

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The United Kingdom EVAR Trial Investigators. Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. *N Engl J Med* 2010;362:1872-80. DOI: 10.1056/NEJMoa0911056.

Supplementary Appendix – EVAR Trial 2

DESCRIPTION OF TRIAL METHODS

Eligibility criteria for participating centres

All participating hospitals had to have performed at least 20 endovascular aneurysm repair (EVAR) procedures and have submitted their 30-day mortality results to the UK national Registry for Endovascular Treatment of Aneurysms (RETA) who reported to the EVAR Trial Management Committee when centres were eligible to participate. Centres were required to nominate a surgeon, radiologist and coordinator for their centre. Before randomisation could commence, each trial coordinator had to attend a 1 day training course in trial recruitment and data collection procedures at the central trial office based at Charing Cross Hospital in London.

Inclusion criteria for patients

- Males or females
- Aged at least 60 years
- Abdominal aortic aneurysm measuring at least 5.5cm in any plane on a computed tomography (CT) scan
- Aneurysm regarded as anatomically suitable for EVAR according to CT scan
- Patient considered anaesthetically unfit for an open repair
- Patients were excluded if they were anaesthetically fit for an open repair but had a hostile abdomen preventing an open repair.

Anatomical suitability for EVAR

EVAR is only feasible in patients who satisfy certain specific anatomical requirements. Factors that are thought to influence the likelihood of technical success include axial length from the aneurysm neck (distance between the lower most renal artery to the start of the aneurysmal dilation), the shape and angulation of the neck, the diameter of the iliac arteries

(for access through the groin) and the potential length and condition of distal arteries used for fixation of the device. In addition, it is important to take account of whether the artery walls are parallel or conical or whether thrombosis, calcification or tortuosity is present at the intended sites of fixation. Pre-procedural imaging is vitally important in preparing the endograft which is assembled remotely by the manufacturer. In general, it is not possible to tailor the endograft during the procedure, as in open repair. Instead, graft measurements must be determined precisely in advance of the operation and the EVAR operator needs to construct an endograft that will be optimally configured for the individual patient(1). For the EVAR Trials, local radiologists were required to assess the baseline CT scan for each patient and determine anatomical suitability for the endovascular device of their choice. Centres were encouraged to use commercially available devices as these all carried CE marks (European Union certification of consumer health and safety requirements) and had undergone certain checks before being released onto the market.

Criteria used to ascribe fitness for open repair

A “traffic light” system was used as the underlying recommendation for entry into EVAR Trial 1 or 2. Cardiac, respiratory and renal function questions were asked on the case record forms and these helped classify the patients into 3 groups:

RED - Failure to be considered suitable for any procedure at that time on the basis of cardiac factors.

AMBER – Failure to satisfy criteria for open repair but possibly suitable for EVAR Trial 2.

GREEN – Satisfying criteria for open repair and probably suitable for EVAR Trial 1.

Supplementary Appendix Table 1 presents the specific questions asked on the case record forms as well as the numbers of patients who recorded a positive response in EVAR Trial 2.

Supplementary Appendix Table 1 – Case record form questions used to ascribe patient fitness for open repair and suitability for EVAR Trial 1 or 2	
	No. of patients with positive response in EVAR Trial 2 N=404
CARDIAC STATUS	
1. Has the patient had a myocardial infarction within the last 3 months?	4
2. Has the patient experienced onset of angina within last 3 months?	44
3. Does the patient have unstable angina at night or at rest?	18
If yes to any of questions 1-3, entry unlikely into either trial at this stage	
4. Is there a past history of myocardial infarction?	
5. Is there a history of cardiac revascularisation?	
6. Is there a past history of angina pectoris?	
7. Is there severe heart valve disease?	
8. Is there significant arrhythmia?	
9. Is there uncontrolled congestive cardiac failure?	
If yes to any of questions 4-9, patient may be more suitable for EVAR 2	285
If no to all of questions 4-9, patient may be suitable for EVAR 1	119
RESPIRATORY STATUS	
10. Is Forced Expiration Volume in 1 second (FEV ₁) <1.0L?	
If yes to question 10, patient may be more suitable for EVAR 2	65
If no to question 10, patient may be suitable for EVAR 1	339
RENAL STATUS	
11. Is serum creatinine >200 µmol/L?	
If yes to question 11, patient may be more suitable for EVAR 2	34
If no to question 11, patient may be suitable for EVAR 1	370
CONFIRMATION OF DECISION TO OFFER EVAR TRIAL 1 OR 2	
12. Having answered questions 1-11, in the views of your anaesthetist and surgeon, is your patient fit for open repair?	Yes No
13. If not, is your patient suitable for EVAR Trial 2?	Yes No
14. Which trial has the patient been offered?	EVAR EVAR 1 2
15. Is the abdomen hostile such that open repair is not an option?	Yes No

Primary outcome and power calculations

All-cause mortality

Power calculations were based upon all-cause mortality. For 90% power at the 5% significance level, a total of 280 patients were required (140 per group) to detect a difference in annual mortality of 25% in the no intervention group (based upon mortality data of patients

with large aneurysm unfit for surgery in the UK Aneurysm Study (2)) and 15% in the EVAR group after an average of 3.3 years follow-up.

Aneurysm-related mortality

Aneurysm-related mortality is a more sensitive measure of effect and this was included as an additional mortality outcome during a Trial Management Committee held on 5th May 2004 without knowledge of the long-term outcome data of the EVAR Trials. A definition for aneurysm-related death was agreed; any death within 30 days of any aneurysm intervention as well as deaths attributed to ICD-10 abdominal aortic aneurysm codes I713-I719. Thus, late deaths such as graft rupture or aorto-duodenal fistula occurring more than 30 days after aneurysm repair also were classified as aneurysm-related. An Endpoints Committee was convened to examine each death certificate received from the Office of National Statistics in relation to the dates of either the primary aneurysm repair or any subsequent re-interventions for graft-related complications. The Committee was blinded to randomised group.

Secondary outcomes

Definition of graft-related complications

A modified version of the White and May classification(3) of endoleaks was used to classify the following endograft complications:

Type 1 - perigraft leak perigraft channel or graft-related endoleak at the proximal or distal end of the graft.

Type 2 – Retrograde endoleak, collateral flow, retroleak or non-grade related endoleak. Leak from patient lumbar, inferior mesenteric or intercostal arteries.

Type 3 – Fabric tear, modular disconnection or poor seal, stent frame fracture or separation, attachment system fracture

In addition to endoleaks, the presence of the following graft-related complications were recorded:

Graft rupture (aortic rupture despite the presence of an aneurysm repair graft), anastomotic aneurysm, graft migration at proximal or distal ends of device, graft kinking, graft thrombosis, graft stenosis, distal embolisation from graft, graft infection, dilatation of the aortic neck, sac or iliac landing zones following graft placement, aortic perforation/dissection and renal infarction.

Definition of graft-related re-interventions

Graft-related re-interventions could occur either during the primary admission for the main aneurysm repair or as a new admission at a later occasion. The decision on whether to intervene for a graft-related complication was left to the local clinician as it was not feasible for the trial protocol to dictate whether it was appropriate to intervene. Factors such as the availability of a suitable treatment solution, patient fitness and patient consent are all likely to have played a role in the decision to intervene but data on reasons for not intervening were not recorded. At the design stage of the trial, data on the cost implications of aneurysm repair had shown that approximately 80% of the costs of the procedure were attributable to 1) costs in operating theatre, 2) use of intensive care and high dependency units (ITU/HDU) and 3) total length of stay(4). The trial funding only provided limited resources for data collection and thus it was decided that data would not be collected for the following:

- Hospital admissions for non-aneurysm-related conditions
- Day case admissions
- Outpatient attendances
- Local general practitioner appointments

Therefore, data (including time in theatre, use of ITU/HDU facilities and total length of stay) were only collected for the primary aneurysm repair as well as for re-admissions for any of the graft-related complications listed in the previous section. Thus, for patients having EVAR, events such as day case admissions for minor procedures or additional investigational imaging were excluded. For patients having open repair, admissions for laparotomy-related complications such as incisional hernia or wound infections were excluded.

Recruitment period

Recruitment commenced on 1st September 1999 with the planned recruitment phase closing on 31st December 2003 when a total of 338 patients had been randomised (20% beyond target). At a previous Trial Management Committee it had been decided that randomisation would continue until release of the 30-day mortality results in EVAR Trial 1 as equipoise remained and the additional recruitment would enhance the power of the trial. For practical reasons it made sense to continue running both trials in parallel rather than stop one and not the other. Thus, recruitment continued until the 30-day mortality results were released for EVAR Trial 1 in August 2004 and this meant that an additional 66 patients were recruited and followed for these final analyses.

Randomisation method

Randomisation was performed using a 1:1 ratio in randomly permuted blocks with varying block sizes constructed using the Stata software package. Randomisation was stratified by centre such that local differences in decisions on anatomical suitability and fitness for open repair would not lead to differences between randomised groups. Randomisation was performed by the trial manager once all baseline data had been received at the central trial management office.

Patient follow-up protocol

All patients were flagged for mortality at the Office for National Statistics (ONS) with provision of centrally coded death certificates to the main trial management centre. Patients having EVAR were followed up at 1 month, 3 months and annually after EVAR deployment and patients having no intervention were followed up annually. At each follow-up appointment, data were recorded for 1) any clinically adverse events (myocardial infarction, stroke, above or below knee amputation or referral for chronic renal dialysis), 2) a CT scan was used to monitor the size of the aneurysm in the no intervention group as well as record basic morphological changes in the neck, sac and iliac diameters and report any graft-related

complications, 3) an annual serum creatinine measurement was taken to monitor any changes in renal function and 4) a EuroQol questionnaire was completed to enable later assessment of cost effectiveness.

Loss to follow-up, data audit and censoring criteria

For the primary mortality outcomes, the follow-up was truncated on 1st September 2009 (minimum of 5 years from close of randomisation) to allow 3 months for the central trial management office to make direct contact with all patients recorded as alive by the UK Office for National Statistics (ONS), in order to ensure they were truly alive and resident in the UK. Patients who were contacted were censored as alive on 1st September 2009 and any patient who could not be contacted or was not seen in 2009 was regarded as lost to follow-up and censored on the date of their last follow-up appointment. This accrued a total of 1413 person-years of follow-up for EVAR Trial 2.

To check that all adverse events, graft-related complications and re-interventions had been reported, a data clerk was employed to audit the trial case record notes against the local hospital notes. Two periods of audit were conducted, one in 2007 and one in 2009. A total of 308 (76%) patient notes were audited with the remaining 96 sets of notes unavailable in archive. All reported events were confirmed and a small number of unreported events were detected and included in the main database.

For the secondary outcomes, patients were required to attend a follow-up appointment and thus these censoring rules were applied:

- For all patients with a follow-up in 2009, the date of their 2009 follow-up was used for censoring.
- For alive patients without a follow-up in 2009, the latest of their date of last follow-up or the date of audit of their notes was used for censoring.

- For dead patients without a follow-up in 2009, the date of death was used for censoring, providing it occurred within the year after their last follow-up or date their notes were audited; otherwise these latter dates were used for censoring.
- Patients who died within the first year after randomisation or AAA repair were censored on the date of death.
- Alive patients without AAA repair were censored on the date of last follow-up or audit whichever occurred latest.

This censoring method reduced the number of person-years accrued to 1351 for EVAR Trial 2 (4% lower than for the mortality analyses).

SUPPLEMENTARY INFORMATION ON STATISTICAL METHODS

For the Cox regression analyses, crude hazard ratios were calculated as well as ones adjusted for baseline age, sex, aneurysm diameter, forced expiration volume in 1 second, log-transformed creatinine, statin use, body mass index, smoking status, systolic blood pressure and serum cholesterol. Baseline data were almost complete with 90% of patients having a complete set of covariates for the adjusted analyses. Two sensitivity analyses were performed to allow inclusion of patients with missing covariates in the adjusted models: first the missing indicator method (5) and second multiple imputation chained equations that included terms for the event outcome and the log of time to event (6-9).

Deviation from the proportional hazards assumption was tested by regressing scaled Schoenfeld residuals against the log of time. Tests of interaction were performed for 30-day, all-cause and aneurysm-related mortality between randomised group and sex, age and aneurysm diameter (the latter two as continuous variables).

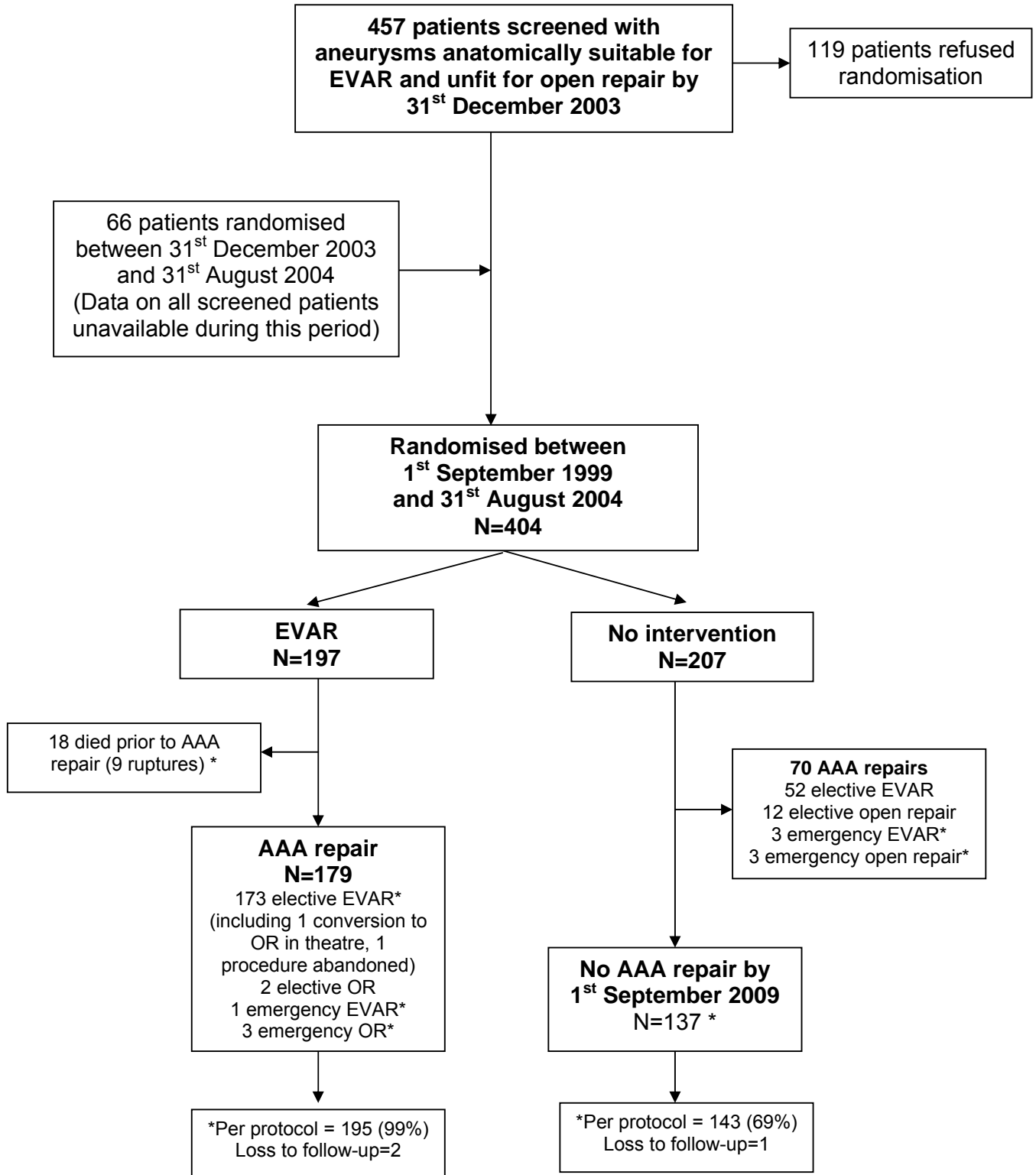
A per protocol analysis was performed on the patients who had complied with their randomised allocation. In the group randomised to EVAR, per protocol patients were defined as those who had an elective EVAR attempted even if they subsequently converted to open

repair during the primary procedure in theatre. Patients who died without aneurysm repair or had an emergency repair were included as per-protocol patients. Patients who had elective open repair in the EVAR group were censored at aneurysm repair. In the group randomised to no intervention, per protocol patients were defined as those who remained without aneurysm repair at the end of the study or who had emergency repair as a result of rupture. Patients undergoing any type of elective aneurysm repair in the no intervention group were censored at the time of repair.

SUPPLEMENTARY RESULTS FOR EVAR TRIAL 2

The CONSORT diagram showing patients screened for the trial as well as the flow of patients through the trial is given in Supplementary Appendix Figure 1. Given that a considerable number of patients in the no intervention group crossed over and had aneurysm repair, a post hoc analysis was performed comparing the baseline fitness of the 70 patients who had aneurysm repair in the no intervention group with the 179 patients who had aneurysm repair in the EVAR group. The Customized Probability Index (CPI) was used to ascribe patient fitness(10;11). This is a validated prognostic score for operative mortality after open repair but it was used in this instance as a marker of patient fitness with higher values indicating worse fitness. The mean (SD) CPI score was 5.8 (9.5) for the 70 non-compliant patients compared with 10.5 (11.8) for the 179 compliant patients, Students t-test p-value=0.004. Thus, patients who crossed over from the no intervention group appeared to be fitter at baseline. Unfortunately, data are not available to determine their fitness level at the later time of aneurysm repair.

The causes of death by randomised group are presented in Supplementary Appendix Table 2. The types of graft-related complications are shown in Supplementary Appendix Table 3 presented by type of aneurysm repair completed during the primary procedure (not by intention-to-treat group) with total numbers of each complication in brackets in the first column.



Supplementary Appendix Figure 1 – Trial profile showing flow of patients screened for and entered into EVAR Trial 2 (per protocol patients marked with an asterisk, 93% overall)

Supplementary Appendix Table 2 – Causes of death by randomised group relative to randomisation (Aneurysm-related deaths highlighted in italics)

Cause of death	EVAR N=145 (25)	No intervention N=160 (53)	Total N=305 (78)
Between randomisation and 6 months			
<i>Procedure related</i>	8	1	9
<i>Aneurysm rupture</i>	7	8	15
IHD #	2	5	7
Stroke	0	2	2
Cancer (lung)	1 (1)	0	1 (1)
Respiratory	5	1	6
Renal	0	1	1
Other	1	1	2
Total	24	19	43
6 months to 4 years			
<i>Procedure related</i>	3	0	3
<i>Aneurysm rupture</i>	6	35	41
<i>Graft rupture after EVAR deployment</i>	1	0	1
IHD #	30	32	62
Stroke	3	2	5
Other PAD #	0	3	3
Cancer (lung)	21 (7)	14 (3)	35 (10)
Respiratory	19	9	28
Renal	2	3	5
Other	7	8	15
Unknown	0	2	2
Total	92	108	200
Beyond 4 years			
<i>Procedure related</i>	0	2	2
<i>Aneurysm rupture</i>	0	7	7
IHD #	10	9	19
Stroke	1	1	2
Cancer (lung)	6 (3)	7 (3)	13 (6)
Respiratory	7	4	11
Other	5	3	8
Total	29	33	62

IHD - ischaemic heart disease, PAD - peripheral arterial disease

Supplementary Appendix Table 3 – Description of first graft-related complications occurring after EVAR by randomised group # in EVAR Trial 2		
Complication (total number of particular complication) ‡	EVARs in EVAR group N=174	EVARs in no intervention group N=55
Graft rupture (2)	0	0
Deployment difficulties or conversion to open repair after primary procedure (3)	2	1
Graft infection (3)	0	0
Migration (6)	1	0
Type 1 endoleak (25) *	11	6
Type 3 endoleak (11) *	5	1
Kinking (4)	1	2
Sac, neck or iliac expansion (11)	3	1
Type 2 endoleak * + sac, neck or iliac expansion (11)	9	1
Type 2 endoleak * (40)	18	6
Graft thrombosis (16)	3	2
Graft stenosis (1)	0	0
Renal infarction (2)	2	0
Anastomotic or false aneurysm (1)	0	1
Other surgery during primary admission (11)	8	1
Unclassifiable endoleak (3)	1	0
Other (5)	3	0
Unknown (3)	2	1
TOTAL (158)	69	23

An additional 5 first complications occurred after open repair.

‡Some patients had more than 1 complication. In these cases, the first complication is presented with complications listed in order of severity. Total numbers of complications across both groups are given in brackets in the first column.

* Type 1 = presence of blood leaking from top or bottom of graft, type 2=other arteries backbleeding into sac, type 3=structural fault or modular disconnection anywhere in main graft or limbs.

COMPARISON OF COSTS BETWEEN RANDOMISED GROUPS

Hospital inpatient costs for aneurysm-related procedures were calculated up to 8 years from randomisation on an intention-to-treat basis. Resource use collected in the trial included the endovascular device, theatre occupation time, blood products used, radiation exposure time, postoperative interventions, length of stay on wards, intensive therapy units and high dependency units for the primary AAA procedure, and in-patient graft-related re-interventions. Unit costs (2009 prices) were obtained from national sources(12-14) and from the results of questionnaires sent to trial centres in May 2004, updated for inflation(15). Censoring criteria were the same as those used for the analysis of graft-related complications and re-interventions. Mean costs accounted for censoring(16) and bootstrap methods were used to estimate the uncertainty in mean costs(17). Mean imputation, conditional on treatment received, was used to impute missing resource use data. Costs were discounted by 3.5% per year. Mean costs are provided for the EVAR 2 Trial in Supplementary Appendix Table 4.

Supplementary Appendix Table 4 - Mean costs of AAA procedures at 8 years for EVAR Trial 2 by intention-to-treat randomised group in GBP 2009 prices								
Cost	EVAR Patients with events	No int. Patients with events	EVAR mean £ n=197	No int. mean £ n=207	Difference £	Standard error of difference	95% CI	
Primary AAA admission*	179	70	13301	4467	8834	901	7068	10599
Other AAA admission**	25	11	1694	702	992	654	-290	2274
Total			14995	5169	9826	1116	7638	12013

*The primary AAA admission is as defined in the CONSORT diagram. The costs of re-interventions during the primary admission are included in the costs of the primary AAA admission. **The costs of abandoned operations (1 EVAR arm, 0 no intervention arm) that were not counted as primary AAA procedures are included with the costs of other AAA admissions.

Web appendix references

- (1) Greenhalgh RM, Powell JT. Endovascular repair of abdominal aortic aneurysm. *N Engl J Med* 2008; 358(5):494-501.
- (2) Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann Surg* 1999; 230(3):289-296.
- (3) White GH, May J. Failure of endovascular repair of abdominal aortic aneurysms: endoleak, adverse events and grading of technical difficulty. Greenhalgh RM. Pub: WB Saunders, London, 1999.
- (4) Holzenbein J, Kretschmer G, Glanzl R et al. Endovascular AAA treatment: expensive prestige or economic alternative? *Eur J Vasc Endovasc Surg* 1997; 14(4):265-272.
- (5) White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Stat Med* 2005; 24(7):993-1007.
- (6) Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. 2nd ed. John Wiley & Sons Inc., 2002.
- (7) Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. *J Clin Epidemiol* 2003; 56(1):28-37.
- (8) Royston P. Multiple Imputation of missing values: Update of ice. *Stata Journal* 2005; 5(4):527-536.
- (9) Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol* 2006; 59(10):1092-1101.
- (10) Kertai MD, Steyerberg EW, Boersma E et al. Validation of two risk models for perioperative mortality in patients undergoing elective abdominal aortic aneurysm surgery. *Vasc Endovascular Surg* 2003; 37(1):13-21.
- (11) Kertai MD, Boersma E, Klein J et al. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. *Arch Intern Med* 2005; 165(8):898-904.
- (12) NHS Scotland: Cost book 2008/2009 (release 24/11/09). Edinburgh: ISD Scotland, 2009.
- (13) NHS Trust reference cost schedules 2007-08. London: Department of Health, 2009.
- (14) National Blood Service. National Blood and Blood Components Price List 2009-2010. London: NBS, 2009.
- (15) Curtis L. Unit costs of health and social care. Canterbury: PSSRU., 2009.
- (16) Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005; 24(1):131-145.
- (17) Efron B, Tibshirani R. *An introduction to the bootstrap*. New York: Chapman & Hall, 1993.