strategies, including blood pressure management, optimal management of breathlessness and encouragement to reduce smoking and maintain an active lifestyle, appear to work well.
3. Larger aneurysms (≥ 6 cm in diameter) require intervention without long delays. Timing of intervention remains challenging, but should be discussed when aneurysms reach 6 cm in diameter if operative risk is low or moderate.
4. ESG and OSR are successful for carefully selected patients, based on age, sex, operative risk and aneurysm diameter.

Further research

1. More detailed analysis of diameter, length and volume of aneurysms, and other anatomical features, to refine decisions around when and how to intervene.
2. Definition of low-, medium- and high-risk patients within each intervention group.
3. Combine ETTAA and long-term routine electronic data to elucidate longer-term survival and hospital admissions and identify predictors of clinical outcomes and cost.
4. Establish a prospective registry, involving specialist centres, to record the outcomes of and predictors for ESG and OSR, allowing the longer-term follow-up of patients pre/post intervention.

Trial registration

This trial is registered as ISRCTN04044627 and NCT02010892.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 6. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction and background to the ETTAA study

Introduction

An estimated 1 in 10,000 patients per year is diagnosed with chronic thoracic aortic aneurysm (CTAA) of the arch or descending thoracic aorta.[1,2] Between 1999 and 2010, hospital admissions for thoracic aortic aneurysm increased from 4.4 to 9.0 per 100,000 inhabitants.[2]

Normal aortic diameter varies by aortic segment, gender, age and body mass index (BMI). An aneurysm is defined as a dilatation to one and a half times the normal size of the vessel. Generally, in the arch or descending thoracic aorta (DTA), aneurysms of diameters of ≥ 4 cm are considered abnormal. Without treatment, aortic aneurysms can continue to expand, usually 'silently', giving no symptoms until the point of dissection (when the aortic wall tears) or rupture. Either of these events is immediately life-threatening, and survival depends on timely diagnosis and intervention. A study of Routine Hospital Episode Statistics of patients in England admitted with a new diagnosis of thoracic aortic aneurysm between 2004 and 2011 reported a 6-month mortality rate among treated patients of 17.7% and among untreated patients of 30%.[3]

In an era of prevalent computerised tomography (CT) scanning, more cases of CTAA are being diagnosed early, offering the opportunity for planned intervention before any life-threatening event can occur. The Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study investigates the effectiveness of the current treatments available. This chapter outlines the nature of the condition and describes the available treatments and the evidence that currently guides clinical practice.

Pathology

Most aneurysms develop chronically, over several years. In the majority of patients, these are asymptomatic but occasionally they give rise to episodic chest or back pain. Severe pain or cardiovascular collapse may be a sign of rupture or dissection. Aneurysms can also occur acutely (i.e. within days) in the context of dissection of a normal-sized aorta, infection or trauma, but such situations fall outside the remit of this project.

Anatomical definitions and classifications

As shown in *Figure 1*, CTAAs are subdivided into ascending aortic, aortic arch and DTA aneurysms. Aneurysms may extend across both thoracic and abdominal segments, in which case they are classified as thoracoabdominal aortic aneurysms. The ETTAA study focuses on CTAAs of ≥ 4 cm in diameter in the arch, descending or thoracoabdominal aorta. Ascending aortic aneurysms are excluded because there is an established body of evidence supporting surgical repair, and no established endovascular treatment for comparison.[4]

Aneurysms do not always exhibit defined abrupt proximal and distal ends but instead have dilated aortic segments that extend into neighbouring segments. In some cases, most of the aorta or the entire aorta may be dilated to some degree, described as ectatic. Aneurysms in which the aorta has dilated evenly around its circumference are described as fusiform, whereas those in which the dilatation is predominantly on one side of the aorta are described as saccular. Thus, aortic dilatation can have diverse patterns, for various reasons. The different pathological features of the aneurysm influences treatment decisions and, therefore, patient outcomes.

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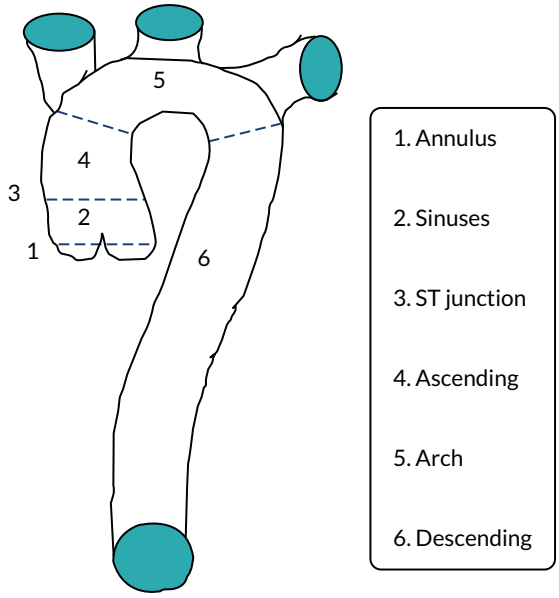

FIGURE 1 Diagram illustrating sections of the thoracic aorta. ST, sinotubular.

Aetiology

Chronic thoracic aortic aneurysm occurs because the aortic wall is in some way abnormal and cannot withstand the normal stresses exerted by the blood pressure. In approximately 80% of CTAAs, the abnormality in the aortic wall is secondary to atherosclerotic plaques, which in turn are associated with smoking, hypertension, hyperlipidaemia and obesity.[5] In the remaining 20% of cases there is a genetic defect in some structural component of the aortic wall, so that it is weaker and dilates in response to normal stresses. Examples include mutated *FBN1* (fibrillin 1 gene), causing Marfan syndrome, and mutated *TGFBR2* (transforming growth factor beta receptor 2 gene), causing Loeys–Dietz syndrome.[6,7] The underlying cause of CTAA is important, as this can direct treatment. For example, in cases of genetically mediated aneurysm, current opinion is that the 'normal' aortic wall above and below the aneurysm, which are landing zones for the stent graft, will continue to dilate and lead to migration of the stent and endoleak, and so surgery is generally preferred. As individual genetic disorders are rare, we grouped them under the umbrella term 'connective tissue disorders' (CTDs).

Presentation and diagnosis

Most aneurysms of the arch or DTA are identified incidentally (on a scan for some other reason), or via screening if CTDs are suspected. Once an aneurysm is detected, monitoring of its progression requires repeated CT imaging or magnetic resonance imaging (MRI), which incurs radiation exposure and a significant cost. Longitudinal surveillance, although limited to small numbers of patients and studies,[8,9] suggests that some aneurysms (whatever their size at diagnosis) appear quiescent, without growth for a prolonged period of time, whereas others progress precipitously. Genetic, acquired and pathological features may increase the rate of growth, but the evidence for this is sparse.

Management

Treatment options

In the case of patients with smaller aneurysms, those who are less fit to undergo chest surgery or endovascular intervention or those who reject such interventions, treatment is confined to lifestyle modification advice (smoking cessation and dietary management) and medical management of

hypercholesterolaemia and hypertension. In the ETTAA study, these non-intervention patients are described as either watchful waiting (WW) or conservative management (CM) patients (see *Chapter 3*). WW patients are monitored with serial (usually annual or biennial) CT or MRI scans with a view to future intervention should the aneurysm grow beyond the intervention threshold. CM patients either are considered to be at very high risk of life-threatening complications from intervention, despite having an aneurysm that is above the guideline thresholds for intervention, or have rejected potential interventions. In such patients aneurysm monitoring may decrease or stop altogether.

As aneurysms grow and the risk of fatal complications such as rupture or dissection increases, two main interventions are available: endovascular stent grafting (ESG) and open surgical repair (OSR).[10]

Open surgical replacement describes procedures in which the chest cavity is opened in order to replace the diseased aortic segment, usually with woven prosthetic tube grafts. Most cases of OSR require cardiopulmonary bypass to support or reroute blood flow while the aorta is operated on. The arch and DTA give rise to important branch arteries to the head, neck, upper limbs and spine and so OSR carries a risk to these organs when the blood supply is interrupted. This risk is usually mitigated by the use of hypothermia and cardiopulmonary bypass. As the mainstay of treatment for CTAAs for over four decades, OSR has been demonstrated to reduce mortality and can be performed reproducibly in cardiac surgical centres.[11,12] Techniques have improved, but OSR still carries a risk of mortality of around 5% and of paraplegia of around 10%.[13]

In ESG, a covered stent or frame (stent graft) is inserted into the arterial system at a peripheral access point (usually the femoral artery in the groin) and guided using X-rays to the aneurysm site. At the target segment, the stent springs open and fixes to the normal aorta above and below the aneurysm, so that the aneurysm is sealed and blood flows through the stent graft. The aneurysm outside the stent graft has no flowing blood and clots; thus, it is excluded from the circulation and the risk of rupture is very low. ESG for CTAAs is a more recent and less invasive technique, with reported risk of in-hospital mortality of 2–10%. It is technically feasible in many patients and excludes the aneurysm from the circulation, with shrinkage or stabilisation of the aneurysm sac in most cases, at least initially. Unfortunately, the procedure cannot be performed in all patients because it has specific anatomical requirements. It is resource intensive, as the stent grafts themselves are expensive, and it requires a hybrid theatre and an appropriate theatre team, but it does lead to a shorter length of stay and usually faster recovery. In the long term, patients who receive ESG need to be monitored as there may be leakage around/between stent components that requires urgent reintervention.

For some patients a hybrid procedure, including both stent components and surgical components, is necessary. For example, a minor surgical procedure may be completed in the patient's neck to protect the cerebrovascular blood supply after arch stenting, thereby facilitating the endovascular placement of a stent into the arch of the aorta. When the ETTAA study began, these hybrids were most prevalent, and such patients were intended for the ESG arm, as the stent graft was considered (clinically) the predominant intervention. Alternatively, an endovascular stent may be placed into the DTA at the same time as the arch is replaced in an open surgical procedure. During the ETTAA study, these approaches became more prevalent when a hybrid graft became available. The hybrid graft is half surgical prosthesis–half stent and is inserted during open surgery, with the patient usually undergoing median sternotomy. In such cases the surgery is the predominant procedure, so these hybrid patients were placed in the OSR arm of the study.

Treatment decisions

Endovascular stent grafting and OSR are considered for arch/DTA aneurysms when the risk of rupture/dissection or death exceeds the risks associated with intervention. Risk of rupture is mostly determined by aneurysm size, measured using CT or MRI.[14,15]

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When the ETTAA study launched in 2014, clinical practice was informed by the 2010 American Heart Association guidelines for the diagnosis and management of thoracic aortic disease[16] and the 2014 European Society of Cardiology Guidelines on the diagnosis and treatment of aortic diseases.[17] These guidelines were written by international panels of clinical experts, based on the available evidence. The American guidelines advised that operative treatment was reasonable for patients at low operative risk who had an arch aneurysm of > 5.5 cm in diameter. The level of evidence supporting this recommendation is classified as 'B – multiple non-randomised studies of surgery versus conservative management' in the hierarchy of evidence.[18] The European guidelines advised that an endovascular procedure ought to be considered in patients for whom it was technically feasible, but that, if surgery (OSR) were the only option, then it should be planned *after* the aortic diameter reached 6.0 cm. The level of evidence for the European guidelines was classified as 'C – consensus of opinion of the experts and/or small studies, retrospective studies, registries' in the hierarchy of evidence.[18] The main body of evidence considered by both committees came largely from data obtained from Yale University publications,[19,20] alongside data from the American International Registry of Acute Aortic Dissections (IRAD) database[21] and, to a lesser extent, the European German Registry for Acute Aortic Dissection Type A (GERAADA) data set[22] and the International Aortic Arch Surgery Study Group's ARCH projects.[23] Analysis of the Yale registry of acute aortic dissections and ruptures indicated that the risk of life-threatening dissection or rupture dramatically increases at a diameter of 6 cm and outweighs the 5–10% risk of death, stroke or paralysis from procedural intervention.[19,20,23]

Taking the two guidelines together, and especially considering that many patients requiring arch surgery may not be considered at 'low surgical risk', the general practice in the UK in 2014 was to consider intervention with OSR or ESG when an arch/DTA aneurysm became > 6 cm in diameter.[16,17] Clinical opinion at the start of the ETTAA study is explored more comprehensively in *Chapter 2*, but it is useful to state here that the risks of intervention are influenced by a variety of factors and are different for every patient. At present, there are no national or international guidelines addressing patient selection for WW, CM, ESG or OSR. In the absence of such guidelines, specialist multidisciplinary teams (MDTs) play a key role in assessing the risk–benefit profile of each patient before recommending a treatment pathway (*Figure 2*). Ultimately, the choice of treatment is made by the patient after appropriate explanation and discussion.

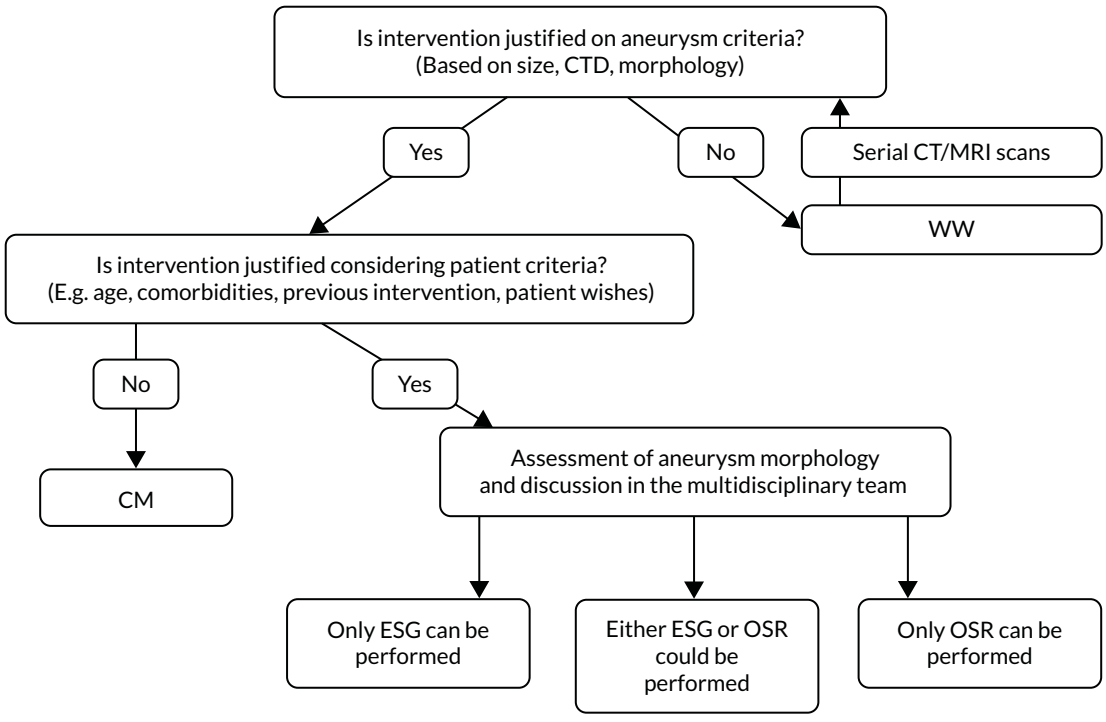

FIGURE 2 Multidisciplinary team decision-making process for treatment for CTAAs.

Natural history of arch/descending thoracic aorta aneurysms

To determine the benefits and effectiveness of intervention for arch/DTA aneurysms, it is necessary to understand what would happen without intervention. Unfortunately, contemporary studies of the natural history of CTAAs are rare. The most up-to-date analysis of this disease comes from the Yale registry and was published in 2015.[24] With aneurysms of > 6 cm in diameter, the Yale group suggests that the annual risks of dissection, rupture and death are 3.6%, 3.7% and 10.8%.[19] There is, however, increasing evidence that aneurysm diameter is not the only important predictor of risk; a 2011 review of the IRAD database showed that 60% of patients with arch/DTA dissections had aortic diameters of < 5.5 cm at the time of dissection, *below* the accepted threshold for intervention.[25] After aortic size, presence of CTDs and aneurysm growth rate have been associated with an increased risk of aortic dissection/rupture, along with chronic obstructive pulmonary disease (COPD), hypertension and older age. All of these factors must be considered when judging the relative risks and benefits of management options.

Mean aortic arch growth rates have been reported in the range 0.09–0.56 cm per year, and mean DTA growth in the range 0.12–1.44 cm per year. Rare reports of regression of DTA aneurysms (up to 0.12 cm per year) were confined to cases of chronic dissection where thrombosis in the layers of the aortic wall accounted for the shrinkage.[26–28] Key factors that have been associated with aneurysm growth include aneurysm size, patency and size of the false lumen, number and location of tears around the arch, peak wall stress, comorbidities (hypertension, CTD, COPD), patient characteristics (age, sex, smoking history) and anticoagulant treatment. Owing to a lack of high-quality, consistently-recorded data, no large-scale multivariate regression analysis has been possible and no clear relationship between the risk factors and growth rate has emerged.[8] Two studies have generated prediction models for future aneurysm size using initial diameter and based on single-centre data; neither has been validated in a prospective clinical cohort.[29,30]

Outcomes following intervention

Systematic review of outcomes

As part of the ETTAA study, a systematic review was conducted in January 2016 to assess the available evidence regarding the effectiveness of ESG compared with OSR for CTAA in the aortic arch or DTA. The review protocol was registered in the PROSPERO database (CRD42017054565)[31] and details can be found in the published article.[32]

Briefly, no randomised studies comparing ESG and OSR have been published. Cohort studies and case–control studies matched on key outcomes were included if patients had elective treatment for arch/DTA aneurysms and some attempt had been made to adjust for selection bias. Five comparative cohort studies met the inclusion criteria, reporting a total of 3955 ESG and 21,197 OSR patients. In accordance with the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool,[33] one study was judged to be at moderate risk of bias[34] and the remaining four were judged to be at severe risk of bias because of the potential for confounding.[35–39] Early mortality rates (30 days or to discharge) ranged from 3.1% to 6.1% after ESG and from 1.5% to 20% after OSR, with extreme rates arising from small studies. The meta-analysis of unadjusted short-term all-cause mortality favoured ESG [odds ratio 0.75, 95% confidence interval (CI) 0.55 to 0.1.03]. Adjusting for heterogeneity between small and large studies, the odds ratio did not change substantially (0.71, 95% CI 0.51 to 0.98). Meta-analysis of long-term all-cause mortality could not be carried out owing to differences in how results were reported. Overall, the long-term mortality was higher for ESG in larger studies and higher for OSR in smaller studies. For example, in von Allmen *et al.*'s study[36] of 618 patients, the hazard ratio (HR) for ESG relative to OSR up to 5 years, adjusting for age and sex, was 1.45 (95% CI 1.08 to 1.94; $p = 0.013$). Conversely, the Gore TAG study of 234 patients reported identical survival of 63% to 5 years for the

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two groups (log-rank $p = 0.625$),[35] and the study of 28 patients by Piffaretti *et al.*[39] reported higher (non-significant) long-term survival with ESG. Freedom from reinterventions in the long-term also favoured OSR.

Overall, studies reporting short-term non-fatal complications suggested fewer events following ESG, although limited data prevented meta-analysis (*Table 1*).[35–39] However, Hughes *et al.*'s 2014 study[38] of 8967 patients reported lower odds of neurological complications (odds ratio 0.48, 95% CI 0.26 to 0.86; $p = 0.015$), pulmonary complications (odds ratio 0.38, 95% CI 0.21 to 0.67; $p = 0.001$) and cardiac complications (odds ratio 0.24, 95% CI 0.15 to 0.37; $p < 0.001$) for ESG patients. The Gore TAG study[35] reported a substantial endoleak rate for ESG patients of 8.5%.

Although this systematic review was, to our knowledge, the first to consider evidence from non-randomised studies directly comparing ESG and OSR for treatment of elective arch/DTA aneurysms in CTAA patients, it identified increasingly dated evidence only, and this was limited by either small size or severe risk of bias. The conflicting evidence reinforced the need for updated evidence on UK practice and comparisons of short- and long-term outcomes of ESG and OSR.

Additional important studies reporting outcomes

Five relatively large, recent cohort studies[40–44] reported clinical and cost outcomes but were not eligible for the systematic review because of the inclusion of a heterogeneous cohort. All five studies acknowledged important differences between ESG and OSR cohorts, which resulted in biased comparisons. ESG tended to be chosen for older patients with more comorbidity, many of whom may have been unsuitable for OSR. Despite this, the risk of death, paraplegia or other complications

TABLE 1 Short-term complications in published studies eligible for the meta-analysis

Complication	Number (%) of events					
	Gore TAG 2007[35]		Piffaretti *et al.* 2007[39]		Hughes *et al.* 2014[38]	
	ESG group ($N = 140$)	OSR group ($N = 94$)	ESG group ($N = 17$)	OSR group ($N = 11$)	ESG group ($N = 712$)	OSR group ($N = 8255$)
Neurological						
Paraplegia/paraparesis	4 (3)	13 (14)	NR	NR	NR	NR
Cerebral vascular accident	5 (4)	5 (4)	2 (9)	1 (12)	NR	NR
Neurological: unspecified	NR	NR	NR	NR	20 (2.8)	273 (3.3)
Respiratory						
Respiratory failure	5 (4)	19 (20)	NR	NR	NR	NR
Pneumonia	NR	NR	2 (12)	3 (27)	NR	NR
Pulmonary: unspecified	NR	NR	NR	NR	17 (2.4)	462 (5.6)
Cardiac						
Myocardial infarction	0 (0)	1 (1)	0 (0)	1 (9)	NR	NR
Cardiac: unspecified	NR	NR	NR	NR	28 (2.9)	1252 (15.2)
Other						
Endoleaks	12 (8.5)	NR	NR	NR	NR	NR
Peripheral vascular disease	20 (14)	4 (4)	NR	NR	NR	NR

NR, not reported.

appeared to be lower after ESG than after OSR. Conversely, the need for reintervention was greater after ESG as a result of technical failures of the stent over time, and with each reintervention there was an added risk of complication owing to either the increased complexity of the procedure or the deteriorating health of the patient. One UK[44] and one US[41] study compared the costs of ESG against those of OSR procedures in the context of CTAAs. Both studies found open surgery to be more expensive by approximately US$6700 and £1650, but they considered in-hospital cost only, excluding reintervention. No formal economic evaluation has been performed. Therefore, there is a lack of economic data to guide decision-makers in allocating the scarce resources available.

Relationship with abdominal aortic aneurysms

Because aneurysms in the abdominal aorta are more prevalent, the evidence base for intervention with both endovascular aneurysm repair (EVAR) and open surgery is stronger for abdominal aortic aneurysms (AAAs). In particular, the EVAR-1 randomised clinical trial (RCT) compared these techniques, initially showing a significant but short-lived benefit for the patients receiving EVAR. At the end of 15 years, the effect was reversed, with a significant advantage in overall survival for those who had received OSR, because of late complications and rupture in the EVAR group. Based on cost-effectiveness analysis of EVAR compared with open repair, draft guidelines for aneurysm repair from the National Institute for Health and Care Excellence (NICE), published in 2018,[45] concluded that EVAR is not cost-effective and should not be used in fit or unfit patients with a non-ruptured aneurysm. After unprecedented stakeholder concern and intervention from NICE, the guidelines were revised and finally published.[46] The guidelines state that 'where open surgical repair can't be carried out – for example because of medical or anaesthetic risks – EVAR can be considered'[46] (© NICE 2020 *NICE Publishes its Guideline on the Diagnosis and Management of Abdominal Aortic Aneurysms*. Available from www.nice.org.uk/news/article/nice-publishes-its-guideline-on-the-diagnosis-and-management-of-abdominal-aortic-aneurysms. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication). However, cost-effectiveness is clearly an increasingly important issue, given increasing health-care costs, and studies that attempt to find cost-effective improvements are needed.

The ETTAA study

Both ESG and OSR are effective in some patients with CTAAs, but both are associated with significant complications. Currently, there is no consensus on either best management strategy or timing of interventions and there are no UK-specific economic studies that assess outcomes beyond the chosen procedure. Further evidence regarding the cost-effectiveness of ESG and OSR is needed, given the increasing demand for treatment (an ageing population with a rising prevalence of CTAAs)[2] and limited NHS resources. The relatively low incidence of aneurysms in the thoracic aorta means that the feasibility of a trial is unclear. Therefore, the ETTAA study was designed as an observational study to document current practice in the management of CTAAs of the arch/DTA in the NHS, and to compare the clinical effectiveness and cost-effectiveness of the available treatment strategies, adjusting for selection bias.

Aims of the ETTAA study

The overall aims of the ETTAA study are to describe the pathways undertaken by current NHS patients who are diagnosed with CTAAs, to estimate the natural history of patients prior to endovascular or open surgical procedures and to compare clinical outcomes and cost-effectiveness between the intervention groups.

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Specifically, we aimed to answer the following questions:

- Without procedural intervention for CTAAs, what is the risk of aneurysm growth, dissection, rupture, permanent neurological injury or death, and how does health-related quality of life (HRQoL) change over time?
- If a patient receives ESG or OSR, what is the risk of dissection, rupture, permanent neurological injury or death?
- What factors affect aneurysm growth pre intervention?
- Can aneurysm- or patient-related predictors of treatment outcomes be determined?
- What is the most cost-effective strategy in patients eligible for both ESG and OSR?
- What further research is required?

The report is organised as follows. *Chapter 2* reports a study of clinical expert opinion on the current management of CTAAs. *Chapter 3* provides an overview of methods employed in the ETTAA study and a description of the resulting cohort. *Chapters 4–7* describe the specific methods and results of the analysis of clinical and HRQoL outcomes (see *Chapter 4*), post-intervention clinical and HRQoL outcomes (see *Chapter 5*) and bias-adjusted clinical and HRQoL outcomes (see *Chapter 6*), and of the health economic analysis (see *Chapter 7*). *Chapter 8* provides a discussion of the results and implications for service and future research.

Chapter 2 Expert clinical views at the start of the ETTAA study

Introduction

The ETTAA study was designed to identify the strengths and weaknesses of established practice. An integral consideration when comparing the outcomes in different treatment groups is how patients are selected for treatment. This chapter reports on a consensus study that aimed to understand how aneurysm features and patient characteristics influence treatment decisions in the UK. The main objective was to understand when there is clinician consensus regarding appropriate treatment methods for patients with CTAAs according to predefined criteria, what thresholds for intervention are commonly adopted and when clinicians are in equipoise between different treatment methods and, therefore, further research is required.

Methods

Preparation of resources

An initial design period involved production of study resources, including assembling an expert panel, defining clinical criteria and designing the study questionnaire. Thereafter, the consensus study was carried out in two rounds, combining features of both the Delphi survey technique and the nominal group technique.[47] The Delphi technique uses questionnaires and anonymised responses from experts to identify consensus where it exists. The nominal group technique allows further refinement of consensus in a face-to-face meeting of the panel (the nominal group), where experts discuss reasons for their decisions with the group and have the opportunity to revise their decision. The two rounds are described in greater detail below. The initial Delphi survey was conducted during autumn 2015 and the nominal group technique meeting was held in January 2016.

Assembling the expert panel

Invitations to form an expert panel were sent to cardiothoracic and vascular surgeons, cardiologists, interventional radiologists and anaesthesiologists who participated in thoracic aortic MDTs at 29 UK centres recruiting patients to the ETTAA study. These centres had already been identified as having significant experience in managing patients with arch, DTA and thoracoabdominal aneurysms during recruitment to the ETTAA study. Respondents were specialists who had expertise and significant experience in open or endovascular surgery, or both.

Defining case scenarios

Vascular and cardiothoracic surgeons in the ETTAA team compiled a list of patient and aneurysm factors that they considered influential in making treatment decisions regarding CTAAs. Initially, more than 20 factors were identified. However, to include all possible combinations of factors and levels would generate many millions of case scenarios (cases). Although these combinations (case scenarios) allow granularity of the information obtained by the consensus exercise, the elicitation of all combinations would result in fatigue/disengagement of members of the expert panel and so was not feasible. Thus, comorbidities related to the risk of surgical intervention or the operative fitness of the patient were included under the umbrella term of 'high, medium or low risk of (open surgery) intervention'. After discussion, five characteristics with two to five levels remained (*Table 2*).

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TABLE 2 Clinical and patient characteristics used for defining 360 case scenarios

Characteristic	Level
CTD	Present
	Absent
Aneurysm location	Aortic arch
	DTA
	Thoracoabdominal aorta
Age (years)	< 65
	65–75
	76–85
	> 85
Aneurysm size (maximum orthogonal diameter in cm)	< 5.0
	5.1–6.0
	6.1–7.0
	7.1–8.0
	> 8.0
Risk of open surgery	Low
	Medium
	High

Questionnaire design

A total of 360 case scenarios were developed in a factorial design of the attributes given in *Table 2* and considered a good compromise between granularity and feasibility. These scenarios were grouped into six sections based on aneurysm location and presence or absence of CTD. The order in which experts completed the sections was randomised to minimise bias due to responder fatigue. The questionnaires were e-mailed to participants to be printed, completed and returned by post or e-mail.

Round 1: Delphi survey

For each clinical scenario, participants scored the 'appropriateness' of all four management options by indicating how strongly they considered each treatment option to be 'appropriate' on a scale of 1–9, where one represented 'not at all appropriate', five represented 'just appropriate' and nine represented 'most appropriate' (see *Report Supplementary Material 1* for an example of a completed Delphi survey). Experts were guided to score for all four treatment methods for each clinical scenario and to avoid just marking the most 'appropriate'. When an expert recorded 'most appropriate' for more than one management approach, this suggested equipoise for that expert.

When completing the scores, experts were asked to represent the opinion of their local multidisciplinary team as far as possible and to follow established definitions for clinical attributes. For each scenario, experts could assume that WW, CM, ESG and OSR were available, with no anatomical/morphological contraindications. 'Hybrid' interventions that included a component of conventional surgery as well as an endovascular stent graft were classified as OSR if they involved opening a body cavity (e.g. visceral artery bypass, re-implantation of innominate artery origin) and otherwise as endovascular repair (e.g. carotid to subclavian bypass through neck incision). No specific stipulations were given regarding methods of assessing the risk of intervention, but panel members were asked to follow local standard clinical practice.

Data analysis: round 1

The anonymised results of round 1 were summarised as medians, interquartile ranges and whole ranges using box-and-whisker plots. For example, *Figure 3* depicts the scoring for a clinical scenario with a median 'appropriateness' score of eight for OSR (range 4–9, interquartile range 7–9).

To assess disagreement and appropriateness (and, thus, define consensus) the Research ANd Development (RAND)/University of California Los Angeles appropriateness method was used.[48] This considers the dispersion of individual scores and identifies scenarios in which expert responses are clustered at either end of the 9-point Likert scale, so that consensus is evident. Fitch *et al.*[48] argue that in cases when agreement is good, the distribution of responses should be narrow, and in cases where there is disagreement, the distribution should be wider. The width of the distribution is measured by the range between the 30th and 70th percentile, known as the interpercentile range (IPR). However, Fitch *et al.*[48] found that, in general, the IPR required for disagreement was smaller when responses were symmetrical than when they were asymmetrical, with respect to the middle of the distribution. To overcome this, they developed the asymmetry-adjusted IPR (IPRAS), which includes a correction factor for asymmetry. In this method, disagreement between experts is concluded for the *i*th scenario if the IPR > IPRAS for that scenario, or, conversely, IPR ≤ IPRAS indicates consensus. Clinical scenarios for which consensus was demonstrated in round 1 were noted and these were not taken into round 2.

Round 2: nominal group technique

Round 2 was completed at a face-to-face meeting of the expert panel moderated by one of the investigators (SRV). For each clinical scenario entering round 2, 'appropriateness' scores of the treatment options from round 1 were displayed as box-and-whisker plots, as demonstrated in *Figure 3*. The expert panel was given 60 seconds to study each summary, after which a brief discussion was held in which individual experts explained the reasons for their treatment choice. The role of the moderator was to clarify ambiguities, ensure a balanced discussion, give everyone a chance to express their opinion to the group and explore reasons for divergent views. It was decided prospectively that each expert would be given a maximum of 60 seconds of uninterrupted time to express opinions. Experts were concise, discussions were constructive and curtailment by the moderator was never required. After each discussion, individual experts were asked to select their single most 'appropriate' management strategy or to indicate more than one treatment method if there was equipoise between them.

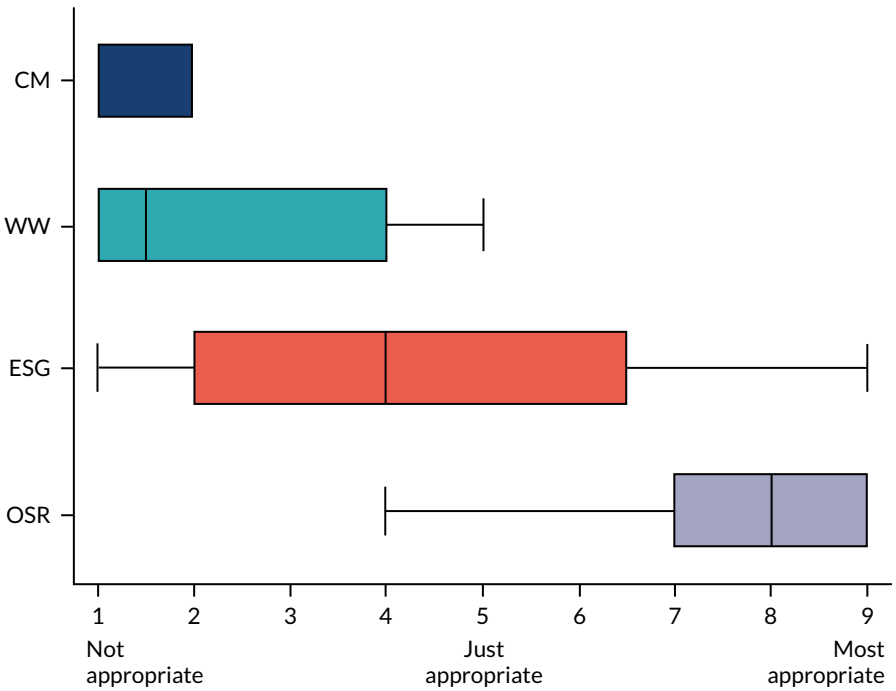

FIGURE 3 Example of round 1 results for one clinical scenario: aneurysm size of 7.1–8 cm in diameter, in the aortic arch, in a patient with no connective tissue disorder, aged < 65 years and of low surgical risk.

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Data analysis: round 2

In round 2 consensus was defined if the same management was chosen by ≥ 70% of participants; otherwise, there was no consensus. If there was no consensus, and ≥ 33% of participants thought that (the same) two management options were equally effective, equipoise about the choice of management was defined.

Results

Round 1: Delphi survey

Twenty experts from 13 centres returned round 1 scores. The expert panel consisted of an anaesthetist, an interventional radiologist, five cardiac surgeons and 13 vascular surgeons. Among the 360 scenarios considered, consensus was reached in 167 (46%) and the remaining 193 were discussed in round 2. The consensus achieved in round 1 was predominantly that WW was most appropriate for cases involving smaller aneurysms (< 6.0 cm in diameter), OSR was most appropriate for arch aneurysms in low-risk scenarios and ESG was most appropriate for DTA aneurysms in low- or medium-risk patients without CTDs.

Round 2: nominal group technique

Twelve experts, nine vascular surgeons and three cardiac surgeons took part in round 2, during which consensus was reached for a further 80 (22%) scenarios and equipoise between two different treatment modalities was noted for 34 (9%) scenarios, leaving neither consensus nor equipoise for a total of 79 scenarios (22%). Outcomes at the end of round 2 are presented in *Tables 3* (aneurysms of ≤ 6.0 cm in diameter) and *4* (aneurysms of > 6.0 cm in diameter).

Aneurysms of ≤ 6.0 cm in diameter (144 scenarios; see *Table 3*)

Watchful waiting was generally the preferred management for patients with aneurysms of ≤ 6.0 cm in diameter (110/144, 76% scenarios), regardless of the presence of CTDs or the location of the aneurysm (arch, DTA or thoracoabdominal). Notable exceptions, mainly for older patients, were:

- CM was preferred for most high surgical risk patients, aged > 85 years, for all aneurysm sites.
- OSR was preferred for patients with CTDs, with arch aneurysm of 5.0–6.0 cm in diameter and > 85 years of age, if at low or medium surgical risk.
- Equipoise was found between WW and OSR for older patients with CTDs and with low surgical risk and aneurysms of 5.1–6.0 cm in diameter.

No consensus was reported for 10% of the clinical scenarios in which aneurysms were of < 6.0 cm in diameter. This was mainly for low- to medium-risk patients aged > 85 years or patients with CTDs aged < 65 years.

Aneurysms of > 6.0 cm in diameter (see *Table 4*)

For patients with aneurysms of > 6.0 cm in diameter, clinical decisions were influenced by, in order, aneurysm site, surgical risk and age group, rather than by aneurysm size (see *Table 4*).

Aortic arch

In terms of aneurysms of > 6.0 cm in diameter experts favoured OSR over ESG in the arch, regardless of CTD status, for low- or medium-risk patients aged > 75 years, as well as for most low-risk patients aged ≤ 75 years. Clinicians were in equipoise between OSR and ESG for medium-risk patients aged 65–75 years with arch aneurysms of > 6.0 cm in diameter. There was uncertainty and a general lack of consensus about what to offer patients at high surgical risk, with the exception that experts generally preferred CM for high-risk non-CTD patients aged ≤ 75 years. There was also little consensus among experts on treatment for younger (aged < 65 years) patients at medium surgical risk (with or without CTD) or for younger low-risk patients with aneurysms of 6.1–7.0 cm in diameter.

TABLE 3 Final consensus for patients with aneurysms of ≤ 6.0 cm in diameter

Aneurysm site	Aneurysm size (cm)	Patient age (years)	No CTD			CTD		
			Low risk	Medium risk	High risk	Low risk	Medium risk	High risk
Aortic arch	< 5.0	< 65	WW	WW	WW	WW	WW	WW
		65–75	WW	WW	WW	WW	WW	WW
		75–85	WW	WW	WW	WW	WW	WW
		> 85	WW	No consensus	CM	WW	No consensus	CM
	5.1–6.0	< 65	WW	WW	WW	No consensus	No consensus	WW
		65–75	WW	WW	WW	WW	WW	WW
		75–85	WW	WW	WW	WW/OSR	WW	WW
		> 85	WW	WW	No consensus	OSR	OSR	WW
DTA	< 5.0	< 65	WW	WW	WW	WW	WW	WW
		65–75	WW	WW	WW	WW	WW	WW
		75–85	WW	WW	WW	WW	WW	WW
		> 85	No consensus	No consensus	CM	WW	CM	CM
	5.1–6.0	< 65	WW	WW	WW	No consensus	No consensus	No consensus
		65–75	WW	WW	WW	WW	WW	WW
		75–85	WW	WW	WW	WW/OSR	WW/OSR	WW
		> 85	WW	WW	WW	WW/OSR	WW/OSR	WW
Thoracoabdominal aortic aneurysms	< 5.0	< 65	WW	WW	WW	WW	WW	WW
		65–75	WW	WW	WW	WW	WW	WW
		75–85	WW	WW	WW	WW	WW	No consensus
		> 85	No consensus	CM	CM	WW	No consensus	CM
	5.1–6.0	< 65	WW	WW	WW	WW	WW	WW
		65–75	WW	WW	WW	WW	WW	WW/CM
		75–85	WW	WW	WW	WW	WW	WW
		> 85	No consensus	No consensus	CM	WW/OSR	WW	CM

Descending thoracic aorta

There was consensus that ESG should be offered to non-CTD patients with DTA aneurysms of > 6.0 cm in diameter. CM was recommended only for high-risk patients aged ≤ 65 years. There was little or no consensus on how to treat DTA aneurysms in CTD patients aged ≤ 75 years, although experts agreed that ESG should be recommended for older CTD patients at high operative risk. In general, for CTD patients, there was equipoise between ESG and OSR for those aged 75–85 years at medium surgical risk, and consensus for OSR for those aged > 85 years at low/medium surgical risk.

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TABLE 4 Final consensus for patients with aneurysms of ≥ 6.0 cm in diameter

Aneurysm site	Aneurysm size (cm)	Patient age (years)	No CTD			CTD		
			Low risk	Medium risk	High risk	Low risk	Medium risk	High risk
Aortica arch	6.1–7.0	< 65	No consensus	No consensus	CM	No consensus	No consensus	No consensus
	7.1–8.0		OSR	No consensus	CM	OSR	No consensus	No consensus
	> 8.0		OSR	CM/ESG	CM	OSR	No consensus	ESG/OSR
	6.1–7.0	65–75	OSR	ESG/OSR	No consensus	OSR	OSR	No consensus
	7.1–8.0		OSR	ESG/OSR	CM/ESG	OSR	ESG/OSR	CM/ESG
	> 8.0		OSR	ESG/OSR	CM	OSR	ESG/OSR	CM/ESG
	6.1–7.0	76–85	OSR	OSR	No consensus	OSR	OSR	No consensus
	7.1–8.0		OSR	OSR	ESG	OSR	OSR	No consensus
	> 8.0		OSR	OSR	No consensus	OSR	OSR	No consensus
	6.1–7.0	> 85	OSR	OSR	No consensus	OSR	OSR	No consensus
	7.1–8.0		OSR	OSR	No consensus	OSR	OSR	No consensus
	> 8.0		OSR	OSR	ESG/OSR	OSR	OSR	ESG
DTA	6.1–7.0	< 65	ESG	ESG	CM	No consensus	No consensus	No consensus
	7.1–8.0		ESG	ESG	CM	ESG	No consensus	No consensus
	> 8.0		ESG	ESG	CM	No consensus	No consensus	No consensus
	6.1–7.0	65–75	ESG	ESG	No consensus	ESG	ESG	No consensus
	7.1–8.0		ESG	ESG	ESG	No consensus	No consensus	No consensus
	> 8.0		ESG	ESG	ESG	No consensus	No consensus	CM/ESG
	6.1–7.0	76–85	ESG	ESG	ESG	ESG/OSR	ESG/OSR	ESG
	7.1–8.0		ESG	ESG	ESG	ESG	ESG/OSR	ESG
	> 8.0		ESG	ESG	ESG	OSR	ESG/OSR	ESG
	6.1–7.0	> 85	ESG	ESG	ESG	OSR	OSR	ESG
	7.1–8.0		ESG	ESG	ESG	OSR	OSR	ESG
	> 8.0		ESG	ESG	ESG	OSR	ESG/OSR	ESG

TABLE 4 Final consensus for patients with aneurysms of ≥ 6.0 cm in diameter (*continued*)

Aneurysm site	Aneurysm size (cm)	Patient age (years)	No CTD			CTD		
			Low risk	Medium risk	High risk	Low risk	Medium risk	High risk
Thoracoabdominal aortic aneurysms	6.1–7.0	< 65	No consensus	No consensus	No consensus	No consensus	No consensus	No consensus
	7.1–8.0		No consensus	ESG	ESG	No consensus	No consensus	No consensus
	> 8.0		No consensus	ESG	ESG	OSR	No consensus	No consensus
	6.1–7.0	65–75	No consensus	No consensus	No consensus	No consensus	No consensus	No consensus
	7.1–8.0		ESG	ESG	CM	No consensus	No consensus	No consensus
	> 8.0		ESG	ESG	CM/ESG	No consensus	No consensus	No consensus
	6.1–7.0	76–85	ESG/OSR	ESG/OSR	ESG	OSR	OSR	No consensus
	7.1–8.0		ESG/OSR	ESG/OSR	ESG	OSR	OSR	No consensus
	> 8.0		ESG/OSR	ESG	ESG	OSR	OSR	No consensus
	6.1–7.0	> 85	No consensus	ESG/OSR	ESG	OSR	OSR	CM
	7.1–8.0		OSR	ESG/OSR	ESG	OSR	OSR	CM
	> 8.0		ESG/OSR	ESG/OSR	ESG	OSR	OSR	CM

Thoracoabdominal aneurysms

There was no consensus on treatment for thoracoabdominal aneurysms of 6.1–7.0 cm in diameter for patients aged < 65 years, regardless of CTD status. For younger non-CTD patients (aged ≤ 75 years) with aneurysms of > 7.0 cm in diameter, ESG was often recommended, except for high-risk patients, for whom CM was considered. For older (aged > 75 years) non-CTD patients, ESG was supported for patients at high surgical risk, whereas both ESG and OSR were considered 'appropriate' for patients at low or medium surgical risk. For CTD patients aged ≤ 75 years, there was no consensus on 'appropriate' treatment. For older (aged > 75 years) CTD patients at low or medium risk, OSR was the treatment of choice, with the oldest high-risk patients considered suitable for CM.

Summary of findings

This chapter reports expert opinion among UK specialists regarding the most 'appropriate' management for 360 clinical scenarios relating to thoracic aortic and thoracoabdominal aortic aneurysms. Pathophysiology, natural history of disease, technical aspects relevant to open surgery and ESG are different between the aortic arch, DTA and thoracoabdominal aorta, so they need to be considered separately.

For patients with aneurysms of < 6.0 cm in diameter, there was clear consensus for WW in the majority of patient scenarios, including those in the arch and irrespective of the presence or absence of CTDs. This differs from ascending aortic aneurysms, for which the threshold for surgical intervention in

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CTD patients is lower (5.0 cm) than for non-CTD patients. This may reflect the fact that surgical repair of the ascending aorta can be offered with much lower operative risks than arch repair.

For larger aneurysms in the aortic arch, OSR was the treatment of choice in older patients provided that operative risk was acceptable, but there was little consensus among experts on the management of younger patients or high-risk patients. Aneurysms of the arch pose particular challenges for ESG as multiple cerebral emboli are associated with the use of endovascular stents and, therefore, there is a high risk of stroke.[49,50] Thus, OSR was preferred in the majority of cases where intervention was considered 'appropriate'.

Conversely, there was consensus that ESG should be offered to patients with DTA aneurysms of > 6.0 cm in diameter. This is unsurprising given that the risk of paraplegia is significantly lower with ESG than with OSR and that the DTA procedure is more straightforward than ESG in the arch. Experts also recorded consensus for ESG for large aneurysms in the DTA in CTD patients at high operative risk, despite conventional 'wisdom' that implanting stents in the intrinsically weak aortic tissue of CTD patients should be avoided.[51–53]

For the oldest patients, CTD played an influential role in decisions. Clinicians tended to prefer intervention for smaller aneurysms in patients with CTDs, possibly because of concerns that complications are seen with aneurysms of smaller diameters in this population. The presence of CTDs poses a particular threat to the durability of ESG, compared with absence of CTDs.[54] The consensus reflects a reluctance to use ESG in patients with CTD, particularly in younger and lower-risk cohorts. However, the anatomical features of the DTA conferred a consensus for ESG, even in the presence of CTDs, especially if operative risk was high.

Thoracoabdominal aneurysms are currently treated by ESG in anatomically suitable patients.[55] A consensus for the use of this technique was noted for patients without CTD, with OSR remaining the preferred choice in the majority with CTD.

Unsurprisingly, our findings are in line with recommendations in previously published guidelines,[17] but they provide greater detail. They also reflect the importance of aneurysm diameter in the timing of intervention, the perceived benefits of endovascular techniques and the consequences of CTDs.

Our study has some methodological limitations. During study design, we could not identify an objective, widely understood measure of surgical risk. Decisions relied on each participant's perception of surgical risk category, which may have differed between experts, particularly if they were from different centres or surgical specialties. The methods require us to categorise patient and aneurysm characteristics, but each patient and aneurysm repair might be considered unique, and we were not able to capture all important aspects affecting management decisions. In addition, we did not include aneurysm growth rate as an indication for operation because it would have greatly increased the number of clinical scenarios and growth cannot always be distinguished from random variation in aneurysm measurement. Although we drew participants from as wide a range as possible, all experts practised at UK NHS centres, and worked in multidisciplinary teams that included open surgical and endovascular expertise. Consensus was based on 12–20 participants who may not fully represent their local practice. Analysis of the empirical data from the ETTAA study will demonstrate how closely UK clinical practice aligns with the reported consensus in this study.

One reason for undertaking an early Delphi study was to identify patients for whom clinicians have equipoise between ESG and OSR. Perceived equipoise was found in only a few scenarios by our definition, although we stress that the study is based on practice reported by experts rather than on more objective data. The size of patient groups for which there is equipoise is also unclear. *Chapters 3–7* report analysis of CTAA patient management in the NHS, both before and after undergoing a procedure.

Chapter 3 Cohort construction, data and study management and general methods

Introduction

In this chapter we describe the methods for constructing the ETTAA cohort and provide an overview of the design and analysis of planned work packages. The methods for each work package are described in greater detail in the relevant chapters. We also describe the main characteristics of recruited patients and their procedures. We stress here that the ETTAA study was designed as an observational study and we did not intervene in routine practice; rather, we describe management strategies and outcomes for existing patients. As with any observational study, biases can arise from measured and unmeasured confounders, informative dropouts, missing data and other selection strategies; our emphasis is on accommodating biases in the analysis as far as possible and on acknowledging residual bias in results where necessary.

Aims of the project overall

The overall aims of this project are to describe the pathways undertaken by current NHS patients who are diagnosed with CTAA, to compare outcomes between the main treatment groups using modern methods for addressing the biases inherent in non-randomised studies, and to provide inputs for a health economics model.

The specific questions are listed in *Chapter 1*, along with planned work.

To meet the aims of the ETTAA study, we had the following objectives:

- to follow patients with CTAA, prospectively recording management, patient characteristics, clinical events, HRQoL and use of health and social services throughout the duration of the study
- to quantify clinical outcomes in each management cohort (WW, CM, ESG, OSR) in terms of survival, clinical events and quality of life
- to identify patient-specific or aneurysm-specific features that might predict poor outcome in each treatment group by risk-modelling methods
- to estimate the clinical effectiveness and cost-effectiveness of competing treatments to define optimal management strategies for patients in whom more than one treatment is considered appropriate.

Methods

Inclusion and exclusion criteria

Inclusion criteria

Included patients were those aged ≥ 18 years presenting to an NHS hospital with an existing or a new CTAA in the arch or DTA of a diameter ≥ 4 cm (including aneurysms secondary to atherosclerotic degeneration, after acute dissection and secondary to aortopathy). Patients were eligible as long as they had not undergone intervention for the index aneurysm. If a patient had already received treatment for an aneurysm on a different part of the aorta (e.g. ascending, abdominal), then that patient was eligible. The arch was defined as between the brachiocephalic artery and the left

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subclavian artery. The DTA was defined as between the left subclavian artery and the coeliac axis. If the aneurysm of maximum diameter was located in the thoracoabdominal aorta (21 patients), then the patient was included if the index aneurysm in the DTA was ≥ 4 cm in diameter. If the DTA and arch both had aneurysms of the same size, the aortic arch was considered to be the location of the maximal aneurysm size.

Exclusion criteria

Patients were excluded if they were unable or unwilling to give written informed consent, were suffering from acute dissection or malperfusion syndromes (e.g. myocardial infarction, acute stroke or limb ischaemia) or had had a previous intervention for the same aneurysm.

Setting

All NHS hospitals that treat or manage patients with CTAA in a MDT setting or specialist clinic were eligible to participate in the study.

Patient and centre recruitment

Centres were recruited after completion of a feasibility questionnaire confirming that they treated patients with CTAA by ESG, OSR or both. In addition, hospitals that cared for patients using WW or CM were eligible to participate if they referred patients for intervention to a centre also participating in the ETTAA study. The initial intention was to recruit 8–10 large centres but, owing to slow recruitment, it became necessary to open the study to 30 hospitals.

Patient eligibility for the study was assessed either in a MDT setting or in a specialist clinic at participating centres. Eligible patients were enrolled, and consent to collect and retain the patient's data was taken by local research personnel. Consent was obtained face to face or by post/telephone with the consent form posted to the research team.

Study groups

Patients were divided into four groups, depending on the planned management at the time of recruitment:

1. WW – patients with smaller aneurysms at low risk of rupture who were not expected to undergo a surgical or endovascular procedure as part of the current management plan, but for whom these interventions may be a future option should the aneurysm expand.
2. CM – patients with aneurysms of a size where risk of rupture is significant, who were not expected to undergo a surgical or endovascular procedure as part of the current or future management plan due to patient choice, comorbidities or procedural risk.
3. ESG – patients for whom the risks around intervention were considered lower than the risks of rupture, who were referred to a vascular surgeon for aneurysm repair.
4. OSR – patients for whom the risks around intervention were lower than the risks of rupture, who were referred to a cardiac surgeon for aneurysm repair.

During the study some patients transferred between groups, particularly from WW to active intervention (ESG or OSR), so that the final analysis was based on the numbers of patients in each group at end of the study period, with the exception of the analysis of aneurysm growth rates (see *Chapter 4* for more details).

Management and interventions

Watchful waiting

Watchful waiting patients with aneurysms considered 'below threshold' for intervention were treated with lifestyle modification advice (smoking cessation and dietary management) and medical management

of hypercholesterolaemia and hypertension. Patients underwent surveillance of the aneurysm (by CT or MRI scans at intervals chosen by the local team) and MDT review (as per local practice).

Conservative management

Conservative management included lifestyle modification advice (smoking cessation and dietary management) and medical management of hypercholesterolaemia and hypertension. CM prohibited any endovascular or open surgical procedure. In this group, features of the aneurysm would have normally triggered intervention, but patient-related features (including comorbidities or patient choice) prohibited it; thus, CM is different from WW.

Endovascular stent grafting

Endovascular stent grafting included any endovascular repair of the aneurysm via transluminal introduction of a stent graft under X-ray guidance. It included any primary endovascular procedure comprising a combination of a conventional surgical component and a transluminal repair (described as a hybrid procedure in some publications). It was completed by a vascular surgeon or an interventional radiologist, usually in a 'hybrid' theatre equipped with an imaging scanner intensifier (with a fixed C-arm). It could also be performed in a catheter laboratory or surgical theatre with a mobile C-arm. It excluded open procedures via sternotomy or thoracotomy.

Open surgical replacement

Open surgical replacement comprised replacement of the aneurysmal aorta with a prosthetic conduit, requiring sternotomy or thoracotomy with circulatory support. OSR was completed in a surgical theatre by a cardiac or vascular surgeon. It also included cases where an adjacent segment of aorta was stabilised by implanting a stent at the time of surgery, through the surgical incision.

Hybrids

A hybrid treatment means that the intervention has both stent and surgical components (see *Chapter 1* for examples). Where surgery involved only a minor incision, for example to guide stent placement, ESG was the predominant procedure, and these patients were included in the ESG group. Where the hybrid graft was half surgical prosthesis-half stent, inserted during open surgery involving median sternotomy, surgery was the predominant procedure and these patients were included in the OSR group.

Populations

Patient group allocation at recruitment

Once consented, patients took one of two typical pathways depending on whether or not an intervention had been planned and a date of procedure fixed. At recruitment, patients were assigned to CM by the recruiting centre if future management was not expected to involve an intervention, or to WW if future management could include an intervention but further imaging was to be completed before any procedure was planned. These patients entered a non-intervention period, during which baseline characteristics, medical history and HRQoL were recorded at the point of consent and at follow-up visits planned at 3, 6, 12, 18, 24, 36 and 48 months while the patient remained in the non-intervention period. Each patient had either a CT or MRI scan to measure aneurysm size at baseline, and this was then repeated according to local management protocols, expected to occur approximately once per year.

Patients who had a known date of intervention at recruitment were assigned to the ESG or OSR group by the recruiting centre. For patients in the OSR or ESG group an additional assessment was undertaken at 1 month post intervention, with all other measurements taken at the same stages as for WW and CM patients. Procedure data, important complications, subsequent hospital admissions and serious adverse events (SAEs) were recorded by the participating centres as they occurred.

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Crossover between groups

Owing to the observational nature of the study, patients switched groups according to local centre management protocols. Patients switching from WW to an intervention group were analysed as part of the non-intervention period up to the date of the procedure. Thereafter, patients entered a post-intervention period, with the timing of follow-up reset so that time zero was the date of the procedure to align with those who went straight to procedure.

Planned analyses

In accordance with the protocol, six work packages were planned to:

1. model aneurysm growth in WW and CM patients during the non-intervention period
2. quantify clinical outcomes within each treatment group (CM, ESG, OSR) and to assess the risk factors for each
3. compare propensity score-matched patients from each treatment group to estimate clinical effectiveness for patients in whom more than one treatment is appropriate
4. estimate cost-effectiveness of competing treatments to define optimal management strategies for patients in whom more than one treatment is considered appropriate
5. assess the subjective level of agreement among experts regarding best management for hypothetical patients using a RAND–Delphi exercise (see *Chapter 2*)
6. analyse aneurysm growth data from Yale University in collaboration with Professor John Elefteriades.

Amendments to the work packages

Work package 6 was not completed as initial analysis showed that the database included only 23 scans in 11 patients who satisfied the ETTAA study inclusion and exclusion criteria. This work package is not discussed further. For other work packages, aneurysm measurements were completed in sufficient numbers at only four locations (ascending, arch, descending thoracic and thoracoabdominal). Other locations are not reported in this monograph. See *Report Supplementary Material 2* for a full list of protocol amendments and *Report Supplementary Material 3* for a list of departures from the original protocol.

Outcomes

The primary and secondary outcomes for work packages 1–5 are listed briefly below with definitions.

1. Primary: aneurysm diameter in the aortic arch and DTA. Secondary: survival, time to intervention, clinical complications and HRQoL. Exploratory: aneurysm diameter in the ascending aorta and the thoracoabdominal aorta.
2. Primary: survival. Secondary: clinical complications, reinterventions, re-admission and HRQoL.
3. Primary: survival. Secondary: complications, reinterventions, re-admission, length of stay and HRQoL.
4. Primary: incremental cost per QALY gained. Secondary: HRQoL.
5. Primary: expert opinion on best treatment for any given theoretical patient scenario.

Definitions of outcome measurements

Aneurysm diameter

Study centres were asked to provide a copy of the chest CT or MRI radiological scan conducted closest to the time of recruitment to the ETTAA study (baseline scan) and the accompanying report needed to confirm that the patient had an eligible aneurysm of ≥ 4 cm in diameter. Centre co-ordinators were then asked to provide copies of any additional scans during patient follow-up. Note that all CT/MRI scans were conducted as part of routine care and, therefore, neither the timing of the scan nor the

scan request itself was determined by participation in the ETTAA study. CT/MRI scans were anonymised and sent on DVD (digital versatile disc) to St George's Hospital (London) or Royal Papworth Hospital Core Laboratory for the measurement of aortic diameters (in centimetres) to ensure that differences between multiple radiographers, hospitals and measurement techniques were minimised. In the original plan St George's was to measure all scans but, owing to staffing issues, scans not analysed at the end of recruitment (30 June 2018) were transferred and analysed at Royal Papworth Hospital. A standard protocol was agreed and CT scan measurements at both centres were made using the same 3mensio (Pie Medical Imaging BV, Maastricht, the Netherlands) software (see *Report Supplementary Material 4* for the scan measurement protocol). A total of five operators analysed CT scans [two at St George's Hospital ($n = 269$ scans) and three at Royal Papworth Hospital ($n = 1268$ scans)]. All MRI scans were measured at Royal Papworth Hospital by two radiology consultants ($n = 125$). If neither core laboratory nor co-ordinating centre analysis was available, measurements were taken from the scan results provided by the participating hospital ($n = 70$). Although published evidence suggested that results from CT and MRI were comparable, statistical analyses of scan diameters were adjusted for scan modality.[56]

Survival time in the non-intervention period

This was the time between the date of recruitment and the date of death or censoring. Patients were censored at date of the procedure or withdrawal or the last patient follow-up if any of these preceded death. The date and cause of death were reported by the participating centre.

Survival time in the intervention period

This was the time between the date of the procedure and the date of death or censoring. Patients were censored at withdrawal or on the date of the last post-procedure follow-up if this preceded death. The date and cause of death were reported by the participating centre.

Procedure-related data

For all interventions on the ascending, arch, DTA or thoracoabdominal aorta, the dates of admission, intervention and discharge, details of operative and postoperative care and clinical outcomes between admission and discharge were recorded by local centre staff from hospital medical records.

Time to intervention

This was the time interval between the date of recruitment and the date of the intervention.

Length of hospital stay for the index procedure

This was the interval in days between date of the index procedure and date of discharge from hospital or transfer to a non-hospital setting (e.g. a care home). This was separated into intensive care unit (ICU), high-dependency unit (HDU) and ward stay.

Clinical complications

All clinical complications related to the aneurysm or interventions were collected by centre staff from hospital records during the initial and follow-up hospital admissions, including myocardial infarctions, gastrointestinal, neurological or spinal events, thrombi, infections, vocal cord palsy and return to theatre, as well as requirement for cardiac support, prolonged ventilation and renal support. ESG complications were classified as access vessel injury, stent graft complication, endoleak, fistulae, aneurysm complication and other. In addition, the following were recorded: date of the event, theatre time, relationship to the procedure or treatment (not related, unlikely to be related, possibly related, probably related, definitely related), cause of event and management. Additional complications, which may arise outside the hospital, including vessel injury, endoleaks, aneurysm complications, stent graft complications and fistulae, were reported by participating centres. All complications were reviewed centrally by ETTAA clinicians (PS, SRL). Further details of complications are given in *Appendix 1*.

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Readmissions to hospital

Readmissions after discharge were obtained by centre staff from hospital records. Information on dates of admission, days in ICU, HDU and ward, reason for admission, relationship to aneurysm or treatment and presenting symptoms were recorded. Further interventions on the ascending, arch, descending thoracic or thoracoabdominal aorta were also recorded.

Health-related quality of life

The completion of the EuroQoL-5 Dimensions, five-level version (EQ-5D-5L) was scheduled at baseline, at 3, 6 and 12 months and annually thereafter pre intervention and at 1, 3, 6 and 12 months and annually thereafter post intervention.[57] EQ-5D-5L records mobility, self-care, usual activities, pain/discomfort and anxiety/depression on a five-level Likert scale. Owing to varying times between recruitment and procedure, follow-up was not always synchronised with planned assessment times. See *Chapters 4–7* for further details.

Quality-adjusted life-years

The results from the EQ-5D-5L were converted into health state utilities using UK population tariffs[58] and used to estimate quality-adjusted life-years (QALYs) using the area-under-the-curve approach. QALYs at 12 months were estimated for patients who completed EQ-5D-5L score in the first year post intervention.

Resource use

Data on resource use from a UK NHS perspective were recorded for the procedure and any subsequent admissions to hospital for aneurysm-related or cardiac-related events. Other resource use was scheduled to be recorded at 1, 3, 6, 12, 18, 24, 36, 48 and 60 months post procedure for the use of primary care and Personal Social Services (PSS). Costs of health-care services were taken from standard sources such as NHS reference costs, Healthcare Resource Group (HRG) tariffs and manufacturer/supplier costs and from the centres themselves. See *Chapter 7* for further details of health economic analyses.

Demographic and baseline variables collected

The baseline variables explored as predictors in modelling and for propensity score development are listed below.

Patient related

Sex, age, height, weight, BMI and smoking history.

Aneurysm related

Type of scan (CT or MRI), aneurysm diameter and location, and location of largest aneurysm.

Cardiovascular related

Diagnosis of hypertension, diabetes, left ventricular (LV) function, coronary artery disease, previous cardiac/aortic intervention, extracardiac arteriopathy, valvular heart disease, and medication (antihypertensive, anticoagulant, statin) at baseline and each follow-up visit.

Other markers of comorbidity

Chronic obstructive pulmonary disease (COPD), New York Heart Association (NYHA) classification of heart disease and CTD. Serum creatinine and haemoglobin levels at baseline and follow-up visits, if recorded.

Operative risk related

Logistic EuroSCORE and formal/informal care (as a proxy for frailty).

Health-related quality of life

EQ-5D-5L score.

Data collection

At baseline, medical history was taken by research personnel to identify a patient's eligibility. Procedure details and related complications, clinical outcome data and EQ-5D-5L questionnaires were collected prospectively until the study ended, either during hospital attendances or by post/telephone and from hospital databases.

Aneurysm imaging using CT or MRI was undertaken in accordance with local practice, and anonymised copies of scans from the time of diagnosis were sent to the study team.

For patients who transferred from WW to ESG or OSR, a reassignment form was completed at the time the clinical decision was made. Following reassignment, assessment visits were scheduled relative to the reassignment date. For patients waiting over 3 months for surgery, pre-procedure follow-up assessments were completed every 3 months.

Follow-up visits had to be conducted within the following windows:

- 1- and 3-month follow-up: ± 1 week
- 6-, 12-, 18- and 24-month follow-up: ± 2 weeks
- 36-, 48- and 60-month follow-up: ± 4 weeks.

Data were transferred into ETTAA's electronic database by the local principal investigator (PI) or a delegated researcher.

Statistical methods

Original planned sample size and revision in October 2016

Although the ETTAA study was an observational study, we provided sample size estimates based on comparing survival between ESG and OSR. From UK registry data, 360 elective operations and stents were performed each year in the UK for arch and DTA aneurysms.[2] Based on log-rank tests, assuming proportional hazards and uninformative censoring, we calculated the smallest possible effect sizes that would be statistically significant at (two-sided) 5% error rate, with 80% power, assuming a fixed sample size and a range of predicted incidence of events in the OSR group.

Table 5 gives the range of the minimum HRs detectable for a given expected event incidence in OSR. The first set of estimates uses pre-study predictions of the final sample size (ESG, $n = 293$; OSR, $n = 147$). The second set uses October 2016 predictions of sample size (ESG, $n = 170$; OSR, $n = 112$). With these numbers, moderate to large effects (HR > 0.5) could be detected, providing that the event incidence (e.g. deaths) during the study in the OSR group was at least 30%.

TABLE 5 Minimum HR detectable with 80% power and 5% significance, a given sample size (see footnote) and different event incidence during the study for OSR

	OSR group probability of observing an event during the study									
	50%	45%	40%	35%	30%	25%	20%	15%	10%	5%
HR based on original expected sample size[a]	0.66	0.64	0.62	0.60	0.57	0.54	0.49	0.43	0.34	0.16
HR based on revised expected sample size[b]	0.59	0.57	0.55	0.52	0.49	0.45	0.40	0.33	0.22	0.02

a Original predictions assumed 293 ESG patients and 147 OSR patients.
b Revised predictions assumes 170 ESG patients and 112 OSR patients.

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In response to requests from the National Institute for Health Research (NIHR), we also estimated the power of the study to detect the minimum clinically important difference (MCID) in HRQoL. Assuming a MCID of 0.1 in the EuroQoL utility measure,[59] with 5% significance and a sample size of 170 ESG and 112 OSR the power was > 90% for either two-sided *t*-test or Wilcoxon-Mann–Whitney *U*-test (the latter would account for potential ceiling effects in HRQoL). The more sophisticated modelling methods to be used, adjusting for confounders, mean that 90% is a lower bound for power. Given this number of procedures, we expected 81 CM and 730 WW patients to be recruited during the study.

Data quality assurance

The assessment of data quality was complicated by the observational nature of the ETTAA study and the movement of patients between groups over time. Data completeness was assessed using summaries of individual case report forms (CRFs) returned. Data checks broadly followed recommendations in Kirkwood and Sterne.[60] Outliers in continuous variables were detected using ranges and plotting distributions within each group. Unresolved outliers that were extreme and separated from the distribution of a variable were removed and considered missing. Categorical variables were tabulated and unexpected values were queried with centres. Consistency checks between two or more variables were performed (e.g. bivariate plots, cross-tabulations). Dates were checked against planned timing assessments and interventions, as well as relative to other assessments in the same person. All queries were checked with centres and amended in the ETTAA database.

Data summaries

Detailed methods are provided in each chapter; here we give a brief overview of the descriptive methods. Throughout, variables were summarised as the total participants per group and overall, with means and standard deviations (SDs) if normally distributed, or median and interquartile range otherwise. Categorical data were presented as frequencies and proportion in each level. Time-to-event data were summarised as the actuarial survival probability or incidence during the non-intervention and post-intervention periods using Kaplan–Meier estimates. Post-intervention survival was also calculated separately for deaths within 30 days of an intervention. To assess whether or not patients allocated to different management groups were comparable, baseline variables were compared across the four groups using one-way analysis of variance, Pearson's chi-squared test or a generalisation of Fisher's exact test, as appropriate.[61]

Multiple-centre issues

For the analysis of aneurysm growth and HRQoL over time, clustering by centre was investigated using normal random effects in a three-level hierarchy (scan within patient within hospital) (see *Chapter 4*). For time-to-event outcomes in work package 1, gamma-distributed frailty terms for centres were investigated. For all other analyses, between-centre variation in outcomes could not be assessed owing to the small number of patients contributed by most centres.

Subgroup analysis

Sensitivity analysis included the subgroup of patients who were potentially suitable for both OSR and ESG (see *Chapter 6*).

Missing data

The extent of missing data per variable was quantified as the number of cases divided by the number of patients who were in the study at the point of assessment. All essential variables for work packages 1–3 are expected to be complete or to have low missing rates (< 8%). Variables for which > 25% of data were unavailable or missing were not used in modelling but were summarised and reported.

Missing data patterns were explored (e.g. monotonic, intermittent). Missing data mechanisms, missing at random (MAR) and missing completely at random (MCAR) were investigated using standard statistical tests (log-rank, Student's *t*-test, Mann–Whitney *U*-test, Pearson's chi-squared test, Fisher's exact test) to assess the associations between missing variable status (yes/no) and outcomes. To inform imputation models,

associations between pairs of covariates and predictors of missingness were assessed using correlations and other standard statistical tests. Missing covariates were analysed together irrespective of the reasons (death, withdrawal, loss to follow-up, test not completed). For the analysis of aneurysm growth and HRQoL (work packages 1 and 2), all patients with at least two measurements were included in random-effects models. No adjustment was made for missing measurements as estimates from such models are unbiased provided that the data are MAR conditional on the observed data.[62] For work packages 2 and 3, the analysis found little evidence against the hypothesis that data were MCAR (see *Appendix 2*), so the complete-case analysis is presented throughout. Sensitivity analysis assuming MAR used multiple imputation with chained equations (MICE). Imputation models included the outcome variable as well as all important covariates from exploratory analysis. Each imputation model performed predictive mean matching to impute missing data. Values were simulated for each missing variable and the resulting models were combined using Rubin's rules.[63]

Results

Recruitment

Centre recruitment

Between 24 March 2014 and 24 July 2018, 886 CTAA patients were recruited from 30 centres (see *Appendix 3* for a list of participating centres). Studies covered the majority of England but did not recruit from the devolved nations (*Figure 4*). Although some centres specialised in either vascular or cardiac surgery, many centres recruited patients to all four management groups.

FIGURE 4 Locations of the 30 centres participating in the ETTAA study.

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The Consolidated Standards of Reporting Trials (CONSORT)-style flow charts in *Tables 6* and *7* show the number of cases assigned to each group pre (see *Table 6*) and post intervention (see *Table 7*). A total of 112 (12.6%) patients were assigned to CM, of whom 46 died during follow-up. The remaining 774 (87.4%) patients were eligible and willing to receive the intervention. Of these 774 patients, 150 (19.4%) subsequently received ESG, 135 (17.4%) subsequently received OSR and 83 (10.7%) died before any intervention. Plots of actual against target recruitment are provided in *Appendix 4*.

TABLE 6 Pre-procedure follow-up relative to date of recruitment, according to intention to intervene ($N = 886$)

Procedure follow-up relative to date	Number of patients	Percentage of total
***Intervention or WW* (N = *774*)**		
3 months		
Completed	525	67.8
Died	12	1.6
Procedure	182	23.5
Withdrew	8	1.0
Missing	47	6.1
Censored	0	0.0
6 months		
Completed	482	62.3
Died	24	3.1
Procedure	212	27.4
Withdrew	11	1.4
Missing	45	5.8
Censored	0	0.0
12 months		
Completed	418	54.0
Died	43	5.6
Procedure	244	31.5
Withdrew	15	1.9
Missing	54	7.0
Censored	0	0.0
18 months		
Completed	323	41.7
Died	58	7.5
Procedure	256	33.1
Withdrew	19	2.5
Missing	51	6.6
Censored	67	8.7

TABLE 6 Pre-procedure follow-up relative to date of recruitment, according to intention to intervene (*N* = 886) (*continued*)

Procedure follow-up relative to date	Number of patients	Percentage of total
24 months		
Completed	251	32.4
Died	64	8.3
Procedure	268	34.6
Withdrew	21	2.7
Missing	56	7.2
Censored	114	14.7
36 months		
Completed	159	20.5
Died	77	9.9
Procedure	278	35.9
Withdrew	23	3.0
Missing	30	3.9
Censored	207	26.7
48 months		
Completed	66	8.5
Died	83	10.7
Procedure	284	36.7
Withdrew	23	3.0
Missing	29	3.7
Censored	289	37.3
60 months		
Completed	1	0.1
Died	83	10.7
Procedure	285	36.8
Withdrew	23	3.0
Missing	14	1.8
Censored	368	47.5
CM (N = 112) *3 months*		
Completed	98	87.5
Died	6	5.4
Procedure	0	0.0
Withdrew	0	0.0
Missing	8	7.1
Censored	0	0.0

continued

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TABLE 6 Pre-procedure follow-up relative to date of recruitment, according to intention to intervene ($N = 886$) (*continued*)

Procedure follow-up relative to date	Number of patients	Percentage of total
6 months		
Completed	92	82.1
Died	9	8.0
Procedure	0	0.0
Withdrew	2	1.8
Missing	9	8.0
Censored	0	0.0
12 months		
Completed	85	75.9
Died	15	13.4
Procedure	0	0.0
Withdrew	4	3.6
Missing	8	7.1
Censored	0	0.0
18 months		
Completed	60	53.6
Died	23	20.5
Procedure	0	0.0
Withdrew	6	5.4
Missing	11	9.8
Censored	12	10.7
24 months		
Completed	51	45.5
Died	28	25.0
Procedure	0	0.0
Withdrew	7	6.3
Missing	6	5.4
Censored	20	17.9
36 months		
Completed	28	25.0
Died	40	35.7
Procedure	0	0.0
Withdrew	7	6.3
Missing	2	1.8
Censored	35	31.3
48 months		
Completed	8	7.1
Died	46	41.1

TABLE 6 Pre-procedure follow-up relative to date of recruitment, according to intention to intervene ($N = 886$) (*continued*)

Procedure follow-up relative to date	Number of patients	Percentage of total
Procedure	0	0.0
Withdrew	7	6.3
Missing	1	0.9
Censored	50	44.6
60 months		
Completed	0	0.0
Died	46	41.1
Procedure	0	0.0
Withdrew	7	6.3
Missing	0	0.0
Censored	59	52.7

Percentages have been rounded to nearest 0.1%, so the total percentage is not always exactly 100%.

TABLE 7 Post-procedure follow-up relative to procedure date ($N = 285$)

Procedure follow-up relative to date	Number of patients	Percetange of total
ESG (N = 150) *1 month*		
Completed	102	68.0
Died	9	6.0
Withdrew	0	0.0
Missing	39	26.0
Censored	0	0.0
3 months		
Completed	113	75.3
Died	12	8.0
Withdrew	1	0.7
Missing	23	15.3
Censored	1	0.7
6 months		
Completed	109	72.7
Died	15	10.0
Withdrew	1	0.7
Missing	21	14.0
Censored	4	2.7

continued

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TABLE 7 Post-procedure follow-up relative to procedure date (*N* = 285) (*continued*)

Procedure follow-up relative to date	Number of patients	Percetange of total
12 months		
Completed	100	66.7
Died	25	16.7
Withdrew	1	0.7
Missing	13	8.7
Censored	11	7.3
18 months		
Completed	73	48.7
Died	29	19.3
Withdrew	1	0.7
Missing	18	12.0
Censored	29	19.3
24 months		
Completed	44	29.3
Died	34	22.7
Withdrew	1	0.7
Missing	13	8.7
Censored	58	38.7
36 months		
Completed	21	14.0
Died	40	26.7
Withdrew	1	0.7
Missing	11	7.3
Censored	77	51.3
48 months		
Completed	5	3.3
Died	40	26.7
Withdrew	1	0.7
Missing	2	1.3
Censored	102	68.0
OSR (N = 135) *1 month*		
Completed	71	52.6
Died	15	11.1
Withdrew	2	1.5
Missing	47	34.8
Censored	0	0.0

TABLE 7 Post-procedure follow-up relative to procedure date ($N = 285$) (*continued*)

Procedure follow-up relative to date	Number of patients	Percetange of total
3 months		
Completed	82	60.7
Died	17	12.6
Withdrew	2	1.5
Missing	29	21.5
Censored	5	3.7
6 months		
Completed	92	68.1
Died	21	15.6
Withdrew	2	1.5
Missing	17	12.6
Censored	3	2.2
12 months		
Completed	81	60.0
Died	26	19.3
Withdrew	4	3.0
Missing	16	11.9
Censored	8	5.9
18 months		
Completed	62	45.9
Died	28	20.7
Withdrew	4	3.0
Missing	17	12.6
Censored	24	17.8
24 months		
Completed	49	36.3
Died	32	23.7
Withdrew	4	3.0
Missing	0	0.0
Censored	50	37.0
36 months		
Completed	28	20.7
Died	35	25.9
Withdrew	4	3.0
Missing	4	3.0
Censored	64	47.4

continued

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TABLE 7 Post-procedure follow-up relative to procedure date ($N = 285$) (*continued*)

Procedure follow-up relative to date	Number of patients	Percetange of total
48 months		
Completed	11	8.1
Died	36	26.7
Withdrew	4	3.0
Missing	3	2.2
Censored	81	60.0

Percentages have been rounded to nearest 0.1%, so the total percentage is not always exactly 100%.

Characteristics of the cohort at recruitment

Both prevalent and incident aneurysms were included in the cohort. Among the 871 patients with a record, the median time between diagnosis and recruitment was 9.1 months (range 4.0 months to 21.6 years).

Baseline predictors

A full breakdown of patient characteristics is given in *Appendix 6*, with summaries in *Tables 8–10*. Overall, the cohort comprised 321 (36.2%) women and 565 men and the mean age of the CTAA patients recruited was 70.9 (SD 10.9) years, with CM patients significantly older and OSR patients significantly younger on average (see *Table 8*). The groups also differed in height, weight (but not BMI) and requirements for additional care, which may relate to the differences in age.

TABLE 8 Summaries of patient characteristics at recruitment according to final management group

	Patient subgroup (number of patients with a registration scan)				
Characteristic	WW ($N = 489$)	CM ($N = 112$)	ESG ($N = 150$)	OSR ($N = 135$)	*p*-value
Age (years)					
Mean (SD)	70.8 (10.7)	76.6 (9.9)	72.0 (8.6)	64.9 (11.6)	< 0.0001
Minimum, maximum	32.3, 92.5	26.1, 92.5	49.6, 89.2	31.6, 83.5	
Sex, *n* (%)					
Female	174 (35.6)	48 (42.9)	50 (33.3)	49 (36.3)	0.4297
Male	315 (64.4)	64 (57.1)	100 (66.7)	86 (63.7)	
Care, *n* (%)					
Formal	10 (2.0)	5 (4.5)	0 (0.0)	1 (0.7)	0.0020[a]
Informal	50 (10.2)	18 (16.1)	12 (8.09)	7 (5.2)	
None	425 (86.9)	88 (78.6)	138 (92.0)	125 (92.6)	
Missing	4 (0.8)	1 (0.9)	0 (0.0)	2 (1.5)	
Smoker (current or past), *n* (%)					
Yes	343 (70.1)	71 (63.4)	113 (75.3)	89 (65.9)	0.1518
No	142 (29.0)	40 (35.7)	36 (24.0)	45 (33.3)	
Missing	4 (0.8)	1 (0.9)	1 (0.7)	1 (0.7)	

a Formal and informal care groups combined for hypothesis test.

Note

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TABLE 9 Summaries of comorbidities at recruitment according to final management group

Comorbidity	Patient subgroup (number of patients with a registration scan)				*p*-value
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	
Connective tissue disorder, *n* (%)					< 0.0001
Yes	30 (6.1)	3 (2.7)	2 (1.3)	20 (14.8)	
No	459 (93.9)	109 (97.3)	148 (98.7)	115 (85.2)	
Coronary artery disease, *n* (%)					0.3712
CABG	26 (5.3)	10 (8.9)	7 (4.7)	8 (5.9)	
Medication	46 (9.4)	9 (8.0)	14 (9.3)	8 (5.9)	
No	377 (77.1)	85 (75.9)	123 (82.0)	116 (85.9)	
PCI	27 (5.5)	6 (5.4)	5 (3.3)	2 (1.5)	
Missing	13 (2.7)	2 (1.8)	1 (0.7)	1 (0.7)	
Extracardiac arteriopathy, *n* (%)					0.4940
No	406 (83.0)	91 (81.3)	123 (82.0)	118 (87.4)	
Yes	71 (14.5)	20 (17.9)	26 (17.3)	16 (11.9)	
Missing	12 (2.5)	1 (0.9)	1 (0.7)	1 (0.7)	
Valvular heart disease, *n* (%)					0.0013
No	389 (79.6)	87 (77.7)	134 (89.3)	96 (71.1)	
Yes	89 (18.2)	23 (20.5)	15 (10.0)	38 (28.2)	
Missing	11 (2.3)	2 (1.8)	1 (0.7)	1 (0.7)	
LV function, *n* (%)					< 0.0001
Good	199 (40.7)	41 (36.6)	64 (42.7)	79 (58.5)	
Moderate	30 (6.1)	14 (12.5)	13 (8.7)	19 (14.1)	
Poor	11 (2.2)	2 (1.8)	2 (1.3)	0 (0.0)	
Not measured	241 (49.3)	55 (49.1)	70 (46.7)	36 (26.7)	
Missing	8 (1.6)	0 (0.0)	1 (0.7)	1 (0.7)	
Diabetes, *n* (%)					0.2350[a]
No	432 (88.3)	105 (93.8)	137 (91.3)	126 (93.3)	
Non-IDDM	52 (10.6)	7 (6.3)	13 (8.7)	8 (5.9)	
IDDM	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
Missing	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypertension, *n* (%)					0.7856
Yes	424 (86.7)	7 (86.6)	135 (90.0)	119 (88.2)	
No	63 (12.9)	15 (13.4)	15 (10.0)	16 (11.9)	
Missing	2 (0.4)	0 (0)	0 (0.0)	0 (0)	
COPD, *n* (%)					0.1772
Yes	87 (17.8)	26 (23.2)	32 (21.3)	18 (13.3)	
No	397 (81.2)	86 (76.8)	118 (78.7)	117 (86.7)	
Missing	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	

continued

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TABLE 9 Summaries of comorbidities at recruitment according to final management group (*continued*)

Comorbidity	Patient subgroup (number of patients with a registration scan)				*p*-value
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	
NYHA class, *n* (%)					0.4187
I	198 (40.5)	39 (34.8)	68 (45.3)	54 (40.0)	
II	175 (35.8)	41 (36.6)	47 (31.3)	52 (38.5)	
III	86 (17.6)	27 (24.1)	20 (13.3)	17 (12.6)	
IV	16 (3.3)	3 (2.7)	4 (2.7)	3 (2.2)	
Missing	14 (2.9)	2 (1.8)	11 (7.3)	9 (6.7)	
Serum creatinine level (μmol/l)					0.0068
Mean (SD)	96.0 (32.8)	104.9 (39.8)	92.6 (31.9)	85.7 (27.3)	
Minimum, maximum	45.0, 227.0	44.0, 225.0	43.0, 200.0	32.0, 186.0	
Missing, *n* (%)	309 (63.2)	60.0 (53.6)	42.0 (28.0)	48 (35.6)	
Haemoglobin level (g/l)					0.0420
Mean (SD)	127.5 (19.1)	128.4 (15.8)	131.7 (16.2)	133.6 (17.3)	
Minimum, maximum	76.0, 175.0	98.0, 171.0	77.0, 176.0	90.0, 165.0	
Missing, *n* (%)	326 (66.7)	64 (57.1)	44 (29.3)	50 (37.0)	

CABG, coronary artery bypass grafting; IDDM, insulin-dependent diabetes mellitus; PCI, percutaneous coronary intervention.
a Insulin-dependent and non-insulin-dependent patients combined for hypothesis test.

Note
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TABLE 10 Summaries of cardiac drugs at recruitment according to final management group

Drug group	Patient subgroup (number of patients with a registration scan), *n* (%)				*p*-value
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	
Beta-blocker use					
Yes	255 (52.2)	51 (45.5)	74 (49.3)	72 (53.3)	0.5608
No	234 (47.9)	61 (54.5)	76 (50.7)	63 (46.7)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Angiotensin-converting enzyme inhibitor use					
Yes	116 (23.7)	39 (34.8)	45 (30.0)	40 (29.6)	0.06342
No	373 (76.3)	73 (65.2)	105 (70.0)	95 (70.4)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Angiotensin receptor blocker use					
Yes	94 (19.2)	26 (23.2)	28 (18.7)	32 (23.7)	0.5416
No	395 (80.8)	86 (76.8)	122 (81.3)	103 (76.3)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Calcium channel blocker use					
Yes	176 (36.0)	35 (31.3)	55 (36.7)	47 (34.8)	0.7909
No	313 (64.0)	77 (68.8)	95 (63.3)	88 (65.2)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

TABLE 10 Summaries of cardiac drugs at recruitment according to final management group (*continued*)

Drug group	Patient subgroup (number of patients with a registration scan), *n* (%)				*p*-value
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	
Other antihypertensives					
Yes	65 (13.3)	24 (21.4)	24 (16.0)	17 (12.6)	0.1384
No	424 (86.7)	88 (78.6)	126 (84.0)	118 (87.4)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Any antihypertensive					
Yes	412 (84.3)	94 (83.9)	131 (87.3)	116 (85.9)	0.7900
No	77 (15.7)	18 (16.1)	19 (12.7)	19 (14.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Statins					
Yes	283 (57.9)	72 (64.3)	106 (70.7)	51 (37.8)	< 0.0001
No	204 (41.7)	40 (35.7)	44 (29.3)	84 (62.2)	
Missing	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	

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In addition to age, there were important differences between the management groups in comorbidities/biomarkers (see *Table 9*) and cardiac medication (see *Table 10*). Among those with CTDs, only two had ESG, compared with 20 who had OSR. As might have been expected, the CM group were less likely to have good LV function and more likely to have comorbidities such as COPD, higher NYHA classification and higher mean serum creatinine level, although the differences overall were not always statistically significant. Conversely, OSR patients were less likely to have COPD or take statins and more likely to have good LV function. Between 86% and 90% of patients had documented hypertension and were treated.

Some baseline variables were not measured by centres, resulting in large numbers of missing data. For example, LV function was not recorded for approximately half of the WW, CM and ESG groups and for one-quarter of the OSR group because echocardiography was not performed routinely at this stage in all centres. Similarly, serum creatinine and haemoglobin levels at recruitment were missing for 456 (51.5%) and 484 (54.6%) patients, respectively, because these biomarkers were not measured routinely in some centres. Otherwise, the missing data level was < 8% for all baseline variables.

Details of the available scans

Reading of baseline scans was mandated for aneurysms in the arch and DTA, but it was restricted by resources for other locations in the thoracic aorta. *Table 11* provides summaries of the measurements at recruitment for the four aortic segments with consistent data collection, along with the largest diameter at any of the four sites. Aneurysms in the arch and those extending into the ascending aorta were smaller in WW and ESG patients than in patients receiving CM and OSR. Overall, aneurysms in the DTA were similar in CM, ESG and OSR and smaller in the WW group, but significantly larger in all groups than those in the arch. Aneurysms that extended into the thoracoabdomen were approximately 2 cm smaller on average.

Details of the procedures

Between 9 April 2014 and 18 June 2019, 150 patients underwent ESG as the first (index) procedure and 135 underwent OSR. Because the co-ordinating centre is primarily a cardiac surgery centre and

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TABLE 11 Summaries of aneurysm diameters at recruitment by location according to final management group

Aneurysm location	Patient subgroup (number of patients with a recruitment scan)				*p*-value
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	
Ascending aorta					< 0.0001
Frequency	404	101	134	113	
Mean diameter, cm (SD)	4.0 (0.8)	4.4 (1.1)	3.9 (0.5)	4.7 (1.2)	
Minimum, maximum, cm	2.5, 7.7	2.9, 8.9	2.8, 5.7	2.5, 7.9	
Missing, *n* (%)	85 (17.4)	11 (9.8)	16 (10.7)	22 (16.3)	
Aortic arch					< 0.0001
Frequency	472	105	140	126	
Mean, cm (SD)	3.9 (0.8)	4.5 (1.3)	3.7 (0.8)	4.5 (1.2)	
Minimum, maximum, cm	2.3, 9.4	2.5, 10.6	2.5, 8.3	2.5, 9.5	
Missing, *n* (%)	17 (3.5)	7 (6.2)	10 (6.7)	9 (6.7)	
DTA					< 0.0001
Frequency	486	111	150	133	
Mean diameter, cm (SD)	5.1 (1.1)	5.9 (1.4)	6.0 (1.1)	5.8 (1.4)	
Minimum, maximum, cm	2.8, 9.4	2.4, 10.0	3.4, 9.7	2.5, 9.0	
Missing, *n* (%)	3 (0.6)	1 (0.9)	0 (0.0)	2 (1.5)	
Thoracoabdominal					0.0090
Frequency	388	96	130	100	
Mean diameter, cm (SD)	3.4 (0.8)	3.8 (1.1)	3.5 (1.0)	3.6 (0.9)	
Minimum, maximum, cm	1.9, 7.2	2.3, 6.7	1.9, 6.7	1.8, 6.4	
Missing, *n* (%)	101 (20.7)	16 (14.3)	20 (13.3)	35 (25.9)	
Largest aneurysm					< 0.0001
Frequency	489	112	150	135	
Mean diameter, cm (SD)	5.3 (1.0)	6.3 (1.2)	6.0 (1.1)	6.3 (1.0)	
Minimum, maximum, cm	2.8, 9.4	4.2, 10.6	3.7, 9.7	4.0, 9.5	
Missing, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

opened before other centres, OSR procedure dates began 5 months earlier than ESG procedures. Descriptive data for procedures are shown in *Table 12*. One ESG recipient had a hybrid procedure involving a carotid-to-carotid bypass; similarly, 12 OSR patients had a combined procedure in which a stent was inserted via a median sternotomy. Procedures were planned to be completed in stages for 39 ESG and 34 OSR patients; of these, 14 ESG and 2 OSR were started prior to recruitment.

Over 85% of patients were treated electively, with a minority having urgent or emergency procedures. OSR was almost always completed in theatre, whereas ESG was completed in theatre, a catheter laboratory or a hybrid theatre combining the traditional operating theatre with an interventional radiology suite. The predominant mode of access for OSR was a median sternotomy, although thoracotomy/thoracolaparotomy was reported for 34 patients. Thirty-seven OSR patients had concomitant procedures, including aortic valve replacements and bypass grafts, which could have been carried out only during open surgery.

TABLE 12 Summaries of procedures during the ETTAA study

	Patient subgroup (number of patients having index procedure)		
	ESG ($N = 150$)	OSR ($N = 135$)	*p*-value
First procedure date	12 November 2014	9 April 2014	
Last procedure date	5 June 2019	12 June 2019	
Hybrid procedure, *n* (%)	1 (0.7)	12 (9.0)	
Staged procedure, *n* (%)	39 (26.0)	34 (25.2)	
Index procedure = second/third stage	14	2	
Priority, *n* (%)			
Elective	131 (87.3)	115 (85.2)	0.0840
Urgent	13 (8.7)	19 (14.1)	
Emergency	6 (4.0)	1 (0.7)	
Concomitant procedures, *n* (%)			
Aortic valve surgery	0 (0.0)	12 (8.9)	0.0005
Aortic valve plus CABG surgery	0 (0.0)	2 (1.5)	
Aortic valve plus other surgery	0 (0.0)	8 (5.9)	
CABG	0 (0.0)	10 (7.4)	
Other surgery	1 (0.7)	5 (3.7)	
None reported	149 (99.3)	98 (72.6)	
Operating facilities, *n* (%)			
Operating room	24 (16.0)	125 (92.6)	< 0.0001
Operating room with C-arm	26 (17.3)	1 (0.7)	
Hybrid theatre	73 (48.7)	7 (5.2)	
Catheter laboratory	21 (14.0)	1 (0.7)	
Missing	6 (4.0)	1 (0.7)	
Surgical incisions required, *n* (%)			
Sternotomy	0 (0.0)	97 (71.9)	< 0.0001
Thoracotomy	0 (0.0)	19 (14.1)	
Thoracolaparotomy	0 (0.0)	15 (11.1)	
Other	0 (0.0)	4 (3.0)	
None	150 (100.0)	0 (0.0)	
Missing	0 (0.0)	0 (0.0)	
Reported access site for stenting, *n* (%)			
Femoral artery	128 (85.3)	5 (3.7)	< 0.0001
Iliac artery	7 (4.7)	0 (0.0)	
Brachial	4 (2.7)	0 (0.0)	
Other	2 (1.3)	4 (3.0)	
None recorded	9 (6.0)	126 (93.3)	

continued

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TABLE 12 Summaries of procedures during the ETTAA study (*continued*)

	Patient subgroup (number of patients having index procedure)		
	ESG ($N = 150$)	OSR ($N = 135$)	*p*-value
Aortic arch procedures, *n* (%)			
Repair/replacement	37 (24.7)	102 (75.6)	< 0.0001
None	111 (74.0)	33 (24.4)	
Missing	2 (1.3)	0 (0.0)	
DTA procedures, *n* (%)			
Repair/replacement	139 (92.7)	82 (60.7)	< 0.0001
None	11 (7.3)	51 (37.8)	
Missing	0 (0.0)	2 (1.5)	
Ascending aorta procedures, *n* (%)			
Repair/replacement	0 (0.0)	58 (42.9)	< 0.0001
None	149 (99.3)	76 (56.3)	
Missing	1 (0.7)	1 (0.7)	
Thoracoabdominal aorta procedures, *n* (%)			
Repair/replacement	14 (9.4)	10 (7.4)	0.001
None	135 (90.0)	116 (85.9)	
Missing	1 (0.7)	9 (6.7)	
Subsequent procedures: second third	12 ESG	24 ESG, 4 OSR 3 ESG	

CABG, coronary artery bypass grafting.

A variety of endovascular stent grafts were implanted and, for some patients, branched, fenestrated and scalloped grafts were employed. The site of access for main stent body insertion was the femoral artery in the majority of ESG procedures (see *Table 12*). In 136 patients in whom the relationship with the left subclavian artery was recorded, 84 (61.8%) were landed distal to the subclavian artery, 36 (26.5%) underwent bypass and 16 (11.8%) had coverage of the left subclavian artery without bypass. One ESG patient had another endovascular procedure but no other details were provided by the time of data lockdown.

There were marked differences in aneurysm site between the two intervention groups. Aneurysms were more likely to be treated with OSR if they were in the aortic arch (102 vs. 37 patients) and less likely to be treated with OSR if they were in the DTA (82 vs. 139 patients). If aneurysms extended into the ascending aorta, then they were invariably treated by OSR. Both procedures were used for aneurysms extending to the thoracoabdominal aorta (see *Table 12*).

Some patients required reintervention during the study. Twelve patients who received ESG as the index procedure required a second ESG between 0.6 and 35.4 months after the first procedure. In addition, 25 OSR patients had a second procedure (21 ESG and 4 OSR) between 0.4 and 36.1 months after the first procedure; of these, three received a further ESG at 1.1, 11.5 and 11.9 months after the second procedure.

Further details of outcomes of surgical procedures, including complications and NHS resources used, are reported in *Chapters 5* and *7*.

Summary of findings

This chapter describes the construction of the ETTAA cohort and the classification of patients into management groups depending on their risk of aneurysm-related events and their suitability for open-heart surgery. Although recruitment was lower than expected, we were close to meeting the targets for the ESG and OSR intervention groups, and high levels of baseline data collection were achieved for all but a small number of variables that were not measured routinely at all centres.

Groups differed in their baseline characteristics, reflecting clinician opinions expressed during the Delphi study in *Chapter 2*. In particular, expert clinicians expressed a preference for OSR for aneurysms in the arch and ESG for aneurysms in the DTA, which was broadly consistent with clinical practice during the study. In practice, the WW group had smaller (on average) aneurysms and lower aneurysm-related risk factors at recruitment; conversely, patients assigned to the CM group had greater risk factors for a poor outcome. Specifically, CM patients were older, more likely to be receiving formal or informal care (a marker of frailty), more likely to be in NYHA class II-IV and less likely to have good LV function than other groups.

It was clear that there were significant differences between the two intervention groups. For some variables the procedure groups overlapped despite important differences; for example, OSR patients were younger, more likely to have good LV function and less likely to be smokers, have statins prescribed or suffer from COPD, but these were not exclusive to OSR patients. Importantly, for some risk factors there was little or no overlap between these two intervention groups. For example, only two CTD patients had ESG, just over one-quarter of OSR patients had concomitant valve or coronary artery surgery which could not have been done in an endovascular procedure and all patients whose aneurysm extended into the ascending aorta had OSR. This lack of overlap between the groups has a major impact on the validity of any direct comparisons between them, which will be discussed in detail in subsequent chapters.

All analysis in this chapter concerned information collected at recruitment or during the interventions. However, there was often a prolonged interval between recruitment and either intervention or the end of the study, during which aneurysms and HRQoL were monitored. *Chapter 4* reports changes over time and other clinical outcomes during this non-intervention period.

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Chapter 4 Pre-procedure outcomes, aneurysm growth and health-related quality of life

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Introduction

This chapter reports on the analysis of data arising prior to any intervention taking place. Specifically, we provide estimates of aneurysm growth and changes in HRQoL over time for different treatment groups, survival, neurological events and incidence of aneurysm-related ruptures and dissections.

Aims of pre-procedure analyses

The aims of this chapter are to:

- model growth of aneurysms over time in the four sections of the aorta (ascending, arch, DTA and thoracoabdominal) in all patient groups prior to any intervention
- describe survival patterns in the absence of major interventions by patient group
- describe the time between diagnosis, recruitment and intervention
- describe major aneurysm-related events of rupture and dissection
- model change in HRQoL measured by the EQ-5D-5L utility over time prior to any intervention.

Methods

Population

All patients who were recruited into the study were included in the analysis of pre-intervention outcomes. Patients contributed data from either the date of diagnosis (aneurysm growth) or the date of recruitment (HRQoL, survival, clinical events) until one of the following occurred: first intervention, death, major clinical event, withdrawal or end of the study.

Outcomes

The primary outcome of interest was growth in the CTAA diameter using measurements made at diagnosis and at all subsequent time points prior to intervention.

Secondary outcomes were survival, clinical complications and HRQoL trajectories over time as defined in *Chapter 3*.

Statistical analysis

Aneurysm growth

All patients with CTAA diameter measurements from either CT or MRI scanning were included in the analysis. The date of the first scan recorded was considered time zero; these scans were completed between 4.0 months and 21.6 years prior to recruitment. Scans up to death, rupture, dissection or surgery (ESG or OSR) were included. Analysis was restricted to the four sections of the aorta that were recorded routinely.

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Longitudinal assessments of aneurysm diameters were analysed using linear random-effects models. Centre-specific and patient-specific random effects for the intercept and time variables were explored. Variation in outcomes attributable to centres was close to zero, so this was not included. Heterogeneity in random effects was assessed by allowing the variance components to differ between aneurysm sites. Non-linear growth was assessed by including time-squared in the model, but the small number of cases with more than two measurements precluded more complicated models of growth. Baseline variables were assessed as fixed effects in the model that included time. These were sex, age at scan, height, weight, BMI, hypertension, smoking (current, no, ex-smoker), COPD (yes, no), CTD (yes, no), coronary artery disease, extracardiac arteriopathy, valvular heart disease, type of scan (CT, MRI) and aneurysm location (arch, DTA, ascending aorta, thoracoabdominal aorta). All continuous variables except time of assessment were centred around their mean. A linear term was included for NYHA, with NYHA class rescaled so that class I took the value zero. The rationale for this was to ensure that (1) the overall intercept for the models was interpreted as the mean for patients in NYHA class I (and all other covariates set to zero) and (2) risk increased linearly with each one-class increase in NYHA classification. Treatment group was not included in this analysis of aneurysm growth because the group allocation occurred after time zero.

Initially, exploratory analysis involved plotting empirical distributions and aneurysm trajectories by aneurysm site. The normality of the distributions of baseline and subsequent measurements were confirmed by Q–Q plots and summary statistics. Unresolved extreme values were excluded (one weight/BMI).

Longitudinal random-effects models have two inter-related parts: the covariance structure and the mean structure.[65,66] First, the best covariance structure was investigated after 'saturating' the mean part of the model, including all variables and two-way interactions. Then a range of random-effects models, with and without variance heterogeneity, was fitted using restricted maximum likelihood, with nested models compared using likelihood ratio tests. Thereafter, the mean structure was simplified by removing variables sequentially, starting with polynomial and interaction terms, based on *z*-statistics.

If Y_{it} represents the diameter (in cm) of an aneurysm in an individual $i = 1, \ldots, n$, at time $t = 0, 1, \ldots, T_i$, (measurement time), then the model with best fit had the form:

$$Y_{it} = \beta_0 + \beta_1 \tau_{it} + \theta^T x_i + u_i + \varepsilon_{it}, \quad (1)$$

where:

- τ_{it} is actual time of the measurement for patient i at the tth time point
- x_i is a vector of baseline variables including aneurysm site for patient i
- $(\beta_0, \beta_1, \theta)$ are coefficients for the fixed effects
- $u_i | x_i, \tau_{it} \sim N(0, \sigma_u^2)$ are patient-level random effects
- $\varepsilon_{it} | u_i, x_i, \tau_{it} \sim N(0, \sigma_\varepsilon^2)$ are residual errors.

Model fit was assessed informally by histograms and Q–Q plots of standardised residual errors and random effects and by comparing fitted and observed trajectories for individuals. We note that estimates from resulting analyses are unbiased provided that measurements are missing at random conditional on observed measurements in the model. Missing data will not be considered further in longitudinal models.

Health-related quality of life

Patients with EQ-5D-5L utilities at recruitment and at least one subsequent follow-up time were analysed using the same methodology as for aneurysm diameters, with three exceptions: (1) time zero was the date of recruitment to the ETTAA study, (2) fixed age at recruitment rather than age at time of assessment was included and (3) management group was included in the analysis. Again, centre effects were not included in HRQoL models because variation in outcomes attributable to centres was zero. The resulting final model for utilities had the form:

$$U_{it} = \beta_0 + \beta_1 \tau_{it} + \theta^T x_i + u_{0i} + u_{1i} \tau_{it} + \varepsilon_{it}, \quad (2)$$

where:

- τ_{it} is the time of the measurement for patient at the tth time point
- x_i is a vector of baseline variables including aneurysm site and intended management for patient
- $(\beta_0, \beta_{1,} \theta)$ are coefficients for the fixed effects
- $u_{0i}|x_i, \tau_{it} \sim N(0, \sigma^2_{u0})$ and $u_{1i}|x_i, \tau_{it} \sim N(0, \sigma^2_{u1})$ are patient-level random effects for patients on the intercept and time slope respectively, μ_{0i} and μ_{1i} were independent
- $\varepsilon_{it}|u_{0i}, u_{1i}, x_i, \tau_{it} \sim N(0, \sigma^2_{\varepsilon})$ are residual errors that vary by management group (level 1 heterogeneity).

Again, estimates from this analysis are unbiased provided that data are missing at random conditional on observed data. Model fit was assessed using fitted and residual plots.

Death, rupture, dissection and neurological events

The numbers of deaths and hospital admissions from recruitment and prior to any intervention were summarised as the number and event rate, with ruptures, dissections and neurological events reported separately. For survival and aneurysm-related survival, the cumulative incidence was summarised using the Kaplan–Meier method. Relationships between baseline risk factors and outcomes were assessed informally from incidence plots and compared using log-rank tests. After assessing the validity of proportional hazards assumptions using Schoenfeld residuals, Cox proportional hazards models were developed to assess the relationship between incidence of events and baseline variables. First, all baseline variables that were significant in exploratory analysis were included in the models, and then removed sequentially, based on z-statistics, until the best parsimonious model was obtained. Centre effects were assessed by including gamma frailty terms in the Cox survival models. The primary analysis was complete case, with main results checked using multiple ($m = 12$) imputation for missing data. See *Chapter 3* and *Appendix 2* for details of missing data analysis.

A key assumption of survival analysis is that censoring is independent of risk of death, which is unlikely to hold if high-risk patients are more likely to undergo procedures. In sensitivity analysis we refitted the final model using Fine and Gray's[67] subdistribution hazards model, with ESG and OSR treated as competing risks. In addition, we provided predicted survival rates for the composite outcome of death or intervention with ESG or OSR.

Joint analysis of aneurysm growth and the composite of death, rupture and dissection

Our intention is to investigate whether or not aneurysm growth is related to clinical events (ruptures, dissections, deaths) by developing joint random-effects models for growth and time-to-event processes.[68] As stated in the statistical analysis plan, this was not part of the original application and will be reported separately from this monograph.

Results

Aneurysm growth from first scan

Descriptive analysis

A total of 1789 scans reporting measurements of aneurysm diameter for at least one section of the aorta were returned by 886 patients. After excluding scans after interventions ($n = 10$), scans using techniques other than CT or MRI ($n = 11$) and one scan whose follow-up date was over 8 years after the first scan, data from 1767 scans in 882 (99.5%) patients were analysed. These included 6433 measurements of aneurysm diameter: 1537 in the ascending aorta, 1698 in the arch, 1761 in the DTA and 1437 in the thoracoabdominal aorta. The time between first scan and subsequent scans ranged from 3 days to 7.35 years. Mean (SD) diameters at baseline for patients with at least two scans was 4.11 (0.87) in the ascending, 3.98 (0.85) in the arch, 5.26 (1.09) in the DTA and 3.48 (0.81) in the

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thoracoabdominal aorta. There was little difference between baseline measurements for those with and without repeat scans.

Figure 5 shows diameter measurements at the four aneurysm sites over time. Diameters at the first scan varied substantially between patients at all sites, with DTA aneurysms showing greater average diameter and more variation between patients; thoracoabdominal aneurysms were slightly smaller on average. Trajectories over time are difficult to disentangle, although on average diameters appeared to increase only slightly over time.

Results of modelling

The final model describing the diameter measurement trajectories in the absence of treatment is shown in *Appendix 7*; the results are summarised below.

In the final model, at time zero all covariate values are zero if the aneurysm is measured using CT, the patient is of average age (70.9 years) and height (171 cm), has never smoked, and does not have a CTD, COPD or valvular heart disease. For these 'zero' aneurysms, the average diameter at first scan (time zero) was 4.14 cm in the ascending aorta, 4.13 cm in the arch, 5.29 cm in the DTA and 3.37 cm in the thoracoabdominal aorta (*Table 13*, first row).

At the time of the first scan (time zero), older age, being taller, having comorbidities such as CTD, COPD and valvular heart disease and being a past or current smoker were all associated with larger aneurysms in one or more aortic sites, although these effects varied between sites. *Table 13* shows the average diameters (95% CIs) in these subgroups. For example, at first scan, age was associated with bigger aneurysms in the ascending aorta and DTA, but less so in the arch and only slightly in the thoracoabdominal aorta. Aneurysms in the DTA and thoracoabdominal aorta (but not in the other sites) were larger on the

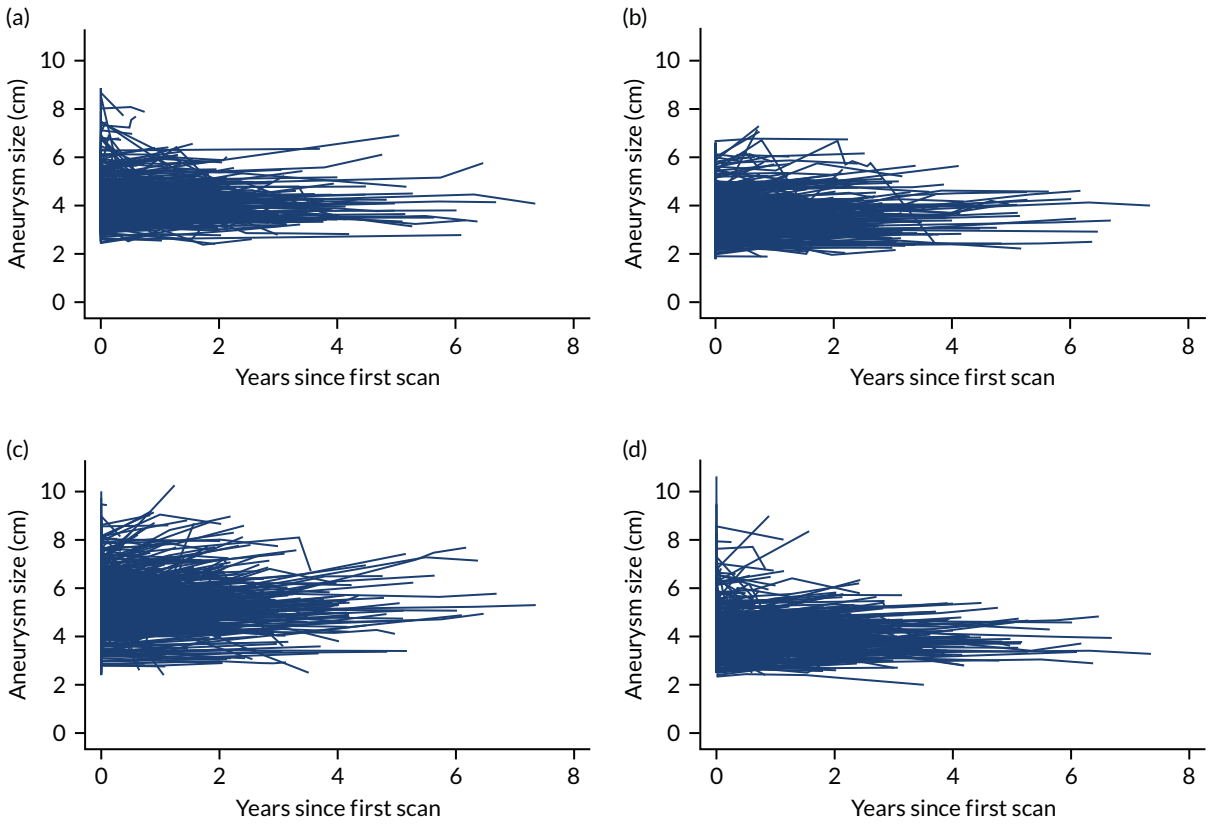

FIGURE 5 Aneurysm diameters over time, by location in the thoracic aorta. (a) Ascending aorta; (b) suprarenal abdominal aorta; (c) descending thoracic aorta; (d) aortic arch.

TABLE 13 Mean (95% CI) aneurysm diameter (cm) at first scan by site and baseline covariates

Variable	Ascending aorta	Aortic arch	Descending thoracic aorta	Thoracoabdominal aorta
All covariates zero[a]	4.14 (4.03 to 4.25)	4.13 (4.02 to 4.24)	5.29 (5.18 to 5.40)	3.37 (3.25 to 3.49)
Average age + 10 years	4.33 (4.20 to 4.46)	4.22 (4.10 to 4.34)	5.46 (5.34 to 5.58)	3.41 (3.28 to 3.54)
Connective tissue disorder	4.12 (3.85 to 4.39)	4.14 (3.88 to 4.40)	5.52 (5.26 to 5.78)	3.93 (3.65 to 4.21)
COPD	4.19 (4.00 to 4.38)	4.09 (3.91 to 4.27)	5.56 (5.38 to 5.74)	3.35 (3.16 to 3.54)
Valvular heart disease	4.39 (4.21 to 4.57)	4.16 (3.99 to 4.33)	5.17 (5.00 to 5.34)	3.35 (3.17 to 3.53)
Current smoker	4.15 (3.95 to 4.35)	4.04 (3.84 to 4.24)	5.52 (5.33 to 5.71)	3.65 (3.45 to 3.85)
Ex-smoker	4.04 (3.90 to 4.18)	4.01 (3.88 to 4.14)	5.41 (5.28 to 5.54)	3.49 (3.35 to 3.63)

a Male of average age and height, never smoked, with no comorbidities (CTD, COPD, valvular heart disease), measured by CT scan.

first scan if the patient had CTD than if they did not. DTA aneurysms were larger on the first scan if the patient had COPD, but this effect was not evident in other vessels. Ascending aorta aneurysms on the first scan were larger if the patient had valvular heart disease. Again, this effect was not evident in other sites. Even after adjusting for these baseline variables, there was significant variation in aneurysm size at first scan between patients (random-effects SD 0.54 cm). That is, aneurysm diameters at time zero lie within ± 1.08 cm of the average for that site for 95% of patients, even after adjustment for baseline variables.

On average, aneurysms in the DTA grew by 0.07 cm per year (95% CI 0.03 to 0.12 cm per year), compared with 0.04 cm (95% CI −0.002 to 0.07 cm per year) in the arch and 0.10 cm (95% CI 0.06 to 0.14 cm per year) in the thoracoabdominal aorta. Average growth for aneurysms in the ascending aorta was −0.001 cm per year (95% CI −0.04 to 0.04 cm per year) during the study (see *Appendix 7*). *Figure 6* summarises the average growth trajectories in each site, showing that aneurysms in the DTA were substantially larger throughout, and grew faster than aneurysms in the arch or ascending aorta (all else being equal). There was no evidence that aneurysm growth accelerated or decelerated during this study. At first scan, there was no difference between aneurysm diameters measured by CT and MRI, all other variables being equal. However, over time the average difference between diameters measured by the two modalities increased by 0.11 cm per year, with MRI measurements being smaller (see *Appendix 7*).

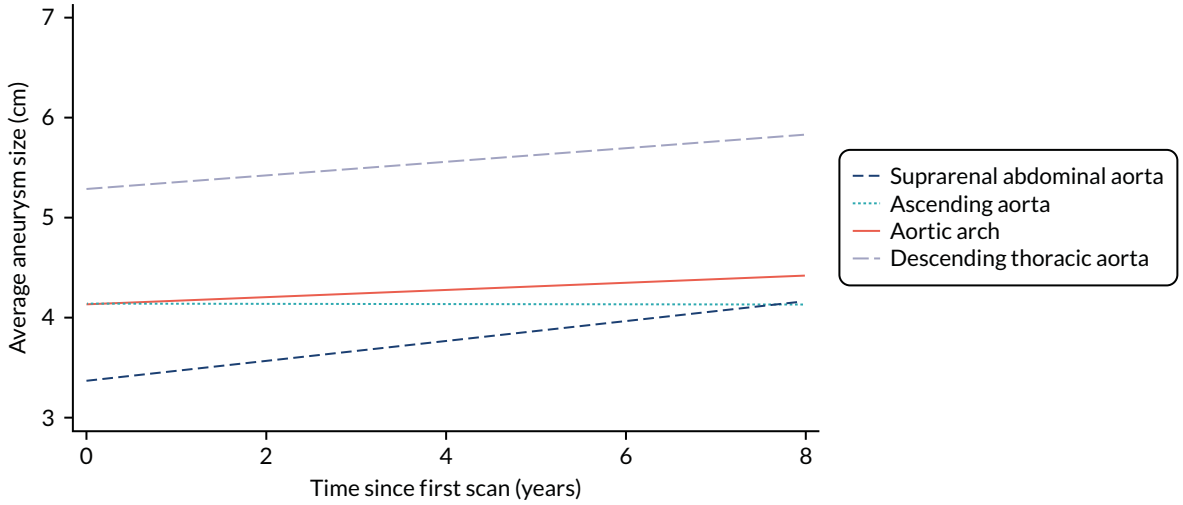

FIGURE 6 Average model-predicted growth trajectories from first scan by aneurysm site, assuming assessment by CT and all other baseline variables set to zero. Adapted from Sharples *et al.*[64] © The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial re-use distribution and reproduction in any medium provided the original work is properly cited. The figure includes minor additions and formatting changes to the original figure.

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Survival, hospital admissions and aneurysm-related events

Survival: descriptive analysis

In this analysis, follow-up time was from the date of recruitment to the first of death, rupture, dissection, procedure or censoring date. Pre intervention, 129 patients died during a total of 1498.2 patient-years of follow-up, a rate of 8.6% per patient-year (*Table 14*). Of these, 83 were in the WW group (7.4% of deaths per patient-year) and 46 were in the CM group (20.0% of deaths per patient-year).

Aneurysm was the primary or contributory cause of death in 64 (49.6%) patients; 45 were ruptured, 11 were dissected, three were ruptured and dissected and five reported aneurysm-related cause of death but no specific event. Thirty-nine aneurysm-related deaths were in the WW group (3.5% per patient-year) and 25 were in the CM group (10.9% per patient-year). One person had a dissected aorta but died from sepsis and aplastic anaemia; this death was not classified as aneurysm related. The results changed only slightly in sensitivity analysis that included this death as aneurysm related (not shown).

The 1- and 3-year cumulative incidence rates for all-cause death were 7.6% (95% CI 5.9% to 9.8%) and 22.4% (95% CI 18.8% to 26.6%), respectively, and for aneurysm-related death were 3.6% (95% CI 2.4% to 5.2%) and 11.7% (95% CI 9.0% to 15.2%), respectively. CM patients had much higher overall and aneurysm-related death rates than patients assigned to WW (*Figure 7*). Note that 19 patients do not appear in these figures because they were consented on the day of the intervention.

Survival: results of modelling

The variables associated with all-cause and aneurysm-related deaths were similar (*Table 15*). As expected, in univariable models the hazard for CM was over three times that for WW. Moreover, in univariable models, hazards were significantly higher for women, patients reporting formal/informal care and patients with previous cardiac interventions, COPD, higher NYHA classification, larger aneurysms, older age and smaller frame. The relationship between age and risk of death was not linear,

TABLE 14 Number of patients with readmissions and clinical outcomes prior to any procedure

	Patient subgroup			
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)
Total time at risk (years)	1119.8	229.7	77.1	71.4
Deaths (rate per patient-year)	83 (0.07)	46 (0.20)	–	–
Aneurysm-related deaths (rate per patient-year)	39 (0.03)	25 (0.11)		
All admissions, *n* (rate per patient-year)	243 (0.22)	71 (0.31)	36 (0.46)	13 (0.18)
People with at least one admission, *n* (%)	147 (30.1)	41 (36.6)	22 (14.6)	12 (9.0)
Admissions, definitely/probably aneurysm related, *n* (rate per patient-year)	25 (0.02)	11 (0.05)	14 (0.18)	2 (0.03)
Patients admitted, definitely/probably aneurysm related, *n* (%)	17 (3.5)	9 (8.0)	11 (7.3)	2 (1.5)
Non-fatal ruptured aneurysms	2	–	–	–
Non-fatal dissected aneurysms	4	1	2	–
Non-fatal neurological events	5	1	–	2

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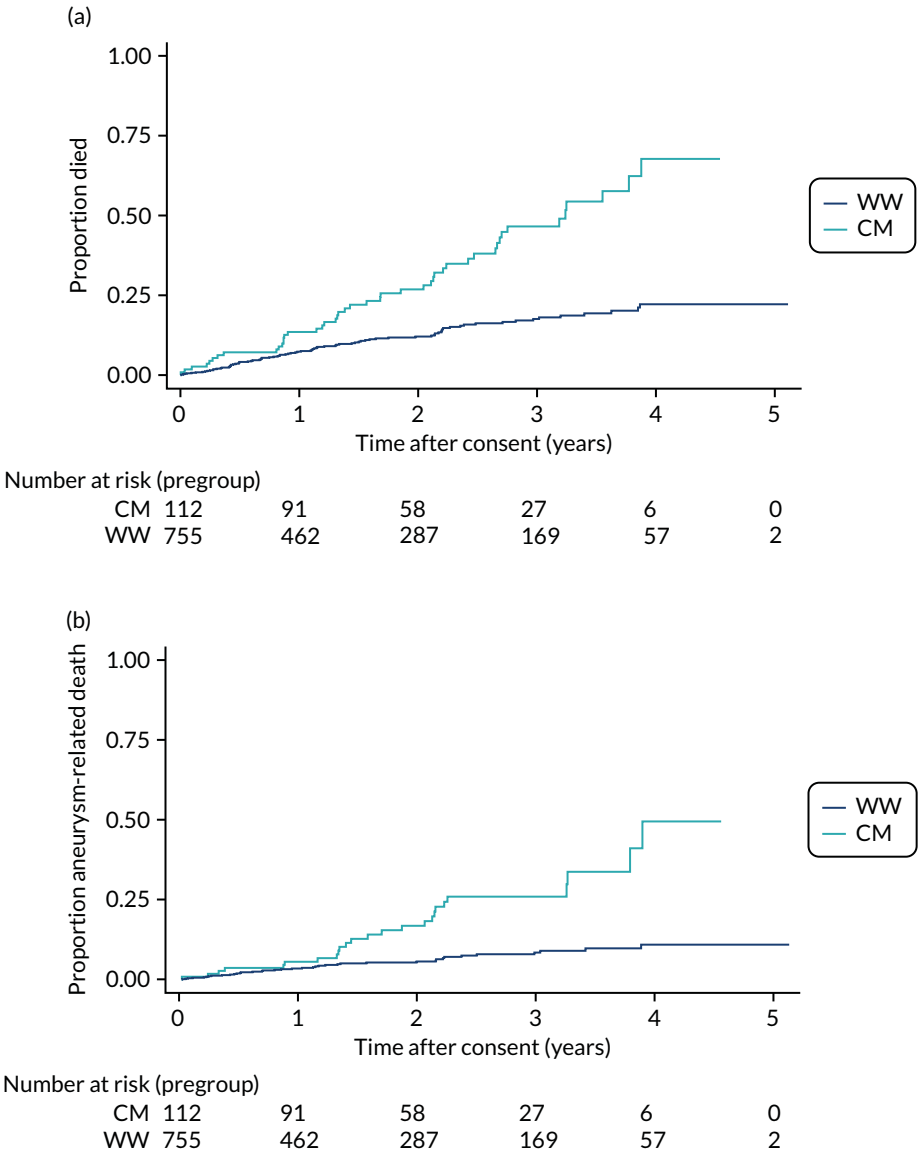

FIGURE 7 Kaplan–Meier cumulative incidence curves for death from any cause and aneurysm-related deaths by CM and non-CM management (labelled WW). (a) Kaplan–Meier deaths from any cause; and (b) Kaplan–Meier aneurysm-related deaths.

with patients aged > 80 years at particularly high risk, so that age was categorised for analysis. It is likely that the higher risk with lower height and weight measurements reflects a loss of muscle mass due to ageing. Variables not significant at the 5% level in both survival outcomes are not reported.

Many of the variables in *Table 15* were correlated, and the final multivariable models for all-cause and aneurysm-related deaths are shown in *Table 16*. Apart from age and sex, aneurysm size was the strongest risk factor for all-cause and aneurysm-related deaths. *Figure 8* shows the predicted survival for patients with different aneurysm sizes at baseline. This shows that, for example, the probability of survival to 1 year exceeds 95% for maximum aneurysm diameters of 4–5.5 cm and 90% for diameters up to 6.5 cm. The 1-year risk of death increases rapidly for aneurysms of > 6.5 cm in diamater. The 3-year survival probability exceeds 90% for small (4–4.5 cm) aneurysms and 80% for aneurysms of 5–5.5 cm in diameter. Predicted 3-year survival was 79% for aneurysms of 6 cm in diameter, falling to 42% for aneurysms of 8 cm in diameter.

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TABLE 15 Univariable Cox regression results for all-cause and aneurysm-related deaths: complete-case analysis

Variable	All-cause deaths		Aneurysm-related deaths	
	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
CM	3.05 (2.12 to 4.37)	< 0.001	3.55 (2.15 to 5.87)	< 0.001
Female sex	1.93 (1.36 to 2.72)	< 0.001	2.61 (1.59 to 4.29)	< 0.001
Use of formal/informal care	2.15 (1.40 to 3.29)	< 0.001	1.92 (1.02 to 3.61)	0.042
Previous cardiac interventions CABG/PCI	2.17 (1.43 to 3.29)	< 0.001	1.28 (0.63 to 2.59)	0.492
COPD	2.28 (1.56 to 3.34)	< 0.001	2.14 (1.24 to 3.69)	0.007
NYHA per class	1.47 (1.21 to 1.79)	< 0.001	1.35 (1.02 to 1.79)	0.037
Maximum aneurysm size per cm	1.94 (1.71 to 2.21)	< 0.001	2.16 (1.81 to 2.59)	< 0.001
Age (years) at consent		< 0.001		< 0.001
61–70	2.03 (0.76 to 5.43)		1.34 (0.42 to 4.29)	
71–80	4.18 (1.68 to 10.41)		2.49 (0.87 to 7.11)	
> 80	8.43 (3.35 to 21.23)		5.08 (1.75 to 14.74)	
Height per 10 cm	0.66 (0.56 to 0.77)	< 0.001	0.60 (0.48 to 0.76)	< 0.001
Weight per kg	0.97 (0.96 to 0.98)	< 0.001	0.96 (0.94 to 0.98)	< 0.001
BMI per kg/m^2	0.95 (0.91 to 0.99)	0.008	0.91 (0.86 to 0.97)	0.002

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Note

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TABLE 16 Final multivariable Cox regression results for all-cause and aneurysm-related deaths: complete-case analysis

Variable	All-cause deaths		Aneurysm-related deaths	
	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
Female sex	1.79 (1.25 to 2.57)	0.001	2.67 (1.61 to 4.42)	< 0.001
NYHA per class	1.23 (1.00 to 1.52)	0.052		
Maximum aneurysm size per cm	1.90 (1.65 to 2.18)	< 0.001	2.19 (1.81 to 2.65)	< 0.001
Age at consent (years)				
61–70	2.50 (0.76 to 5.43)	< 0.001	1.30 (0.41 to 4.14)	0.0103
71–80	3.49 (1.26 to 9.66)		1.47 (0.51 to 4.23)	
> 80	7.01 (2.50 to 19.62)		3.36 (1.15 to 9.87)	

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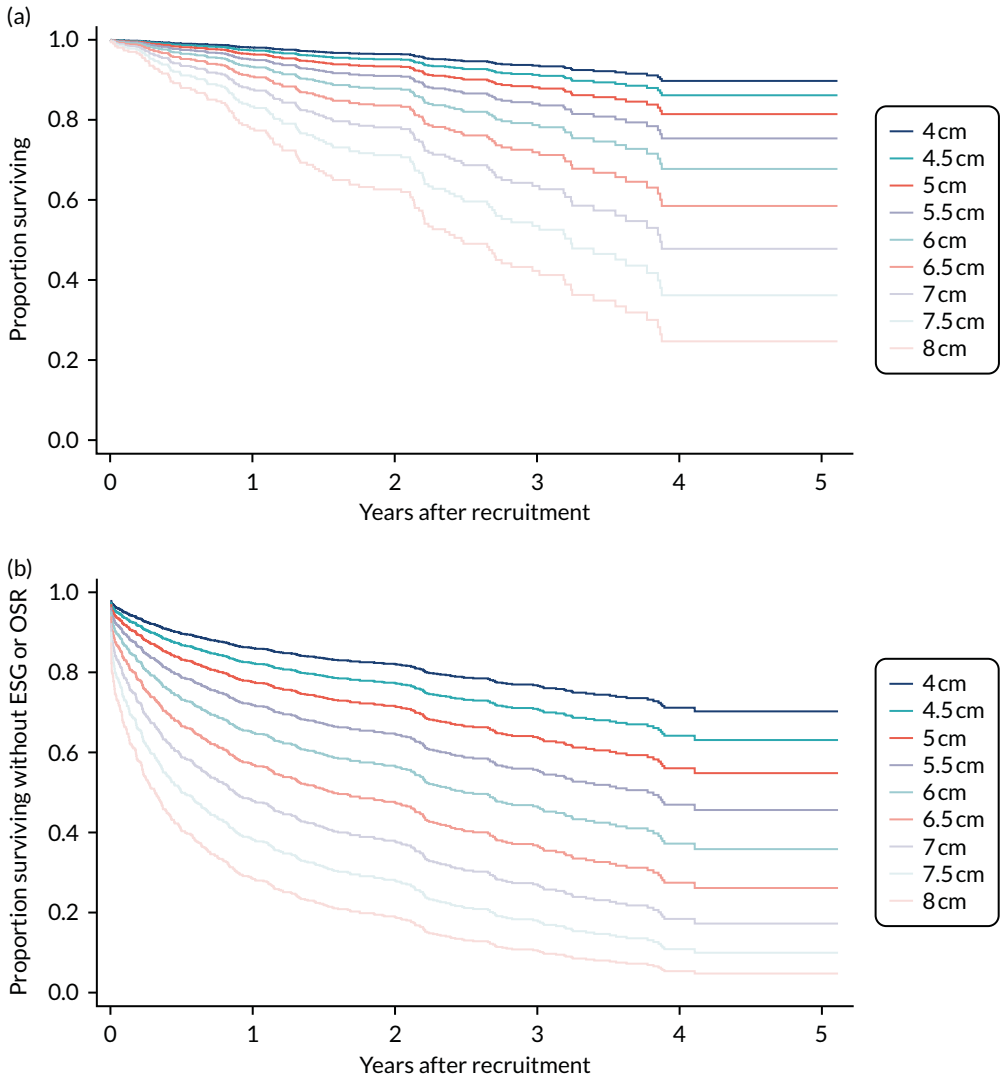

FIGURE 8 Predicted overall survival (a) and time to composite event of death, ESG or OSR (b) by maximum aneurysm at baseline, using Cox regression, with all other variables set to their average. Adapted from Sharples *et al.*[64] © The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial re-use distribution and reproduction in any medium provided the original work is properly cited. The figure includes minor additions and formatting changes to the original figure.

These predictions will underestimate the death rates if people undergoing procedures are at greater risk than people with similar characteristics who do not undergo procedures. Thus, we also provide predicted time to the composite outcome of death or intervention. This provides a worst-case scenario as it assumes that a patient would die on the day of the procedure if this were not performed.

There was weak evidence that increasing NYHA class was associated with increasing risk of all-cause death. In particular, CM and a range of comorbidity markers were not significant in the final model once age, sex, aneurysm size and NYHA class were included. The relatively small number of deaths meant that these models had limited power to detect small to moderate risk factors for death.

Frailty models showed that, given the small number of events, there was no evidence of variation between hospitals in the death rates, so this was not included in the models presented.

All survival models above used complete-case analysis. The results of repeating the analysis using multiple imputation for missing covariates were almost identical (see *Appendix 2*), showing that

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the results were not sensitive to missing data, provided that the assumption of MAR conditional on observed covariates holds. If there is some unknown missing data mechanism that depends on characteristics that were not measured in the ETTAA study, some bias in results could result. We consider this unlikely, given the comprehensive covariate adjustment in the imputation process.

We also refitted the final models with ESG and OSR treated as competing risks. This did not affect the main messages from this analysis, but the effect of baseline maximum aneurysm size was lower for both overall survival (HR 1.58, 95% CI 1.37 to 1.82; $p < 0.001$) and aneurysm-related survival (HR 1.81, 95% CI 1.51 to 2.17; $p < 0.001$).

Hospital admissions

Hospital admissions and non-fatal clinical events prior to any procedure are reported in *Table 14* WW and CM patients respectively, and patients who went on to have interventions after this period. During the pre-procedure period, 363 admissions were reported in 222 patients; WW and patients who subsequently had OSR recorded admission rates of 0.22 and 0.18 per patient per-year of follow-up. Adjusting for age and sex, the difference between groups in overall pre-procedure admission rates was significant ($p = 0.016$). Taking WW as the reference group, the relative admission rate was 1.31 (95% CI 0.89 to 1.92) for CM patients, 2.10 (95% CI 1.30 to 3.42) for subsequent ESG recipients and 0.90 (95% CI 0.46 to 1.76) for subsequent OSR recipients. This may reflect the greater number of comorbidities in CM and (subsequent) ESG patients.

Fifty-two (definitely or probably) aneurysm-related hospital admissions were recorded in 39 separate patients. The aneurysm-related readmission rate was 0.18 per patient per-year in the patients who subsequently had ESG and was significantly lower in the other three groups ($p = 0.0003$ likelihood-ratio test, negative binomial regression). Only two non-fatal ruptures and seven dissections were reported. Three of these events were within 1 month of a CT scan and had maximal aneurysm diameters of 5.64 cm, 6.91 cm and 8.29 cm. In the other six events the maximal aneurysm sizes ranged from 4.56 cm to 6.98 cm, but scans had not been carried out within 6 months of the event. Eight non-fatal neurological events were reported (four cerebrovascular accidents and four transient ischaemic attacks).

Health-related quality of life over time from recruitment

Descriptive analysis

During the study, 3732 pre-procedure HRQoL questionnaires were returned by 886 patients. After blank forms ($n = 256$), duplicate entries ($n = 11$) and incomplete forms ($n = 35$) were excluded, 3492 (93.6%) questionnaires remained. Overall, 855 of 886 (96.5%) patients completed between one and nine EQ-5D-5L questionnaires. Of these 855 patients, 179 completed a single questionnaire, leaving 676 (79.1%) who contributed to the longitudinal analysis. *Figure 9* shows the HRQoL trajectories over time pre procedure for the four treatment groups. These plots show recognised ceiling effects (maximum health) and very wide variation between patients at recruitment. Patterns over time are difficult to unravel from the plots, but CM patients appear to have lower HRQoL at baseline and there is some sign of a general decline in all groups.

At least two pre-intervention EQ-5D-5L questionnaires were completed by 450 WW, 105 CM, 82 ESG and 64 OSR patients. Mean (SD) utilities at recruitment for these patients were 0.73 (0.23), 0.68 (0.25), 0.77 (0.24) and 0.76 (0.18), respectively. According to Szende *et al.*,[69] the population average in the UK is 0.785 for people aged 65–74 years and 0.734 for people aged ≥ 75 years, so the ETTAA cohort reported slightly worse HRQoL than the UK population of similar age. Future ESG and OSR patients had similar average HRQoL, despite the 5-year difference in average age. Patients allocated to intervention groups often left the pre-intervention phase before a second assessment had been made; ESG patients were less likely than other patients to complete baseline forms.

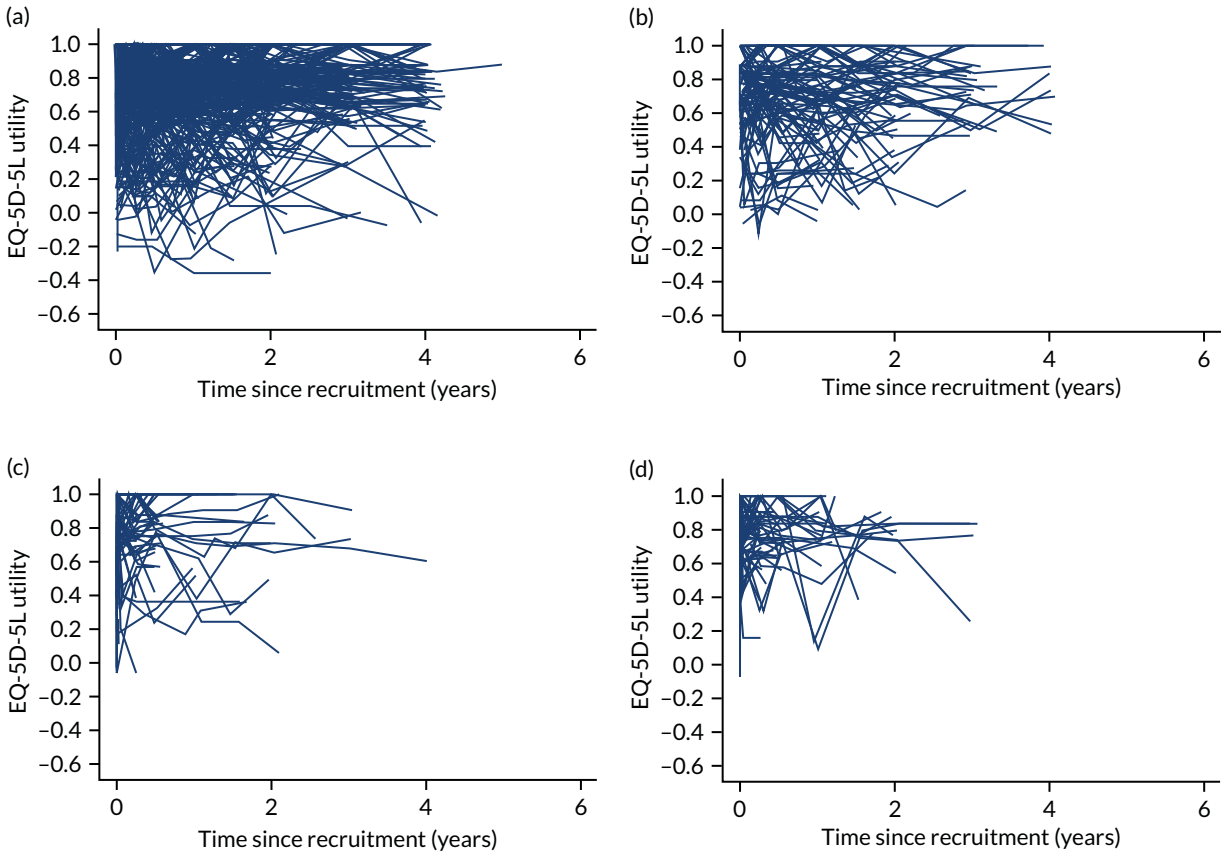

FIGURE 9 The EQ-5D-5L utilities over time, according to management group: (a) WW; (b) CM; (c) ESG; and (d) OSR.

Results of modelling

The final model describing HRQoL trajectories in the absence of treatment is shown in the *Appendix 7*, and a brief summary is provided here.

At time zero, all covariate values are zero if the patient is male, is of average age (70.9 years), is in the WW group, has never smoked, does not receive formal/informal care and is in NYHA class I. For these 'zero' patients, average HRQoL at recruitment (time zero) was 0.85 (95% CI 0.82 to 0.88) (*Table 17*).

At recruitment (time zero), across all management groups, there was weak evidence that women had lower HRQoL (−0.029, 95% CI −0.55 to −0.003). The average age at recruitment was just under 71 years and HRQoL at recruitment actually increased slightly with age (0.013 per decade, 95% CI 0.000 to 0.025),

TABLE 17 Model estimates of the mean HRQoL (95% CI) at time of consent to the ETTAA study by final management group and baseline covariates

Variable	WW group	CM group	ESG group	OSR group
All covariates zero[a]	0.85 (0.82 to 0.88)	0.83 (0.78 to 0.89)	0.86 (0.81 to 0.92)	0.82 (0.76 to 0.87)
Formal/informal care	0.64 (0.58 to 0.70)	0.71 (0.61 to 0.81)	0.65 (0.51 to 0.79)	0.82 (0.68 to 0.96)
NYHA class				
II	0.76 (0.73 to 0.79)	0.71 (0.67 to 0.75)	0.70 (0.65 to 0.75)	0.76 (0.71 to 0.81)
III	0.67 (0.63 to 0.71)	0.58 (0.52 to 0.64)	0.54 (0.46 to 0.62)	0.71 (0.64 to 0.78)
IV	0.58 (0.53 to 0.63)	0.45 (0.35 to 0.55)	0.37 (0.25 to 0.49)	0.66 (0.54 to 0.78)

a Male of average age, no formal/informal care, never smoked and NYHA class I.

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possibly as a result of selection policies. In terms of patients *not* requiring formal/informal care, the management groups had similar average HRQoL at recruitment (all else being equal). There was weak evidence that current smokers had worse HRQoL (−0.047, 95% CI −0.091 to −0.004) at recruitment than ex-smokers or never-smokers in all management groups. Reported requirement for formal/informal care had a very large impact on HRQoL at recruitment in WW, CM and ESG patients, but HRQoL was not adversely affected by the reported need for care in OSR patients (see *Table 17*). In the WW group, HRQoL at recruitment was lower by −0.089 (95% CI −0.11 to −0.069) for each one-class increase in NYHA classification. The interaction between management group and NYHA class shows that the relationship with increasing NYHA class is even stronger in CM and ESG patients than in WW patients, but slightly less strong in OSR patients (see *Table 17*).

For the relatively fit patients with zero covariates at baseline, HRQoL did not change significantly over time (estimated decrease −0.010 per year, 95% CI −0.022 to 0.003 per year). However, the interaction between follow-up time and age showed that for two patients who differ in age by 10 years, the older patient has a faster decrease in HRQoL of −0.013 (95% CI −0.019 to −0.007) per year (all else being equal). As a result, the higher HRQoL (baseline, 0.013; change in the first year, −0.013) between age groups increased over time thereafter. Moreover, there was reasonably strong evidence that current smokers had a faster decline in HRQoL than non-smokers and ex-smokers (estimated regression parameter −0.034, 95% CI −0.057 to −0.01; $p = 0.004$) per year. *Figure 10* shows the estimated trajectories for variables that affected rate of decline in HRQoL. This shows that, in this cohort, smoking has a much greater influence on HRQoL than a 10-year increase in age.

Significant random effects indicated that HRQoL varied significantly between patients both at recruitment and in the rate of decline over time, in addition to the variation that could be attributed to the variables in the model. There were also some differences between the management groups in how much patients varied around the average at recruitment.

Perhaps of greater interest were the variables that did not significantly affect HRQoL, including aneurysm size and comorbidities such as COPD, coronary heart disease and valvular heart disease, although age and the use of formal/informal care (reflecting frailty) were associated with these comorbidities and possibly acted as surrogates.

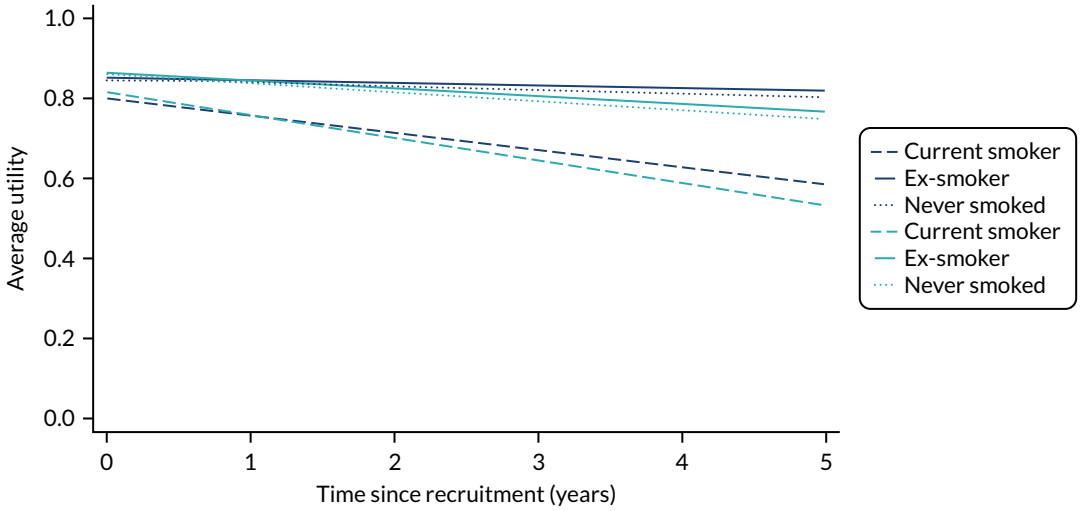

FIGURE 10 Model-estimated HRQoL over time by smoking history and age (dark blue is average age of 70.9 years, light blue is average age + 10 = 80.9 years), with all other covariates set to zero (patient is WW, male, no formal/informal care, NYHA class I).

Summary of findings

This analysis shows that CTAA patients present with widely varying aneurysm sizes. Some of the variation can be explained by patient age, height, smoking history and comorbidities, as well as the site of the aneurysm. In addition, there was variation between aneurysms at presentation that was not explained by the baseline variables recorded in the ETTAA study (significant random intercepts). At presentation, aneurysms in the DTA were significantly larger than in all other sections of the aorta, and they grew faster over time. This may result from the differences in tissue types in different sections of the aorta. Alternatively, the more linear anatomy of this section of the vessel may allow greater expansion before the aneurysm becomes clinically apparent or results in rupture or dissection. We did not observe growth of aneurysms in the ascending aorta. Our inclusion criteria allowed previous intervention for aneurysms in the ascending aorta, and 21.2% of patients had received previous surgery on the ascending aorta or aortic root. A complication in the analysis of this segment is that growth was measured from diagnosis, which may well have preceded surgery in the ascending aorta. A post hoc analysis restricted to measurements in the ascending aorta only showed that there was almost no growth in patients who did not report previous surgery (0.018 cm per year) and a significant decrease in those who did receive surgery (–0.092 cm per year). This suggests that at least some surgery took place between diagnosis (time zero) and entry into the ETTAA study. Unfortunately, the date of previous surgery was not recorded.

The relationship between results from MRI and CT scans over time is difficult to explain. One possible explanation is that, after the initial scan, clinicians may direct patients with slower-growing aneurysms towards MRI and refer patients for CT if growth appears to be accelerating. This potential selection bias induces a difference in aneurysm size over time.

Almost all patients (88%) had hypertension at consent and were treated with one or more antihypertensive medications. Thus, our analysis was not able to identify significant effects of specific antihypertensive drugs. The observational nature of the study may also result in treatment by indication bias, whereby higher-risk patients are treated with more powerful or more expensive drugs, underestimating the treatment effects of the drugs. Such bias is difficult to adjust for unless there are very detailed data on the reasons for the use of single drugs or combination treatments.

The all-cause death rate during this period was relatively high, at 8.6% per patient-year. This compares with the 1-year probability of death for English men aged 71 years of 2.1% and for women 1.4%.[70] Around half the observed deaths in the ETTAA study had a rupture, dissection or other aneurysm-related cause. Comparisons of CM and non-CM patients showed that clinicians successfully identify patients at higher risk from their characteristics and clinical history. As might be expected each 1-cm increase in aneurysm size doubled the hazards of all-cause and aneurysm-related death in the absence of surgical intervention. We note that the relationship between aneurysm size and (log) hazard was linear over the range of aneurysm sizes observed. However, patients leave this analysis when aneurysms become large enough for intervention or through death, so that the pattern of growth outside this range is not known and extrapolation is not valid. The very large and accelerating increase in hazards with each decade increase in age was also expected. The higher risk of death for women in this age group was less predictable and may indicate that women presented at a later stage in their disease or when they also had other comorbidities. There is no evidence that women had longer follow-up after consent than men, so any delays due to (patient or clinician) selection were more likely to have occurred prior to referral to participating MDTs.

We included management group in the analysis of clinical events and HRQoL, even though this was not always decided at baseline. Although this is generally not recommended by statisticians, our rationale was to explore the empirical data rather than establish causal relationships between baseline variables and outcomes. Results should be interpreted with this in mind. From *Chapter 3*, ESG patients on average were older, had poorer LV function, and were more likely to be current smokers and have COPD.

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The index aneurysm was also more likely to be in the DTA for this group; on this basis ESG patients were more likely to have faster-growing aneurysms before the procedure. The analysis of pre-procedure clinical events and HRQoL also showed that ESG patients had a faster decrease in HRQoL, especially if they also reported formal/informal care or a high NYHA class, and more admissions to hospital for aneurysm-related and other causes prior to the intervention. These factors will be important and must be taken into account when comparing intervention groups in *Chapters 5*, *6* (clinical outcomes) and *7* (cost-effectiveness).

Chapter 5 Post-procedure outcomes for intervention groups

Introduction

This chapter provides further details of patients who underwent ESG or OSR and investigates variables associated with post-procedure survival and HRQoL outcomes in each group separately, using traditional regression methods. The Delphi study reported in *Chapter 2* showed that there was consensus among clinicians about management options for patients with specific aneurysm and patient-related characteristics. Here we assess whether or not clinician opinion is borne out by clinical practice and summarise differences in outcomes between interventions. This analysis is in preparation for comparisons in *Chapters 6* and *7* of outcomes for patients who could undergo both interventions.

Aims of analysis of outcomes following a procedure

The aims in this chapter are to:

- quantify post-procedure clinical outcomes of survival (primary outcome), complications, reinterventions, readmission and HRQoL within treatment groups ESG and OSR separately
- assess variables associated with survival and HRQoL
- compare patient characteristics and clinical histories of ESG and OSR patients for future comparison.

Methods

Population

All patients who underwent at least one ESG or OSR procedure were included in this analysis from the date of hospital admission for the index procedure to death, withdrawal or the end of the ETTAA study. Consistent with the observational study protocol, patients were analysed according to the treatment received, irrespective of management plans at recruitment.

Outcomes

The primary outcome was survival from the date of the index procedure to either death or censoring date. Secondary outcomes were clinical complications, death within 30 days of procedure, reinterventions, readmissions to hospital for aneurysm or cardiac causes, length of stay and HRQoL from procedure to end of follow-up, as defined in *Chapter 3*.

Statistical analysis

Survival

Owing to the small number of deaths within 30 days, these were summarised with other procedure complications. Overall survival was summarised by Kaplan–Meier incidence plots, and exploratory comparisons used log-rank tests. The association between potential risk factors and survival was modelled by Cox proportional hazards models, after confirming validity of the proportional hazards assumption using Kaplan–Meier plots and Schoenfeld residuals. Initial exploratory analysis identified variables where the z-statistic from the univariable Cox model had a p-value of < 0.2. These variables were considered for the multivariable model using backward selection based on z-statistics. The final

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model was re-estimated using multiple imputation using chained equations with 30 imputed data sets (see *Chapter 3* and *Appendix 2*).

Complications, reinterventions, readmission and length of stay

Complications following all procedures were pooled and analysed as a binary response for each patient (none/any) and as counts (number of complications per patient). Reintervention included planned and unplanned additional procedures and other reasons for return to theatre. Length of hospital stay was measured from date of procedure to the date of discharge or transfer. Readmissions to hospital for (definitely/probably) aneurysm-related or other cardiac events were summarised as rates per patient-year at risk and confidence intervals for the following time periods: 0–3, 4–6 and 7–12 months and annually thereafter. They included reinterventions (ESG followed by another ESG, or OSR followed by either another OSR or ESG).

Owing to the small number of patients and events, simple tests comparing proportions or event rates were performed for complications, clinical events and readmissions and no modelling was undertaken. For readmissions to hospital the relative rate of readmission was estimated using negative binomial regression to allow for repeated readmissions for individual patients and included time at risk, index procedure, age and sex.

Health-related quality of life

Repeated measures of HRQoL assessed by EQ-5D-5L utilities were analysed using linear mixed models as described in *Chapter 4*. Continuous time was assumed, with actual rather than nominal times of measurement. Preliminary analysis revealed a temporary decrease in utilities in the OSR group after surgery; to model this, a marker variable for early postoperative assessment (first 6 weeks) was considered, together with an interaction between group and early postoperative assessment. Preoperative patient characteristics and clinical variables measured closest to the index procedure were investigated for this analysis. The final model had the following form.

$$U_{it} = \beta_0 + (\beta_1 + \beta_{1F} female_i)\tau_{it} + (\beta_2 + \beta_{2P} OSR_i)\delta_{it} + \theta^T x_i + u_i + \varepsilon_{it}, \quad (3)$$

where:

- τ_{it} is the time (from the procedure) of the tth measurement from patient i and δ_{it} is a marker of whether that measurement was in the first 6 weeks
- x_i is a vector of procedure baseline variables including early postoperative assessment, aneurysm site and treatment group for patient i
- (β_0, β_1, β_{1F}, β_2, β_{2P}, θ) are coefficients for the fixed effects, including interactions between sex and time (β_{1F}) and between procedure and the first 6 weeks (β_{2P})
- $u_i | x_i \sim N(0, \sigma_u^2)$ are random intercepts
- $\varepsilon_{it} | u_i, x_i \sim N(0, \sigma_\varepsilon^2)$ are residual errors, with σ_ε^2 differing between the two intervention groups.

Again, estimates from this analysis are unbiased provided that data are *missing at random*, conditional on observed data. Model fit was assessed by fitted and residual plots.

Results

Baseline predictors

Baseline variables at consent for the two intervention groups were provided in *Tables 8–10*. These variables recorded before but closest to the procedure are summarised in the *Appendix 8*, although changes from baseline were small.

There were important differences between the two groups at the time of their procedures. Excluding missing covariates, compared with OSR patients, ESG patients were older (mean age difference 7.1 years, 95% CI 4.7 to 9.5 years; $p < 0.0001$), were smaller (mean height difference −3.7 cm, 95% CI −6.3 to −1.2 cm; $p = 0.0041$ and mean weight difference −5.3 kg, 95% CI −9.2 to −1.4 kg; $p = 0.0075$) and were more likely to be current or past smokers (75.8% vs 66.4%; $p = 0.080$). The differences in height and weight were partially explained by the higher proportion of CTD patients in the OSR group, although the differences remained significant when these patients were removed (mean height difference −2.7 cm, 95% CI −5.2 to −0.1 cm; $p = 0.0381$ and mean weight difference −5.0 kg, 95% CI −9.1 to −0.9 kg; $p = 0.0172$). ESG patients were more likely to have valve disease (89.9% vs. 71.6%; $p < 0.0001$), COPD (21.3% vs. 13.3%; $p = 0.087$) and stage III/IV NYHA (22.3% vs. 16.0%; $p = 0.217$). Patients with connective tissue disorders almost invariably underwent OSR (14.8% vs. 1.3%; $p < 0.0001$). A very high proportion of patients (90.7% ESG, 85.2% OSR) had hypertension; there was no difference between groups in the numbers who were prescribed antihypertensive medications (88.7% vs. 85.2%; $p = 0.486$). ESG patients were more likely to report use of statins (69.3% vs. 42.2%; $p < 0.0001$). Serum creatinine and haemoglobin measurements were missing for approximately 19% of cases in each group. For those with complete data ESG patients had similar renal function (mean serum creatinine difference −7.1 µmol/l, 95% CI −16.0 to 1.8 µmol/l; $p = 0.1191$) but lower levels of haemoglobin (mean haemoglobin difference −6.8 g/l, 95% CI −11.2 to −2.4 g/l; $p = 0.0026$) than OSR patients.

Despite differences in age and other covariates between the groups, mean (SD) HRQoL utilities before the procedures were the same, 0.73 (0.24) for ESG and 0.73 (0.26) for OSR.

Description of outcomes

Outcomes from the procedure

Endovascular stent grafting patients spent a median of 3.15 (quartiles 2.07, 5.08) hours in surgery compared with 8.52 (quartiles 7.25, 9.70) hours for OSR patients ($p < 0.0001$). Ten (6.7%) ESG and 15 (11.1%) OSR patients died within 30 days of the procedure ($p = 0.2107$). Two of the ten ESG patients were discharged alive but died at home within 30 days.

Non-fatal complications during the procedure and associated admission are listed in *Table 18*. In the OSR group one patient had a ruptured aneurysm and one had a dissection. In the ESG group there were 14 intraoperative stent-related complications in 14 different patients recorded during the primary stenting procedure: six endoleaks (three of type I and three of type II), treated either by insertion of an additional stent ($n = 2$), re-ballooning ($n = 2$) or conservatively ($n = 2$); five injuries to the access vessel [two bleeding (one requiring surgery), one pseudoaneurysm, one dissection (treated by insertion of an additional stent) and one 'peripheral arterial disease – small external iliac artery'] and three complications of the stent graft [one migration, one incomplete procedure (no details given) and one 'balloon moulding to smooth stent'].

Post procedure, OSR patients required a significantly longer stay in ICU [median 5 days (quartiles 3, 10 days) vs. median 0.5 (quartiles 0, 3) days; $p < 0.0001$] and a longer stay in hospital than ESG patients [median 16 days (quartiles 10, 23 days) vs. median 7 days (quartiles 4, 12 days), $p < 0.0001$]. OSR patients were more likely to have cardiac, gastrointestinal, neurological and infection complications, and to require cardiac, pulmonary and renal support during admission, than ESG patients. Return-to-theatre rates were slightly higher in the OSR group, but not significantly so (see *Appendix 9*; $p = 0.3722$). The main reasons for return to theatre were access injuries, aneurysm complications and endoleaks after ESG, and aneurysm injuries and other acute surgical complications after OSR. The total number of complications was much larger in the OSR group (240 vs. 98; relative rate 2.72, 95% CI 2.04 to 3.68; $p < 0.0001$). Overall, 58 (38.7%) ESG and 103 (76.3%) OSR patients had an adverse event during the index procedure admission ($p < 0.0001$).

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TABLE 18 Summaries of complications during the index procedure admission

	Patient subgroup (number of patients)	
	ESG ($N = 150$)	OSR ($N = 135$)
Number of deaths within 30 days, *n* (%)	10 (6.7)	15 (11.1)
During index procedure		
Number of complications		
Dissection	0	1
Rupture	0	1
Stent complications	3	–
Stent access vessel injury	5	–
Endoleak	6	–
During index procedure admission		
Number of complications		
Myocardial infarction	9	2
Gastrointestinal	7	12
Neurological	5	13
Cerebrovascular accident	4	11
Transient ischaemic attack	1	2
Spinal cord injury	5	4
Paraparesis	2	0
Paraplegia	3	4
Thromboembolic event	3	7
Deep-vein thrombosis	0	3
Pulmonary embolism	1	3
Not recorded	2	1
Infection	17	44
Vocal cord palsy	2	7
Number of patients requiring additional support		
Inotropes/intra-aortic balloon pump	27	79
Prolonged ventilation	5	37
Renal support	2	15
Return to theatre	16	20
Total number of events	98	240
Total number of people with ≥ 1 event (%)	58 (38.7)	103 (76.3)

Survival, hospital readmissions and aneurysm-related events

Survival post procedure: descriptive analysis

The primary outcome was overall survival after the procedure. During follow-up, 40 ESG and 36 OSR patients died, of whom 17 and 25, respectively, died from aneurysm-related causes; these included deaths within 30 days (*Table 19*). The 1-year overall death rate was 17.5% (95% CI 12.2% to 24.8%) after ESG and 20.7% (95% CI 14.6% to 28.9%) after OSR; the 3-year death rate was 34.7% (95% CI 26.1% to 45.1%) after ESG and 31.9% (95% CI 23.7% to 42.2%) after OSR (*Figure 11a*). For aneurysm-related deaths, the 1-year rate was 10.2% (95% CI 6.2% to 16.6%) after ESG and 12.3% (95% CI 10.9% to 24.1%) after OSR;

TABLE 19 Number of patients with re-admissions and clinical events after the index procedure

	Patient subgroup	
	ESG ($N = 150$)	OSR ($N = 135$)
Total time at risk (years)	265.2	253.4
Deaths overall (rate/year)	40 (0.15)	36 (0.14)
Aneurysm-related deaths (rate/year)	17 (0.06)	25 (0.10)
All readmissions, *n* (rate/year)	111 (0.42)	87 (0.34)
People with at least one readmission, *n* (%)	61 (40.7)	43 (31.9)
Readmissions, definitely/probably aneurysm related, *n* (rate/year)	40 (0.15)	23 (0.09)
Patients readmitted, definitely/probably aneurysm related, *n* (%)	26 (17.3)	17 (12.6)
Non-fatal ruptured aneurysms	0	0
Non-fatal dissected aneurysms	3	1
Non-fatal neurological events	4	0

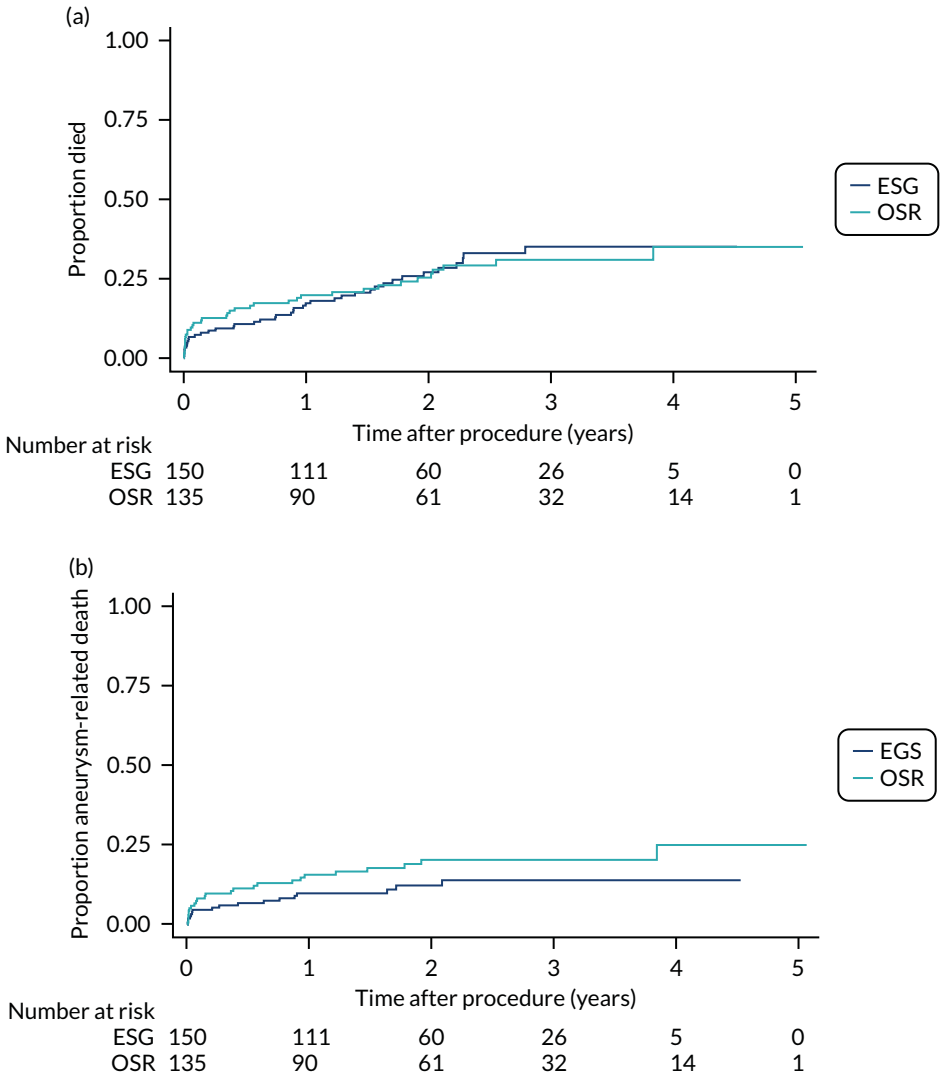

FIGURE 11 Kaplan–Meier cumulative incidence curves for post-intervention death from any cause and aneurysm-related deaths by ESG and OSR groups. (a) Kaplan–Meier deaths from any cause; and (b) Kaplan–Meier aneurysm-related deaths.

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the 3-year rate was 14.3% (95% CI 8.8% to 22.7%) after ESG and 20.6% (95% CI 14.3% to 29.3%) after OSR (*Figure 11b*). Despite the slightly higher aneurysm-related death rate for OSR patients in the first 30 days, there was no significant difference between the groups in time to death overall (log-rank $p = 0.9918$) or in aneurysm-related death (log-rank $p = 0.1107$).

Survival: results of modelling

Table 20 shows the variables for which the *p*-value of the HR test (H_0: HR = 1) was, at most, 0.2 in univariable models for all-cause deaths and aneurysm-related deaths; we also include OSR, despite the higher *p*-value. For only 2 out of 150 (1.3%) ESG procedures, the location of the maximum aneurysm diameter was the ascending aorta or arch, so these two variables have considerable overlap. Therefore, these were combined into a three-level variable (ESG in the DTA, OSR in the DTA, any procedure in the ascending aorta/arch). Similarly, patients were treated with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), but rarely with both, so these were also analysed together as a three-level variable (neither drug, ACE inhibitor only or ARB with or without ACE inhibitor).

In univariable Cox models for all-cause mortality, the two procedures had similar survival probabilities, despite the older age and higher risk profile of ESG patients. There was weak evidence that aneurysms where the maximum diameter was in the DTA/thoracoabdominal aorta conferred a higher risk of death. The strongest associations with all-cause death were age at procedure, higher NYHA class and

TABLE 20 Univariable Cox regression results for post-intervention all-cause and aneurysm-related deaths during follow-up: complete-case analysis

	All-cause deaths		Aneurysm-related deaths	
Variable	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
OSR	1.00 (0.64 to 1.57)	0.992	1.64 (0.87 to 3.04)	0.115
Maximum aneurysm site DTA/TCAA	2.00 (0.92 to 4.34)	0.082		
Ascending/arch procedure	(Reference category)	0.134	(Reference category)	0.043
OSR in DTA/TCAA	2.29 (1.01 to 5.23)		2.70 (0.93 to 7.87)	
ESG in DTA/TCAA	1.81 (0.81 to 4.06)		1.33 (0.45 to 3.98)	
Age (per decade)	1.37 (1.08 to 1.74)	0.010		
Female			1.83 (1.00 to 3.36)	0.052
Weight (per kg)	0.99 (0.98 to 1.00)	0.152		
BMI (per kg/m^2)	0.96 (0.91 to 1.01)	0.141		
Per month since recruitment	1.03 (1.01 to 1.05)	0.003	1.03 (1.01 to 1.06)	0.010
NYHA per class	1.41 (1.08 to 1.84)	0.013	1.28 (0.89 to 1.84)	0.184
COPD	1.50 (0.89 to 2.55)	0.131		
ACE inhibitor	0.60 (0.35 to 1.05)	0.071		
ARB	1.61 (0.98 to 2.65)	0.059	1.57 (0.80 to 3.06)	0.190
Neither	(Reference category)	0.069		
ACE inhibitor only	0.64 (0.36 to 1.17)			
ARB ± ACE inhibitor	1.40 (0.83 to 2.37)			
Any antihypertensive medication	1.95 (0.85 to 4.49)	0.116		

TCAA, thoracoabdominal aorta.

longer time between recruitment to the ETTAA study and procedure. The median time between recruitment and procedure was longer for OSR patients than for ESG patients (82 vs. 64 days), although this difference was not significant at traditional levels ($p = 0.5682$).

The smaller number of aneurysm-related deaths meant that only the procedure/location of maximum aneurysm diameter, female sex and time since recruitment were weakly significant in univariable analyses for this outcome.

The final multivariable models for all-cause and aneurysm-related deaths are shown in *Table 21*. For all-cause mortality, procedures for aneurysms in the ascending aorta/arch (mostly OSR) had lowest risk, whereas OSR for maximum aneurysms in other vessels had highest risk. Age at procedure conferred an increase in risk, with a HR of 1.48 (95% CI 1.12 to 1.94) for each 10-year increase in age, and the hazard was multiplied by 1.39 (95% CI 1.06 to 1.82) for each one-class increase in NYHA class. Owing to the smaller number of aneurysm-related deaths, neither age nor NYHA class was significantly associated with this outcome, but female patients were found to have a higher risk of aneurysm-related death. The length of time in the study before the procedure was associated with higher risk of both all-cause and aneurysm-related death. These associations were almost identical after the imputation of missing covariates (see *Appendix 2*).

For clarity it is worthwhile to refit these multivariable models including procedure group but excluding aneurysm site; the HR for OSR was 1.27 (95% CI 0.78 to 2.09; $p = 0.332$) for overall deaths and 1.59 (95% CI 0.86 to 2.96; $p = 0.140$) for aneurysm-related deaths. Thus, overall there is a non-significant increase in all-cause and aneurysm-related deaths among OSR patients.

Readmissions after discharge from the index procedure

Table 19 shows the readmissions after discharge from the index procedure. During a total of 265.2 years of follow-up, ESG patients were readmitted 111 times, a rate of 0.42 (0.35, 0.49) per patient-year (i.e. on average 42% of patients admitted to hospital per year of follow-up). This was higher than the rate for OSR patients (0.34, 95% CI 0.27 to 0.41) per patient-year. The relative hospital readmission rate (adjusted for time at risk) was 0.70 (95% CI 0.44 to 1.11; $p = 0.133$); further adjustment for age and sex increased the relative rate of readmission slightly, to 0.75 (95% CI 0.46 to 1.21; $p = 0.237$). Furthermore, 40.7% of ESG patients were readmitted during follow-up compared with 31.9% of OSR patients ($p = 0.1398$). A similar pattern was observed for aneurysm-related readmissions. No ruptures and only one dissection were reported as the reason for aneurysm-related readmissions.

TABLE 21 Final multivariable Cox regression results for all-cause and aneurysm-related deaths: complete-case analysis

	All-cause deaths		Aneurysm-related deaths	
Variable	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
Ascending/arch procedure	(Reference category)	0.031	(Reference category)	0.041
OSR in DTA/TCAA	2.82 (1.15 to 6.89)		2.86 (0.97 to 8.45)	
ESG in DTA/TCAA	1.61 (0.68 to 3.84)		1.43 (0.48 to 4.30)	
Age (per decade)	1.48 (1.12 to 1.94)	0.005		
Female			2.03 (1.10 to 3.75)	0.024
NYHA (per class)	1.39 (1.06 to 1.82)	0.018		
Pre-operation time in study (per month)	1.03 (1.01 to 1.05)	0.005	1.03 (1.01 to 1.06)	0.019

TCAA, thoracoabdominal aorta.

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Figure 12 shows the pattern of readmissions over time after procedure for the two groups. In the first 3 months, ESG patients were more likely to be readmitted, and thereafter the readmission rates were similar.

Once readmitted, ESG patients spent a median of 6 days (quartiles 2 to 12) in hospital, compared with 5.5 days (quartiles 2 to 10) for OSR patients (Mann–Whitney *U*-test $p = 0.8236$). However, ESG patients were more likely to spend some of the inpatient stay in ICU (25 vs. 7; $p = 0.0064$).

Table 19 shows that 12 ESG patients underwent a second ESG during the study period at a median of 93.5 days after the index procedure (range 18–1076 days). Similarly, four OSR patients had a second OSR at 58, 149, 217 and 371 days post index procedure. Twenty-one OSR patients had a subsequent ESG; one was in the same admission, and the remaining 20 were a median of 173 days (range 11–1100 days) after the index procedure. Three OSR patients had ESG as a third procedure at 208, 908 and 1399 days after the index procedure. OSR patients had more complications during readmissions. All 40 reinterventions were reported as planned as part of a staged procedure. Complications after second and third procedures are summarised in *Appendix 5*.

Post-procedure health-related quality of life

Descriptive analysis

For this analysis the preoperative HRQoL assessment nearest to the date of the procedure was included as a potential predictor of postoperative HRQoL. Forty-three patients had no postoperative assessment of HRQoL; the remaining 242 patients completed between 1 and 12 postoperative questionnaires, resulting in a total of 1082 assessments.

Utility measurement trajectories for individual patients are plotted in *Figure 13*. Again, the ceiling effect at utility = 1 (maximum health) is observed, and there is evidence of wide variation in HRQoL at time zero. Patterns over time were not clear from the trajectories, but initial analysis suggested that both linear and quadratic terms for change over time should be considered for inclusion and that these may differ between the sexes. A marker variable of early postoperative assessment (first 6 weeks) was considered, as was an interaction between group and early postoperative assessment. Again, there was evidence that HRQoL at procedure was more variable in the ESG group.

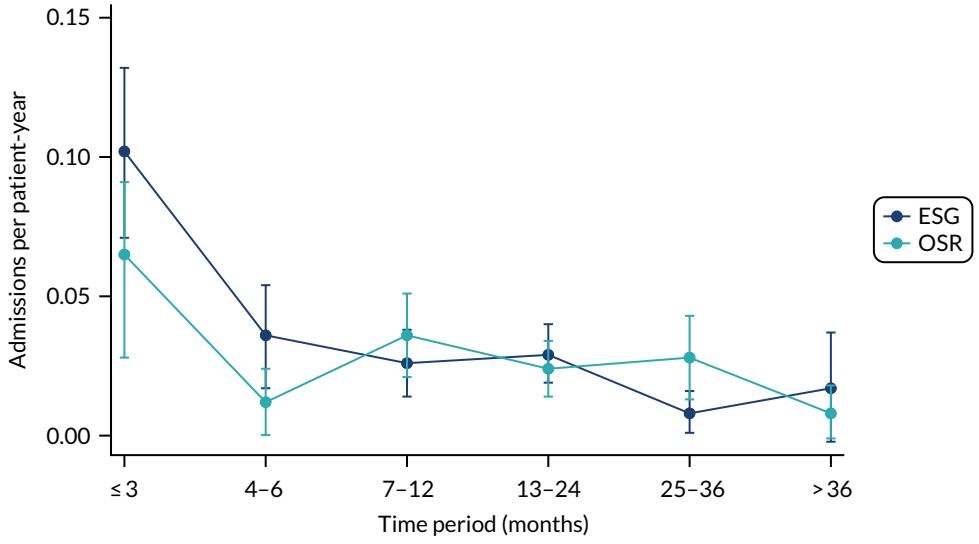

FIGURE 12 Readmissions to hospital (per patient-year at risk) by group and by time after the index procedure.

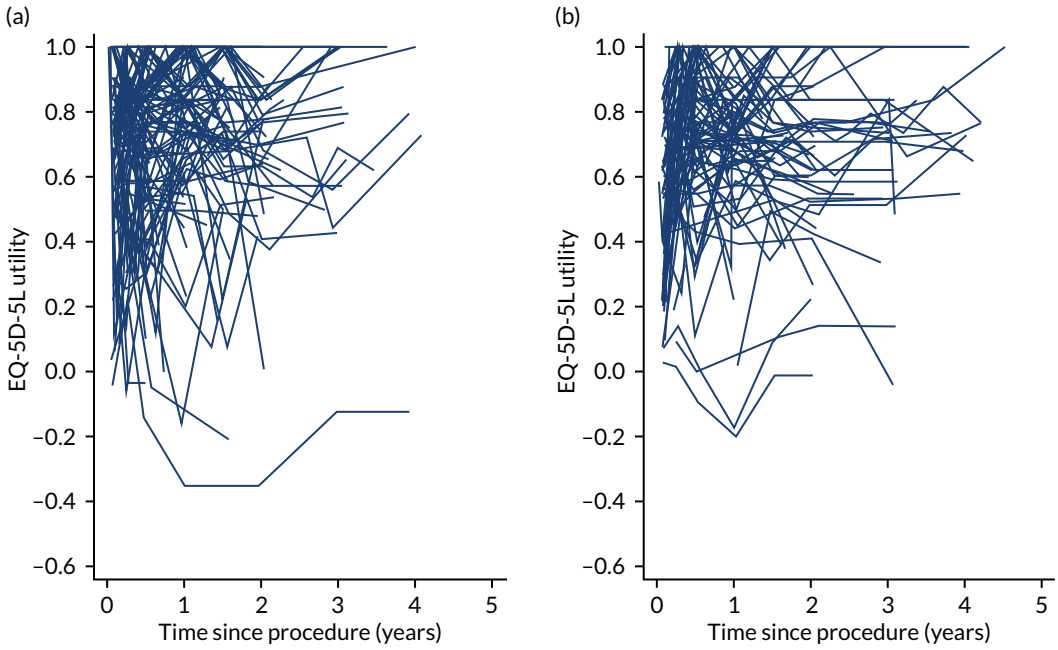

FIGURE 13 Post-procedure EQ-5D-5L utilities over time by intervention group. (a) ESG; and (b) OSR.

Health-related quality-of-life modelling

The final model for postoperative HRQoL is provided in full in *Appendix 10*. Briefly, for a male, non-smoking ESG patient, in NYHA class I, with average preoperative utility of 0.73, the average postoperative HRQoL immediately post ESG was estimated to be 0.785 (95% CI 0.725 to 0.844). This decreased very slightly by −0.001 (95% CI −0.012 to 0.013) per year, with little evidence of acceleration or deceleration. There was a slight non-significant dip in HRQoL of −0.017 (95% CI −0.062 to 0.027) in the first 6 weeks. HRQoL between patients showed significantly more variation in the ESG group than in the OSR group. These results did not change substantially if the analysis excluded second and third stages of a staged procedure.

For OSR patients, there was a substantial, significant decrease in HRQoL in the first 6 weeks after the procedure of −0.160 (95% CI −0.199 to −0.121; $p < 0.001$). Otherwise, the difference between the two procedures during follow-up was not significant (all else being equal). Although female and male OSR patients had the same decrease in HRQoL in the first 6 weeks, the pattern over time was different; women had a slight increase in HRQoL over time, whereas men did not change after the first 6 weeks (*Figure 14*). Finally, in common with pre-procedure analysis, current smokers and those in higher NYHA

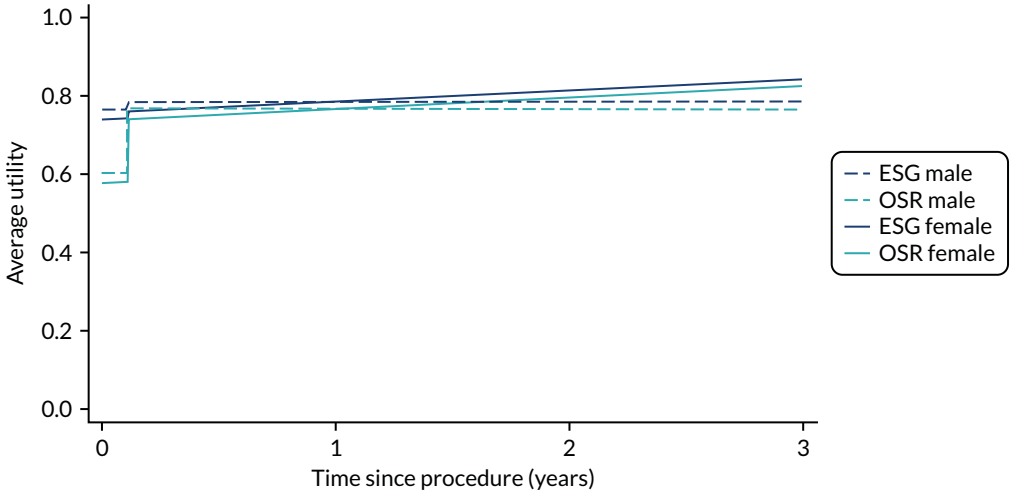

FIGURE 14 Average estimated post-procedure EQ-5D-5L utility over time by sex and intervention group.

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classes had significantly lower HRQoL throughout, with decrements of −0.095 (95% CI −0.171 to −0.020) for current smokers and −0.034 per NYHA class (95% CI −0.066 to −0.003).

Summary of findings

The main differences in clinical outcomes between interventions were (1) higher readmissions in the short term for ESG patients, and (2) the substantially higher incidence of postoperative complications, longer initial hospital stay and subsequent reinterventions in the OSR group. The latter were predictable differences given the more invasive nature of OSR, and they have implications for the economic analysis reported in *Chapter 7*.

Chronic thoracic aortic aneurysm patients were at high risk of death, had a range of comorbidities and had somewhat impaired HRQoL measured by EQ-5D-5L utility at the time of the intervention, compared with a UK age- and sex-matched population. Their management was complicated, with most having treatment in more than one segment of the aorta, 40 out of 285 (14.0%) requiring staged procedures and 13 out of 285 (4.6%) undergoing hybrid (open surgery and endovascular) procedures.

As suggested by the Delphi study report in *Chapter 2* and initial summaries of the cohort in *Chapter 3*, there was clear selection of younger patients for the more invasive intervention (OSR). Consistent with older age, ESG was associated with frailty (smaller frame, lower haemoglobin level) and higher levels of comorbidity (valve disease, COPD, higher NYHA class, use of statins). Although some factors were common to both intervention groups (hypertension), there was almost no overlap of others (ascending aorta surgery, CTD), so that the validity of direct comparisons of the interventions is in doubt and unadjusted results should be interpreted cautiously.

Despite this, outcomes for ESG patients were largely comparable to those for OSR patents. The invasive nature of OSR was associated with a slightly higher risk of death within 30 days (11.1% vs. 6.7%) and more complications reported during postoperative hospital stay (240 vs. 98). Although more ESG patients were readmitted to hospital, especially early after discharge, the overall rate of readmission was not significantly greater in this group and fewer ESG patients had reinterventions for aneurysm-related procedures (12 vs. 28). This may be a result of relatively short follow-up post procedure in this study, as well as the stricter selection of older patients for an intervention.

Overall, OSR patients had higher all-cause and aneurysm-related death rates, but the differences were not significant in this study. When the maximum diameter was in the ascending aorta or arch, this was almost invariably treated with OSR. These patients had significantly lower all-cause and aneurysm-related mortality rates than both OSR and ESG patients who had maximal diameter aneurysms in the DTA/thoracoabdominal aorta. The higher mortality rate after OSR of the DTA/thoracoabdominal aorta may have resulted from the selection of OSR for patients with more extensive disease in this segment, including some CTDs, or patients whose aortic anatomy made stent implant difficult. We should highlight that most patients had surgery/stenting in more than one location and these results refer to the location of the maximum diameter. As expected, survival was influenced by age at procedure. Somewhat less predictably, a longer interval between entry to the study and intervention increased the risk of all-cause and aneurysm-related mortality. The timing of intervention is not straightforward, and there may be a tendency for patients with more complicated surgical management requirements to have delayed surgery. For ETTAA patients, post hoc analysis suggested that longer interval was associated with surgery in the DTA/thoracoabdominal aorta (especially OSR in these vessels), staged procedures, current smoking, previous coronary artery bypass grafting (CABG)/percutaneous coronary intervention (PCI) for coronary artery disease and concomitant valve disease. Owing to low power, none of these was a significant risk factor for all-cause or aneurysm-related death individually, but time interval before intervention may capture their combined effects on outcome. In addition, as patients

wait longer for the intervention, they may develop both increased aneurysm diameter and length, and increased severity of comorbidities over time.

There was a large initial decrease in HRQoL for OSR patients, a feature reported in other cardiothoracic surgery trials,[71,72] including the EVAR 1 trial.[73] This decrease is related to limitations conferred by hospital stay and post-surgical complications. Beyond this period ESG and OSR had similar HRQoL, all else being equal. We should highlight that, in contrast to health economics analyses, we do not impute zeros for patients who have died here. The strongest predictor of postoperative HRQoL was preoperative HRQoL. Both were related to current smoking and NYHA class, which reflects the extent of heart failure by assessing breathlessness, particularly during physical activity. Recommending smoking cessation and optimising the treatment of heart failure may ease these symptoms to some extent, as reported in the OXVASC study,[74] and has been shown to improve outcomes after surgery.[75,76]

The biggest limitation in these analyses was the small number of patients and events, which caused two main problems; first, there was low power to detect differences in outcomes between intervention groups; and, second, there was limited ability to adjust for confounding in regression models. Moreover, a detailed review of aneurysm scans and patient histories showed that many patients were suitable for only one of the two interventions of interest. To ensure a 'fair' comparison between the two intervention groups, it is necessary to exclude any patients who were not suitable for both procedures and apply alternative analysis methods that reduce bias resulting from residual confounding. Propensity score matching or weighting are convenient and relatively straightforward methods, and these are applied in *Chapter 6*.

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Chapter 6 Direct comparison between intervention groups

Introduction

Important differences between the populations undergoing ESG and OSR raised concerns that any comparisons are biased because of unobserved or inadequately controlled confounding. Here we assess the sensitivity of results to alternative analyses that target comparability between groups.

In these analyses it is important to exclude any patients for whom OSR (or ESG) is contraindicated, that is, their probability of receiving OSR (or ESG) is zero (the positivity assumption in propensity methods[77]). It may be plausible to assume that clinician equipoise exists to some extent in the remaining cohort. Then we can either compare the procedures within this cohort or apply propensity score methods to adjust for any residual confounding.

Aims of comparative analysis of outcomes following a procedure

The aims in this chapter are to:

- describe how a subset of ETTAA patients who could have had either ESG or OSR was defined; these are referred to as the 'no-contraindication' cohort
- compare the clinical outcomes of survival, readmission and HRQoL for no-contraindication patients in the treatment groups ESG and OSR
- use propensity score methods to compare the clinical outcomes for no-contraindication patients in the treatment groups ESG and OSR.

Methods

Population

All patients who underwent ESG or OSR procedures as defined in *Chapter 5* were eligible. Patients were excluded if they had a zero or close to zero probability of having either of the procedures. Initially, patients were excluded based on variables that were found to be non-overlapping in the exploratory analysis. All remaining ESG patients were then assessed by a cardiac surgeon; anyone aged > 85 years, with BMI < 20 kg/m^2 or > 35 kg/m^2, with impaired mobility, assessed by the EQ-5D-5L item response severe difficulty walking/self-care, or of NYHA class IV was considered unfit to receive OSR and was excluded. CT/MRI scans for all except seven OSR patients were re-assessed by a vascular surgeon and patients with aneurysms with aortic morphology that could not be managed with ESG were excluded. Seven scans could not be retrieved and analysed by the end of follow-up and these patients were considered suitable for both procedures on the basis of the operation and clinical history CRFs and were included. Finally, because we were interested in the question of whether an open surgical or an endovascular procedure was the better approach for a new patient, any patients for whom the index procedure was the second or third part of a staged procedure were excluded.

Outcomes

Owing to the reduced sample size, outcomes were restricted to all-cause and aneurysm-related mortality, hospital readmissions and HRQoL, as defined in previous chapters.

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Statistical analysis

Initially, the final statistical models developed in *Chapter 5* were refitted for the comparison cohort only. Then, to reduce any residual bias caused by uncontrolled confounders, we completed a propensity score analysis based on methods described in Leyrat *et al.*[78] and Mitra and Reiter.[79] Propensity scores were calculated using binary logistic regression on the probability of OSR, including multiple predictors.[80] Theoretically, there is no limit on the number of predictors than can be used to predict propensity, but, owing to the small sample, we restricted the model to all variables related to the main outcomes (mortality and HRQoL) as well as major associates of treatment. The ability of a propensity score to balance the confounding variables between treatment groups was assessed and the model was refined by adding variables to reduce imbalance.[81,82] The final model included age at procedure, sex, height, need for formal/informal care (as a marker of frailty), COPD, NYHA class, diabetes, hypertension, smoking history, maximum aneurysm size, maximum aneurysm location and preoperative time in the ETTAA study. To assess the sensitivity of the results to different methods, we refitted the main outcome analyses by:

i. matching ESG and OSR participants in a 1 : 1 ratio using the nearest neighbour (with replacement) and excluding any patients without a match
ii. inverse probability of treatment weighting (IPTW), in which the propensity score was used to weight individual responses as follows: $w_i = z_i/ps_i + (1 - z_i)/(1 - ps_i)$, where z_i denotes treatment (1 = OSR, 0 = ESG) for individual i
iii. IPTW excluding patients with extreme weights ($w_i > 5$) that conferred a large influence on results
iv. including the propensity score in regression equations as a covariate.[83]

For matching, we used a calliper width of 0.2 SDs of the logit(propensity score).

The analysis was further complicated by incomplete baseline measurements. Following Leyrat *et al.*[78] our strategy for accommodation of partially complete baseline measurements was as follows:

- Create 30 complete data sets using multiple imputation.
- Calculate the propensity score for each complete data set.
- For predictive mean matching, identify the set of matched patients over all imputed data sets, estimate treatment effects on these matched pairs and combine using Rubin's rules.[62,63]
- For IPTW or regression adjustment, estimate treatment effects for each imputed data set and combine using Rubin's rules.

Variables in the imputation models were the same as those included in the propensity score, as well as serum creatinine. We used 30 imputation data sets because of the relatively large number of patients with missing creatinine.

Results

Definition of no-contraindication cohort

Figure 15 shows how the final no-contraindication cohort was derived. Almost all (20/22) CTD patients and all patients who had either surgery in the ascending aorta or concomitant cardiac surgery had OSR. These violated the positivity assumption required for both comparability and propensity score methods (i.e. they were essentially unsuitable for ESG) and were excluded from the analysis before clinician review.

Overall, 35 ESG patients were excluded from the comparison cohort because they had CTDs ($n = 2$), or the index procedure was stage 2 ($n = 8$) or 3 ($n = 2$) of a staged procedure, or the cardiac surgeon considered them unsuitable for OSR (aged > 85 years, $n = 1$; BMI < 20 kg/m^2 or > 35 kg/m^2, $n = 11$; severe mobility problems, $n = 9$; NYHA class IV, $n = 2$). The remaining 115 (76.7%) ESG patients were considered suitable for OSR in principle.

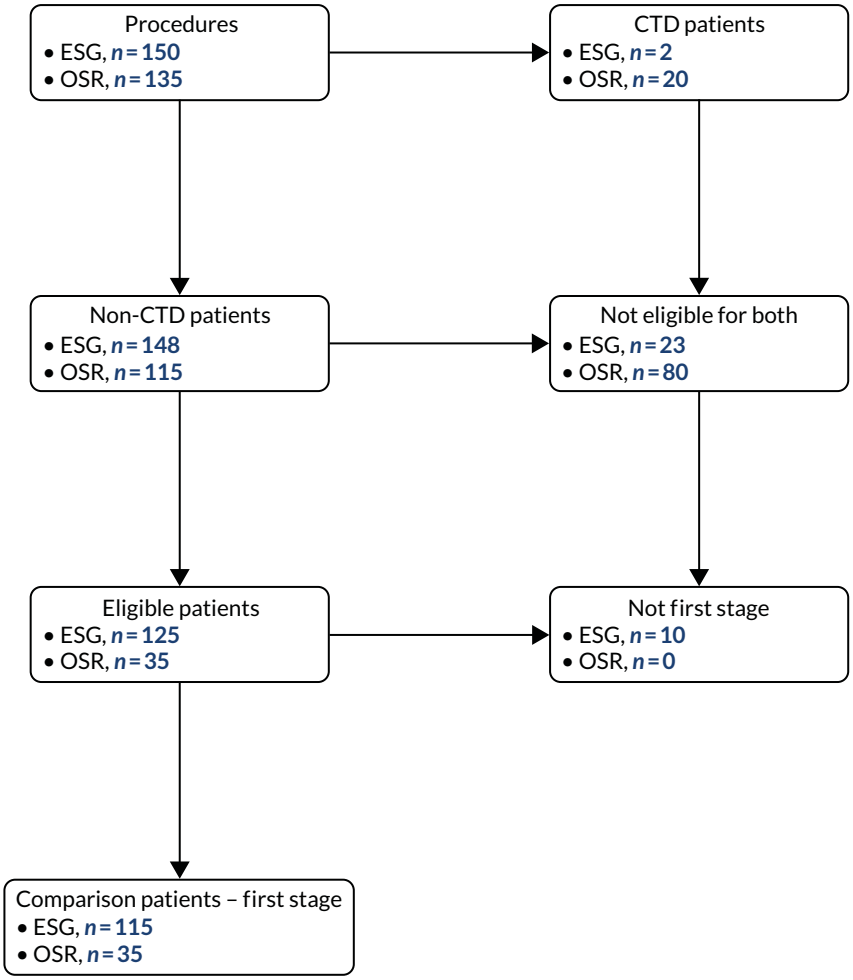

FIGURE 15 Cohort of no-contraindication ESG and OSR patients.

Of the 135 OSR patients recruited, 100 were excluded from the comparison cohort because they were not suitable for ESG due to CTDs ($n = 20$), ascending aorta surgery ($n = 57$) or concomitant cardiac surgery ($n = 7$), or based on morphology ($n = 16$). The remaining 35 (25.9%) were included in the no-contraindication cohort.

Despite the exclusion of patients with contraindications to one or other of the procedures, important differences in baseline variables between the groups remained. The difference between the groups in age at procedure increased to 10.5 years (95% CI 6.9 to 14.1 years), with the mean slightly reduced to 62.6 years for OSR patients and slightly increased to 73.1 years for ESG patients. ESG patients were smaller and were more likely to have diabetes, report a need for informal care and be treated with statins. However, ESG patients were treated quicker, were less likely to have raised serum creatinine and had slightly smaller maximum aneurysm size on average (*Table 22*).

Effect of confounding on propensity score methods

A propensity score was developed for each of the 30 imputed data sets. The residual between-group differences had important implications for propensity score methods; in the 30 imputed data sets, imbalance (difference in propensity scores > 0.1) was observed for two to seven variables. The main variables with residual imbalance between groups were time between consent and procedure (30 data sets), age at procedure (26 data sets) and maximum aneurysm size (24 data sets). This meant that, for propensity score matching, only 46–54 patients formed matched pairs in the imputed data sets, making

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TABLE 22 Major differences between ESG and OSR patients in the no-contraindication cohort

	Patient subgroup (number of patients in no-contraindication cohort)		
	ESG ($n = 115$)	OSR ($n = 35$)	p-value
Age (years)			< 0.0001
Mean (SD)	73.1 (8.4)	62.6 (12.2)	
Minimum, maximum	49.8, 85.8	33.3, 84.6	
Height (cm)			0.0205
Mean (SD)	169.5 (10.0)	174.0 (10.0)	
Minimum, maximum[a]	149, 188	147, 195	
Weight (kg)			0.0024
Mean (SD)	78.4 (14.5)	87.8 (18.7)	
Minimum, maximum[b]	49, 111	41, 130	
Care, *n* (%)			0.337
Informal	6 (5.2)	0 (0.0)	
None	109 (94.8)	35 (100.0)	
Diabetes, *n* (%)			0.068
Non-insulin dependent	11 (9.6)	0 (0.0)	
None	104 (90.4)	35 (100.0)	
Statin use, *n* (%)			0.016
Yes	82 (71.3)	17 (48.6)	
No	33 (28.7)	18 (51.4)	
Preoperative time in the ETTAA study (months)			0.1641
Median (quartiles)	1.8 (0.1, 7.4)	4.7 (0.1, 13.2)	
Minimum, maximum	0, 49.1	0, 36.5	
Serum creatinine			0.0045
Mean (SD)	86.9 (30.8)	107.7 (42.9)	
Minimum, maximum[c]	44, 194	54, 221	
Maximum aneurysm size (cm)			0.0341
Mean (SD)	6.12 (1.20)	6.62 (1.28)	
Minimum, maximum	3.7, 9.7	4.2, 10.3	
Maximum aneurysm site, *n* (%)			0.002
Ascending aorta/arch	2 (1.7)	6 (17.1)	
Descending aorta/suprarenal	113 (98.3)	29 (82.9)	

a Four missing.
b Five missing.
c Twenty-four missing.

this method inefficient. IPTW reweights outcomes according to their propensity to be matched and, therefore, included all patients in the no-contraindication cohort, but it can give undue influence to patients with propensity scores close to 0 or 1; IPTW excluding patients with extreme weights is a good compromise and resulted in the loss of only seven to eight patients. Including propensity score in the analysis models retains all patients but may be less effective in adjusting for confounding.[84]

Survival and hospital readmissions

During the follow-up of 150 no-contraindication patients, 31 ESG and 8 OSR patients died, of whom 14 and 5, respectively, died from aneurysm-related causes. Eight (7.0%) ESG and three (8.6%) OSR patients died within 30 days. In exploratory analysis (*Figure 16*), there were no differences between the groups in time to death overall (log-rank $p = 0.6608$) or aneurysm-related death (log-rank $p = 0.7533$).

Survival: results of modelling

Table 23 shows the adjusted HRs for OSR relative to ESG for all-cause and aneurysm-related deaths in the no-contraindication cohort. The results for the full data set are included for comparison. For the no-contraindication cohort alone, there was a small decrease in all-cause mortality for OSR, but this may result from inadequate adjustment of the 10-year age difference. Once propensity scores were included, risk of death for OSR patients was generally higher, although estimates of HRs vary and are measured imprecisely; CIs are particularly wide for the propensity matching method because of the very small sample sizes. Adjusting for the propensity score in the no-contraindications cohort results in estimates close to the full data set, but may be subject to residual bias.[84] Despite these differences, the CIs overlap substantially and no clear differences between procedures emerge.

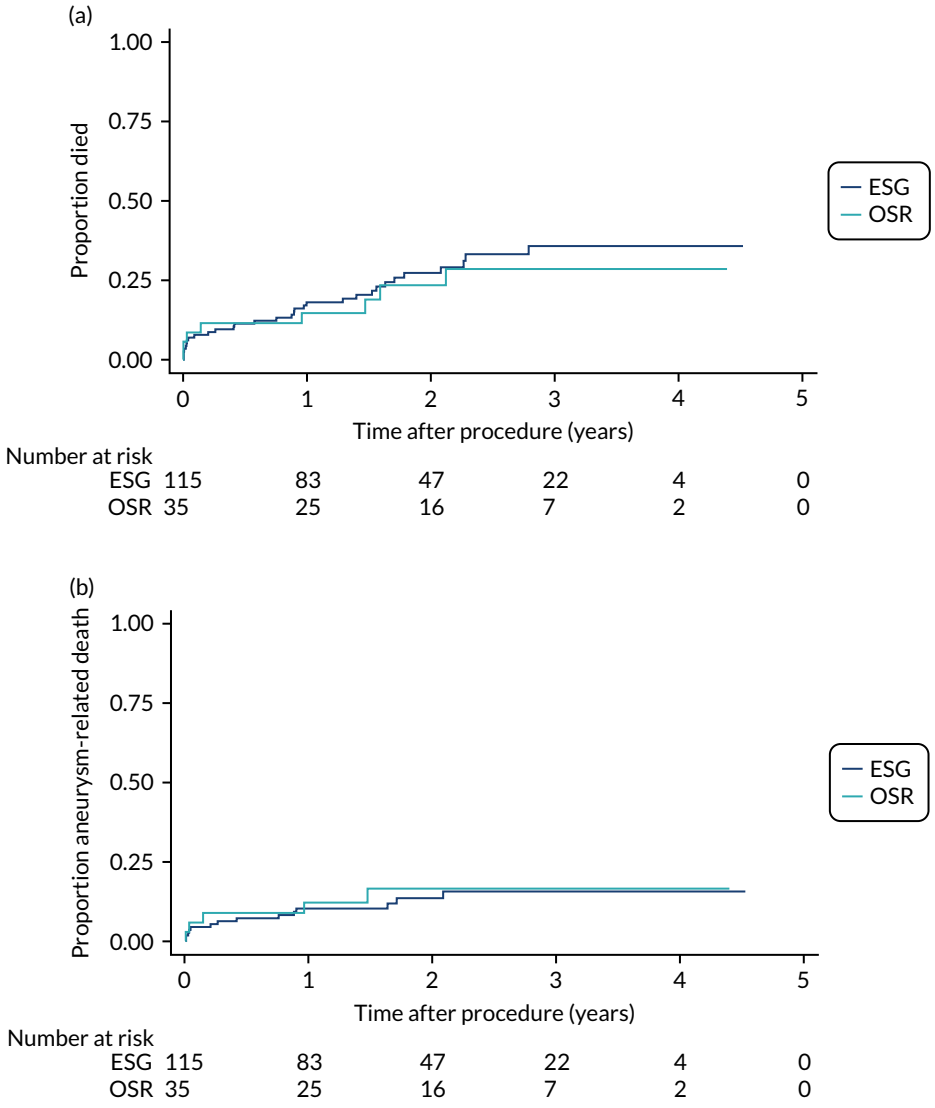

FIGURE 16 Kaplan–Meier cumulative incidence curves for post-intervention deaths from all-cause and aneurysm-related deaths by ESG and OSR groups (no-contraindication patients only). (a) Kaplan–Meier deaths from any-cause; and (b) Kaplan–Meier aneurysm-related deaths.

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TABLE 23 Hazard ratios for OSR from multivariable Cox regression models for post-intervention all-cause and aneurysm-related deaths

Model	All-cause deaths (adjusted for age, NYHA class and time from consent to procedure)		Aneurysm-related deaths (adjusted for sex and time from consent to procedure)	
	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
All patients: complete-case analysis ($n = 264$)	1.27 (0.78 to 2.09)	0.332	1.59 (0.86 to 2.96)	0.140
All patients: MICE for missing covariates ($n = 285$)	1.28 (0.79 to 2.07)	0.314	1.59 (0.86 to 2.96)	0.140
Patients with no contraindications: complete case ($n = 137$)	0.87 (0.36 to 2.09)	0.754	1.20 (0.43 to 3.34)	0.733
Patients with no contraindications, MICE for missing covariates ($n = 150$)	0.91 (0.39 to 2.11)	0.823	1.20 (0.43 to 3.43)	0.733
Patients with no contraindications: MICE for missing covariates and PS matched[a] ($n = 48–54$)	1.39 (0.38 to 5.11)	0.620	2.51 (0.32 to 19.6)	0.379
Patients with no contraindications: MICE for missing covariates and IPTW ($n = 150$)	1.43 (0.50 to 4.07)	0.510	1.56 (0.39 to 6.25)	0.532
Patients with no contraindications: MICE for missing covariates and IPTW excluding extremes[b] ($n = 142–143$)	1.09 (0.40 to 2.96)	0.865	1.54 (0.50 to 4.77)	0.457
Patients with no contraindications: MICE for missing covariates and PS adjusted ($n = 150$)	1.23 (0.47 to 3.24)	0.679	1.58 (0.43 to 5.77)	0.492

PS, propensity score.
a Note that the number of matched pairs varied between imputed samples, but ranged from 24 to 27.
b The number with weights greater than five was seven or eight, depending on the imputed sample.

Readmissions after discharge from the index procedure

Table 24 reports readmissions after discharge from the index procedure in the no-contraindication cohort. The results are very similar to those for the overall cohort for ESG as most patients remain in the analysis. The subset of OSR patients with no contraindications to ESG have lower readmission rates, which is likely to be due to the younger age distribution. Adjusting for age and sex, the relative readmission rate for OSR compared with ESG is 0.53 (95% CI 0.23 to 1.21; $p = 0.132$), and restricted to aneurysm-related admissions this is 0.22 (95% CI 0.04 to 1.30; $p = 0.094$). The number of ESG patients readmitted was greater for any cause ($p = 0.0709$) and for aneurysm-related causes ($p = 0.1627$).

TABLE 24 Number of patients with each outcome after the index procedure: no-contraindication patients only

Outcome	ESG group ($N = 115$)	OSR group ($N = 35$)
Total time at risk (years)	201.9	63.4
All readmissions, number (rate/year)	87 (0.43)	16 (0.25)
People with at least one readmission, *n* (%)	47 (40.9)	8 (22.9)
Readmissions, definitely/probably aneurysm related, number (rate/year)	30 (0.15)	2 (0.03)
Patients readmitted, definitely/probably aneurysm related, *n* (%)	19 (16.5)	2 (5.7)
Non-fatal ruptured aneurysms, *n*	0	0
Non-fatal dissected aneurysms, *n*	2	0
Non-fatal neurological events (all transient ischaemic attack), *n*	3	0

Post-procedure health-related quality of life

Descriptive analysis

Postoperative HRQoL was available for 129 no-contraindication patients, who completed a total of 548 questionnaires. The results of refitting the final model from *Chapter 5* using only these patients are shown in *Table 25* (full models can be obtained from the authors). The estimated difference between ESG and OSR in no-contraindication patients within 6 weeks of procedure and after 6 weeks is reported. In common with the full data analysis in *Chapter 5*, there was a larger decrease in HRQoL for OSR patients within 6 weeks. For this subset of patients, the difference between procedures was much larger both within and beyond the 6-week 'recovery' period and this was significant for many of the comparison models fitted. In particular, within 6 weeks OSR patients reported a very large and highly significant decrease in HRQoL in this no-contraindications cohort. After 6 weeks, the difference between ESG and OSR patients decreases, but is still of the order of 0.1–0.15 units and is significant across most models.

Summary of findings

The main finding of this chapter were that (1) ESG patients were more likely to be readmitted to hospital during follow-up and (2) OSR patients had slightly higher risk of death and substantially poorer HRQoL, both early post operation and beyond the first 6 weeks, even though they were 10 years younger on average.

This chapter aimed to identify a cohort of comparable ESG and OSR patients, which might be used to reflect equipoise among clinicians. After excluding contraindications to one of the procedures, the sample size was reduced substantially, particularly for OSR patients, resulting in very limited power for comparisons. Moreover, ESG and OSR groups in the no-contraindication cohort had important differences in age and age-related comorbidities, which suggests that age is an important factor in decisions about which intervention is appropriate in clinical practice.

TABLE 25 Effect of procedure on post-intervention EQ-5D-5L utilities in the first 6 weeks and after 6 weeks post procedure

	Difference in EQ-5D-5L utility (OSR – ESG) in first 6 weeks		Difference in EQ-5D-5L utility (OSR – ESG) after first 6 weeks	
Model	Estimate (95% CI)	*z*-test *p*-value	Estimate (95% CI)	*z*-test *p*-value
All 285 patients: complete case	−0.160 (−0.199 to −0.121)	< 0.001	−0.018 (−0.065 to 0.028)	0.433
All 285 patients: MICE for missing covariates	−0.167 (−0.223 to −0.102)	< 0.001	−0.018 (−0.062 to 0.026)	0.416
No contraindications ($n = 150$): complete case	−0.255 (−0.371 to −0.139)	< 0.001	−0.098 (−0.179 to −0.017)	0.020
No contraindications ($n = 150$): MICE	−0.261 (−0.371 to −0.151)	< 0.001	−0.102 (−0.177 to −0.028)	0.007
No contraindications ($n = 150$): MICE and PS matched	−0.344 (−0.509 to −0.178)	< 0.001	−0.091 (−0.200 to 0.017)	0.100
No contraindications ($n = 150$): MICE and IPTW	−0.248 (−0.366 to −0.130)	< 0.001	−0.085 (−0.163 to −0.008)	0.032
No contraindications ($n = 150$): MICE and IPTW excluding extremes	−0.307 (−0.428 to −0.185)	< 0.001	−0.146 (−0.241 to −0.050)	0.003
No contraindications ($n = 150$): MICE and PS adjusted	−0.277 (−0.402 to −0.152)	< 0.001	−0.118 (−0.212 to 0.024)	0.014

PS, propensity score.

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Although propensity score methods are designed to reduce bias due to confounding in observational studies, they can be unreliable for small samples (in common with many statistical methods). In propensity score matching, only 46 to 54 patients formed matched pairs, resulting in both low power and a more highly selected cohort. IPTW uses all patients and excluding those with very high weights resulted in loss of only seven to eight patients, while adjusting for propensity score in the analysis models retained all. Thus, the weighting and adjustment methods are likely to yield the more reliable results.

From the information available in the ETTAA study, just over half (150/285) of the patients who had an intervention may have had either procedure; we cannot tell from the data whether clinicians were in equipoise, and the decision around ESG or OSR appears to be largely driven by patient age. Our results provide estimates of relative outcomes for these two procedures, which vary between different analysis models, and are imprecisely estimated due to the small samples. The results generally align with the full data analysis (at least qualitatively) from *Chapter 5*. Concerns about residual confounding remain, but only a randomised trial would provide unbiased comparisons, and this is unlikely to be feasible given the low prevalence of CTAA. Cost-effectiveness analysis will provide further insight into the value of these interventions.

Chapter 7 Health economic analysis

Overall aims of the economic evaluation

This chapter reports the health economic analysis that was performed as part of the ETTAA study using the cohort of patients with no contraindications to either procedure.

Planned analysis

Originally, and according to protocol, the aim of this analysis was to estimate the cost–utility of two alternative surgical methods of treating patients with arch/descending thoracic aortic aneurysm. In the economic evaluation, the costs and effects associated with ESG were to be compared with those associated with OSR to define the optimal management strategies for patients who could be eligible for both treatments and for whom, therefore, there was a choice.

The economic analysis aimed to compare the incremental cost per QALY gained with different threshold values for society's willingness to pay for a QALY, including those commonly adopted by NICE.[85] Both a 'within'-study patient-level analysis and a state-transition model to extrapolate findings over patients' lifetimes were proposed. To facilitate this analysis, data were collected from individual study participants, participating centres and external sources in order to estimate costs. QALYs were to be estimated from serial responses to the EQ-5D-5L.

Resource utilisation and the associated costs were collected from an NHS and PSS perspective and concentrated on the micro-costing of the surgical procedures themselves in secondary care. The utilisation of any subsequent secondary, primary and personal social services during the follow-up period was also recorded. Data on resource use were captured on bespoke CRFs [see *Report Supplementary Material 5* for CRFs (use of secondary care services, and incidence and frequency of cost-generating events, e.g. hospital readmissions)]. Further CRFs were completed at 3, 6, 12, 18, 24, 36, 48 and 60 months to capture the use of primary care and PSS. The unit costs of resources were obtained from standard sources such as NHS reference costs, HRG tariffs, manufacturers/suppliers and from the centres themselves. For each participant, measures of resource use were to be combined with unit costs to estimate the total cost for that participant.

In terms of QALY estimation, EQ-5D-5L scores were collected prospectively at baseline and at 1, 3, 6, 12, 18 and 24 months, and then annually until the study ended. The responses for each participant were converted into health state utilities using UK population tariffs via crosswalk mapping[58] and used to estimate QALYs using the area-under-the-curve approach.[86]

For the within-trial analysis, bootstrapping methods were to be used to estimate the imprecision around estimates of incremental costs, QALYs and incremental cost per QALY. For the model-based analysis, a probabilistic sensitivity analysis was to be conducted. The results of both the within-trial and the model-based analyses were to be presented as plots of incremental cost and QALY and cost-effectiveness acceptability curves.

Revised analysis

To ensure a fair comparison between OSR and ESG as a primary procedure, the cohort of patients who had a surgical procedure (presented in *Chapter 6*) were assessed by clinical experts to determine whether they would have been eligible to receive both procedures (see *Figure 15*). *Chapter 6* describes reasons that patients who received one procedure would have been ineligible for the other and the numbers of participants excluded for that reason. In brief, the reasons why OSR patients were ineligible for ESG included aneurysm repair extending into the ascending aorta, concomitant cardiac

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procedures and unsuitable aortic morphology. The reasons why ESG patients were ineligible for OSR included BMI < 20 kg/m^2 or > 35 kg/m^2; NYHA class IV dyspnoea; or age ≥ 85 years. In addition, 10 ESG patients had primary procedures that were the second or third stage of a planned staged procedure. These patients were excluded as they would have biased the analysis of costs and QALYs. Overall, 115 ESG patients and 35 OSR patients were judged potentially eligible for both procedures.

As there were only 35 no-contraindication participants in the OSR group, the results of a comparative cost–utility analysis were judged to be imprecise and potentially misleading.[87] Therefore, the aims of the economic evaluation were recast to:

- Provide a non-comparative, descriptive 'within-study' analysis of the available cost and QALY data for participants eligible to receive both OSR and ESG as the first (index) procedure, without formally comparing the two procedures statistically. Specifically, the following were estimated –
  - health-care costs of primary surgical procedures (average and median costs per surgical group)
  - health-care and PSS costs that were definitely or probably related to the index procedure/the aneurysm at all follow-ups including average total costs at 12 months by surgical group
  - utilities at all follow-up points and average total QALYs at 12-month follow-up by surgical group.
- Estimate a regression model to explore the predictors of NHS costs for both OSR and ESG that may aid future economic evaluation modelling studies.
- Estimate the costs and benefits of obtaining further information (about overall cost-effectiveness and costs and QALY individually) based on data obtained from the ETTAA study via value of information (VoI) analyses.[88]

Given the potentially misleading results from conducting a comparative cost-effectiveness analysis, none was attempted.[85] Instead, we sought to utilise the limited information from the ETTAA study and conduct a VoI analysis in order to inform proposed future research into the relative cost-effectiveness of OSR compared with ESG and to identify potential sources of uncertainty. However, the results of this analysis should be seen in the context of a lack of a fair comparison in the ETTAA population, and are presented to aid any future research.

All health economic analysis has been designed and conducted to best practice conforming to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[89]

Within-study descriptive analysis of costs and quality-adjusted life-years methods

Health economic data collection

Identification and measurement of resource use

Resource utilisation was identified and measured using information derived from expert clinical opinion and from data collected in study specific CRFs. Three categories of resource use were considered:

1. Resources necessary to provide the primary procedures including medical devices, surgical equipment, staff and consumables.
2. Resources necessary to provide postoperative care until hospital discharge. This included length of hospital stay during the primary admission, including critical and specialist unit bed-days. Furthermore, all reinterventions associated with the aneurysm during the primary admission, including time in the operating theatre or endovascular suite, devices and consumables, were included in this category.
3. Use of health and personal social care until final follow-up, including readmissions related to the aneurysm. This category also included costs of resource utilisation within primary, community, secondary and PSS settings regardless of whether this was related to the aneurysm or other conditions.

Resource use in the primary surgical procedures

The costs of the two surgical interventions (OSR and ESG) were micro-costed for each participant included in this part of the study.[90,91] Micro-costing attempts to measure costs of a service as accurately as possible. The process involves identifying all of the resources involved in the provision of care, accurately measuring each resource and valuing the resources used.[92] The CRF captured participant-level data on theatre time, type of graft, blood products used and perioperative complications. Other information needed for the micro-costing came by considering what resources would be needed for a typical surgical procedure of each type. These data were collected using an iterative series of resource use capture pro formas (see *Report Supplementary Material 5*) and expert clinical opinion. Resource utilisation included staffing mix, reusable (e.g. some surgical instruments) and disposable (e.g. grafts) equipment and the overheads (heat, power, light, cleaning) of theatres. For capital and reusable equipment, the equivalent annual costs were estimated based on the life expectancy of the equipment, assuming a 3.5% discount rate per year.[85] The equivalent annual cost was then divided by the expected annual usage to obtain a cost per recipient. Procedure resource use is presented in *Appendix 11*.

Resource use postoperatively until discharge

Resource use postoperatively until hospital discharge was captured at the patient level using two study-specific CRFs. The post-procedure and discharge CRF (see *Report Supplementary Material 5*) captured the number of days in hospital, days in an ICU or a HDU, postoperative blood product use, and any adverse events (including cardiac and renal failure). It also captured the use of any diagnostic investigations. If a patient suffered an adverse event requiring a return to theatre, the theatre time and the reason for return to theatre were captured in the return-to-theatre CRF. These events were micro-costed using the same methods as described above for the primary surgical procedure. Postoperative resource use until discharge is presented in *Appendix 11*.

Use of health and personal social care resources during follow-up

Use of health and personal social services up until final follow-up or the end of the study was collected at the patient level using the study-specific follow-up CRF (see *Report Supplementary Material 5*) at 3, 6, 12, 18, 24, 36, 48 and 60 months post discharge from the index surgical procedure. This included the use of primary and community care [general practitioner (GP) and nurse visits both at a health care facility and at home, physiotherapy and occupational therapy community visits], secondary care [accident and emergency (A&E) visits, outpatient appointments related to the primary procedure, diagnostic imaging], and formal and informal social care (hours per week) up to patient death, censoring or the end of the study. These data are presented for each resource use category up to each follow-up point in *Appendix 11*. If a patient was readmitted to hospital for reasons probably or definitely related to aneurysms, a hospital admission CRF captured length of stay by level of care (general ward, HDU and ICU). Details of the number of hospital readmissions and reasons for each surgical procedure are also presented in *Appendix 11*.

If a patient underwent another procedure during follow-up, this was captured using the same CRFs as used for the primary procedure. This is recorded in *Appendix 11* as additional procedures. In addition, following discussion with experts, we assumed that each patient who underwent an ESG procedure had a CT scan and a vascular outpatient visit at 1 month post discharge and annually thereafter. Similarly, it was assumed that a patient who had undergone a primary OSR procedure had a CT scan and a cardiology outpatient appointment at 6 months post discharge and annually thereafter.

Formal and informal caregiving

Data on the provision and number of hours per week of formal care (e.g. social worker, care assistant) and informal care from family or friends were collected on the study CRF. These were then extrapolated for each follow-up period (i.e. each patient's care was assumed to remain the same across all subsequent time periods) and multiplied by an hourly cost of formal and informal caregiver time.

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Valuation of NHS and informal caregiving resource use

Unit costs

Unit costs were obtained from a variety of sources, including national databases[93] and published studies[94] (see *Appendix 11*). All unit costs were inflated, where necessary, to 2018–19 prices using the health care and community health services inflation index[94] and are reported in Great British pounds.

Primary surgical procedure

The unit costs used to value the required resources utilised in the index procedure are presented in *Appendix 11*.

Unit costs postoperatively until hospital discharge

The unit costs of a day in a general ward, HDU or ICU were based on the *NHS Reference Costs 2017 to 2018*[95] and inflated accordingly. The unit costs of any diagnostic tests and investigations (e.g. X-ray, CT scans) likewise were taken from the *NHS Reference Costs 2018 to 2019*.[93] Postoperative blood product use was costed from the NHS Blood and Transplant Price list 2018/2019.[96]

With the exception of a return to theatre, any adverse events occurring in the admission were not explicitly costed as it was assumed that these would be adequately captured by prolonged length of hospital stay and by the costs of tests and investigations described above. If a patient suffered an adverse event requiring a return to theatre, then the same methods were used to identify the unit costs of resources used. Unit costs post procedure until discharge, return to theatre costs, are presented in *Appendix 11*.

Unit costs following discharge

The unit costs of NHS primary and community care, NHS secondary care, social service formal care and informal care by family members/friends are presented in *Appendix 11*.

For use of primary and community care, the unit costs varied according to type of contact (e.g. GP, nurse) and where the contact took place (health-care setting or participant's home). The unit costs of these were obtained from a standard source collated for use in economic evaluation.[94] For the use of secondary care services, including A&E visits, outpatient appointments and diagnostic imaging related to the aneurysm, the costs came from *NHS Reference Costs 2018 to 2019*.[93]

The unit cost of formal caregiver time was obtained from the PSS Research Unit publication, *Unit Costs of Health and Social Care*.[94] The national minimum wage of £7.83 was taken as a proxy for the value of informal caregivers' time.[97]

For each of the hospital admissions, a HRG approach was utilised, whereby weighted mean costs for patients for each HRG were derived from the *NHS Reference Costs 2018 to 2019* (see *Appendix 11*).[93]

If a patient underwent another full ESG or OSR procedure, then the same micro-costing approach was used as described for the index procedure (these costs are reported separately from hospital admissions).

Estimation of total costs per patient

The cost analysis was divided into three stages (primary surgical procedure, post procedure until discharge and follow-up) based on a chronological sequence of events related to the procedures.

For each study participant, all components of costs stratified by category of resource use were computed by multiplying the units of resource use by their unit costs. These were then summed for each stage of the cost analysis. The primary procedure cost is presented as the average costs for each element of resource use with a subsequent average total cost per participant. The same approach was

used to present the costs for the post-procedure-until-discharge stage. These two stages of the costing are based on all of those eligible for inclusion in this comparative analysis (OSR, $n = 35$; ESG, $n = 115$).

The follow-up CRFs for costs asked patients to report resource use 'since the last follow-up'. Therefore, if a CRF was not completed at one planned visit, data could be retrieved at the subsequent visit.

The cumulative follow-up costs are reported at each follow-up period (e.g. at 1, 3, 6, 12, 18, 24, 36, 48, 60 months post discharge) using all data available at each follow-up time point. However, we note that cost estimates for informal care are a concern, as the intensity of care as reported on the CRF may be imprecise (in some instances, for example, patients reported 24-hour care 7 days a week). Hence, although we report costs from an NHS and PSS perspective, the PSS costs may be less reliable.

The costs for the three stages (primary surgical procedure, post procedure until discharge and follow-up) were then summed over all resource use categories to obtain a total annual cost for each participant at 12 months from both an NHS and an NHS and a PSS perspective. This was because the minimum follow-up for the study was 12 months, with variable duration of follow-up thereafter.

Derivation of descriptive cost statistics

For each surgical group, the mean (SD) and median [interquartile range (IQR)] costs are presented for each cost element. The analysis of the costs of the study was conducted using Stata® 15.1 (StataCorp LP, College Station, TX, USA).

Quality of life

The EQ-5D-5L questionnaire was administered at baseline and at 1, 3, 6, 12, 24, 36 and 48 months following a procedure. If a participant died, then they were assigned a zero score from the date of death. For each participant, utilities were collected across three distinct pathways:

1. Pre-procedure follow-ups after consent at 3, 6, 12, 18, 24, 36, 48 months.
2. After the index procedure, follow-up was 'reset' and occurred at 1, 3, 6, 12, 18, 24, 36 and 48 months after the index procedure.
3. After each additional procedure (second or third procedure), follow-up was 'reset' and occurred at 1, 3, 6, 12, 18, 24, 36 and 48 months after the additional procedure.

In some cases, however, the 'resets' did not occur as planned, resulting in misaligned follow-ups. To aid analysis and to use as many available data as possible, the time of all follow-ups was calculated from the date of primary procedure; that is, date of the primary procedure was taken to be time zero. Time of follow-up after the primary (index) procedure was then categorised and aligned to nominal time points 1, 3, 6, 12, 18, 24, 36 and 48 months after the index procedure. For example, 1-month follow-ups were those that actually occurred between 0 and 60 days after the index procedure. In addition, as in the analysis of clinical outcomes in *Chapters 5* and *6*, baseline was taken as the most recent utility measure prior to the index procedure. *Appendix 11* provides the categories of the time post procedure assigned to the different nominal follow-up time points.

The mean (SD) and median (IQR) of the EQ-5D-5L utility scores were calculated at nominal measurement times (i.e. baseline and 1, 3, 6, 12, 24, 36 and 48 months) using the measurements available at those time points. Owing to the small sample size, especially in the OSR group, multiple imputation of missing outcomes was not undertaken.

The mean (SD) and median (IQR) QALYs at 12 months were estimated for each surgical group for those patients who had a follow-up at baseline, 1 month, 12 months and any follow-up point in between, including a score of zero if they had died during follow-up. QALYs for each participant were estimated as the area under the curve, constructed by interpolating between utilities at nominal

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measurement times. There was no comparison between total QALYs for each surgical procedure because of the limited number of data available. The analysis of the EQ-5D-5L and QALY data was conducted using R, version 6.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Missing cost and quality-of-life data

The data available for comparative purposes were very limited, and there were considerable missing data for study participants (*Table 26*), particularly after 12 months' follow-up. Every patient who provided utility data at each follow-up also provided a follow-up CRF for resource use and hence for costs. There was only a very small number of patients ($n = 11$) who provided resource use and not utility data for some of the follow-up points. Up to 12 months, there was a larger proportion of missing data in the OSR cohort relative to the ESG cohort for both resource use and quality-of-life data. An examination of the data highlighted that patients who were in hospital at 1 month in the OSR group had subsequent missing data points for both resource use and quality of life. The reasons for this are unknown but could include not being sent a questionnaire, being in hospital or being too ill to complete a questionnaire. As expected, there are more censored data at later follow-up points.

Given, the nature and extent of missing data, no imputation was attempted. The exceptions to this were that if the missing data were related to standard resources that are normally used during the treatment pathway, it was assumed that these resources were used and, therefore, costs were added. Furthermore, where length of theatre time and length of stay were missing, averages of similar events were used for each procedure type.

As specified previously, to maximise the data used to estimate EQ-5D-5L QALYs utilities at baseline, 1, 3, 6 or 12 months were utilised.

Results of descriptive analysis

Cost analysis at all time points

The total average cost per recipient by each area of resource use for each of the three stages of the study is presented in *Appendix 11*. This shows that costs of theatre time and the corresponding staff time are higher on average for the OSR procedure, as are the costs of blood products. Stent costs are much higher on average for the ESG group relative to the average cost of grafts in the OSR group.

TABLE 26 Numbers of patients included in the cost analysis by surgical group

	ESG group				OSR group			
Follow-up period	Complete data	Cumulative deaths	Missing	Censored	Complete data	Cumulative deaths	Missing	Censored
Baseline	115	0	0	0	35	0	0	0
1 month	74	8	33	0	16	4	15	0
3 months	76	9	29	1	19	4	11	1
6 months	81	11	19	4	24	4	6	1
12 months	74	17	14	10	20	4	8	3
18 months	59	19	10	27	16	5	4	10
24 months	35	22	14	44	11	7	4	13
36 months	17	23	12	63	5	7	5	18
48 months	3	23	6	83	0	7	4	24

The mean (SD) total costs of the primary OSR procedure was £17,239 (£8043) and for the primary ESG was £26,536 (£9877). The cost of the ESG procedure was largely driven by the stent costs, which accounted for 79% of the average total cost of an ESG procedure.

Appendix 11 shows the total average costs per patient postoperatively until discharge for each surgical procedure broken down into categories of resource use. With the exception of return-to-theatre costs, average costs were higher in all resource use categories in the OSR group relative to ESG. The largest cost driver for OSR procedures was ICU resource use, which accounted for 71%. Furthermore, a larger percentage of patients in the OSR group were transferred to other hospital settings for further treatment (e.g. rehabilitation).

The average total costs after discharge by follow-up period and resource use category are shown in *Appendix 11*. The average total NHS costs for the first 12 months following the primary procedure were higher in the ESG group. These were driven by the extra costs of patient admissions to hospital, including the costs of additional procedures (85% of total NHS costs).

There was no discernible pattern in the average total costs of formal and informal care. These costs may also be inaccurate.

The average total costs for the primary procedure, post procedure until discharge and follow-up at 12 months are presented in *Table 27* for the participants who were suitable for either procedure. Particularly for the OSR group, mean costs are highly skewed to the right for most categories because of a small number of participants who incurred very high costs.

Analysis of quality of life

Owing to the very small numbers of patients reporting utility values at all time points, particularly in the OSR group, utilities [means (SD) and medians (IQR)] are reported for every patient who completed an EQ-5D-5L questionnaire at each time point, or were known to have died by a given time (*Table 28*). Patient numbers include all those who had completed a utility CRF at each time point, including a zero value for those who died. This excludes those who were censored for any reason. Utility values were lower at all follow-up points for OSR than for ESG. At 1 month post surgery, HRQoL dropped from

TABLE 27 Total average cost (£) per patient for all resource use at 12-month follow-up

Resource use cost (by stage)	ESG group		OSR group	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Sample size, *n*	115		35	
Primary procedure cost	26,536 (9877)	24,733 (19,300–35,173)	17,239 (8043)	15,359 (10,350–21,874)
Post procedure until discharge cost	7484 (7848)	5516 (2873–8526)	28,636 (23,083)	13,997 (10,480–28,040)
Total NHS cost up to discharge	34,020 (14,301)	30,620 (25,180–42,806)	45,875 (43,023)	36,488 (23,093–48,724)
Follow-up (up to 12 months)				
Sample size, *n*	91		24	
Follow-up cost (NHS resources)	5206 (11,585)	696 (495–1387)	5039 (11,994)	1105 (784–1821)
Formal care	202 (794)	0 (0–0)	9221 (37,547)	0 (0–0)
Informal care	1234 (3817)	0 (0–40)	1729 (3254)	265 (0–1295)
Total follow-up cost	6642 (11,927)	825 (506–7958)	15,989 (38,247)	2213 (1000–14,326)

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TABLE 28 EQ-5D-5L utility scores for all patients at each follow-up period by surgical group and QALYs at 12 months

	EQ-5D-5L utility scores					
	Patient numbers (*n*)[a]		EQ-5D-5L, mean (SD)		EQ-5D-5L, median (IQR)	
Time point	ESG alive (dead)	OSR alive (dead)	ESG	OSR	ESG	OSR
Baseline[b]	111 (0)	35 (0)	0.75 (0.24)	0.68 (0.24)	0.77 (0.68–0.91)	0.74 (0.64–0.84)
1 month	72 (8)	15 (4)	0.64 (0.32)	0.33 (0.28)	0.74 (0.51–0.86)	0.29 (0.05–0.56)
3 months	73 (9)	19 (4)	0.68 (0.32)	0.49 (0.30)	0.79 (0.63–0.87)	0.56 (0.31–0.70)
6 months	80 (11)	22 (4)	0.65 (0.33)	0.56 (0.36)	0.77 (0.50–0.88)	0.69 (0.34–0.79)
12 months	73 (17)	20 (4)	0.65 (0.37)	0.49 (0.37)	0.77 (0.5–1.00)	0.68 (0.17–0.78)
18 months	59 (19)	15 (5)	0.57 (0.39)	0.41 (0.33)	0.72 (0.02–0.88)	0.56 (0.00–0.65)
24 months	35 (22)	11 (7)	0.45 (0.40)	0.32 (0.32)	0.57 (0.00–0.81)	0.25 (0.00–0.62)
36 months	17 (23)	6 (7)	0.34 (0.42)	0.27 (0.34)	0.00 (0.00–0.77)	0.00 (0.00–0.60)
48 months	3 (23)	0 (7)	0.10 (0.280)	0 (0)	0.00 (0.00–0.00)	0.00 (0.00–0.00)

	EQ-5D-5L QALYs			
	ESG (*n* = 65)		OSR (*n* = 18)	
Time point	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
12 months	0.62 (0.32)	0.70 (0.47–0.88)	0.46 (0.35)	0.62 (0.03–0.73)

a Number of patients providing a utility score at each follow-up.
b Baseline is defined as the most recent completed EQ-5D-5L prior to the procedure.

baseline, with a fall of > 50% in HRQoL in the OSR group. HRQoL also reduced at 1 month in the ESG group, although this drop was not as large (15%). HRQoL in both groups increased until 6 months post procedure in the OSR group and until 12 months post procedure in the ESG group as people recovered from their primary procedure. Average utilities in both groups for the remaining follow-ups then started to decrease. This may be because of the impact of complications, readmissions and deaths (which are assigned a zero score). It must be noted that the sample sizes were small and so estimates were imprecise and potentially unreliable, particularly after the first 12 months. *Table 28* shows that the estimated mean QALYs at 12 months were larger in the ESG group than in the OSR group, although this was based on very small (and possibly not representative) numbers of patients who had complete data up to 12 months.

Predicting NHS expenditure costs for UK patients receiving open surgical replacement and endovascular stent grafting procedures

Introduction and rationale

The aim of this part of the economic analysis was to identify the key determinants of costs to the NHS of an OSR procedure and, separately, of an ESG procedure up until hospital discharge. Therefore, a separate regression model was used for each surgical procedure. Regression models were used where the dependent variable was the NHS costs for an OSR or an ESG procedure up until discharge. Potential determinants of NHS costs up to discharge were included as independent (explanatory) variables. These analyses are shown to illustrate more fully what the main predictors of these costs were and also to provide a resource for future economic evaluation modelling.

Methods

Planning the analysis

The first step was to examine the distribution of total surgical costs to help decide which type of statistical model would best suit the observed distribution of the data. Based on the observed distribution, a generalised linear model with gamma distribution with an identity link function of the total NHS costs was considered to be the most appropriate. This approach was chosen as cost data are typically heavily skewed to the right and this approach is less influenced by outlying observations.

To identify the main drivers of cost, a long list of variables thought to make the most significant contribution to the total NHS costs of each of the procedures was constructed. Using graphical methods and simple statistical summaries, the relationships between the most important predictive variables (to identify collinearity) and between each variable and the total costs were explored. Thereafter, predictive variables were introduced into each regression model using stepwise forward selection.[98] Variables for entry into the regressions were chosen at each step in accordance with the Akaike information criterion.

Possible explanatory variables and model structure

Appendix 11 presents the explanatory variables that were tested to build the regression model, as well as the reason for their selection. These variables were based on initial assumptions about the factors that might have an impact on the total NHS cost of each surgical procedure up until discharge and were divided into two main categories: patient characteristics and resource use. Given that there were fewer patients in the OSR arm, a more limited regression model was used to avoid overfitting. The initial cost regression models are presented in *Equations 4* and *5*, but their final forms depended on which model fitted the data and provided robust predictions of costs (i.e. would be calibrated with the observed data):

$$\begin{aligned}\text{COST}_{\text{ESG}} = {} & \beta_0 + \beta_1\text{AGE} + \beta_2\text{SEX} + \beta_3\text{BMI} + \beta_4\text{DIABETES} + \ + \beta_5\text{SMOKING HISTORY} \\ & + \beta_6\text{NYHA} + \beta_7\text{HYPERTENSION} + \beta_8\text{PAI} + \beta_9\text{COPD} + \beta_{10}\text{UTILITY},\end{aligned} \tag{4}$$

$$\begin{aligned}\text{COST}_{\text{OSR}} = {} & \beta_0 + \beta_1\text{AGE} + \beta_2\text{SEX} + \beta_3\text{UTILITY} + \beta_4\text{SMOKING CURRENT} \\ & + \beta_5\text{SMOKING HISTORY},\end{aligned} \tag{5}$$

where COST is the NHS expenditure costs from admission until discharge for the index procedure; AGE is the patient age at the time of the intervention (centred continuous variable), SEX is the patient sex (dichotomous variable: 1 if male; 0 otherwise); UTILITY is the baseline utility for the patient (continuous variable multiplied by 100); DIABETES indicates whether or not patients have any diabetes (dichotomous variable: 1 if diabetic; 0 otherwise); SMOKING current indicates whether or not patients are current smokers (dichotomous variable: 1 if current smoker; 0 otherwise); SMOKING HISTORY indicates if a patient has smoked in the past but is no longer a smoker (dichotomous variable: 1 if smoking history; 0 otherwise); NYHA is the patient's NYHA score (continuous variable with recalibrated NHYA score of 1 = 0 up to a maximum of 3); HYPERTENSION indicates whether or not patients had hypertension prior to intervention (dichotomous variable: 1 has hypertension; 0 otherwise); PAI indicates whether or not patients had a previous aortic intervention; COPD indicates whether or not patients have COPD (dichotomous variable: 1 has COPD; 0 otherwise).

The regression coefficients describe the direction and magnitude of the relationship between each variable and the NHS cost of each surgical procedure until hospital discharge. All analysis of costs was conducted using the statistical software R, version 6.2.

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Results

Current smoking status was the only variable associated with costs in the ESG model. The model estimated that current smokers have an increased cost on average of £10,447 (95% CI £2449 to £20,495) compared with non-smokers/past smokers. In the OSR cost model, there was no evidence of significant predictors. See *Appendix 11* for model coefficients.

Value-of-information analysis

Methods

To inform the VoI analysis, we used a subset of patients for whom we had near-complete data about resources and quality of life from baseline to 12 months. Details of this patient subset are shown in *Appendix 11* and the data definitions are the same as used throughout this chapter. We also developed a simple model to extrapolate the results to 36 months. This model used annual follow-up costs (ESG, £245; OSR, £337), 12–24 month unadjusted common mortality rate (5%), reintervention rates (yearly 3% OSR and 15% ESG) and 12-month utilities. Utility at 12 months was carried forward into years 2 and 3, and the mean cost of an aneurysm-related admission was estimated at £36,005.

Although we considered that cost–utility data would be of limited use and potentially misleading due to the limited data available for a comparative analysis, the principles of economic evaluation can be used to estimate the expected value of perfect information (EVPI) and the expected value of partial perfect information (EVPPI). Although these estimates suffer from the same limitations as the incremental cost–utility data on which they are based, they do show (for the small sample) the breakdown between the uncertainty associated with health outcomes and resource utilisations. Therefore, they are reported with the caveat that they are based on a small sample, but they may inform future research. EVPI and EVPPI were estimated using a bootstrapping technique whereby subpopulations of study participants were sampled with replacement from the overall study population. It is emphasised that the VoI analysis has been presented using the limited ETTAA data set purely to inform decision-making regarding future research and should not be interpreted as a definitive comparative analysis.

The EVPI for each patient is the net benefit of the decision made with perfect information about the uncertain parameters and the decision made based on existing evidence. For the study population, it is the net benefit of the overall optimal treatment choice across all bootstrap iterations less the net benefit lost when the overall optimal choice was not optimal in a particular iteration. The EVPI at the population level, the expected benefit accruing to all future patients, was calculated by multiplying the individual EVPI by the expected future population where there would be a choice about which of the two interventions to use. The annual population in the UK who might benefit from either treatment was assumed to be 100 (based on a plausible limit of the number of procedures the equipment could be used for in 1 year in a given centre), but sensitivity analyses were undertaken with eligible populations of 50 and 200. Initial analysis assumed that the consequences of intervention would last for 12 months. A second analysis assumed that the consequences would last for 3 years, with these second- and third-year impacts being determined using the data derived in the descriptive analysis presented above but incorporated into a simple Markov model predicting death and reintervention. The EVPPI was calculated to show the value of removing all uncertainty around two groups of parameters, namely costs and QALYs.

All VoI analyses were conducted in Stata 15.1 and used a threshold value of £20,000 per QALY.[85] The analyses used generalised linear models to estimate bootstrapped total costs and QALYs at the time points noted above. The bootstrapping took repeated random sampling with replacement of individuals from the data set and estimating a cost-effectiveness ratio for each sample. These samples capture the uncertainty in the overall estimate of cost-effectiveness and inform the VoI, each representing a possible decision about the marginal cost-effectiveness of the two surgical options.

The perspective of the analysis was that of the NHS (i.e. PSS and patient costs were excluded from this analysis). As the total costs and QALYs estimated extended beyond 1 year, each was discounted at 3.5%.[85] To estimate effect, each bootstrap iteration drew a set of matched patients for the analysis. Using multiple imputation, 45 sets of propensity-weighted patients were created. During each bootstrap iteration of the VoI analysis, the bootstrap sample was merged with a random (1 out of 45) set of propensity scores as estimated in *Chapter 6* to estimate marginal costs and QALYs, and hence net benefits and the EVPI and EVPPI.

Results of the value-of-information analyses

For the VoI analyses, the population deemed eligible for either procedure and with complete resource use and EQ-5D-5L up to 12 months was used (OSR, $n = 18$; ESG, $n = 65$); 800 bootstraps were used for the estimation of EVPI and EVPPI at the 12-month follow-up, and a further 800 bootstraps were used for estimates of the EVPI and EVPPI at the 36-month follow-up.

The results for the propensity-scored primary analyses are shown in *Table 29* and the accompanying 12-month and 36-month cost-effectiveness planes are shown in *Figures 17* and *18*. Each point on the cost-effectiveness plane shows the average difference in costs and effects from each bootstrap iteration. Points in the north-east and north-west represent circumstances in which OSR is more expensive than ESG, and points in the north-east and south-east quadrants indicate circumstances in which OSR has higher HRQoL compared with ESG.

TABLE 29 Bootstrapped cost-effectiveness and VoI analysis

	12-month follow-up	36-month follow-up
Cost difference (OSR – ESG) (£), mean (95% CI)	7870 (−7810 to 22,280)	−710 (−16,390 to 13,670)
QALY difference (OSR – ESG), mean (95% CI)	−0.017 (−0.274 to 0.254)	−0.062 (−0.894 to 0.764)
Non-parametric incremental cost-effectiveness ratio (£)	ESG dominates OSR	11,518[a]
EVPI – 100 patients (£)	84,200	493,600
EVPPI QALY – 100 patients (£)	17,400	390,300
EVPPI costs – 100 patients (£)	72,425	328,200

a This represents compensation for QALY lost.

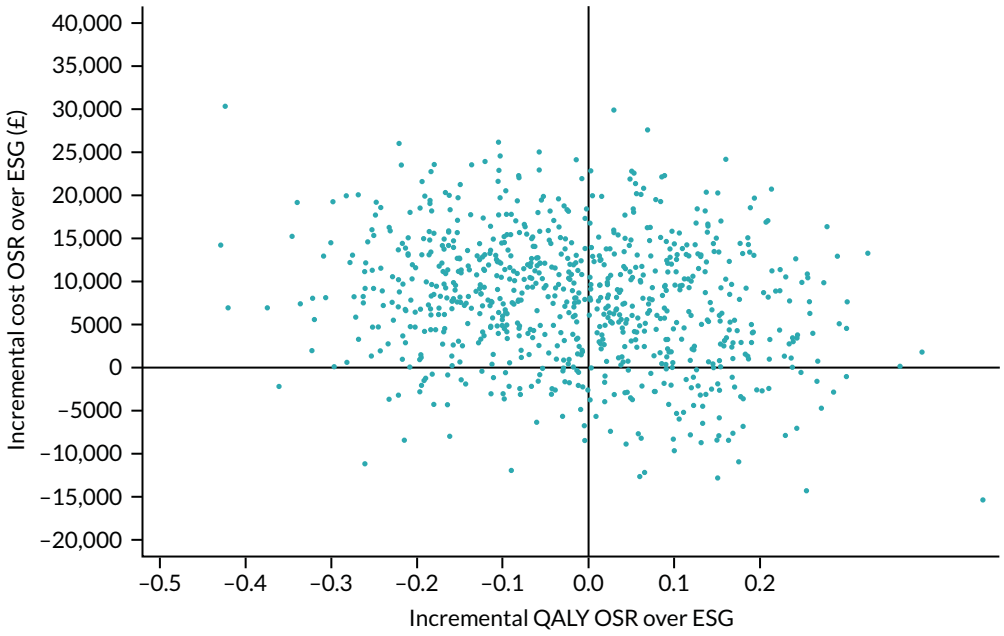

FIGURE 17 Cost-effectiveness plane for the 12-month VoI model. Cost-effectiveness plane OSR – ESG (generalised linear model). Incremental cost-effectiveness ratio: ESG dominates OSR.

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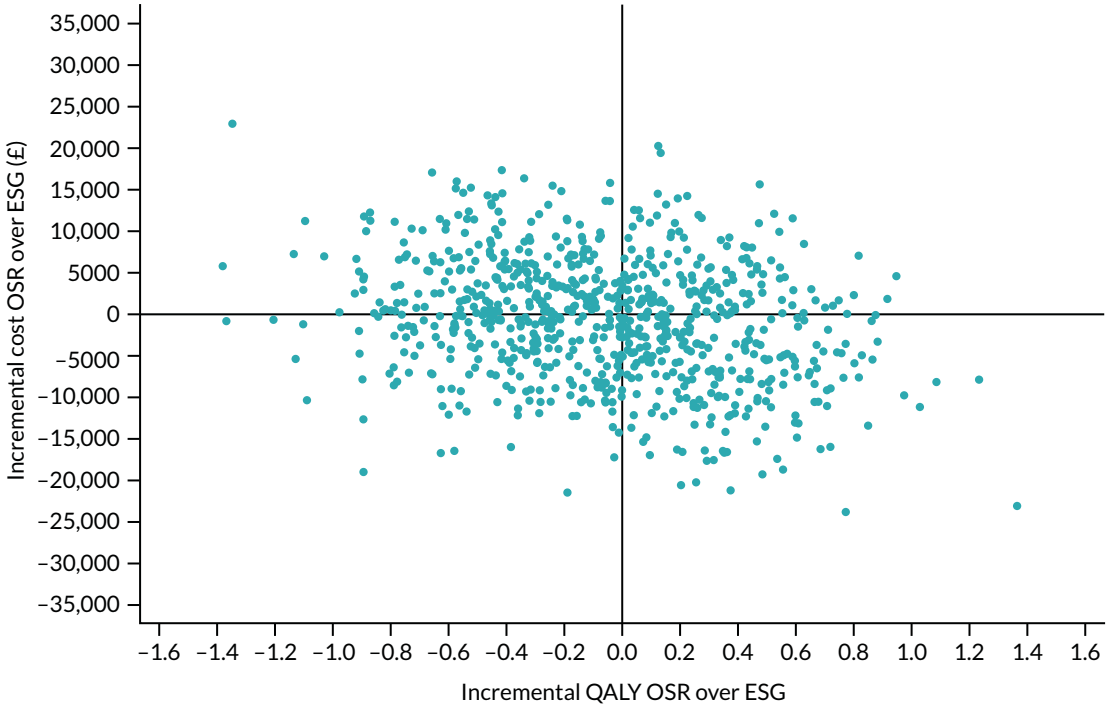

FIGURE 18 Cost-effectiveness plane for the 36-month VoI model. Cost-effectiveness plane OSR – ESG (generalised linear model). Incremental cost-effectiveness ratio: −£11,518.

Over 12 months, ESG dominates OSR in this exploratory analysis. It is, on average, associated with higher costs and statistically significantly greater QALYs. The EVPI of £84,200 reflects the distribution of points on the cost-effectiveness plane and that few exist outside the north-west and north-east quadrants. EVPPI confirms that most of the uncertainty derives from uncertainty about costs rather than about QALYs and is, therefore, less sensitive to willingness-to-pay thresholds.

Over 3 years, ESG no longer dominates OSR. OSR is on average less costly but less effective. The incremental cost-effectiveness ratio of £11,518 is the incremental cost per QALY gained for the comparison of the more effective but more costly ESG compared with the less costly and less effective OSR. In this analysis, the VoI increases, with EVPPI estimates for cost parameters increasing the most. Extending the time frame from 12 months to 10 years sees the total EVPI increase to £1,628,800.

Over 12 months, there is considerably more uncertainty around the net benefit associated with resource consequences than with quality of life. However, this relative gap closes in our simple 36-month model as reintervention costs of ESG offset the higher initial costs of OSR.

Summary of findings

The ability to conduct any comparative analysis was limited by the small number of patients in the data set who were eligible for both surgical procedures, particularly OSR. This resulted in much of the analysis being conducted on each surgical group separately.

The primary procedure costs and costs during follow-up were higher for the ESG procedure than for OSR. Seventy-nine per cent of the ESG primary procedure costs were accounted for by stent costs and 85% of the follow-up costs were accounted for by hospital admissions, including additional procedures. Costs post procedure to discharge were higher in the OSR group, with > 70% of these costs accounted for by ICU costs. HRQoL was higher in the ESG group than in the OSR group at all time points, with EQ-5D-5L QALYs higher at the 12-month follow-up.

The regression analysis of costs for both OSR and ESG identified little evidence that patient characteristics were associated with costs. Only current smoking status was associated with costs in the ESG model. The ability of this analysis to identify evidence was limited by the few data available for analysis, and the CIs surrounding the impact of individual characteristics are wide and contain economically important increases or decreases in costs.

The VoI analysis estimated the absolute value of removing all uncertainty from the analysis. The values estimated, regardless of the analyses conducted, were modest. The greatest value would be from removing uncertainty around costs, but our 36-month model suggests that the relative benefits would fall over time. Generally, if the VoI estimates are correct, then further research may not be worthwhile; any further research would be costly and may not exceed any benefits gained from it. However, the analysis conducted makes two critical assumptions. First, it assumes that the data used in the analysis may be imprecise but are not biased. Second, it assumes that the model accurately captures the decision problem. The small sample of patients may be biased by the fact that HRQoL values are imputed only for patients who die, which is likely to introduce bias in both the point estimate and the variance. In addition, the simple, limited-time-frame Markov model used may overly simplify reality and, hence, underestimate decision uncertainty, particularly given the inherent assumptions about previous events.

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Chapter 8 Discussion

Summary of research findings

In our study, participating centres collectively referred 886 CTAA patients, with a combined follow-up of 2016.8 patient-years. The incidence of CTAA is expected to rise as the age distribution of the UK population increases and associated comorbidities become more prevalent. When the ETTAA study began, published research on management of CTAA was sparse, consisting of small single-centre studies or larger unselected registry studies (see *Chapter 1*). All comparisons of treatment options used observational designs with limited adjustment for confounding. The ETTAA study aimed to provide an analysis of service provision in the NHS and to report outcomes for patients diagnosed with CTAA both before and after the intervention.

Without procedural intervention for chronic thoracic aortic aneurysm, what is the risk of aneurysm growth, dissection, rupture, permanent neurological injury or death, and how does health-related quality of life change over time?

Chronic thoracic aortic aneurysm patients were at high risk of death, had a range of comorbidities and had somewhat impaired HRQoL measured with EQ-5D-5L utility at the time of the intervention. Rate of aneurysm growth varied by location but was generally slow in this cohort of patients.

After diagnosis with arch/descending CTAA but before intervention (if planned), the death rate was high (8.6% per patient-year) compared with the general population with similar age distribution in England; for example, in 2015–17, the 1-year probability of death in England among people aged 71 years was 2.1% for men and 1.4% for women.[70] Thus, death rates for ETTAA patients were over four times the death rate for the general population of similar age. Approximately half of the deaths prior to a procedure in the ETTAA study were from aneurysm-related causes. The hazards of death in the absence of surgical intervention were significantly associated with aneurysm size, older age at presentation, female sex and (to a lesser extent) higher NYHA class. Other than aneurysm size and patient sex, these predictors of risk may simply be surrogates for comorbidity. Predictions from fitted models suggested that 3-year survival without treatment is > 90% for patients with small aneurysms (4–4.5 cm in diameter), falling to 88% for aneurysms of 5 cm, 79% for aneurysms of 6 cm, 63% for aneurysms of 7 cm and 42% for aneurysms of 8 cm. Together with the increased risk of poor post-intervention outcomes for longer waiting times, this indicates that intervention should be discussed once aneurysms exceed 6 cm in diameter, provided that operative risk is considered low/moderate.

Consistent with their older age, CM patients and those who went on to have ESG had more hospital admissions, including aneurysm-related admissions. Patients who were managed conservatively were judged to be sicker and less likely to benefit from intervention than other patients, so the higher admission and death rates in this group testify to the judgement of the clinicians. Non-fatal acute ruptures, dissections and neurological injuries were uncommon. Combining fatal and non-fatal cases, there were 69 ruptures or dissections, or both combined, in a combined total of 1489 years of patient follow-up pre intervention, a rate of 4.6% per patient-year at risk. This is broadly consistent with the benchmark study from Yale University, IRAD, GERAADA and reports of the Australasian experience.[19,21–23]

Health-related quality of life as measured using the EQ-5D-5L varied substantially at presentation, but, on average, the mean was slightly lower than UK age- and sex-matched population estimates. Heterogeneity at presentation could be partially explained by age, sex, smoking and NYHA class, but there was substantial unexplained variation. Moreover, the decline in HRQoL was faster for older patients and current smokers, but there was also unexplained variation between patients in the rate of change over time. Patients destined for ESG had lower HRQoL at presentation, all other factors being

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equal, although a few patients waited more than 6 months before intervention, at least partly due to delays in production of custom-made stents.

What factors affect aneurysm growth pre intervention?

The mean aneurysm size at presentation was partly related to known covariates such as age, smoking, CTD and COPD, with only location of the aneurysm related to both baseline diameter and growth rate.

The mean aneurysm size at study entry varied widely as a result of patients being identified at different stages in the evolution of their disease, and there was significant variation that was not explained by the variables measured in the ETTAA study. Almost all patients had documented hypertension, so the impact of hypertension on aneurysm growth (or any other outcome) could not be evaluated; hypertension is, however, an established causal factor in the development and outcome of aneurysms, and treatment should be optimised.[74] Given their older average age, poorer LV function, smoking history, COPD and prevalence of DTA aneurysms, patients who went on to have ESG are likely to have had faster-growing aneurysms before the procedure.

Differences in aortic pathology and morphology in different sections of the aorta meant that aneurysms in the DTA were significantly larger and more variable at presentation and grew faster than those in the arch or thoracoabdominal aorta; no growth was found in the ascending aorta, which largely results from previous interventions in this segment. Mode of surveillance (MRI or CT scans) was the only other variable associated with growth over time, which is likely to be a result of the selection for MRI of patients with slower-growing aneurysms and referral for CT more likely if growth appears to be accelerating. Slower-growing aneurysms are anticipated to require longer-term follow-up and, therefore, clinicians aim to reduce radiation exposure by choosing MRI scans for the patient. However, when an aneurysm is approaching an indication for surgery, CT images are superior for interventional planning. With these exceptions, there was no evidence of measured or unmeasured covariates affecting growth of the aneurysm, which partly results from the short-term follow-up in most patients and possible earlier intervention in patients who have signs of faster growth. Other studies suggested that growth is related to various risk factors including age, smoking, CTD, COPD and hypertension (see *Chapter 1*). The ETTAA study included surveillance imaging from diagnosis when growth may have been slower, so that ability to detect factors associated with growth was limited. Studies of growth in the infrarenal aorta have also failed to consistently find useful predictors of increased growth rate.[99]

Detailed studies of the aneurysm/vasculature (patent or partially patent false lumen, larger false lumen diameter/saccule formation within the false lumen, number and location of tears around the arch, peak wall stress) could not be undertaken in this observational study and so we could not assess their relationship to size or growth. Moreover, treatment by indication bias may have hindered our ability to assess whether or not medical treatments slowed growth. It is important to note that patients leave this analysis when their aneurysms are fast-growing or become large enough for intervention, or when they die, so the pattern of growth outside this range is not known and extrapolation is not justified.

If a patient has endovascular stent grafting or open surgical repair, what is the risk of dissection, rupture, permanent neurological injury or death, and how does health-related quality of life change over time?

Differences in patient populations meant that ESG and OSR outcomes could not be directly compared. ESG patients had lower risk of death within 30 days (6.7% vs. 11.1%) but subsequent survival was comparable; incidences of non-fatal dissection, rupture and neurological injury was rare; and, after an initial dip after OSR, *survivors* in the two groups had comparable mean HRQoL.

Arch/descending CTAA often required complicated intervention, with most requiring ESG or OSR in more than one segment of the aorta. In addition, 11.2% required concomitant cardiac surgery, 14.0% required staged procedures and 4.6% required hybrid procedures. Although there was clear selection of younger, 'fitter' patients for OSR, outcomes for ESG and OSR patients were largely comparable.

The invasive nature of OSR was associated with a slightly higher risk of death within 30 days, but few aneurysm-related procedural complications were reported. The main differences in clinical outcomes between interventions were higher readmissions in the short term for ESG patients, and the substantially higher incidence of postoperative complications, longer initial hospital stay and subsequent reinterventions in the OSR group. Although ESG patients were more likely than OSR patients to be readmitted to hospital early after discharge, their overall rate of readmission was not significantly higher, despite the 7- to 10-year age difference. This is at odds with the literature on infrarenal AAA repair, in which the complication rate and subsequent need for reintervention are higher.[100] This perhaps reflects the differences in natural history of the thoracic and abdominal aorta. After excluding patients who had a contraindication to one of the procedures, the results were qualitatively unchanged, although the smaller sample size resulted in more variable estimates of outcomes and low precision.

A large initial decrease in HRQoL followed OSR, a feature reported in other cardiothoracic surgery and vascular surgery trials,[71,72] including the EVAR 1 trial,[73] and is related to the longer hospital stay and post-surgical complications. Beyond this period, ESG and OSR had similar HRQoL in the full data analysis; conversely, the subset of OSR patients who were also eligible for ESG had significantly poorer HRQoL. The results for patients who were eligible for both ESG and OSR were based on small numbers and the difference between the groups from the full data analysis is more reliable. We also highlight that these analyses include only surviving patients and are not restricted to the nominal planned measurement times.

Can aneurysm- or patient-related predictors of treatment outcomes be determined?

Aneurysm location, age, sex, NYHA class and time before intervention were most closely related to survival after intervention, while previous HRQoL, smoking and NYHA class were related to HRQoL.

Patients receiving OSR had higher all-cause and aneurysm-related death rates overall, and this was more significant for DTA aneurysms than for arch aneurysms. Poorer survival after OSR in the DTA was partly influenced by treatment of CTD patients who have weaker vessel walls in this segment. Similar effects were noted in analyses that excluded patients with CTD (among other contraindications), even after the application of propensity score methods, suggesting that other factors were also in play. In observational studies it is difficult to delineate treatment effects from patient selection effects. As well as age at procedure, post-intervention survival was associated with a longer interval between entry to the study and intervention. The timing of intervention is challenging, our analysis showed that delays were associated with surgery in the DTA/thoracoabdominal aorta (especially OSR in these vessels), staged procedures, current smoking, previous CABG/PCI for coronary artery disease and concomitant valve disease, but most were not significant. It is likely that during the wait aneurysms will continue to grow and patients will continue to deteriorate over time, which may also contribute to this finding. Ultimately, it may be that vasculopathy of the DTA is simply a worse disease than vasculopathy of the arch, given the potential impact of the former aneurysms on spinal, renal, mesenteric and lower limb blood flow.

The strongest predictor of postoperative HRQoL was preoperative HRQoL, both of which were related to current smoking and NYHA grading of breathlessness. Recommending smoking cessation and treating causes of breathlessness may ease these symptoms to some extent and, therefore, optimise HRQoL.[74] This is supported by evidence that smoking cessation prior to other major procedures improves short-term outcomes.[75,76]

What is the most cost-effective strategy in patients eligible for both endovascular stent grafting and open surgical replacement?

No comparative cost-effectiveness analysis was feasible. However, detailed micro-costing of ESG and OSR highlights that the ESG procedure itself is more costly than an OSR procedure, with the costs of the stents being the main driver. However, the total costs from admission to discharge on average were higher for the OSR procedure, largely as a result of increased ICU days.

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Despite the rigorous work that was undertaken in developing this cohort of patients, relatively few participants were eligible to receive both treatments. We planned to complete a within-study economic evaluation and a sophisticated microsimulation model. However, owing to the limited data available, the analysis was restricted to describing the costs and QALYs for those who had initially received an ESG or OSR in the 'no contraindication' cohort, conducting a regression analysis to explore the key drivers of costs, and a VoI analysis. Standard methods of VoI analysis were used (see *Chapter 7*), and the analysis was based on the assumption that only 100 people would be eligible for both procedures per year.

Over 12 months' follow-up, mean EQ-5D-5L scores were lower than median scores, indicating that some people in both groups had very low scores. For OSR patients, mean EQ-5D-5L score was much lower 1 month after surgery than at baseline, as patients were still recovering from surgery. Mean EQ-5D-5L scores increased thereafter but, on average, were still lower than baseline scores. This differs from the results of HRQoL trajectories in *Chapters 5* and *6* because patients who died were assigned a utility value of zero in the economic analysis and the analysis did not include measurements outside the nominal measurement times. For the ESG group, even at 1 month, EQ-5D-5L scores were not much lower than at baseline. Over a 12-month follow-up period, mean and median QALYs were greater in the ESG group than in the OSR group. For the analysis underpinning the estimates of the EVPI and EVPPI, ESG appears to be the dominant intervention, being both cheaper and more effective than OSR at 12 months and with an incremental cost per QALY of < £12,000 for ESG compared with OSR at 36 months. The value of the EVPI and EVPPI is very modest, given the likely costs of any research project that might be conducted, especially as any research would remove only part of the uncertainty. These results should, however, be treated with caution (see *Strengths and weaknesses*).

How does this compare with existing literature and what does it add?

To our knowledge, this is the first analysis to scrutinise the clinical effectiveness and cost-effectiveness of elective treatments for chronic arch/descending aneurysms. Previous publications have identified the higher costs but shorter length of stay and reduced morbidity with ESG, but these reports conflated both acute and chronic pathologies. The ETTAA study has identified that clinicians are clear about which patients can benefit most from ESG and which can benefit most from OSR. There are also clear and objective technical parameters that determine whether or not an aneurysm can be treated with ESG at all. Finally, in many important aspects, the results of the ETTAA study are a straightforward extrapolation of the findings of studies of the management of AAAs.[100,101] With this in mind, the ETTAA study has established the costs and clinical outcomes associated with the two interventions and has also demonstrated the futility of directly comparing the two interventions.

The other contribution of the ETTAA study has been to describe the natural history of medically treated arch/DTA CTAA under surveillance. The 8.6% per patient-year risk of death and the 4.6% risk of fatal/non-fatal rupture or dissection are similar to the data from published literature. Having described the patterns of growth and risks associated with medical management, the ETTAA study will facilitate the future planning, location and organisation of specialist aortic centres to cater to the projected increase in demand. This is based on substantial literature showing that high-volume specialist centres improve clinical outcomes in complex aortic interventions.[102,103]

Strengths and weaknesses

The main strength of this study was the engagement of 30 centres with specialist aortic aneurysm provision and the diverse and rigorously applied research methods, including a Delphi study, an economic analysis, an analysis of the natural history of aneurysm growth and clinical outcomes before intervention, and the comparison of outcomes after ESG and OSR, using both traditional regression methods and contemporary methods to address bias in patient selection.

The biggest limitations in the comparison of ESG and OSR were the observational nature of the study and the relatively small number of patients, which meant that there was low power to detect differences in outcomes and limited ability to adjust for confounding in regression models using traditional adjustment methods. One of the difficulties with non-experimental studies is that we observe activity based on current clinical mores, so that cause-and-effect relationships are difficult to disentangle. Although we used a variety of methods designed to reduce bias, these can be unreliable for small samples, and analyses were likely to include some level of residual confounding. It is also difficult to compare survival before and after procedures because of the possible selection of higher-risk patients for intervention.

In many situations it appeared that there was little equipoise among clinicians in the choice of patient management. Equipoise was reported for < 10% of scenarios considered in the RAND–Delphi study and around half of the patients who underwent ESG or OSR could not receive the alternative. Even after excluding these patients, clinicians appeared to assign patients largely according to age, fitness for surgery and aneurysm site. It is likely that there was additional selection of patients that was not reflected in the data, particularly as ESG patients, who were 7–10 years older on average, appeared to have similar outcomes to OSR patients, even after adjustment for age and comorbidities. Based on these results, it seems certain that a randomised trial is not feasible in the UK.

A further limitation was the necessity of reporting outcomes for a diverse group of aneurysms (arch and DTA) treated in a number of ways. In general, the treatment of CTAA varies because of significant variation in morphology, and the fact that aneurysms might encompass multiple segments, with very different approaches and risks. In addition, practice and experience vary across centres. The incidence of CTAA is low, so it is impossible to examine the outcomes of a large cohort of patients with morphologically similar CTAAs treated in the same way.

The strength of the economic evaluation is that analyses were based on rigorous and explicit methods that correspond to best practice in terms of identification, measurements and valuation of costs and QALYs. This was hampered by the small number of patients who did not have a contraindication to one or other of the treatments, so the pre-planned economic analysis was not possible. Moreover, estimates of costs and QALYs were made difficult by a complicated data collection schedule that was not always adhered to. More importantly, loss to follow-up was a problem over the longer term, so data past 12 months were very limited. These issues are not uncommon in observational studies, such as the ETTAA study and occurred despite prospective data collection.

A VoI analysis was attempted. The results and their interpretation should be viewed with caution, as the methods rely on the assumption that the data available are imprecise but provide an unbiased estimate of each parameter. Given the small sample sizes available, and the observational nature of the study, the distribution of costs and QALYs observed may not be an accurate representation of the population distribution of costs and QALYs. Therefore, the EVPI and EVPPI may be biased. Furthermore, the EVPI and EVPPI depend, crucially, on the size of population who would be eligible to receive either OSR or ESG. If this were underestimated, then the population EVPI and EVPPI would be underestimated.

Implications for service

Patients with CTAA have complicated management needs and are best managed by specialist centres with the support of MDT meetings. Patients are largely aged between 50 and 90 years (average of 70 years), with a range of cardiac and thoracic comorbidities, and are at an increased risk of death due to rupture, dissection and other aneurysm-related events. Although clinicians expressed reasonably strong agreement about the best management options, the optimal timing of intervention is difficult to define. These factors, together with the relative rarity of CTAA, suggest that care should be delivered

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by specialist centres with the support of MDT meetings. For optimal patient management it is critical that all patients with a diagnosis of arch/DTA CTAA are discussed in an aortic MDT meeting with cardiac and vascular surgeons, radiologists, interventionalists and cardiologists in attendance, who have experience in treating thoracic disease. The ETTAA data have demonstrated that both ESG and OSR can have good outcomes (at least to 3 years) for some patients and that MDT decision-making is reliable. Thus, there should be a drive towards improved information in primary care about the clinical and HRQoL outcomes of complex aortic interventions.

For small (4–5.5 cm in diameter) aneurysms, current strategies appear to work well, with important aspects being blood pressure management, encouragement to maintain an active lifestyle and smoking cessation. Once aneurysms reach the threshold for intervention (≥ 6 cm in diameter), it is important that this intervention is not delayed, as longer time to intervention is an important modifiable risk factor for a poor outcome. For small aneurysms, an important consideration is the essential value of an imagebank for surveillance scans. Regular imaging, be it CT or MRI, will be essential for choosing, planning and timing the intervention. A national registry of patients with chronic aortic disease tied to an imagebank accessible across the UK would be invaluable for NHS service planning.

Further research

What further research is required?

In priority order:

1. The prediction of aneurysm growth and the timing of intervention is difficult, and aneurysm diameter may not be the best indicator of whether or not rupture will occur. More detailed analysis of the diameter, length and volume of aneurysms, as well as other anatomical features in the ETTAA data set, may help to refine decisions around when and how to intervene. Joint analysis of aneurysm growth and acute clinical events (rupture, dissection and death) would provide valuable information on the timing of interventions.
2. The ETTAA database is now well positioned to describe, from real-world practice, what low, medium and high risk mean in terms of objective variables. This would facilitate a risk–benefit analysis and enable patients to be better informed at consent.
3. Combining post-procedure ETTAA data with longer-term routine electronic data sources would throw light on longer-term survival and hospital admissions to understand whether there is a divergence in survival and reintervention rates, as seen in other studies,[36] and with a view to identifying factors that reduce the risk of these events.
4. For quality improvement, and to better understand the drivers of outcome in each group separately, it would be helpful to have a registry that records all CTAA patients, with a wider (but carefully chosen) set of associated variables recorded to the same protocol. This could augment the existing national cardiac and vascular surgical databases (National Institute for Cardiovascular Outcomes Research and National Vascular Registry) and would enable a more reliable assessment of variables affecting outcomes within each intervention group.[104,105] In particular, drug therapies and the value of optimisation prior to intervention could be investigated in a larger group of patients, with more adequate adjustment made for confounders. A registry that is maintained and adopted by the majority of specialist centres will also allow the longer-term follow-up of patients pre and post intervention.

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Patient and public involvement

Representatives from the Marfan Association UK and Liverpool Aneurysm Support group contributed advice for the grant application and the ETTAA website was designed with their support (ettaastudy.com). Neil Towers, who sits on our Trial Steering Committee, reported last year:

> *I was present at the first steering committee meeting and have attended the planned meetings ever since. I have been given every opportunity to involve myself in discussions and to make suggestions and comments as appropriate. My opinion has regularly been sought on issues relating to the patient and public point of view and I have on occasions discussed items with other members of Liverpool Heart and Chest Hospital Aortic Support Group and given their feedback to the steering committee. As a former emergency aortic dissection patient I understand the relevance of this research and look forward to further involvement together, reading the report and also sharing the findings with the Liverpool Support Group.*
>
> *Reproduced with permission from Neil Towers, personal communication, 2021*

We are indebted to Neil for his steadfast support for the ETTAA study.

ETTAA Collaborative Group

The ETTAA Collaborative Group includes the ETTAA Working Group members (past and present), the Trial Steering Committee, the Data Monitoring Committee and, from the recruitment centres, the PIs and research co-ordinators.

ETTAA collaborators contributions by role code	CI; CR; CPM	LST; LHE	HE; ST	RTA	PHC; SM	CRO; STB	PI	RC	TSC	DMC
Conceptualisation	✓	✓			✓	✓			✓	
Data curation	✓		✓	✓						
Formal analysis		✓	✓			✓				
Funding acquisition	✓	✓			✓	✓				
Investigation	✓	✓		✓			✓	✓		
Methodology	✓	✓	✓	✓	✓	✓				
Project administration	✓	✓	✓	✓	✓				✓	
Resources	✓	✓		✓			✓	✓		
Supervision	✓	✓		✓	✓		✓		✓	✓
Validation	✓	✓	✓	✓						✓
Visualisation (presentation)	✓	✓	✓							
Writing – original draft	✓	✓	✓		✓					
Writing – review and editing	✓	✓	✓							

Shaded ticked markers indicate the ETTAA collaboration groups whose members who took responsibility for the research roles listed in column 1.

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Colin Bicknell	Vascular Surgeon/PI	CR
Carol Freeman	Clinical Project Manager	CPM
Andrew Cook	Public Health Consultant	PHC
Yi-Da Chiu	Statistician	ST
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CI, chief investigator; CPM, clinical project manager; CR, cardiac/vascular surgeon researcher; CRO, cardiac surgeon collaborator; DMC, Data Monitoring Committee; HE, health economist; PHC, public health consultant; RTA, research team associate; SM, senior research and development manager; ST, statistician; STB, statistician (RAND Delphi); TSC, Trial Steering Committee.

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Data-sharing statement

The ETTAA Working Group supports the principles of data sharing. Applications to access data should be submitted via the corresponding author. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Definitions of complications and other clinical events

Observed clinical events during hospital admission

Death
Recorded death by the local centre.

Myocardial infarction
The clinical suspicion of myocardial infarction together with elevated CK-MB (creatine kinase MB isoenzyme) 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) or by the use of an intra-aortic balloon pump.

Prolonged ventilation > 48 hours
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 ESG or surgery.

Renal support

Temporary
Treatment of acute renal failure* by means of a period of haemofiltration that is confined to the hospital admission and not required after discharge.

*Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to intervention; or a rise in levels of serum creatinine of $\geq$ 26 µmol/l within 48 hours; or a $\geq$ 50% rise in levels of serum creatinine known or presumed to have occurred within the past 7 days.

Permanent
Renal dysfunction persisting > 90 days and graded according to estimated glomerular filtration rate, or requirement for haemodialysis sustained for at least 90 days.

Gastrointestinal 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 ischaemia (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 and cholecystitis.

Neurological injury

Central nervous system: brain
Any new, temporary or permanent, focal or global neurological dysfunction ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician; or an abnormality identified by surveillance neuroimaging.

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Transient ischaemic attack, defined as an acute transient neurological deficit conforming anatomically to arterial distribution cerebral ischaemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed > 24 hours after symptom onset; or MRI).

Cerebrovascular accident, 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 haemorrhage.

Central nervous system: spinal cord

Paraplegia: new onset of impairment in motor and sensory function of the lower extremities after aortic intervention.

Paraparesis: new onset of partial impairment in motor or sensory function of the lower extremities after aortic intervention.

Thromboembolic event (deep-vein thrombosis/pulmonary embolism)

Evidence of a 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 periprosthetic abscess), 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, pseudoaneurysm, 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

- Leak at the proximal graft attachment site.
- Leak at the distal graft attachment site.
- Leak around a fenestration, branch end point, or branch-occluding plug (e.g. plug occluding a subclavian artery or iliac artery to prevent flow into an aneurysm sac).

Type II

- Retrograde flow from branch arteries arising from the excluded segment.

Type III

- Modular disconnect or apposition failure (including branch junctions).
- 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 localised to the operated segment of aorta, including (but not necessarily confined to) localised 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 epithelialised surface, and diagnosed according to standard clinical and radiological investigations.

Reintervention

Any intervention undertaken to preserve or restore the function of an endovascular stent graft (e.g. re-ballooning/additional stent/surgery) or surgically implanted aortic graft.

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Appendix 2 Treatment of missing covariates

Exploring missing data patterns

All covariates included in pre- or post-procedure analyses were considered for inclusion in the imputation models. These variables are shown by treatment group in *Table 30*. With the exception of haemoglobin and serum creatinine levels, the number of missing covariates is relatively small (< 8%) for an observational study. The two biomarkers were more likely to be missing in patients in the WW and CM groups than in those receiving an intervention. Height and weight were slightly more likely to be missing for CM patients. NYHA class at baseline was slightly more likely to be missing for patients in the two intervention groups.

We used the built-in function (missing_pattern) of the R package 'mice' to explore the missingness pattern.[106] For the data set used for pre-procedure analysis, there were 33 different patterns of missingness. This showed that 788 (88.9%) patients had complete data, 27 (3.0%) patients had missing NYHA class and were otherwise complete and 23 (2.6%) patients had missing height and weight (and, therefore, missing BMI) but were otherwise complete. All other patterns were observed in small numbers of patients.

For the data set used for post-procedure analysis, the output shows 16 different patterns of missingness. For these analyses, 200 (70.2%) patients had complete data, 44 (15.4%) had missing serum creatinine and haemoglobin levels only and 17 (6.0%) had missing NYHA class only. All other patterns were observed in small numbers of patients.

Missing data mechanisms

We used Little's[107] test to assess whether or not continuous covariates were MCAR. In this test, the means of the covariates are compared between different missing-value patterns. The test is similar to the likelihood-ratio statistic for multivariate normal data; the resulting statistic is asymptotically chi-squared-distributed under the null hypothesis that there are no differences between the means of different missing-value patterns. A p-value of < 0.05 tells us that there is some evidence to conclude that the data are not MCAR. The results in *Table 31* suggest that MCAR cannot be safely assumed for either pre- or post-procedure analyses.

In addition, we used standard statistical tests (log-rank, Student's t-test, Mann–Whitney U-test, Pearson's chi-squared test and Fisher's exact test) to assess the associations between missing variable status (yes/no) and other variables (including outcomes). These analyses showed that survival (either pre or post intervention) was significantly related to missing covariate status for weight, BMI, use of formal/informal care, hypertension and extracardiac arteriopathy. As described above, NYHA class missingness was significantly associated with treatment group. In addition, missing status for specific covariates was related to other measured covariates (data not shown).

Overall, these exploratory analyses suggested that imputation models can be informed by related measured covariates in the data set.

Development of the imputation model

This section provides the technical details of imputation models using MICE.

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TABLE 30 Frequencies of missing covariates at baseline by final management group

	Patient subgroup, *n* (%)			
Missing covariate	**WW (*N* = 489)**	**CM (*N* = 112)**	**ESG (*N* = 150)**	**OSR (*N* = 135)**
Age	0	0	0	0
Sex	0	0	0	0
Height	19 (3.9)	9 (8.0)	4 (2.7)	3 (2.2)
Weight	22 (4.5)	8 (7.1)	5 (3.3)	3 (2.2)
BMI	24 (4.9)	9 (8.0)	6 (4.0)	3 (2.2)
Care	4 (0.8)	1 (0.9)	0 (0.0)	2 (1.5)
Smoker	4 (0.8)	1 (0.9)	1 (0.7)	1 (0.7)
CTD	0	0	0	0
Extracardiac arteriopathy	0	0	0	0
Valvular heart disease	11 (2.3)	2 (1.8)	1 (0.7)	1 (0.7)
Coronary artery disease	13 (2.7)	2 (1.8)	1 (0.7)	1 (0.7)
LV function	8 (1.6)	0	1 (0.7)	1 (0.7)
LV function not measured	241 (49.3)	55 (49.1)	70 (46.7)	36 (26.7)
Diabetes	3 (0.6)	0	0	0
Hypertension	2 (0.4)	0	0	0
COPD	5 (1.0)	0	0	0
NYHA class	14 (2.9)	2 (1.8)	11 (7.3)	9 (6.7)
Beta-blockers	0	0	0	0
ACE inhibitors	0	0	0	0
ARBs	0	0	0	0
Calcium channel blocker use	0	0	0	0
Other antihypertensives	0	0	0	0
Any antihypertensives	0	0	0	0
Statins	2 (0.4)	0	0	0
Serum creatinine	309 (63.2)	60 (53.6)	42 (28.0)	48 (35.6)
Haemoglobin	326 (66.7)	64 (57.1)	44 (29.3)	50 (37.0)
Maximum aneurysm location	0	0	0	0
Maximum aneurysm size	0	0	0	0
Pre-procedure variables			***ESG* (N = *150*)**	***OSR* (N = *135*)**
Surgical priority	–	–	0	0
LV function	–	–	113 (75.3)	68 (50.4)
Serum creatinine	–	–	22 (14.7)	32 (23.7)
Haemoglobin	–	–	21 (14.0)	31 (23.0)

Notes
Note that LV function was not measured for 241 WW, 55 CM, 70 ESG and 36 OSR patients.
Adapted from Sharples *et al.*[64] © The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial re-use distribution and reproduction in any medium provided the original work is properly cited. The table includes minor additions and formatting changes to the original table.

TABLE 31 Significance of Little's MCAR test

Work package (analysis type)	Variables included	*p*-value
Package 1 (pre procedure)	Age, height, weight, BMI, maximum aneurysm diameter, maximum aneurysm sites	0.0277
Package 2 and 3 (post procedure)	Age, height, weight, BMI, maximum aneurysm diameter, maximum aneurysm sites, creatinine level, haemoglobin level	0.0073

For analysis of pre-procedure survival, treatment group, pre-procedure survival time from consent, whether or not aneurysm was related to death, death status before the index procedure and all pre-procedure variables were included in the imputation models.

For analysis of post-procedure survival, procedure type (ESG, OSR or hybrid) and procedure priority were included in the imputation models, in addition to the covariates included in the pre-procedure imputation models above (updated to just before the procedure, if appropriate).

In the MICE procedure, we used predictive mean matching for all covariates included in imputation models except BMI. For the imputation of missing BMI, a fixed formula was used.

The percentages of incomplete data for the variables used in imputation models for pre- and post-procedure analysis were 11.1% and 29.8%, respectively. We therefore set the number of imputations in MICE for the two analyses to 12 and 30. During the imputation process, we ran 10 imputation iterations for each imputed variable. The imputed values in the last iteration were used for generating an imputation data set. Those imputed values generated during the process were used for checking whether or not the values converged by inspecting the trajectories.

Results of survival models after multiple imputation

The results of refitting the final models are given in *Tables 32* and *33* for pre- and post-procedure survival. These results, which are based on the assumption that data are missing at random conditional on variables included in the imputation models, are almost identical to the complete-case results. It is not possible to tell whether data are missing not at random from the measurements available in the ETTAA study, but the small number of missing data in general (apart from for biomarkers) and the similarity in missing data frequencies between comparison groups suggest that the results will be robust, unless there is an extreme non-random missing data mechanism in play.

TABLE 32 Final multivariable Cox regression results for all-cause and aneurysm-related deaths, after multiple imputation for pre-procedure analysis

	All-cause deaths		Aneurysm-related deaths	
Variable	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
Female sex	1.79 (1.25 to 2.54)	0.001	2.55 (1.55 to 4.21)	< 0.001
NYHA per class	1.21 (0.98 to 1.50)	0.073		
Maximum aneurysm size per cm	1.89 (1.64 to 2.17)	< 0.001	2.18 (1.80 to 2.63)	< 0.001
Age at consent (years)		< 0.001		0.027
61–70	2.00 (0.74 to 5.36)		1.30 (0.41 to 4.15)	
71–80	2.80 (1.12 to 7.01)		1.53 (0.53 to 4.41)	
> 80	5.89 (2.33 to 14.89)		3.38 (1.15 to 9.92)	

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TABLE 33 Final multivariable Cox regression results for all-cause and aneurysm-related deaths, after multiple imputation for post-procedure analysis

Variable	All-cause deaths		Aneurysm-related deaths	
	HR (95% CI)	*z*-test *p*-value	HR (95% CI)	*z*-test *p*-value
Ascending/arch procedure	(Reference category)	0.017	(Reference category)	0.041
OSR in DTA/SRAA	2.84 (1.23 to 6.58)		2.87 (0.97 to 8.46)	
ESG in DTA/SRAA	1.55 (0.69 to 3.49)		1.44 (0.48 to 4.31)	
Age (per decade)	1.50 (1.15 to 1.96)	0.003		
Female			2.03 (1.10 to 3.76)	0.024
NYHA (per class)	1.39 (1.06 to 1.81)	0.017		
Preoperative time in study (per month)	1.03 (1.01 to 1.05)	0.009	1.03 (1.01 to 1.06)	0.019

SRAA, suprarenal abdominal aorta.

Appendix 3 Participating centres

TABLE 34 Participating centres and number of patients recruited, by management group

	Management group, *n* (%)			
Centre	**WW (*N* = 489)**	**CM (*N* = 112)**	**ESG (*N* = 150)**	**OSR (*N* = 135)**
Addenbrookes	11 (2.3)	8 (7.1)	8 (5.3)	2 (1.5)
Bedford	7 (1.4)	0 (0.0)	3 (2.0)	1 (0.7)
Birmingham	3 (0.6)	0 (0.0)	1 (0.7)	0 (0.0)
Blackpool	6 (1.2)	3 (2.7)	1 (0.7)	7 (5.2)
Brighton & Sussex	11 (2.3)	7 (6.3)	9 (6.0)	1 (0.7)
Bristol	13 (2.7)	3 (2.7)	11 (7.3)	8 (5.9)
Central Manchester	14 (2.9)	4 (3.6)	4 (2.7)	3 (2.2)
Derby	12 (2.5)	0 (0.0)	0 (0.0)	1 (0.7)
Glenfield	38 (7.8)	1 (0.9)	4 (2.7)	2 (1.5)
Guy's & St Thomas'	12 (2.5)	1 (0.9)	9 (6.0)	5 (3.7)
Hull	1 (0.2)	1 (0.9)	0 (0.0)	1 (0.7)
Imperial	30 (6.1)	10 (8.9)	23 (15.3)	7 (5.2)
King's	8 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Leeds	29 (5.9)	14 (12.5)	13 (8.7)	7 (5.2)
Liverpool Heart & Chest	15 (3.1)	2 (1.8)	0 (0.0)	7 (5.2)
Musgrove Park	17 (3.5)	2 (1.8)	1 (0.7)	0 (0.0)
Newcastle	15 (3.1)	0 (0.0)	8 (5.3)	1 (0.7)
Norfolk & Norwich	37 (7.6)	0 (0.0)	9 (6.0)	5 (3.7)
North Cumbria	1 (0.2)	3 (2.7)	1 (0.7)	2 (1.5)
Papworth	72 (14.7)	12 (10.7)	2 (1.3)	39 (28.9)
Plymouth	19 (3.9)	1 (0.9)	0 (0.0)	3 (2.2)
Royal Free	7 (1.4)	3 (2.7)	6 (4.0)	0 (0.0)
Royal Liverpool	13 (2.7)	0 (0.0)	5 (3.3)	0 (0.0)
Sheffield	16 (3.3)	6 (5.4)	1 (0.7)	3 (2.2)
South Manchester	7 (1.4)	0 (0.0)	2 (1.3)	1 (0.7)
South Tees	8 (1.6)	1 (0.9)	2 (1.3)	0 (0.0)
Southampton	32 (6.5)	12 (10.7)	9 (6.0)	27 (20.0)
St George's	20 (4.1)	5 (4.5)	17 (11.3)	0 (0.0)
Surrey & Sussex	0 (0.0)	6 (5.4)	0 (0.0)	0 (0.0)
York	15 (3.1)	7 (6.3)	1 (0.7)	2 (1.5)

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Appendix 4 Plots of planned against actual recruitment by final management group

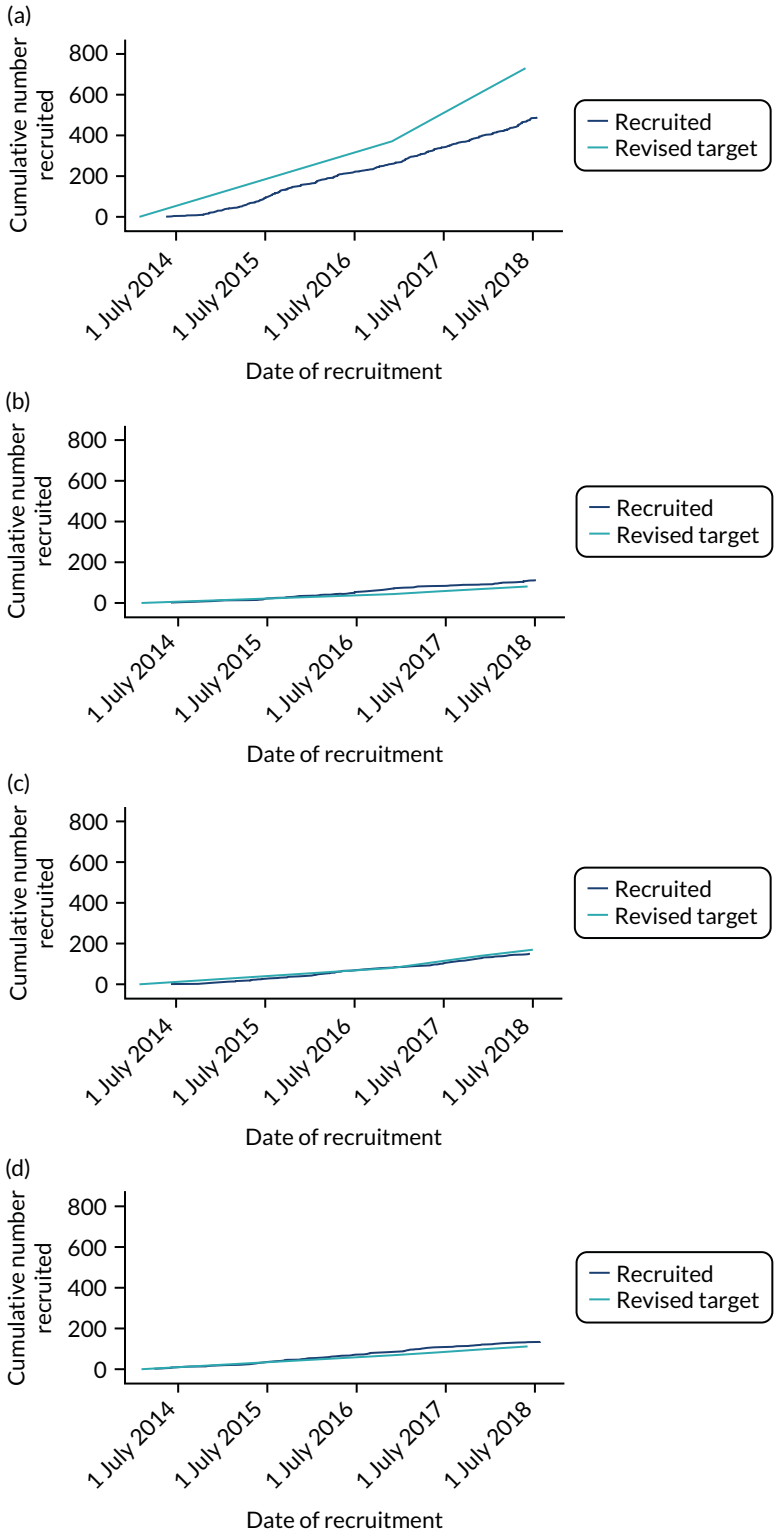

FIGURE 19 Target and actual recruitment over time by management group. (a) WW; (b) CM; (c) ESG; and (d) OSR.

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Appendix 5 Complications after second and third procedures

TABLE 35 Additional procedures and complications after second and third aneurysm procedures during the ETTAA study

Procedure/complication	Patient subgroup (number of patients)	
	ESG ($n = 12$)	OSR ($n = 25$)
Second procedure ESG/OSR	12/0	21/4
Third procedure ESG/OSR	–	3/0
Deaths during admission for procedure[a]	1	2
During additional procedure		
Complications of the procedure		
Endoleak	2	1
During additional procedure admission		
Number of complications		
Gastrointestinal	0	1
Neurological (cerebrovascular accident)	2	0
Spinal cord injury	0	1
Thromboembolic event	1	1
Infection	0	3
Vocal cord palsy	0	1
Inotropes/intra-aortic balloon pump	1	6
Prolonged ventilation	0	3
Renal support	0	1
Return to theatre	2	2
Total number of events	6	19
Total number of people with ≥ 1 event (%)	4 (33.3)	10 (40.0)

a Causes of death: severe visceral ischaemia (ESG); acute kidney injury/respiratory failure (OSR); hypoxic brain injury (OSR followed by ESG in same admission).

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Appendix 6 Descriptive summaries of variables at baseline (recruitment to the ETTAA study)

TABLE 36 Full table of descriptive summaries at recruitment according to final management group

	Patient subgroup (number of patients with a registration scan)				
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	*p*-value
Age (years)					< 0.0001
Mean (SD)	70.8 (10.7)	76.6 (9.9)	72.0 (8.6)	64.9 (11.6)	
Median (IQ)	72.4 (13.1)	77.8 (9.0)	74.3 (11.0)	66.7 (16.1)	
Minimum, maximum	32.3, 92.5	26.1, 92.5	49.6, 89.2	31.6, 83.5	
Sex, *n* (%)					0.4297
Female	174 (35.6)	48 (42.9)	50 (33.3)	49 (36.3)	
Male	315 (64.4)	64 (57.1)	100 (66.7)	86 (63.7)	
Height (cm)					< 0.0001
Mean (SD)	171.3 (10.2)	167.4 (12.5)	170.0 (10.0)	173.7 (11.3)	
Median (IQ)	173.0 (13.0)	165.0 (18.0)	170.0 (16.0)	174.0 (17.0)	
Minimum, maximum	138.0, 205.0	132.0, 216.0	149.0, 201.0	147.0, 210	
Missing, *n* (%)	19 (3.9)	9 (8.0)	4 (2.7)	3 (2.2)	
Weight (kg)					0.0001
Mean (SD)	80.6 (17.2)	74.2 (17.3)	78.6 (15.5)	83.9 (17.5)	
Median (IQ)	79.0 (21.0)	74.5 (18.5)	79.0 (21.0)	85.0 (23.0)	
Minimum, maximum	41.0, 143.0	42.0, 146.0	44.0, 123.0	41.0, 130.0	
Missing, *n* (%)	22 (4.5)	8 (7.1)	5 (3.3)	3 (2.2)	
BMI (kg/m^2)					0.1880
Mean (SD)	27.5 (5.0)	26.5 (4.9)	27.1 (4.3)	27.7 (4.6)	
Median (IQ)	26.9 (6.4)	25.9 (5.7)	27.3 (6.4)	27.6 (6.9)	
Minimum, maximum	13.8, 47.5	18.1, 43.6	18.9, 43.6	16.0, 38.0	
Missing, *n* (%)	24 (4.9)	9 (8.0)	6 (4.0)	3 (2.2)	
Care, *n* (%)					0.002[a]
Formal	10 (2.0)	5 (4.5)	0 (0.0)	1 (0.7)	
Informal	50 (10.2)	18 (16.1)	12 (8.0)	7 (5.2)	
None	425 (86.9)	88 (78.6)	138 (92.0)	125 (92.6)	
Missing	4 (0.8)	1 (0.9)	0 (0.0)	2 (1.5)	
Smoker (current or past), *n* (%)					0.353
Yes	343 (70.1)	71 (63.4)	113 (75.3)	89 (65.9)	
No	142 (29.0)	40 (35.7)	36 (24.0)	45 (33.3)	
Missing	4 (0.8)	1 (0.9)	1 (0.7)	1 (0.7)	

a Formal and informal care combined.

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TABLE 37 Summaries of comorbidities at recruitment according to final management group

	Patient subgroup (number of patients with a registration scan)				
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	*p*-value
CTD, *n* (%)					< 0.0001
Yes	30 (6.1)	3 (2.7)	2 (1.3)	20 (14.8)	
No	459 (93.9)	109 (97.3)	148 (98.7)	115 (85.2)	
Extracardiac arteriopathy, *n* (%)					0.4940
Yes	71 (14.5)	20 (17.9)	26 (17.3)	16 (11.9)	
No	406 (83.0)	91 (81.3)	123 (82.0)	118 (87.4)	
Missing	12 (2.5)	1 (0.9)	1 (0.7)	1 (0.7)	
Valvular heart disease, *n* (%)					0.0013
Yes	389 (79.6)	87 (77.7)	134 (89.3)	96 (71.1)	
No	89 (18.2)	23 (20.5)	15 (10.0)	38 (28.2)	
Missing	11 (2.3)	2 (1.8)	1 (0.7)	1 (0.7)	
Coronary artery disease, *n* (%)					0.3712
CABG	26 (5.3)	10 (8.9)	7 (4.7)	8 (5.9)	
Medication	46 (9.4)	9 (8.0)	14 (9.3)	8 (5.9)	
No	377 (77.1)	85 (75.9)	123 (82.0)	116 (85.9)	
PCI	27 (5.5)	6 (5.4)	5 (3.3)	2 (1.5)	
Missing	13 (2.7)	2 (1.8)	1 (0.7)	1 (0.7)	
LV function, *n* (%)					< 0.0001
Good	199 (40.7)	41 (36.6)	64 (42.7)	79 (58.5)	
Moderate	30 (6.1)	14 (12.5)	13 (8.7)	19 (14.1)	
Poor	11 (2.3)	2 (1.8)	2 (1.3)	0 (0.0)	
Not measured	241 (49.3)	55 (49.1)	70 (46.7)	36 (26.7)	
Missing	8 (1.6)	0 (0.0)	1 (0.7)	1 (0.7)	
Diabetes, *n* (%)					0.2350[a]
No	432 (88.3)	105 (93.8)	137 (91.3)	126 (93.3)	
NIDDM	52 (10.6)	7 (6.3)	13 (8.7)	8 (5.9)	
IDDM	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.7)	
Missing	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypertension, *n* (%)					0.7856
Yes	424 (86.7)	97 (86.6)	135 (90.0)	119 (88.2)	
No	63 (12.9)	15 (13.4)	15 (10.0)	16 (11.9)	
Missing	2 (0.4)	0 (0)	0 (0.0)	0 (0)	

TABLE 37 Summaries of comorbidities at recruitment according to final management group (*continued*)

	Patient subgroup (number of patients with a registration scan)				
	WW (*N* = 489)	CM (*N* = 112)	ESG (*N* = 150)	OSR (*N* = 135)	*p*-value
COPD, *n* (%)					0.1772
Yes	87 (17.8)	26 (23.2)	32 (21.3)	18 (13.3)	
No	397 (81.2)	86 (76.8)	118 (78.7)	117 (86.7)	
Missing	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	
NYHA class, *n* (%)					0.4187
I	198 (40.5)	39 (34.8)	68 (45.3)	54 (40.0)	
II	175 (35.8)	41 (36.6)	47 (31.3)	52 (38.5)	
III	86 (17.6)	27 (24.1)	20 (13.3)	17 (12.6)	
IV	16 (3.3)	3 (2.7)	4 (2.7)	3 (2.2)	
Missing	14 (2.9)	2 (1.8)	11 (7.3)	9 (6.7)	
Serum creatinine level (µmol/l)					0.0068
Mean (SD)	96.0 (32.8)	104.9 (39.8)	92.6 (31.9)	85.7 (27.3)	
Median (IQ)	89.0 (39.0)	97.5 (56.5)	88.0 (34.0)	82.0 (32.0)	
Minimum, maximum	45.0, 227.0	44.0, 225.0	43.0, 200.0	32.0, 186.0	
Missing, *n* (%)	309 (63.2)	60 (53.6)	42 (28.0)	48 (35.6)	
Haemoglobin level (g/l)					0.0420
Mean (SD)	127.5 (19.1)	128.4 (15.8)	131.7 (16.2)	133.6 (17.3)	
Median (IQ)	128.0 (24.0)	129.0 (23.0)	133.0 (20.0)	137.0 (25.0)	
Minimum, maximum	76.0, 175.0	98.0, 171.0	77.0, 176.0	90.0, 165.0	
Missing, *n* (%)	326 (66.7)	64 (57.1)	44 (29.3)	50 (37.0)	

IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.
a IDDM and NIDDM combined.

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TABLE 38 Summaries of cardiac drugs at recruitment according to final management group

	Patient subgroup (number of patients with a registration scan)				
	WW ($N = 489$)	CM ($N = 112$)	ESG ($N = 150$)	OSR ($N = 135$)	*p*-value
Beta-blocker use, *n* (%)					0.5608
Yes	255 (52.2)	51 (45.5)	74 (49.3)	72 (53.3)	
No	234 (47.9)	61 (54.5)	76 (50.7)	63 (46.7)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
ACE inhibitor use, *n* (%)					0.06342
Yes	116 (23.7)	39 (34.8)	45 (30.0)	40 (29.6)	
No	373 (76.3)	73 (65.2)	105 (70.0)	95 (70.4)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
ARB use, *n* (%)					0.5416
Yes	94 (19.2)	26 (23.2)	28 (18.7)	32 (23.7)	
No	395 (80.8)	86 (76.8)	122 (81.3)	103 (76.3)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Calcium channel blocker use, *n* (%)					0.7909
Yes	176 (36.0)	35 (31.3)	55 (36.7)	47 (34.8)	
No	313 (64.0)	77 (68.8)	95 (63.3)	88 (65.2)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Other antihypertensives, *n* (%)					0.1429
Yes	65 (13.3)	24 (21.4)	24 (16.0)	17 (12.6)	
No	424 (86.7)	88 (78.6)	126 (84.0)	118 (87.4)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Any antihypertensive, *n* (%)					0.7900
Yes	412 (84.3)	94 (83.9)	131 (87.3)	116 (85.9)	
No	77 (15.8)	18 (16.1)	19 (12.7)	19 (14.1)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Statins, *n* (%)					< 0.0001
Yes	283 (57.9)	72 (64.3)	106 (70.7)	51 (37.8)	
No	204 (41.7)	40 (35.7)	44 (29.3)	84 (62.2)	
Missing	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	

Appendix 7 Pre-intervention longitudinal models for aneurysm growth and health-related quality of life

TABLE 39 Final models estimates for relation between aneurysm diameter measurements over time and covariates

Parameter fixed effects	Coefficient (SE) (95% CI)	*p*-value (*z*-test)
Main effects		
Intercept	5.29 (0.06) (5.18 to 5.40)	< 0.001
Time per year	0.07 (0.02) (0.03 to 0.12)	0.105
Age at scan (per decade)	0.17 (0.03) (0.11 to 0.22)	< 0.001
Patient height (per 10 cm)	0.06 (0.02) (0.02 to 0.11)	0.004
Smoking history		0.035
Current smoker	0.23 (0.10) (0.05 to 0.42)	
Ex-smoker	0.12 (0.06) (0.00 to 0.25)	
Site (reference DTA)		< 0.001
Ascending	−1.15 (0.06) (−1.26 to −1.03)	
Suprarenal abdominal	−1.92 (0.06) (−2.04 to −1.80)	
Arch	−1.15 (0.06) (−1.27 to −1.04)	
MRI relative to CT	0.00 (0.04) (−0.08 to 0.08)	0.960
Connective tissue disease	0.23 (0.12) (−0.01 to 0.47)	0.056
COPD	0.27 (0.08) (0.12 to 0.42)	< 0.001
Valvular heart disease	−0.12 (0.07) (−0.26 to 0.02)	0.096
Interactions		
Time–MRI interaction	−0.11 (0.03) (−0.18 to −0.04)	0.001
Time–site interaction		< 0.001
Ascending	−0.07 (0.02) (−0.12 to −0.02)	
Suprarenal abdominal	0.03 (0.03) (−0.02 to 0.08)	
Arch	−0.03 (0.02) (−0.08 to 0.02)	
Site–age at scan interaction		< 0.001
Ascending	0.02 (0.03) (−0.04 to 0.07)	
Suprarenal abdominal	−0.13 (0.03) (−0.18 to −0.07)	
Arch	−0.08 (0.03) (−0.13 to −0.02)	

continued

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TABLE 39 Final models estimates for relation between aneurysm diameter measurements over time and covariates (*continued*)

Parameter fixed effects	Coefficient (SE) (95% CI)	*p*-value (*z*-test)
Site–connective tissue disease interaction		< 0.001
Ascending	−0.25 (0.13) (−0.51 to 0.01)	
Suprarenal abdominal	0.33 (0.14) (0.06 to 0.59)	
Arch	−0.23 (0.12) (−0.47 to 0.02)	
Site–COPD interaction		< 0.001
Ascending	−0.22 (0.08) (−0.38 to −0.06)	
Suprarenal abdominal	−0.29 (0.08) (−0.45 to −0.13)	
Arch	−0.31 (0.08) (−0.47 to −0.16)	
Site–valvular heart disease interaction		< 0.001
Ascending	0.37 (0.08) (0.22 to 0.52)	
Suprarenal abdominal	0.10 (0.08) (−0.06 to 0.25)	
Arch	0.14 (0.07) (0.00 to 0.29)	
Site–smoking history interaction		< 0.001
Ascending–current	−0.22 (0.10) (−0.42 to −0.03)	
Suprarenal abdominal–current	0.04 (0.10) (−0.16 to 0.25)	
Arch–current	−0.33 (0.10) (−0.52 to −0.13)	
Ascending–ex	−0.22 (0.07) (−0.35 to −0.09)	
Suprarenal abdominal–ex	0.00 (0.07) (−0.13 to 0.14)	
Arch–ex	−0.25 (0.06) (−0.38 to −0.12)	
Random effects		
SD (intercept)	0.54	
Residual error	0.81	

SE, standard error.

Notes

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TABLE 40 Final models estimates for relation between HRQoL over time and baseline covariates

Parameter fixed effects	Coefficient (SE) (95% CI)	*p*-value (*z*-test)
Main effects		
Intercept	0.849 (0.015) (0.819 to 0.879)	< 0.001
Time per year	−0.010 (0.006) (−0.022 to 0.003)	0.128
Age per decade	0.013 (0.006) (0.000 to 0.025)	0.051
Female sex	−0.029 (0.013) (−0.055 to −0.002)	0.032
Formal/informal care	−0.206 (0.025) (−0.255 to −0.156)	< 0.001
Group (reference WW)		0.5131
CM	−0.018 (0.028) (−0.074 to 0.037)	
ESG	0.015 (0.026) (−0.037 to 0.066)	
OSR	−0.033 (0.028) (−0.088 to 0.023)	
NYHA per class	−0.089 (0.010) (−0.108 to −0.069)	< 0.001
Smoking history		0.042
Current smoker	−0.047 (0.022) (−0.091 to −0.004)	
Ex-smoker	0.003 (0.015) (−0.026 to 0.032)	
Interactions		
Time–age per decade interaction	−0.013 (0.003) (−0.019 to −0.007)	< 0.001
Time–smoking history interaction		0.004
Current smoker	−0.034 (0.012) (−0.057 to −0.010)	
Ex-smoker	0.003 (0.008) (−0.012 to 0.018)	
Care–group interaction		0.009
CM	0.086 (0.051) (−0.014 to 0.186)	
ESG	−0.007 (0.070) (−0.144 to 0.131)	
OSR	0.239 (0.077) (0.088 to 0.390)	
NYHA–group interaction (per class)		0.004
CM	−0.037 (0.023) (−0.083 to 0.009)	
ESG	−0.075 (0.026) (−0.126 to −0.024)	
OSR	0.036 (0.026) (−0.015 to 0.087)	
Random effects		
SD (time slope)	0.038	
SD (intercept)	0.160	
Residual error by group		
WW SD (residuals)	0.121	
CM SD (residuals)	0.133	
ESG SD (residuals)	0.122	
OSR SD (residuals)	0.142	

SE, standard error.

Notes

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Appendix 8 Descriptive summaries for variables measured just before procedures

TABLE 41 Full table of descriptive summaries prior to procedures

	Patient subgroup (number of patients with a registration scan)		
	ESG ($N = 150$)	OSR ($N = 135$)	*p*-value
Age (years)			< 0.0001
Mean (SD)	72.6 (8.6)	65.4 (11.6)	
Median (IQ)	74.5 (10.7)	67.6 (16.1)	
Minimum, maximum	49.8, 89.2	31.7, 84.6	
Sex, *n* (%)			0.6265
Female	50 (33.1)	49 (36.6)	
Male	101 (66.9)	85 (63.4)	
Height (m)			0.005
Mean (SD)	170.0 (10.0)	173.7 (11.3)	
Median (IQ)	170.0 (15.8)	174.0 (17.0)	
Minimum, maximum	149.0, 201.0	147.0, 210.0	
Missing, *n* (%)	4 (2.7)	3 (2.2)	
Weight (kg)			0.007
Mean (SD)	78.6 (15.5)	83.9 (17.5)	
Median (IQ)	79.0 (21.0)	85.0 (22.5)	
Minimum, maximum	44.0, 123.0	41.0, 130.0	
Missing, *n* (%)	5 (3.3)	3 (2.2)	
BMI (kg/m^2)			0.269
Mean (SD)	27.1 (4.3)	27.7 (4.6)	
Median (IQ)	27.3 (6.4)	27.6 (6.9)	
Minimum, maximum	18.9, 43.6	16.0, 38.0	
Missing, *n* (%)	6 (4.0)	3 (2.2)	
Care, *n* (%)			0.3674[a]
Formal	0 (0.0)	2 (1.5)	
Informal	12 (8.0)	9 (6.7)	
None	138 (92.0)	123 (91.1)	
Missing	0 (0.0)	1 (0.7)	
Smoker (current or past), *n* (%)			0.1054
Yes	113 (75.3)	89 (65.9)	
No	36 (24.0)	45 (33.3)	
Missing	1 (0.7)	1 (0.7)	

a Formal and informal care combined.

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TABLE 42 Summaries of comorbidities prior to procedures

	Patient subgroup (number of patients with a registration scan)		
	ESG ($N = 150$)	OSR ($N = 135$)	*p*-value
CTD, *n* (%)			< 0.0001
Yes	2 (1.3)	20 (14.9)	
No	148 (98.7)	115 (85.1)	
Extracardiac arteriopathy, *n* (%)			0.2567
Yes	26 (17.3)	16 (11.9)	
No	123 (82.0)	118 (87.4)	
Valvular heart disease, *n* (%)			0.0002
Yes	134 (89.3)	96 (71.1)	
No	15 (10.0)	38 (28.2)	
Missing	1 (0.7)	1 (0.7)	
Coronary artery disease, *n* (%)			0.6640
CABG	7 (4.7)	8 (5.9)	
Medication	14 (9.3)	8 (5.9)	
No	123 (82.0)	116 (85.9)	
PCI	5 (3.3)	2 (1.5)	
Missing	1 (0.7)	1 (0.7)	
LV function, *n* (%)			0.8189
Good	35 (21.3)	56 (41.5)	
Moderate	5 (3.3)	10 (7.4)	
Poor	0 (0.0)	1 (0.7)	
Missing	113 (75.3)	68 (50.4)	
Diabetes, *n* (%)			0.6959[a]
No	137 (91.3)	126 (93.3)	
NIDDM	13 (8.7)	8 (5.9)	
IDDM	0 (0.0)	1 (0.7)	
Hypertension, *n* (%)			0.2141
Yes	136 (90.7)	115 (85.2)	
No	14 (9.3)	20 (14.8)	
COPD *n* (%)			0.1120
Yes	32 (21.3)	18 (13.3)	
No	118 (78.7)	116 (86.7)	

TABLE 42 Summaries of comorbidities prior to procedures (*continued*)

	Patient subgroup (number of patients with a registration scan)		
	ESG (*N* = 150)	OSR (*N* = 135)	*p*-value
NYHA class, *n* (%)			0.5241
I	62 (41.3)	55 (40.7)	
II	46 (30.7)	50 (37.0)	
III	28 (18.7)	18 (13.3)	
IV	3 (2.0)	2 (1.5)	
Missing, *n* (%)	11 (7.3)	10 (7.4)	
Serum creatinine level (μmol/l)			0.119
Mean (SD)	89.0 (31.1)	96.1 (37.7)	
Median (IQR)	84.5 (36.2)	88.0 (33.5)	
Minimum, maximum	43.0, 194.0	32.0, 229.0	
Missing, *n* (%)	22 (14.7)	32 (23.7)	
Haemoglobin level (g/l)			0.003
Mean (SD)	124.8 (17.1)	131.6 (16.8)	
Median (IQR)	127.0 (21.0)	133.0 (24.0)	
Minimum, maximum	71.0, 168.0	86.0, 168.0	
Missing, *n* (%)	21 (14.0)	31 (23.0)	

IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.
a IDDM and NIDDM combined.

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TABLE 43 Summaries of cardiac drugs prior to procedures

	Patient subgroup (number of patients with a registration scan)		
	ESG ($N = 150$), *n* (%)	OSR ($N = 135$), *n* (%)	*p*-value
Beta-blocker			0.1956
Yes	73 (48.7)	77 (57.0)	
No	77 (51.3)	58 (43.0)	
Missing	0 (0.0)	0 (0.0)	
ACE inhibitor			0.9400
Yes	45 (30.0)	39 (28.9)	
No	105 (70.0)	96 (71.1)	
Missing	0 (0.0)	0 (0.0)	
ARB			0.4511
Yes	29 (19.3)	32 (23.7)	
No	121 (80.7)	103 (76.3)	
Missing	0 (0.0)	0 (0.0)	
Calcium channel blocker			0.3624
Yes	60 (40.0)	46 (34.1)	
No	90 (60.0)	89 (65.9)	
Missing	0 (0.0)	0 (0.0)	
Other antihypertensives			0.2559
Yes	26 (17.3)	16 (11.9)	
No	124 (82.7)	119 (88.1)	
Missing	0 (0.0)	0 (0.0)	
Any antihypertensive			0.4860
Yes	133 (88.7)	115 (85.2)	
No	17 (11.3)	20 (14.8)	
Missing	0 (0.0)	0 (0.0)	
Statins			< 0.0001
Yes	104 (69.3)	57 (42.2)	
No	46 (30.7)	78 (57.8)	
Missing	0 (0.0)	0 (0.0)	

Appendix 9 Reasons for return to theatre

TABLE 44 Return to theatre during index aneurysm procedures

	Patient subgroup (*n*)	
	ESG (*N* = 150)	**OSR (*N* = 135)**
Reason		
Access vessel injury	4	2
Aneurysm complication (includes re-exploration for bleeding/tamponade)	4	13
Fistulae	0	0
Reintervention	0	0
Endoleak	5	0
Stent graft complication	1	0
Other acute surgical complication (e.g. tracheostomy, bronchoscopy, laparotomy)	3	12
Planned abdominal aneurysm intervention	1	0
Total number of events	18	27
Total number of people with ≥ 1 event (%)	16 (10.7)	20 (14.8)

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Appendix 10 Post-intervention longitudinal models for health-related quality of life

TABLE 45 Final models estimates for relation between post-intervention HRQoL over time and pre-procedure covariates

Parameter fixed effects	Coefficient (SE)	95% CI	*p*-value (*z*-test)
Main effects			
Intercept	0.785 (0.030)	0.725 to 0.844	< 0.001
Time per year	−0.001 (0.006)	−0.012 to 0.013	0.913
First 6 weeks	−0.017 (0.023)	−0.062 to 0.027	0.440
OSR	−0.020 (0.024)	−0.066 to 0.026	0.396
Female sex	−0.028 (0.027)	−0.080 to 0.025	0.302
Preoperative HRQoL	0.473 (0.051)	0.374 to 0.572	< 0.001
NYHA per class	−0.034 (0.016)	−0.066 to −0.003	0.033
Smoking history			0.046
Current smoker	−0.095 (0.038)	−0.171 to −0.020	
Ex-smoker	−0.031 (0.028)	−0.085 to 0.023	
Interactions			
Time–female interaction	0.028 (0.013)	0.003 to 0.054	0.029
OSR–first 6 weeks interaction	−0.142 (0.029)	−0.199 to −0.085	< 0.0001
Random effects			
SD (intercept)	0.156		
Residual error by group			
ESG SD (residuals)	0.161		
OSR SD (residuals)	0.126		

SE, standard error.

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Appendix 11 Health economics detailed tables

TABLE 46 Resource use primary surgical procedure

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Fixed costs: theatre usage overheads				
Operating room	Average theatre duration	4 hours 56 minutes	8 hours 53 minutes	ETTAA study procedure CRF
Operating room with C-arm	Average theatre duration	4 hours 52 minutes	N/A	ETTAA study procedure CRF
Catheterisation laboratory	Average theatre duration	4 hours 5 minutes	N/A	ETTAA study procedure CRF
Hybrid theatre	Average theatre duration	3 hours 19 minutes	N/A	ETTAA study procedure CRF
Interventional radiology equipment	Per hour	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Capital equipment				
Cooling head jacket	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Basic vascular tray	Per procedure	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Cardiac major tray	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Diathermy console	Per procedure	1	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Sternal saw	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Defibrillator paddles	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Cell saver machine	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020

continued

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TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Sternal retractors	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Bypass machine	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
3M™ Bair Hugger™ System – 3M (Bracknell, UK)	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Rapid transfuser/ fluid warmer	Per procedure	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Suction machine	Per procedure	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Injection pump	Per procedure	1	4	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Staff				
Consultant surgeon	Per hour	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Assistant surgeon	Per hour	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Consultant anaesthetist	Per hour	Included in theatre cost except catheterisation laboratory	Included in theatre cost	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Anaesthetist registrar	Per hour	Included in theatre cost except catheterisation laboratory	Included in theatre cost	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Consultant radiologist	Per hour	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Assistant/registrar radiologist	Per hour	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Radiographer	Per hour	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Surgical care practitioner	Per hour	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Anaesthetic nurse	Per hour	1	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020 Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Scrub nurse (table)	Per hour	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Scrub nurse (floor)	Per hour	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Health-care assistant	Per hour	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Perfusionist	Per hour	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020

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TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Consumables				
Central lines	Per item	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Arterial lines	Per item	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Nasopharyngeal probe	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Urinary catheter	Per item	1	1	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Diathermy pad	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Swabs	Per item	20	60	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Size 15 knife blade	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Size 10 knife blade	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Cell saver tubing and fluids	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020

TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Side towels	Per item	N/A	2	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Vicryl® stay suture (Johnson & Johnson Medical NV, Brussels, Belgium)	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Cannulae (all sorts)	Per item	N/A	4	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Axillary cannular	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
	Per item	N/A	10	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Prolene® suture (Johnson & Johnson Medical NV, Brussels, Belgium) 5/0	Per item	3	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Prolene suture 3/0	Per item	N/A	5	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Maxolon ADVANZ Pharma (London, UK)	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Monocryl suture (Ethicon, Raritan, NJ, USA)	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Vicryl suture 2/0	Per item	2	2	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020 Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Bypass circuit disposable bits	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Teflon® pledgets/ strips (BD, Franklin Lakes, NJ, USA)	Per item	N/A	10	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020

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TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Bair Hugger blanket	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Haemostatic adjuncts	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Sternal wires	Per item	N/A	3	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Biosyn™ (Biosyn Corporation, Carlsbad, CA, USA)	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Dressings	Per item	N/A	2	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Argyl drain	Per item	N/A	2	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Redivac drain	Per item	N/A	1	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Drain sutures braided nylon	Per item	N/A	4	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Spinal drain	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Suction tube	Per item	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Sheath	Per item	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Angiography hollow needles	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Pigtail catheter	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
J-wire	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Terumo wire	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Super stiff Meier™ wire	Per item	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Extension for injection pump	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Iodinated contrast	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Injection pump contract syringe	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Measuring pigtail catheter	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
12F sheath	Per item	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Saline	Per item	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Sterile bowls for coiling wires	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Moulding balloon	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Syringe 20 ml	Per item	2	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Diathermy forceps	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

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TABLE 46 Resource use primary surgical procedure (*continued*)

Resource or unit intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Blade	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
SURGICEL®	Per item	1	N/A	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Blood products				
Heparin	Per 1000 units/ 1 ml solution	N/A	0	ETTAA study procedure CRF
Protamine	Per sulfate 50 mg/5 ml	N/A	0	ETTAA study procedure CRF
Standard red cells	Per unit	0.46	5.06	ETTAA study procedure CRF
Platelets, pooled	Per unit	0.07	1.63	ETTAA study procedure CRF
FFP	Per unit (275 ml)	0.10	3.51	ETTAA study procedure CRF
Cryoprecipitate, pooled	Per unit (200 ml)	0.03	2.26	ETTAA study procedure CRF
Octaplex® (Octapharma, Manchester, UK)	Per unit (500iu)	N/A	2	ETTAA study procedure CRF
Beriplex® (CSL Behring, Haywards Heath, UK)	Per unit (500iu)	N/A	0.06	ETTAA study procedure CRF
Fibrinogen	Per unit (1 g)	N/A	0.31	ETTAA study procedure CRF
Albumin	Per unit (100 ml of 20%)	N/A	0	ETTAA study procedure CRF
NovoSeven® (Novo Nordisk Inc., Plainsboro, NJ, USA)	Per unit (2 mg)	N/A	0.29	ETTAA study procedure CRF

FFP, fresh frozen plasma; N/A, not applicable.

TABLE 47 Resource use postoperatively until hospital discharge including return to theatres

Resource or intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Type of stay				
ICU	Per day	1.85	10.66	ETTAA study, post-procedure form and discharge CRF
HDU	Per day	1.46	1.77	ETTAA study, post-procedure form and discharge CRF
Ward	Per day	6.38	8.77	ETTAA study, post-procedure form and discharge CRF
Ward after transfer	Per day	0.71	17.89	ETTAA study, post-procedure form and discharge CRF

TABLE 47 Resource use postoperatively until hospital discharge including return to theatres (*continued*)

Resource or intervention	Unit	Mean usage in standard ESG	Mean usage in standard OSR	Resource source
Blood products				
Standard red blood cells	Per unit	0.58	1.66	ETTAA study, post-procedure form and discharge CRF
Platelets, pooled	Per unit	0.24	0.31	ETTAA study, post-procedure form and discharge CRF
FFP	Per unit (275 ml)	0.07	0.66	ETTAA study, post-procedure form and discharge CRF
Cryoprecipitate, pooled	Per unit (200 ml)	0.03	0.11	ETTAA study, post-procedure form and discharge CRF
Albumin	Per unit	0	0.09	ETTAA study, post-procedure form and discharge CRF
Octuplex	Per unit	0	0.06	ETTAA study, post-procedure form and discharge CRF
Pasmalyte	Per unit	0.01	0	ETTAA study, post-procedure form and discharge CRF
Imaging				
CT	Per investigation	0.95	1.17	ETTAA study, post-procedure form and discharge CRF
MRI	Per investigation	0.18	0.06	ETTAA study, post-procedure form and discharge CRF
X-ray (plain films)	Per investigation	1.14	6.54	ETTAA study, post-procedure form and discharge CRF
TOE	Per investigation	0.03	0.09	ETTAA study, post-procedure form and discharge CRF
TTE	Per investigation	0.10	0.46	ETTAA study, post-procedure form and discharge CRF
Angiography	Per investigation	0.10	0.03	ETTAA study, post-procedure form and discharge CRF
Ultrasound	Per investigation	0.19	0.20	ETTAA study, post-procedure form and discharge CRF
Fluoroscopy	Per investigation	0	0.03	ETTAA study, post-procedure form and discharge CRF
Renography	Per investigation	0	0.03	ETTAA study, post-procedure form and discharge CRF
Echocardiography	Per investigation	0.02	0	ETTAA study, post-procedure form and discharge CRF
Return to theatre				
Return to theatre	Per event	0.15	0.20	ETTAA study, return to theatre CRF

FFP, fresh frozen plasma; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph.

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TABLE 48 Resource use of health and personal social care by follow-up including hospital readmissions and additional procedures

Resource or intervention	Unit	Mean usage	
		ESG	OSR
Follow-up: 1 month		***ESG (n = 74)***	***OSR (n = 16)***
Formal care	Per hour	2.91	0
Informal care	Per hour	21.76	31.58
Nurse visits	Per visit	0.54	0.31
Nurse home visits	Per visit	0.97	0.31
GP visits	Per visit	0.69	0.38
GP home visits	Per visit	0.14	0.25
Physiotherapist visits	Per visit	0.01	0
A&E visits	Per visit	0.14	0.13
CT scans	Per visit	1	0
Outpatient appointments vascular surgery (consultant led)	Per visit	1	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	0
Additional procedures	Per event	0.05	0.06
Hospital admissions	Per event	0.11	0
Follow-up: 3 months		***ESG (n = 76)***	***OSR (n = 19)***
Formal care	Per hour	3.97	0
Informal care	Per hour	34.13	61.71
Nurse visits	Per visit	1.46	0.68
Nurse home visits	Per visit	0.24	0.16
GP visits	Per visit	0.88	1.32
GP home visits	Per visit	0.11	0.05
Physiotherapist visits	Per visit	0.13	0.63
A&E visits	Per visit	0.08	0.16
CT scans	Per visit	0	0
Outpatient appointments vascular surgery (consultant led)	Per visit	0	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	0
Additional procedures	Per event	0.01	0.05
Hospital admissions	Per event	0.08	0
Follow-up: 6 months		***ESG (n = 81)***	***OSR (n = 24)***
Formal care	Per hour	0.67	13.63
Informal care	Per hour	137.18	55.23
Nurse visits	Per visit	1.16	1.33
Nurse home visits	Per visit	0.35	2.33
GP visits	Per visit	1.41	2.17
GP home visits	Per visit	0.1	0
Physiotherapist visits	Per visit	0.36	0.54

TABLE 48 Resource use of health and personal social care by follow-up including hospital readmissions and additional procedures (*continued*)

Resource or intervention	Unit	Mean usage	
		ESG	OSR
A&E visits	Per visit	0.11	0.08
CT scans	Per visit	0	1
Outpatient appointments vascular surgery (consultant led)	Per visit	0	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	1
Additional procedures	Per event	0.02	0.08
Hospital admissions	Per event	0.04	0
Follow-up: 12 months		***ESG (n = 74)***	***OSR (n = 20)***
Formal care	Per hour	1.15	378.83
Informal care	Per hour	56.81	120.25
Nurse visits	Per visit	1.36	2.45
Nurse home visits	Per visit	2.09	7.9
GP visits	Per visit	1.78	2.4
GP home visits	Per visit	0.04	0.1
Physiotherapist visits	Per visit	0.55	1.25
A&E visits	Per visit	0.26	0.35
CT scans	Per visit	1	1
Outpatient appointments vascular surgery (consultant led)	Per visit	1	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	1
Additional procedures	Per event	0.01	0
Hospital admissions	Per event	0.07	0
Follow-up: 18 months		***ESG (n = 59)***	***OSR (n = 16)***
Formal care	Per hour	38.1	120.44
Informal care	Per hour	206.68	132.59
Nurse visits	Per visit	1.34	2.69
Nurse home visits	Per visit	1.12	12.44
GP visits	Per visit	1.46	3.06
GP home visits	Per visit	0.02	0.38
Physiotherapist visits	Per visit	0.19	0.13
A&E visits	Per visit	0.15	0.56
CT scans	Per visit	0	0
Outpatient appointments vascular surgery (consultant led)	Per visit	0	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	0
Additional procedures	Per event	0	0
Hospital admissions	Per event	0.02	0

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TABLE 48 Resource use of health and personal social care by follow-up including hospital readmissions and additional procedures (*continued*)

Resource or intervention	Unit	Mean usage	
		ESG	OSR
Follow-up: 24 months		***ESG (n = 35)***	***OSR (n = 11)***
Formal care	Per hour	1.49	94.73
Informal care	Per hour	96.77	71.69
Nurse visits	Per visit	1.03	2.73
Nurse home visits	Per visit	0.11	1.27
GP visits	Per visit	1.63	4.82
GP home visits	Per visit	0.06	0.09
Physiotherapist visits	Per visit	0.4	1.09
A&E visits	Per visit	0.09	0.09
CT scans	Per visit	1	1
Outpatient appointments vascular surgery (consultant led)	Per visit	1	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	1
Additional procedures	Per event	0.03	0.09
Hospital Admissions	Per event	0.03	0
Follow-up: 36 months		***ESG (n = 17)***	***OSR (n = 5)***
Formal care	Per hour	0	0
Informal care	Per hour	16.77	366.17
Nurse visits	Per visit	0.82	1.8
Nurse home visits	Per visit	0	0
GP visits	Per visit	2.53	4
GP home visits	Per visit	0	0
Physiotherapist visits	Per visit	0	1.2
A&E visits	Per visit	0.24	0
CT scans	Per visit	1	1
Outpatient appointments vascular surgery (consultant led)	Per visit	1	0
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	1
Additional procedures	Per event	0.12	0.2
Hospital admissions	Per event	0.18	0
Follow-up: 48 months		***ESG (n = 3)***	***OSR (n = 0)***
Formal care	Per hour	0	N/A
Informal care	Per hour	34.67	N/A
Nurse visits	Per visit	2	N/A
Nurse home visits	Per visit	0	N/A
GP visits	Per visit	3	N/A
GP home visits	Per visit	0	N/A
Physiotherapy visits	Per visit	0	N/A

TABLE 48 Resource use of health and personal social care by follow-up including hospital readmissions and additional procedures (*continued*)

Resource or intervention	Unit	Mean usage	
		ESG	OSR
A&E visits	Per visit	0	N/A
CT scans	Per visit	1	N/A
Outpatient appointments vascular surgery (consultant led)	Per visit	1	N/A
Outpatient appointments cardiothoracic surgery (consultant led)	Per visit	0	N/A
Additional procedures	Per event	0	N/A
Hospital admissions	Per event	0	N/A

TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre

Resource or unit intervention	OSR group	ESG group	Cost (£)	Cost source
Fixed costs				
Operating room for OSR	Yes	N/A	518.00[a]	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Operating room for ESG[b]	N/A	Yes	550.08[a,b]	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Operating room with C-arm[b]	N/A	Yes	550.08[a,b]	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Catheterisation laboratory	N/A	Yes	252.08[b]	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton in 2019 and 2020
Hybrid theatre	N/A	Yes	550.08[a,b]	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Interventional radiology equipment		Yes	32.08	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

Capital equipment costs	*OSR group*	*ESG group*	*Capital*	*Annualised cost*	*Per operating session (253 days)*	*Cost source*
Cooling head jacket	Yes	N/A	12,000 (5 years)	£2657.00	£11.00	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Basic vascular tray	N/A	Yes	7000 (10 years)	£841.65	£3.33	Capital cost from Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

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TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre (*continued*)

Resource or unit intervention	OSR group	ESG group	Capital	Annualised cost	Per operating session (253 days)	Cost source
Diathermy console	Yes	Yes	9000 (5 years)	£1993.00	£7.88	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Sternal saw	Yes	N/A	7500 (5 years)	£1661.00	£6.57	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Cell saver machine	Yes	N/A	5000 (5 years)	£1107.00	£4.38	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Sternal retractors	Yes	N/A	6900 (5 years)	£1528.00	£6.04	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Bypass machine	Yes	N/A	10,500 (5 years)	£2325.00	£9.20	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Bair Hugger™ (3M™, Bracknell, UK) machine	Yes	N/A	3750 (1 year)	£3880.00	£15.35	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Rapid transfuser/fluid warmer	Yes	N/A	15,000 (5 years)	£3322.00	£13.13	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Suction machine	N/A	Yes	500 (5 years)	£111.00	£0.44	Capital cost from Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Injection pump	N/A	Yes	2000 (5 years)	£443.00	£1.75	Capital cost from Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre (*continued*)

Resource or unit intervention	OSR group	ESG group	Cost (£)	Cost source
Defibrillator paddles	Yes	N/A	3.00	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Cardiac major tray	Yes	N/A	50.00	Capital cost from Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Staff costs				
Consultant surgeon	Yes	Yes	109.00	PSSRU 2018/19[94] based on 'consultant: surgical'
Assistant surgeon	Yes	Yes	47.00	PSSRU 2018/19[94] based on 'registrar'
Consultant anaesthetist (included in theatre cost, except catheterisation laboratory)	Yes	Yes	109.00	PSSRU 2018/19[94] based on 'consultant: medical'
Anaesthetist registrar (included in theatre cost, except catheterisation laboratory)	Yes	Yes	47.00	PSSRU 2018/19[94] based on 'registrar'
Consultant radiologist	N/A	Yes	109.00	PSSRU 2018/19[94] based on 'consultant: medical'
Assistant/registrar radiologist	N/A	Yes	47.00	PSSRU 2018/19[94] based on 'registrar'
Radiographer	N/A	Yes	37.00 (band 5)	PSSRU 2018/19[94] based on hospital-based 'scientific and professional staff'
Surgical care practitioner	Yes	N/A	65.00 (band 8a)	PSSRU 2018/19[94] based on 'hospital-based nurses'
Anaesthetic nurse	Yes	Yes	47.00 (band 6)	PSSRU 2018/19[94] based on 'hospital-based nurses'
Scrub nurse (table)	Yes	Yes	38.00 (band 5)	PSSRU 2018/19[94] based on 'hospital-based nurses'
Scrub nurse (floor)	Yes	Yes	38.00 (band 5)	PSSRU 2018/19[94] based on 'hospital-based nurses'
Health-care assistant	N/A	Yes	8.93 (band 2 with 3–4 years' experience)	NHS Employers website[108] 2018/19 hourly rate
Perfusionist	Yes	N/A	62.35	PSSRU 2018/19[94] based on the average of band 7 and band 8a 'hospital-based scientific and professional staff'
Consumables costs				
Central lines	Yes	Yes	25.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Arterial lines	Yes	Yes	25.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020
Nasopharyngeal probe	Yes	N/A	15.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and 2020

continued

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TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre (*continued*)

Resource or unit intervention	OSR group	ESG group	Cost (£)	Cost source
Urinary catheter	Yes	Yes	36.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Diathermy pad	Yes	N/A	1.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Swabs	Yes	Yes	0.50	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Size 15 knife blade	Yes	N/A	10.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Size 10 knife blade	Yes	N/A	10.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Cell saver tubing and fluids	Yes	N/A	235.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Side towels	Yes	N/A	1.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Vicryl® (Johnson & Johnson NV, Brussels, Belgium) stay suture	Yes	N/A	3.15	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Cannula (all sorts)	Yes	N/A	0.50	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Axillary cannula	Yes	N/A	0.50	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
4/0 Prolene® (Johnson & Johnson NV, Brussels, Belgium)	Yes	N/A	7.30	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
5/0 Prolene	N/A	Yes	7.30	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
3/0 Prolene	Yes	N/A	3.15	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Maxalon (ADVANZ Pharma, London, UK)	Yes	N/A	3.15	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Monocryl (Ethicorn, Raritan, NJ, USA) suture	Yes	Yes	25.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
2/0 Vicryl	Yes	Yes	3.15	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Bypass circuit disposable bits	Yes	N/A	650.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020

TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre (*continued*)

Resource or unit intervention	OSR group	ESG group	Cost (£)	Cost source
Teflon pledgets/strips (BD, Franklin Lakes, NJ, USA)	Yes	N/A	1.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Bair Hugger blanket	Yes	N/A	6.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Haemostatic adjuncts	Yes	N/A	25.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Sternal wires	Yes	N/A	42.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Biosyn	Yes	N/A	3.15	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Dressings	Yes	N/A	0.50	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Argyl drain	Yes	N/A	5.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Redivac drain	Yes	N/A	5.00	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Drain sutures braided nylon	Yes	N/A	3.15	Royal Papworth Hospital NHS Trust based on personal communication with Rosie Thornton between November 2019 and June 2020
Spinal drain	N/A	Yes	413.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Suction tube	N/A	Yes	1.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Sheath	N/A	Yes	10.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Angiography hollow needles	N/A	Yes	2.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Pigtail catheter	N/A	Yes	10.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
J wire	N/A	Yes	65.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Terumo wire	N/A	Yes	5.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Super stiff Meier wire	N/A	Yes	70.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020

continued

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TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre (*continued*)

Resource or unit intervention	OSR group	ESG group	Cost (£)	Cost source
Extension for injection pump	N/A	Yes	9.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Iodinated contrast	N/A	Yes	10.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Injection pump contract syringe	N/A	Yes	15.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Measuring pigtail catheter	N/A	Yes	12.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
12F Sheath	N/A	Yes	7.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Saline	N/A	Yes	5.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Sterile bowls for coiling wires	N/A	Yes	30.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Moulding balloon	N/A	Yes	300.00	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Syringe 20ml	N/A	Yes	0.15	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Diathermy forceps	N/A	Yes	195.80	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Blade	N/A	Yes	5.89	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Surgicel	N/A	Yes	55.82	Imperial College Healthcare NHS Trust based on personal communication with Colin Bicknell between January and June 2020
Blood products				
Heparin	Yes	N/A	14.85	BNF NICE 2018/2019[109]
Protamine	Yes	N/A	49.55	BNF NICE 2018/2019[109]
Standard red cells	Yes	Yes	128.99	NHS Blood and Transplant Price list 2018/19[96]
Platelets, pooled	Yes	Yes	185.86	NHS Blood and Transplant Price list 2018/19[96]
Fresh frozen plasma	Yes	Yes	28.46	NHS Blood and Transplant Price list 2018/19[96]
Cryoprecipitate, pooled	Yes	Yes	177.55	NHS Blood and Transplant Price list 2018/19[96]
Octaplex (Octapharma, Manchester, UK)	Yes	N/A	125.00	Royal Papworth Hospital NHS Trust based on personal communication with Priya Sastry in July 2020

TABLE 49 Unit costs of resources and interventions: primary procedure and return to theatre (*continued*)

Resource or unit intervention	OSR group	ESG group	Cost (£)	Cost source
Beriplex (CSL Behring, Haywards Heath, UK)	Yes	N/A	125.00	Royal Papworth Hospital NHS Trust based on personal communication with Priya Sastry in July 2020
Fibrinogen	Yes	N/A	364.00	Royal Papworth Hospital NHS Trust based on personal communication with Priya Sastry in July 2020
Albumin	Yes	N/A	42.50	Royal Papworth Hospital NHS Trust based on personal communication with Priya Sastry in July 2020
NovoSeven® (Novo Nordisk Inc., PLainsboro, NJ, USA)	Yes	N/A	919.00	Royal Papworth Hospital NHS Trust based on personal communication with Priya Sastry in July 2020

N/A, not applicable.
a Consultant anaesthetist + anaesthetic registrar costs included.
b Includes interventional radiology equipment.

TABLE 50 Unit costs of resources and interventions post procedure up until discharge

Resource or unit intervention	Cost (£)	Unit	Cost source
Type of stay			
ICU	1417.63	Per day	From NICE[110] inflated using the PSSRU index[94]
HDU	724.18	Per day	From NICE[110] inflated using the PSSRU index[94]
Ward	416.90	Per day	From NICE[110] inflated using the PSSRU index[94]
Blood products			
Standard red blood cells	128.99	Per unit	NHS Blood and Transplant Price list 2018/19[96]
Platelets, pooled	185.86	Per unit	NHS Blood and Transplant Price list 2018/19[96]
FFP	28.46	Per unit	NHS Blood and Transplant Price list 2018/19[96]
Cryoprecipitate, pooled	177.55	Per unit	NHS Blood and Transplant Price list 2018/19[96]
Imaging			
CT	97.00	Per scan	National Schedule of NHS costs 2018/19.[111] Weighted average of codes RD20A, RD21A, and RD22Z to RD27Z
MRI	341.00	Per scan	National Schedule of NHS costs 2018/19.[111] Weighted average of codes RD08Z to RD10Z
X-ray (plain films)	31.00	Per scan	National Schedule of NHS costs 2018/19.[111] Code: DAPF
TOE	257.00	Per scan	National Schedule of NHS costs 2018/19.[111] Code: EY50Z as 'Complex Echocardiogram'
TTE	257.00	Per scan	National Schedule of NHS costs 2018/19.[111] Code: EY50Z as 'Complex Echocardiogram'
Echocardiogram	64.00	Per scan	National Schedule of NHS costs 2018/19.[111] Code: RD51A as 'Simple Echocardiogram, 19 years and over'
Ultrasound	51.00	Per scan	National Schedule of NHS costs 2018/19. Code: RD47Z 'Vascular Ultrasound'
Renogram	209.00	Per scan	National Schedule of NHS costs 2018/19.[111] Code: RN25A 'Renogram, 19 years and over'
Fluoroscopy	118.00	Per scan	National Schedule of NHS costs 2018/19.[111] Weighted average of codes RD30Z, RD31Z, RD32Z
Angiogram	150.00	Per scan	Royal College of Physicians[112]

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TABLE 51 Unit costs during follow-up

Resource or unit intervention	Cost (£)	Units	Source
Primary/community care			
GP visits (surgery)	39.00	Per average contact time 9.22 minutes	PSSRU,[94] page 120, £39 per surgery consultation
GP visits (home)	100.62	Cost of home visit (23.4 minutes including travel time)	Unit Costs of Health and Social Care 2015,[113] page 176, average home visit is 11.4 minutes with 12 minutes of travel time. Cost on 23.4 minutes of GP time[a]
			PSSRU,[94] page 119, £4.30 per minute[a]
Nurse visit (surgery)	42.00	Per hour	GP practice nurse, PSSRU,[94] page 118, £42 per hour[a]
Nurse visit (surgery)	10.85	Per contact (15.5 minutes)	Unit Costs of Health and Social Care 2015,[113] page 174, 15.5 minutes for contact[a]
			PSSRU,[94] page 118, £42 per hour[a]
Nurse visit (home)	16.38	Per hour	Unit Costs of Health and Social Care 2015,[113] page 176, average home visit is 11.4 minutes with 12 minutes of travel time.[a] Cost on 23.4 minutes of GP time. Assumed the travel and contact time is the same for a nurse as a GP
			PSSRU,[94] page 118, £42 per hour[a]
Physiotherapy/occupational therapy	58.00	Per unit	*NHS Reference Costs 2018 to 2019*,[93] assumed physiotherapy (outpatients code 650)[b]
Formal care	28.00	Per hour	PSSRU,[94] page 134, used home worker and the face-to-face social hours cost per hour[a]
Informal care	7.83	Per hour	Minimum wage as of 2018/19 tax year[114]
Secondary care			
A&E visits	166.00	Per visit	National Schedule of NHS costs 2018/19.[111] Index 'AE'
Outpatient appointments vascular surgery (consultant led)	148.00	Per appointment	National Schedule of NHS costs 2018/19.[111] Service code: 107 in 'total outpatient attendance'
Outpatient appointments cardiothoracic surgery (consultant led)	241.00	Per appointment	National Schedule of NHS costs 2018/19.[111] Service code: 170 in 'total outpatient attendance'
Imaging			
MRI	341.00	Per investigation	National Schedule of NHS costs 2018/19.[111] Weighted average of codes RD08Z to RD10Z
CT	97.00	Per investigation	National Schedule of NHS costs 2018/19.[111] Weighted Average of codes RD20A, RD21A, RD22Z to RD27Z

a Costs including qualifications.
b Unit cost based on consultant-led and non-consultant-led unit costs.

TABLE 52 Unit costs of hospital readmissions

Condition	HRG code	Cost (£)
Pleurisy	Weighted average of DZ28Z and DZ28B (pleurisy)	365
Chest pain	Weighted averages of EB12A to EB12C (unspecified chest pain with a CC score range of 0–11+)	400
Cardiac event	Weighted averages of EB10A to EB10E (actual or suspected myocardial infarction)	1478
Infection and haematemesis	Weighted average WH07A to WH07b (infections or other complications of procedures without and with single and with multiple interventions)	1793
Sepsis	Weighted averages of WJ06A to WJ06J (sepsis without intervention, with intervention and with multiple intervention)	2206
Elective angiography	Weighted average of EY43A to EY43F (standard cardiac catheterisation)	2401
Angiography	Weighted averages of EY41A to EY41D (standard percutaneous transluminal coronary angioplasty)	2689
Groin pseudoaneurysm	Weighted averages of YR11A to YR11D (percutaneous transluminal angioplasty of single blood vessel in CC score range)	2816
Carotid-subclavian bypass	Weighted averages of YQ31A + YQ31B [single open procedure on the carotid artery (CC score of 0–5+)]	5260
Elective carotid-subclavian bypass	Elective weighted averages of YQ31A + YQ31B [single open procedure on the carotid artery (CC score of 0–5+)]	5260
Elective complex endovascular repair of AAA	Elective weighted averages of YR66A to YR67B (standard endovascular repair of AAA and complex)	7321
Endovascular repair of AAA	Weighted averages of YR66A to YR67B (standard endovascular repair of AAA and complex)	7499
Elective open surgery repair of AAA	Elective weighted average of open repair of AAA single and multiple open procedures	9141
Endovascular repair of thoracic or thoracoabdomminal aortic aneurysm (fenestrated)	Weighted averages of YR62A + YR62B + YR63A + YR63B	9314
Complex repair of descending thoracic aorta (fenestrated)	Weighted averages of YR62A + YR62B + YR63A + YR63B	9314
Endovascular repair of thoracic or thoracoabdominal aortic aneurysm	Weighted average of YR61Z and YR60Z (standard and complex endovascular repair of thoracoabdominal aortic aneurysm using branched stent graft)	11,856
Elective complex endovascular repair of thoracic or thoracoabdominal aortic aneurysm	Elective weighted average of YR61Z and YR60Z (standard and complex endovascular repair of thoracoabdominal aortic aneurysm using branched stent graft)	12,493

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TABLE 53 Acceptable ranges for assignment to follow-up points

Follow-up point (months)	Days after index procedure	
	Minimum	Maximum
1	0	60
3	61	121
6	122	244
12	274	456
18	457	639
24	640	821
36	913	1278
48	1279	1643
60	1644	2008

TABLE 54 Total average cost (£) per patient by each area of resource use: OSR and ESG primary procedure

Resource use	ESG group ($n = 115$)		OSR group ($n = 35$)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Total staff time costs	1972 (1399)	1683 (1022–2471)	3611 (1082)	3556 (2885–3915)
Total theatre usage costs including capital and consumable equipment	3517 (1446)	3085 (2461–4167)	6088 (1379)	6018 (5163–6475)
Total graft costs	N/A	N/A	5461 (6696)	1117 (436–12,500)
Total stent costs	20,966 (9001)	20,890 (14,734–28,885)	N/A	N/A
Total blood products usage costs	82 (349)	0 (0–0)	2079 (3378)	869 (117–1819)
Total costs of index surgical procedure	26,536 (9877)	24,733 (19,300–35,173)	17,239 (8043)	15,359 (10,350–21,874)

N/A, not applicable.

TABLE 55 Total average cost (£) per patient by each area of resource use: post procedure until discharge

Resource use	ESG group ($n = 115$)		OSR group ($n = 35$)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Total general ward costs	2661 (2849)	1668 (834–3335)	3657 (2602)	3335 (1876–4169)
Total ICU costs	2626 (4600)	0 (0–4253)	15,108 (20,413)	8506 (5671–15,594)
Total HDU costs	1067 (2639)	0 (0–1448)	1283 (20,413)	0 (0–2173)
Total blood product usage costs	129 (559)	0 (0–0)	322 (625)	0 (0–315)
Total investigations costs	254 (335)	128 (31–363)	499 (547)	350 (163–659)
Total return to theatre costs	460 (1432)	0 (0–0)	310 (1323)	0 (0–0)
Total costs post procedure until discharge	7216 (7399)	5451 (2760–8530)	21,179 (23,083)	13,997 (10,480–27,846)
Total costs of ward days for patients who are transferred on to another care setting	297 (1683)	0 (0–0)	7457 (21,353)	0 (0–0)
Total costs post procedure until discharge including costs for patients who are transferred	7484 (7848)	5516 (2873–8526)	28,636 (23,083)	13,997 (10,480–28,040)

TABLE 56 Total average cost (£) per patient by each area of resource use: during follow-up

	ESG group		OSR group	
Follow-up point	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
1 month				
Sample size, *n*	82		20	
Primary	57 (97)	11 (0–78)	39 (54)	27 (0–42)
Secondary	262 (50)	245 (245–245)	14 (61)	0 (0–0)
Hospital admissions	442 (1961)	0 (0–0)	0 (0)	0 (0–0)
Additional procedures	2097 (9362)	0 (0–0)	912 (4078)	0 (0–0)
Total cost to the NHS	2858 (9581)	284 (245–420)	964 (4076)	28 (0–67)
Formal care	74 (570)	0 (0–0)	0 (0)	0 (0–0)
Informal care	154 (399)	0 (0–0)	198 (245)	115 (0–345)
Total cost	3085 (9640)	323 (245–701)	1162 (4044)	201 (0–511)
3 months				
Sample size, *n*	85		23	
Primary	98 (121)	55 (0–136)	113 (135)	78 (0–158)
Secondary	208 (126)	245 (245–245)	30 (100)	0 (0–0)
Hospital admissions	928 (3125)	0 (0–0)	0 (0)	0 (0–0)
Additional procedures	2504 (10,118)	0 (0–0)	1504 (4992)	0 (0–0)
Total cost to the NHS	3739 (10,514)	267 (245–500)	1647 (4982)	99 (0–283)
Formal care	110 (493)	0 (0–0)	0 (0)	0 (0–0)
Informal care	350 (1434)	0 (0–0)	534 (947)	151 (0–611)
Total cost	4199 (10,589)	284 (245–1507)	2181 (5010)	428 (0–1189)
6 months				
Sample size, *n*	92		28	
Primary	189 (210)	133 (32–256)	237 (282)	128 (47–279)
Secondary	219 (136)	245 (245–245)	372 (95)	338 (338–338)
Hospital admissions	1073 (3310)	0 (0–0)	13 (69)	0 (0–0)
Additional procedures	2650 (10,099)	0 (0–0)	3210 (11,167)	0 (0–0)
Total cost to the NHS	4130 (10,489)	384 (245–724)	3832 (11,153)	508 (385–1019)
Formal care	168 (731)	0 (0–0)	327 (1222)	0 (0–0)
Informal care	1292 (4535)	0 (0–177)	809 (1649)	0 (0–607)
Total cost	5591 (11,279)	438 (245–4031)	4968 (11,100)	803 (385–3835)
12 months				
Sample size, *n*	91		24	
Primary	288 (458)	154 (52–301)	538 (813)	300 (77–567)
Secondary	503 (169)	490 (490–490)	741 (189)	676 (676–710)
Hospital admissions	1379 (4738)	0 (0–0)	15 (75)	0 (0–0)
Additional procedures	3036 (10,802)	0 (0–0)	3745 (12,013)	0 (0–0)

continued

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TABLE 56 Total average cost (£) per patient by each area of resource use: during follow-up (*continued*)

	ESG group		OSR group	
Follow-up point	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
Total cost to the NHS	5206 (11,585)	696 (495–1387)	5039 (11,994)	1105 (784–1821)
Formal care	202 (794)	0 (0–0)	9221 (37,547)	0 (0–0)
Informal care	1234 (3817)	0 (0–40)	1729 (3254)	265 (0–1295)
Total cost	6642 (11,927)	825 (506–7958)	15,989 (38,247)	2213 (1000–14,326)
18 months				
Sample size, *n*	78		21	
Primary	345 (539)	213 (78–346)	838 (1207)	333 (72–1088)
Secondary	487 (206)	490 (490–490)	680 (417)	676 (676–676)
Hospital admissions	1662 (5179)	0 (0–0)	145 (588)	0 (0–0)
Additional procedures	2205 (9589)	0 (0–0)	3501 (12,511)	0 (0–0)
Total cost to the NHS	4699 (10,748)	737 (490–1413)	5164 (12,517)	1287 (676–2440)
Formal care	1042 (5326)	0 (0–0)	4372 (11,742)	0 (0–0)
Informal care	2762 (12,009)	0 (0–0)	2499 (4182)	211 (0–2784)
Total cost	8503 (19,215)	821 (490–8474)	12,034 (17,962)	3099 (676–16,132)
24 months				
Sample size, *n*	57		18	
Primary	399 (621)	248 (54–413)	1020 (1323)	583 (56–1743)
Secondary	743 (171)	735 (735–735)	1075 (434)	1014 (1014–1014)
Hospital admissions	1431 (3567)	0 (0–0)	170 (635)	0 (0–0)
Additional procedures	3878 (12,686)	0 (0–0)	3170 (9880)	0 (0–0)
Total cost to the NHS	6451 (12,943)	1017 (735–3355)	5434 (9855)	2430 (1033–3149)
Formal care	268 (895)	0 (0–0)	6721 (17,328)	0 (0–255)
Informal care	1885 (5911)	0 (0–0)	1912 (3847)	11 (0–2190)
Total cost	8605 (13,904)	1370 (796–8663)	14,068 (22,532)	3722 (1033–18,851)
36 months				
Sample size, *n*	40		12	
Primary	360 (669)	195 (0–327)	729 (951)	153 (0–1219)
Secondary	972 (231)	980 (980–1116)	1381 (468)	1352 (1352–1352)
Hospital admissions	1912 (5118)	0 (0–0)	0 (0)	0 (0–0)
Additional procedures	5143 (14,264)	0 (0–0)	7080 (13,541)	0 (0–4560)
Total cost to the NHS	8386 (14,771)	1173 (980–9047)	9190 (13,652)	2145 (1352–8423)
Formal care	319 (1025)	0 (0–0)	1958 (6659)	0 (0–0)
Informal care	1238 (4744)	0 (0–0)	2146 (5590)	0 (0–1236)
Total cost	9943 (15,318)	1175 (980–10,950)	13,293 (14,926)	3682 (1352–24,118)

TABLE 56 Total average cost (£) per patient by each area of resource use: during follow-up (*continued*)

	ESG group		OSR group	
Follow-up point	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
48 months				
Sample size, *n*	26		7	
Primary	312 (730)	117 (0–315)	470 (846)	0 (0–551)
Secondary	1231 (193)	1225 (1225–1225)	1787 (610)	1690 (1690–1690)
Hospital admissions	2279 (6051)	0 (0–0)	0 (0)	0 (0–0)
Additional procedures	5349 (15,212)	0 (0–0)	2605 (6893)	0 (0–0)
Total cost to the NHS	9172 (15,498)	1418 (1225–8906)	4863 (7714)	1690 (1690–2483)
Formal care	468 (1260)	0 (0–0)	3356 (8708)	0 (0–196)
Informal care	1885 (5816)	0 (0–653)	3 (8)	0 (0–0)
Total cost	11525 (16,047)	1891 (1225–16,281)	8222 (11,177)	1690 (1690–12,245)

TABLE 57 Possible explanatory values for the regression modelling: costs of ESG up until hospital discharge

Variable number	Explanatory variable	Reason for selection
Demographic variables		
1	Age	The age of the patient can affect the health-care resources needed. Older people have more comorbidities and might not respond as favourably to surgery as someone who is relatively younger
2	Sex	There are often differences in resources and, therefore, costs depending on the sex of the patient due to biological differences
3	BMI	BMI outside the healthy range is associated with higher risk factors of surgery
4	Diabetes	Diabetes is often associated with higher health-care costs. Therefore, this was included in the initial modelling
5	Smoking	Smoking status (previous or current smoker) has been shown to have an impact on the resource use during surgical procedures for aneurysm repair
6	NYHA score	NYHA scores are associated with poorer surgical outcomes relative to those with better scores
7	Hypertension	Higher levels of resource utilisation for surgical repair of aneurysms have been associated with hypertension
8	Prior aortic intervention	Previous aortic interventions may result in different resource use needed for interventions
9	COPD	Respiratory function is also associated with poorer clinical outcomes in surgical repair of aneurysms
10	Utility (baseline)	Utility scores give an estimate of HRQoL prior to surgical intervention. For patients with lower HRQoL, it is expected that they may need to utilise more health care resources and, therefore, have an impact on costs

continued

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TABLE 57 Possible explanatory values for the regression modelling: costs of ESG up until hospital discharge (*continued*)

Variable number	Explanatory variable	Reason for selection
Resource use variables		
11	Number of stents	Stent costs in the ESG group accounted for > 70% of the total costs of the primary procedure. Therefore, the number of stents utilised per procedure could directly affect average total costs
12	ICU days	ICU is associated with sicker patients and a higher level of resource use
13	HDU days	HDU is associated with sicker patients and a higher level of resource use
14	Ward days	Longer length of stay in a hospital ward is linked to sicker patients and higher resource use

TABLE 58 Summary of cost information for the VoI analysis

Resource use cost (by stage)	Costs by treatment group (£)			
	ESG ($n = 65$)		OSR ($n = 18$)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Primary procedure cost	26,939 (10,636)	25,092 (16,118–36,624)	18,160 (9611)	16,280 (9692–24,527)
Post procedure until discharge cost	7054 (7555)	5590 (2699–7549)	18,295 (16,211)	12,132 (10,058–22,527)
Follow-up cost NHS	6794 (13,337)	744 (551–2001)	6319 (13,691)	1284 (798–1920)
Total costs NHS	40,788 (18,834)	38,483 (26,376–52,330)	42,774 (23,529)	34,732 (26,083–57,628)

TABLE 59 Summary of EQ-5D-5L QALY information at 12 months for the VoI analysis

ESG group ($n = 65$)		OSR group ($n = 18$)	
Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
0.62 (0.32)	0.70 (0.47–0.88)	0.46 (0.35)	0.62 (0.03–0.73)

TABLE 60 Results of the generalised linear model cost regressions

Variable	Coefficient	SE	*p*-value	95% CI
ESG cost regression				
Intercept	32,362	1337	< 0.001	29,876 to 35,131
Smoking current	10,447	4535	0.023	2449 to 2049
OSR cost regression				
Intercept	46,323	7475	< 0.001	34,303 to 64,687

SE, standard error.

EME
HSDR
HTA
PGfAR
PHR

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