

## 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 versus open repair of abdominal aortic aneurysm. *N Engl J Med* 2010;362:1863-71. DOI: 10.1056/NEJMoa0909305.

# Supplementary Appendix – EVAR Trial 1

## 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 Imperial College (Charing Cross campus) in London.

### Inclusion criteria for patients

- Males or females
- Aged at least 60 years
- Abdominal aortic aneurysm measuring at least 5.5 cm in any plane on a computed tomography (CT) scan
- Aneurysm regarded as anatomically suitable for EVAR according to CT scan
- Patient considered anaesthetically fit for 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 obtain 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 1.

<b>Supplementary Appendix Table 1 – Case record form questions used to ascribe patient fitness for open repair and suitability for EVAR Trial 1 or 2</b>		No. of patients with positive response in EVAR Trial 1 N=1252
<b>CARDIAC STATUS</b>		
1. Has the patient had a myocardial infarction within the last 3 months?		3
2. Has the patient experienced onset of angina within last 3 months?		35
3. Does the patient have unstable angina at night or at rest?		20
<b>If yes to any of questions 1-3, entry unlikely into either trial at this stage</b>		
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?		
<b>If yes to any of questions 4-9, patient may be more suitable for EVAR 2</b>		530
<b>If no to all of questions 4-9, patient may be suitable for EVAR 1</b>		722
<b>RESPIRATORY STATUS</b>		
10. Is Forced Expiration Volume in 1 second (FEV <sub>1</sub> ) <1.0L?		
<b>If yes to question 10, patient may be more suitable for EVAR 2</b>		51
<b>If no to question 10, patient may be suitable for EVAR 1</b>		1201
<b>RENAL STATUS</b>		
11. Is serum creatinine >200 µmol/L?		
<b>If yes to question 11, patient may be more suitable for EVAR 2</b>		33
<b>If no to question 11, patient may be suitable for EVAR 1</b>		1219
<b>CONFIRMATION OF DECISION TO OFFER EVAR TRIAL 1 OR 2</b>		
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 1	EVAR 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 80% power at the 5% significance level, a total of 900 patients were required (450 per group) to detect a difference in annual mortality of 7.1% in the open repair group (based upon data from the UK Small

Aneurysm Trial (2)) and 5% in the EVAR group after an average of 3.3 years follow-up.

Power would be increased to 90% if a total of 1196 patients could be randomised.

### 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 5<sup>th</sup> May 2004 without knowledge of the long-term outcome data in 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 at a later admission. 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 1<sup>st</sup> September 1999 with the planned recruitment phase closing on 31<sup>st</sup> December 2003 when a total of 1082 patients had been randomised (20% beyond target). Approximately 3 months were required for the aneurysm repairs to be performed and 30 days had to elapse in order to calculate the 30-day operative mortality. An additional 2-3 months were required to analyse the results and submit them for publication which occurred at the end of August 2004. At a previous Trial Management Committee it had been decided that randomisation would continue until release of these 30-day mortality results as equipoise remained and the additional recruitment would enhance the power of the trial.

### Excerpt from item 3 of minutes of Trial Management Committee held on 8<sup>th</sup> October 2003.

*“There was more extensive debate about whether 30-day mortality of EVAR 1 should be made available earlier. Analysis of these data could commence from 1<sup>st</sup> April 2004 and it was agreed that 30-day mortality data for EVAR 1 should be released at the Vascular Surgical Society of Great Britain & Ireland and the British Society of Interventional Radiologists in November 2004. A great caveat would be made that these data are just 30-day mortality data and all-cause mortality and durability data would follow in June 2005. There was agreement that randomisation should continue up until the moment that this information reaches the public domain. However it was anticipated that it would be very difficult to continue randomisation beyond this date but that 4 year follow-up would be recommended”.*

### **Randomisation method**

Randomisation was performed using a 1:1 ratio in randomly permuted blocks and 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 open repair 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 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 1<sup>st</sup> 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 1<sup>st</sup> 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 6904 person-years of follow-up.

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 1052 (84%) patient notes were audited with the remaining 200 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.
- Living 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 aneurysm repair were censored on the date of death.
- Living patients without aneurysm 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 6690 (3% lower than for the mortality analyses).

## **SUPPLEMENTARY INFORMATION ON STATISTICAL METHODS**

Logistic regression was used to compare operative and in-hospital mortality for those who had received aneurysm repair and Cox regression was used to compare all-cause mortality, aneurysm-related mortality, graft-related complications and re-interventions. Crude regression estimates were presented as well as ones adjusted for two sets of baseline

covariates: primary adjustment for age, sex, aneurysm diameter, forced expiration volume in 1 second (FEV<sub>1</sub>), log(creatinine) and statin use; secondary adjustment for the primary covariates as well as body mass index, smoking status (current, past and never), systolic blood pressure and serum cholesterol. For the graft-related complications and re-interventions analyses, additional secondary adjustment was made for top neck aortic diameter at the level of the lowest renal artery, neck length (distance between the lowest renal artery and the start of the aneurysm) and common iliac diameter (largest of both legs). The primary and secondary adjustment results were very similar, and the latter are reported. Baseline data were almost complete with 93% of patients having a complete set of covariates for the adjusted analyses.

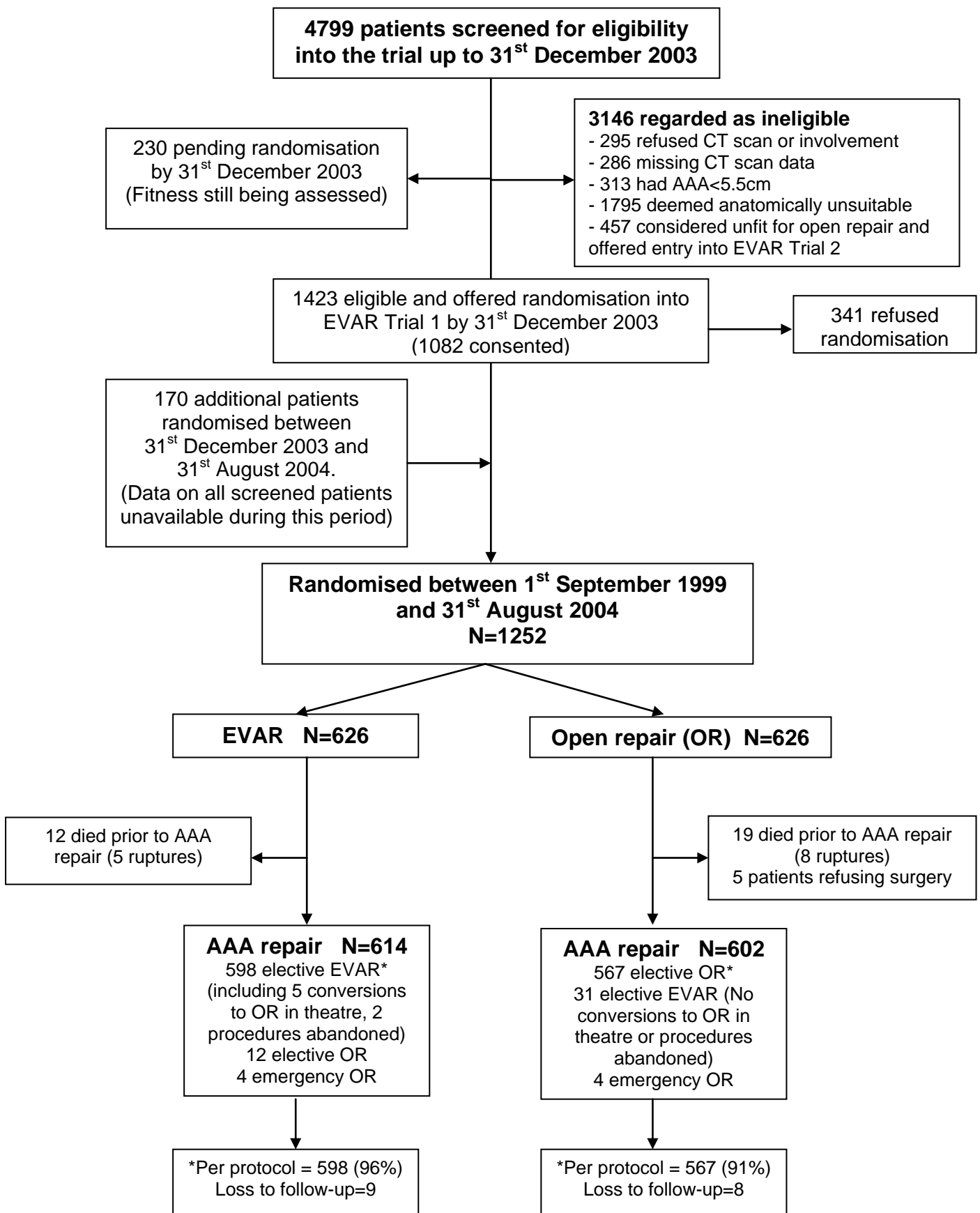
Two sensitivity analyses were performed to allow inclusion of patients with missing covariates in the adjusted models: first the missing indicator method (5) and second multiple imputation chained equations that included terms for the event outcome and the log of time to event (6-9). Deviation from the 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).

## **SUPPLEMENTARY RESULTS FOR EVAR TRIAL 1**

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. Of the 4799 patients screened for eligibility for the trials by 31<sup>st</sup> December 2003, 894 either had an aneurysm less than 5.5 cm, refused assessment or had missing CT data for EVAR suitability. Of the remaining 3905 patients, 1795 were deemed to be anatomically unsuitable for EVAR (46% of the 3905 assessed). The remaining 2110 patients proceeded to an assessment of their fitness for open repair; 457 patients were deemed to be unfit for open repair and offered entry into the sister EVAR 2 trial, 230 anatomically suitable patients were still having their

fitness assessed by 31<sup>st</sup> December 2003 and could not be enrolled by that date and 1423 were considered to be fit enough for the procedure and were offered randomisation into EVAR Trial 1. This was refused by 341 patients leaving a total of 1082 consenting to be randomised into the trial by 31<sup>st</sup> December 2003 (see earlier description of recruitment period). Beyond this time data were not collected for screened patients but only for patients entered into the trial and an additional 170 patients were recruited by 31<sup>st</sup> August 2004.

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 1 (per protocol patients marked with an asterisk\*, 93% overall)**

<b>Supplementary Appendix Table 2 – Causes of death by randomised group relative to time of aneurysm repair (Aneurysm-related deaths highlighted in italics)</b>			
<b>Cause of death</b>	<b>EVAR N=260 (36)</b>	<b>Open repair N=264 (40)</b>	<b>Total N=524 (76)</b>
<b>Prior to aneurysm repair</b>			
<i>Aneurysm rupture</i>	5	8	13
IHD #	1	4	5
Stroke	0	1	1
Other PAD #	1	1	2
Cancer (lung)	5 (0)	2 (0)	7
Respiratory	0	2	2
Other	0	1	1
<b>Total</b>	<b>12</b>	<b>19</b>	<b>31</b>
<b>Within 30 days of aneurysm repair</b>			
<i>Procedure related (elective AAA repair)</i>	8	25	33
<i>Procedure related (emergency AAA repair)</i>	1	1	2
<i>Graft rupture after EVAR deployment *</i>	2	0	2
<b>Total</b>	<b>11</b>	<b>26</b>	<b>37</b>
<b>Between 30-day and 4 years of aneurysm repair</b>			
<i>Procedure related</i>	1	1	2
<i>Procedure related (emergency AAA repair)</i>	1	1	2
<i>Graft rupture after EVAR deployment *</i>	8	2	10
IHD #	31	25	56
Stroke	11	6	17
Other PAD #	7	6	13
Cancer (lung)	38 (20)	47 (20)	85 (40)
Respiratory	10	21	31
Renal	6	1	7
Other	16	9	25
Unknown	1	0	1
<b>Total</b>	<b>130</b>	<b>119</b>	<b>249</b>
<b>Beyond 4 years after aneurysm repair</b>			
<i>Procedure related</i>	4	2	6
<i>Graft rupture after EVAR deployment *</i>	6	0	6
IHD #	27	26	53
Stroke	11	11	22
Other PAD #	7	4	11
Cancer (lung)	22 (9)	29 (9)	51 (18)
Respiratory	15	17	32
Renal	4	2	6
Other	11	9	20
<b>Total</b>	<b>107</b>	<b>100</b>	<b>207</b>

\* all graft ruptures occurred in patients treated with EVAR

# IHD - ischaemic heart disease, PAD - peripheral arterial disease

**Supplementary Appendix Table 3 – Description of first graft-related complications according to the type of operation completed during the primary procedure for EVAR Trial 1**

<b>Complication (total number of particular complication) ‡</b>	<b>Successful EVARs completed N=624 #</b>	<b>Open repairs completed N=592 #</b>
Graft rupture (25)	9	0
Deployment difficulties or conversion to open repair after primary procedure (25)	8	5 #
Graft infection (4)	2	2
Migration (48)	29	0
Type 1 endoleak (62) *	40	0
Type 3 endoleak (28) *	13	0
Kinking (24)	10	1
Sac, neck or iliac expansion (46)	15	12
Type 2 endoleak * + sac, neck or iliac expansion (34)	17	1
Type 2 endoleak * (122)	91	2
Graft thrombosis (41)	20	2
Graft stenosis (10)	4	1
Distal embolisation (2)	1	0
Renal infarction (5)	2	0
Anastomotic or false aneurysm (10)	1	6
Re-exploration of open repair (17)	0	17
Other surgery during primary admission (29)	15	13
Unclassifiable endoleak (6)	5	0
Haematoma (2)	0	1
Other (27)	6	9
<b>TOTAL (567)</b>	<b>288</b>	<b>72</b>

# 629 EVARs attempted, 5 converted to open repair in theatre. 587 open repairs attempted, 5 conversions to 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 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 aneurysm procedure, and in-patient graft-related re-interventions. Unit costs (2009 prices) were obtained from national sources(10-12) and from the results of questionnaires sent to trial centres in May 2004, updated for inflation(13).

Censoring criteria were the same as those used for the analysis of graft-related complications and re-interventions. Mean costs accounted for censoring(14) and bootstrap methods were used to estimate the uncertainty in mean costs(15). 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 1 Trial in Supplementary Appendix Table 4.

<b>Supplementary Appendix Table 4 - Mean costs of aneurysm procedures at 8 years for EVAR Trial 1 by intention-to-treat randomised group in GBP 2009 prices</b>								
Cost	EVAR Patients with events	Open Patients with events	EVAR mean £ n=626	Open mean £ n=626	Difference £	Standard error of difference	95% CI	
Primary AAA admission*	614	602	13019	11842	1177	791	-374	2728
Other AAA admission**	115	20	2283	442	1841	474	913	2770
Total			15303	12284	3019	911	1234	4803

*\*The primary aneurysm 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 aneurysm admission. \*\*The costs of abandoned operations (1 EVAR arm, 1 open repair arm) that were not counted as primary aneurysm procedures are included with the costs of other aneurysm 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) The UK Small Aneurysm Trial Participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 1998; 352(9141):1649-1655.
- (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) NHS Scotland: Cost book 2008/2009 (release 24/11/09). Edinburgh: ISD Scotland, 2009.
- (11) NHS Trust reference cost schedules 2007-08. London: Department of Health, 2009.
- (12) National Blood Service. National Blood and Blood Components Price List 2009-2010. London: NBS, 2009.
- (13) Curtis L. Unit costs of health and social care. Canterbury: PSSRU., 2009.
- (14) Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005; 24(1):131-145.
- (15) Efron B, Tibshirani R. *An introduction to the bootstrap*. New York: Chapman & Hall, 1993.