Version040315

Appendix for

Endovascular strategy versus open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomised trial

IMPROVE trial investigators

Containing:

Patient perspectives on acceptability of randomisation and outcome measures

Seven patients, some with their relatives, were interviewed in early 2008. A summary of the results is shown in Table S1.

Table S1

Patient (sex)	status	Others present at interview	Randomisation acceptable	Key outcome measures
1 male	Post-open repair for rupture	wife	fair	Coming home, back to normal life
2 male	Post-open repair for contained rupture	wife	Yes, if more lives could be saved	Living without further complications
3 male	Post-open repair for rupture	wife	Yes	Fast death or return to normal life – no long-term disability.
4 female	In hospital for elective repair 7.0 cm AAA	daughter	Reasonable as route to better results	Getting out of hospital on my own legs. Looking after grandchildren again.
5 male	Post-EVAR for rupture		yes	Returning to previous level of functioning or a good death. Don't want long-term disability
6 male	In hospital for elective repair 7.8cm AAA		Yes, or whatever the surgeon does best	Getting home quickly, not lingering in a nursing home
7 male	Post-open repair for rupture	Wife, daughter	yes	Time to say goodbye or returning to life as before op.

Cost-effectiveness analysis

Overview

The cost analysis took a UK NHS and Personal Social services perspective [1] and included costs up to 1-year post-randomisation, for all randomised patients. Resource use measures were taken from the IMPROVE case-report forms (CRFs) for the initial hospital admission, re-admissions and outpatient visits to the study hospitals that were related to ruptured abdominal aortic aneurysm (ruptured AAA). Other outpatient visits and community service use (visits to the family doctor, and home nursing) were taken from responses to a Health Services Questionnaire administered to surviving ruptured AAA patients at 3 and 12 months post-randomisation.

The specific resource use categories included were:

i) *Medical devices and consumables* for each intervention (see Table S2 for a full list).

ii) *Hospital length-of-stay during the primary admission*, including time in theatre (minutes) and days in critical care and routine wards. For each day in critical care the number of organs supported was also recorded, which enabled each critical care bed-day to be assigned to the appropriate Healthcare Resource Group [2].

iii) *Re-interventions during the primary admission* included the cost of time in the operating theatre and of the devices and consumables used. In the primary admission the costs of all re-interventions were included whether or not they were defined as directly related to the ruptured AAA.

iv) *Re-admissions* costs included the costs of critical care and time on routine wards. The base-case only included the costs of those re-admissions recorded in the CRFs, which were defined as directly related to the ruptured AAA. In a sensitivity analysis, we included re-admissions unrelated to the ruptured AAA from information collected from patients' responses to a Health Services Questionnaire administered at 3 and 12 months post-randomisation.

v) *Outpatient visits and community service use*. In the base-case, we included this resource use for reasons both related and unrelated to AAA.

Unit costs

The unit costs of the stents and consumables used for rupture repair were taken from manufacturers' list prices and published sources (Table S2). Salary costs for rupture repair were calculated by combining staffing levels reported from a survey of 10 IMPROVE trial centres (www.imperial.ac.uk/medicine/improvetrial) with published staffing costs. The costs per critical care bed-day by Healthcare Resource Group were taken from the 'Payment by Results' database [3]. Unit costs for outpatient visits, and community service use were obtained from a recommended published source for Health and Social Care costs [4].

Quality-of-life

Health-related quality-of-life (QoL) was measured according to a generic measure, the EQ-5D, which requires patients to describe their health on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D instrument chosen was the ED-5D with 3 levels

(EQ-5D-3L) which for each dimension requires patients to state whether they have 'no problems' 'some problems' or 'severe problems'. Each patient's described health at each timepoint was valued according to health state preferences from the general population to calculate EQ-5D utility scores, which are anchored on a scale from 0 (death) to 1 (perfect health) [5]. The mean EQ-5D at 3 and 12 months post randomisation was contrasted between the randomised groups, with unpaired t-tests (Table 2). Quality-Adjusted Life years (QALYs) were calculated by valuing each patient's survival time by their QoL at 3 and 12 months according to the 'area under the curve' approach [6].

QALYs at 3 months

For survivors at 3 months, QALYs were calculated using the EQ-5D scores at 3 months, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and 3 months. This implies that at day 30, the EQ-5D utility score is approximately one third of the EQ-5D at 3 months. For decedents between randomisation and 3 months, we assumed zero QALYs.

QALYs at 12 months

For those surviving up to 12 months, we assumed a linear interpolation, using the EQ-5D scores at 3 months and 12 months. For decedents between 3 months and 12 months where an EQ-5D score at 3 months was available, a linear interpolation was applied between the 3 month EQ-5D, and the date of death, where a zero EQ-5D score was applied.

Missing data

Missing data in baseline covariates, resource use and QoL variables were handled with multiple imputation using chained equations (MICE)[7]. Under this approach each variable was imputed conditional on fully observed baseline variables such as age and gender, and all other imputed variables. Table S3 reports all the variables considered for multiple imputation, and for each variable, the number of missing values, and the imputation model chosen.

The major incomplete resource use components, such as time in the operating theatre, length of stay in critical care or on routine wards (within either primary admission or readmission), and the use of community care, were addressed with multiple imputation. For those ruptured AAA patients for whom aneurysm repair was commenced, missing resource use components were imputed from those ruptured AAA patients with observed resource use data. Patients who did not have a ruptured AAA and had no information recorded on being in critical care, were assumed to stay on a routine ward for their entire hospital stay.

Patients with proven ruptured AAA who failed to return the QoL questionnaire administered at 3 or 12 months, had their EQ-5D scores imputed from other ruptured AAA survivors. For example, of the ruptured AAA patients who had repair commenced and were eligible for the 3 month follow-up, 66 did not complete the EQ-5D questionnaire. For these 66 patients with missing EQ-5D scores at 3 months, EQ-5D scores were imputed using EQ-5D data from those 252 ruptured AAA patients who fully completed the EQ-5D questionnaire at 3 months (see Figure 1, Table S3). Hence, these imputations did not use information from those patients who had died prior to either time point (who were assigned an EQ-5D score of zero), those ruptured AAA patients who did not have a repair commenced, or from patients who had symptomatic AAA. For patients who were alive but otherwise ineligible for follow-up, we assumed the EQ-5D score at either timepoint was the average of the EQ-5D at baseline for AAA patients presenting for elective repair [8], i.e. that their EQ-5D scores were 0.75, 0.75 and 0.74 at baseline, pre-operatively and at 3 and 12 months post-operatively respectively.

Cost-effectiveness

Total costs at 1-year were calculated by combining the resource use with unit costs at 2012 prices (£ GBP), and then converted to US dollars (£1: $1.4215) [9] . This conversion rate was according to purchasing power parities (PPPs), which avoided the impact of short-term currency fluctuations, and recognised the relative purchasing power of the USA compared to UK in 2012. In the base case, incremental costs were reported as unadjusted mean differences between randomised arms, together with 95% confidence intervals (Table 2).

We also reported unadjusted differences in QALYs between the endovascular strategy and open repair groups (Table 2). The differences in average costs and QALYs between the randomised groups were used to calculate the Incremental Net Monetary Benefits (INB). We valued the incremental QALY according to the threshold willingness to pay for a QALY gain recommended by NICE (£30,000 per QALY) [1], and subtracted from this the incremental cost (Table 2). INBs were reported overall, and for the same pre-specified subgroups as for the clinical endpoints (Figure S3 and Table S9). An incremental net benefit greater than zero suggests the intervention is cost-effective at £30,000 per QALY gain.

The uncertainty around the differences in average costs and QALYs between the randomised groups was illustrated on the cost-effectiveness plane (Figure 5). We estimated the incremental costs and QALYs with a seemingly unrelated regression model [10]. To express the uncertainty in the estimation of the incremental costs and QALYs, we used the estimates of the means, variances and the covariance from the regression model, to generate 500 estimates of incremental costs and QALYs from the joint distribution of these endpoints, assuming Asymptotic Normality. We then plotted these incremental costs and QALYs on the cost-effectiveness plane. We also reported cost-effectiveness acceptability curves, by calculating the probability that, compared to open repair, the endovascular strategy is cost-effective, at alternative levels of willingness to pay for a QALY gain (Figure S4).

Assumptions considered in the base case analysis and corresponding sensitivity analyses

Table S10 lists the main assumptions made in the base case scenario, and how each was relaxed in sensitivity analyses. The results of the sensitivity analysis are reported as mean INB with corresponding 95% CIs (Figure S5).

1. Covariate adjustment. The base case reported unadjusted mean differences of both incremental costs and QALYs, assuming randomisation had ensured no imbalances in key prognostic factors such as age, gender and Hardman Index. In the sensitivity analysis, we adjusted for any chance imbalances in these covariates using seemingly unrelated regression.

2. Distributional assumptions on costs and QALYs. The base case assumed that costs and QALYs were normally distributed when reporting the 95% CIs around incremental Costs and QALYs. In sensitivity analyses we assessed the robustness of the cost-effectiveness results to alternative distributional assumptions about both outcomes. Following methodological guidance, the sensitivity analysis considered a Gamma distribution for costs as they had a right-skewed distribution. For QALYs, the sensitivity analysis also considered a Gamma distribution because a large proportion of decedents had zero QALYs, and the remainder of the distribution was again right-skewed.

3. Staffing levels in the operating theatre. In the base case, we assumed the minimum staff required in the operating theatre, to undertake both endovascular and open repair. The staffing input

required was informed by a survey of 10 IMPROVE sites. In sensitivity analyses, we allow for additional staff used in some IMROVE centres according to the results of the survey.

4. Prices of devices endovascular procedure (stent grafts). In the base case, unit costs for the devices and consumables of endovascular intervention were taken from manufacturing list prices, assuming all hospitals would pay the same for these items, irrespective of the volume of cases. In sensitivity analysis, we considered a cost per case for the device of £4,000 to £10,000, which may reflect for example differential prices according to the volume of cases.

5. Patients with no proven rupture. For patients without a proven ruptured AAA, resource use beyond the primary admission and QoL data were not collected. In the base case the following assumptions were made:

- For survivors at 3 months, QALYs were calculated by assuming the EQ-5D score was the mean QoL at 3 months for patients included in the EVAR1 trial of elective endovascular versus open repair, which included patients who had asymptomatic as well as symptomatic AAA [8]. Similarly for survivors at 1-year, we assumed their EQ-5D score was the mean QoL at 12 months for EVAR 1 patients.

- Patients who did not have an AAA operation were assumed to stay on a routine (General Medical) ward for the whole of the primary admission.

- After primary admission, these patients were assumed to have no re-interventions/re-admissions, and 1 outpatient visit.

To assess whether the overall cost-effectiveness results were sensitive to the inclusion of these patients and the requisite assumptions, we ran a sensitivity analysis where we excluded them from the sample.

6. Re-admissions. The base case only included costs from ruptured AAA related re-admissions to study centres that were recorded in the CRFs. Sensitivity analysis allowed for other readmissions, by using information collected in the Health Services Questionnaire, where patients recorded the number of ruptured AAA readmissions, and whether or not they had readmissions unrelated to the RAA, but did not record the duration of the hospitalisation. For these readmissions, we assumed the average re-admission cost from those readmissions recorded in the CRFs.

Table S2: Unit costs (£ GBP) for 1-year analyses

Description	Unit	Open repair	Endovascular strategy	Source
Medical devices & parts				
Endovascular stent and parts	Patient		5 700	Medtronic©, Cook Medical©[a]
Vascular graft (straight)	Patient	623		Maquet©
Vascular graft (bifurcated)	Patient	901		Maquet©
Consumables				
Endovascular package	Patient		600	Maquet©, Cook Medical©
Mechanical retractor	Patient	90		Health-Care Equipment©
Cell Salvage	Patient	74		Davies et al 2006[11]
Surgical instrument set	Patient	51	51	HealthCare Equipment©
Anaesthetics & other drugs	Patient	184	41	British National Formulary [12]
Contrast agent	ml	0.10	0.10	IMPROVE centres[b]
Blood	unit	132	132	NHS Blood & Transplant[13] 2012[13]
Platelets	unit	205	205	NHS Blood & Transplant 2012
Fresh frozen plasma	unit	25	25	NHS Blood & Transplant 2012
CT scan	unit	105	105	NHS reference costs 2012[4]
Emergency room	Minute	0.40	0.40	Dixon et al 2009[14]
Overheads				
Theatre	Minute	2.65	2.65	IMPROVE centres
Staff[c]				
Surgeon (consultant)	Minute	2.20	2.20	PSSRU 2012 [Curtis 2012] [3]
Surgeon (registrar)	Minute	1.16	1.16	PSSRU 2012
Anaesthetist (consultant)	Minute	2.20	2.20	PSSRU 2012
Anaesthetist (registrar)	Minute	1.16	1.16	PSSRU 2012
ODA	Minute	0.58	0.58	PSSRU 2012
Scrub Nurse	Minute	0.72	0.72	PSSRU 2012
Runner	Minute	0.58	0.58	PSSRU 2012
Senior House Officer	Minute	0.83		PSSRU 2012
Radiologist (consultant)	Minute		2.20	PSSRU 2012
Radiologist (registrar)	Minute		1.16	PSSRU 2012
Radiographer	Minute		0.58	PSSRU 2012
Radiologist Nurse	Minute		0.72	PSSRU 2012
Critical care				
ITU/HDU – 1 organ supported	Bed-day	630	630	NHS reference costs 2012 (DH
ITU/HDU – 2 organs supported	Bed-day	870	870	NHS reference costs 2012
ITU/HDU – 3 organs supported	Bed-day	1214	1214	NHS reference costs 2012
ITU/HDU – 4 organs supported	Bed-day	1410	1410	NHS reference costs 2012
ITU/HDU – 5 organs supported	Bed-day	1587	1587	NHS reference costs 2012
ITU/HDU – 6 organs supported	Bed-day	1759	1759	NHS reference costs 2012
ITU/HDU – 7 organs supported	Bed-day	2000	2000	NHS reference costs 2012
Other hospital care				
Inpatient Coronary care unit	Bed-day	436	436	NHS reference costs 2012
Inpatient Stroke unit	Bed-day	309	309	NHS reference costs 2012
Inpatient Routine ward[d]	Bed-day	260	260	NHS reference costs 2012
Outpatient doctor visit	visit	139	139	PSSRU 2012
Outpatient nurse visit	visit	85	85	PSSRU 2012
Outpatient Haemodialysis	session	65	65	NHS Blood & Transplant 2012
Community care				
Nursing home	Bed-day	105	105	PSSRU 2012
Family doctor visit[e]	visit	55	55	PSSRU 2012
Nurse at home visit[e]	visit	18	18	PSSRU 2012

[a]Average (range from £5 400 to £6 500) list price of the endovascular stents and parts most supplied to NHS Hospitals for ruptured AAA (Medtronic Endurant and Cook Medical Zenith Flex). [b]Local and general anaesthesia components were taken from one IMPROVE centre. [c]Typical levels of staff use in theatre were recorded in 10 IMPROVE centres [15]. [d]Same tariff was applied to routine ward in both primary and secondary hospitals. [d]Assuming 15-minute appointments.

Table S3: Variables considered for multiple imputations and imputation model considered.[a]

Variable	Missing values[a] N (%)	Imputation model
Baseline variables and vital status		
Randomised group (Endovascular strategy vs. Open repair)	0 (0%)	None required
Age	0 (0%)	None required
Sex	0 (0%)	None required
Loss of consciousness during care episode	27 (4%)	Logistic regression
Admission haemoglobin	6 (1%)	Predictive mean matching
Admission creatinine	13 (2%)	Predictive mean matching
Acute myocardial ischaemia	52 (8%)	Logistic regression
Maximum aortic diameter	95 (15%)	Predictive mean matching
Aneurysm neck diameter[b]	230 (38%)	Predictive mean matching
Aneurysm proximal neck angle[b]	132 (22%)	Predictive mean matching
Aneurysm neck length[b]	132 (22%)	Predictive mean matching
Death within 1 year	2 (0%)	None done
Resource use variables		
Primary admission-time in theatre	22 (4%)	Predictive mean matching
Primary admission- days in critical care	13 (2%)	Predictive mean matching
Primary admission-days in routine ward	48 (8%)	Predictive mean matching
Primary admission-Re-intervention time in theatre	22 (4%)	Predictive mean matching
Re-admissions at 3months - days in critical care	20 (6%)	Predictive mean matching
Re-admissions at 12months - days in critical care	32 (11%)	Predictive mean matching
Re-admission at 3months- days in routine ward	19 (6%)	Predictive mean matching
Re-admission at 12months- days in routine ward	31 (10%)	Predictive mean matching
Outpatient visits at 3 months	37 (12%)	Predictive mean matching
Outpatient visits at 12 months	47 (16%)	Predictive mean matching
Family doctor visits at 3 months	75 (24%)	Predictive mean matching
Family doctor visits at 12 months	83 (28%)	Predictive mean matching
Nurse at home visits at 3 months	62 (19%)	Predictive mean matching
Nurse at home visits at 12 months	68 (23%)	Predictive mean matching
Quality-of-life (QoL) variables		
EQ-5D at 3 months	66 (21%)	Predictive mean matching
EQ-5D at 12 months	72 (24%)	Predictive mean matching

[a]For baseline variables, vital status and primary admissions, the overall sample size was all randomised patients (n=613). For other resource use and QoL variables, the relevant sample sizes were those patients eligible for the 3 and 12 month follow-up (n=318, 3 months, and n=301, 12 months respectively). [b] Measurements from the Core Laboratory

Table S4: Baseline characteristics of the randomised groups: mean (SD) or N (%) unless otherwise stated

Variable	Missing	Endovascular strategy N=316	Open repair N=297
Age (years)	0	76.7 (7.4)	76.7 (7.8)
Sex	0		
Male		246 (78)	234 (79)
Female		70 (22)	63 (21)
Admission blood pressure (mmHg)	12		
Systolic		110.3 (32.9)	110.5 (31.2)
Diastolic		65.3 (21.4)	66.7 (22.5)
Admission haemoglobin (g/dl)	6	11.2 (2.5)	11.2 (2.3)
Admission creatinine; micromol/l median (IQR)	13	117 (94, 152)	115 (93, 151)
Acute myocardial ischaemia on ECG?	52		
Yes		22 (7.6)	23 (8.5)
No		269 (92.4)	247 (91.5)
Loss of consciousness during care episode	27		
Yes		29 (9.5)	21 (7.5)
No		276 (90.5)	260 (92.5)
Hardman Index (0-5)	74		
0		93 (33%)	71 (28%)
1		130 (46%)	124 (48%)
2		46 (16%)	48 (19%)
3		11 (4%)	12 (5%)
4		2 (1%)	2 (1%)
5		0 (0%)	0 (0%)
CT scan performed	0		
Yes		305 (97)	265 (89)
No		11 (3)	32 (11)
Maximum aortic diameter, cm (Core Lab measured).	95	8.5 (1.9)	8.3 (1.8)

Table S5: Reasons for re-intervention by randomised group and time period for 502 ruptured AAA patients with repair started

Reasons for re-intervention *Footnotes for endograft & other specific reinterventions*	**Total N=174 reintervention episodes in 114/502 patients with 192 procedures**	**Endovascular strategy (30 days)**	**Endovascular strategy (1-12 months)**	**Open repair group (30 days)**	**Open repair group (1-12 months)**
Control bleeding					
Aneurysm-related	**22**	9[a]	3[b]	9[c]	1[d]
Other	**9**	2	1	4	2
Tracheostomy	**10**	5	0	5	0
Limb ischaemia	**43**	23	1	17	2
Mesenteric or colonic ischaemia	**37**	14	1	19	3
Abdominal compartment syndrome	**47***	17	0	27	3
Other: AAA related					
Endovascular	**6**	2[e]	2[f]	2[g]	0
Wound related	**2**	0	1	0	1[h]
Transabdominal	**3**	0	1	2	0
Extraanatomic	**2**	0	0	1	1
Other: not AAA-related (specific cause)	**2**	0	0	2[j]	0
Coronary procedures	**4**	1	0	2	1
Minor procedure	**5**	0	2	3	0

* including 1 patient with 11 reinterventions
a including 1 type I endoleak and 2 type II endoleaks.
b including 2 type I endoleaks and 1 type II endoleaks
c including 1 type 1 endoleak following an Endovascular strategy, with conversion to axillobifemoral graft
d type 1 endoleak
e 1 for stroke and 1 for right limb kinking
f 2 limb extensions without evidence of endoleak
g 2 insertion of inferior vena cava filters
h incisional hernia repair
j 1 resection for colon cancer, 1 acute cholecystitis

Table S6: Quality-of-life (EQ-5D) health state profiles for patients with proven rupture who commenced an operation, were alive and fully completed the questionnaire at 3 and 12 months post-randomisation. '1' refers to 'no problems; '2' refer to 'some problems' and '3' to 'severe' problems.

	3-months[ɬ]		12-months[‡]	
EQ-5D component	**Endovascular strategy** N=138	**Open repair** N=114	**Endovascular strategy** N=127	**Open repair** N=102
Mobility, N (%)				
1	74 (54%)	51 (45%)	63 (50%)	55 (54%)
2	64 (46%)	60 (53%)	65 (51%)	48 (47%)
3	1 (1%)	3 (3%)	0 (0%)	2 (2%)
Self-care, N (%)				
1	116 (84%)	76 (67%)	112 (88%)	82 (80%)
2	21 (15%)	34 (30%)	15 (12%)	20 (20%)
3	1 (1%)	5 (4%)	1 (1%)	4 (4%)
Usual activities, N (%)				
1	60 (43%)	49 (43%)	59 (46%)	61 (60%)
2	71 (51%)	51 (45%)	63 (50%)	36 (35%)
3	8 (6%)	15 (13%)	5 (4%)	9 (9%)
Pain/Discomfort, N (%)				
1	82 (59%)	58 (51%)	76 (60%)	62 (61%)
2	53 (38%)	52 (46%)	51 (40%)	36 (35%)
3	4 (3%)	4 (4%)	1 (1%)	7 (7%)
Anxiety/Depression, N (%)				
1	101 (73%)	83 (73%)	93 (73%)	74 (73%)
2	37 (29%)	27 (24%)	33 (26%)	27 (26%)
3	1 (1%)	4 (4%)	2 (2%)	2 (2%)

[ɬ] 30 (18%) and 36 (24%) patients had incomplete 3-month questionnaires in endovascular strategy and open repair, respectively (see CONSORT diagram, Figure 1). [‡] 34 (21%) and 38 (27%) patients with incomplete 12-month questionnaires in endovascular strategy and open repair groups, respectively (see CONSORT diagram, Figure 1). Results are presented for the samples with complete information; the number of complete responses/eligible patients are as follows: at 3-months: Endovascular strategy: 138/168 (82%); Open repair: 114/150 (76%) 12-months: endovascular strategy: 127/161 (79%); open repair: 102/140 (73%).

Table S7: Quality-of-life (EQ-5D) utility scores, QALY and life-years up to 1-year for patients with fully observed outcomes (complete cases).

	Endovascular strategy		Open repair		Mean difference [95% CI]	P-value
Outcome	N	Mean (SD)	N	Mean (SD)		
EQ-5D [a] at 3 months for ruptured AAA survivors	138	0.76 (0.23)	114	0.69 (0.30)	0.073 [0.007, 0.138]	0.0296
EQ-5D at 12 months for ruptured AAA survivors	127	0.78 (0.19)	102	0.74 (0.32)	0.043 [-0.024, 0.110]	0.211
Life-years for all randomised patients	316	0.61 (0.03)	295	0.59 (0.03)	0.022 [-0.053, 0.098]	0.558
QALY (12 months) for ruptured AAA survivors	114	0.68 (0.16)	89	0.63 (0.22)	0.043 [-0.010, 0.097]	0.112
QALY for ruptured AAA survivors and deceased	209	0.37 (0.36)	189	0.30 (0.35)	0.071 [0.001, 0.141]	0.0445
QALY for all randomised patients[b]	266	0.36 (0.35)	243	0.30 (0.34)	0.053 [-0.008, 0.113]	0.086

[a] The EQ-5D is a QoL measure anchored on a scale that includes 0 (death) and 1 (perfect health). [b] This includes patients without proven rupture, who were assumed to have, on average, the same quality-of-life of elective patients.

EQ-5D questionnaires were sent only to those discharged from hospital or convalescent care. At 3 months more patients in the open repair group remained either in hospital or convalescent care (with poor quality of life), contributing to the lower response rate in the open repair group.

Table S8 Resource use and costs (£ GBP) up to 1 year, reported across all patients randomised. Mean (SD) unless stated

	Resource use		Cost	
Component	Endovascular strategy (n=316)	Open repair (n=297)	Endovascular strategy (n=316)	Open repair (n=297)
Primary admission				
Time in emergency room (mins)[a]	93 (370)	73 (157)	135 (138)	118 (50)
Devices and consumables			4337 (2913)	2540 (2053)
Time in theatre (mins)[b]	157 (100)	180 (108)	2057 (1299)	2110 (1276)
Days in critical care	5.1 (10.6)	7.4 (11.1)	6300 (16289)	9280 (15003)
Days on routine ward[c]	7.3 (12.2)	7.5 (12.5)	1973 (3213)	2044 (3406)
Number patients with at least one re-intervention, N (%)	58 (18%)	56 (19%)		
Number re-interventions	0.26 (0.6)	0.32 (1.0)	545 (1388)	642 (1765)
Transfer to secondary hospital[e], N (%)	10 (3%)	36 (12%)		
Number days	0.7 (4.5)	4.7 (21.0)	174 (1158)	1208 (5452)
Re-admissions				
Number readmissions, N (%)	26 (8%)	12 (4%)		
Number readmissions	0.1 (0.5)	0.05 (0.2)	284 (1805)	119 (863)
Total days in hospital	14.0 (21.6)	20.1 (31.6)		
Total hospital cost (£)			15804 (19318)	18 062 (20296)
Outpatient & community care				
Outpatient visits	3.2 (5.7)	2.9 (8.5)	397 (718)	292 (483)
Days in nursing home	0 (0)	1.8 (22.0)	0 (0)	192 (2309)
Family doctor visits	2.8 (3.9)	2.5 (3.8)	153 (216)	139 (209)
Community Nurse visits	2.2 (6.7)	2.1 (7.4)	40 (120)	38 (134)
Outpatient and community care total costs			590 (902)	661 (1468)
Grand total cost (£)			16394 (19543)	18723 (20599)
Incremental cost [95% CI]			- 2329 [-5489, 922]	

Results are reported after multiple imputation. Unit costs are reported in e-Table 1. [a] Includes costs of CT scan and contrast agent. [b] For those who actually received an endovascular procedure the unit costs of the theatre time were £885/hour and £675/hour for those who actually received open repair (for further details see supplement on IMPROVE website). [c] Patients who did not undergo aneurysm repair (8.9%) were assumed to stay on a routine ward throughout the hospitalisation (details of sensitivity analyses are available in Figure S5, Table S10). [d] While the proportion of patients with re-interventions is similar between groups, patients undergoing open Repair had, on average, a higher number of re-interventions per patient.
[e] Includes those discharged to "other" facilities, mainly rehabilitation facilities.

Table S9: Incremental net benefit [95% CI] (£ GBP) within the first year of randomisation, by subgroups, at recommended willingness to pay threshold stipulated by NICE [1] (£30,000 per QALY).

Subgroup		Incremental cost [95% CI]	Incremental QALY [95% CI]	Incremental net benefit [95% CI][a]	P=
Age	Age ≤ 77	- 2032 [-6579, 2514]	0.025 [-0.050, 0.101]	2797 [-2252, 7846]	P=0.719
	Age > 77	-2560 [-7005, 1885]	0.064 [-0.012, 0.140]	4483 [-501, 9467]	
Sex	Male	-3264 [-6831, 302]	0.025 [-0.035, 0.086]	4025 [37, 8012]	P= 0.661
	Female	1882 [-4861, 8626]	0.133 [0.020, 0.247]	2112 [-5421, 9646]	
Hardman Index	Hardman=0	-2513 [-8383, 3357]	0.034 [-0.064, 0.131]	3525 [-3064, 10114]	P=0.631
	Hardman=1	-2561 [-7277, 2155]	0.020 [-0.061 0.101]	3161 [-2115, 8437]	
	Hardman=2+	-863 [-7350, 5623]	0.114 [0.004, 0.224]	4290 [-2898, 11478]	

[a] Results are following multiple imputation. Estimates were obtained from a regression model which included a randomised group by subgroup interaction term. P-values were reported for this interaction coefficient.

Table S10: Alternative assumptions for sensitivity analyses.

	Base case	Sensitivity analysis
Baseline covariates	Unadjusted analysis	Adjusted for age, sex and Hardman Index
Distributional assumptions	Costs and QALYs Normally distributed	Costs and QALYs Gamma distributed
Theatre staff	See footnote	Alternative according to survey responses[15]
Endovascular devices	Manufacturer list price (£5,700)	Cost per case ranging from £4,000 to £10,000
Patients with no-AAA operation or symptomatic with semi-elective operation	Included in the analysis	Excluded from the analysis
Re-admissions from Health Services Questionnaires	Excluded from the analysis	Included in the analysis

Information about theatre staff was obtained from a survey of 10 centres participating in the trial [15]: The base case considered that open repair was conducted with 2* anaesthestists, 2* vascular surgeons, 1 nurse, 2 other theatre staff and endovascular repair with 2* anaesthestists, 2* vascular surgeons, 1 nurse, 2 other theatre staff, 1 radiographer, 1 radiologist. *includes one training grade. In the sensitivity analysis we included additional staff for each intervention according to the survey results. In open repair we considered 2 additional surgeons (1 consultant, 1 registrar), 1 nurse and 2 other staff (2nd runner and house officer). In the endovascular strategy we considered an additional Radiologist (Registrar level) and 1 other staff (2nd runner).

Figure S1: Kaplan-Meier estimates for AAA-related survival, by randomised group, across all patients randomised.

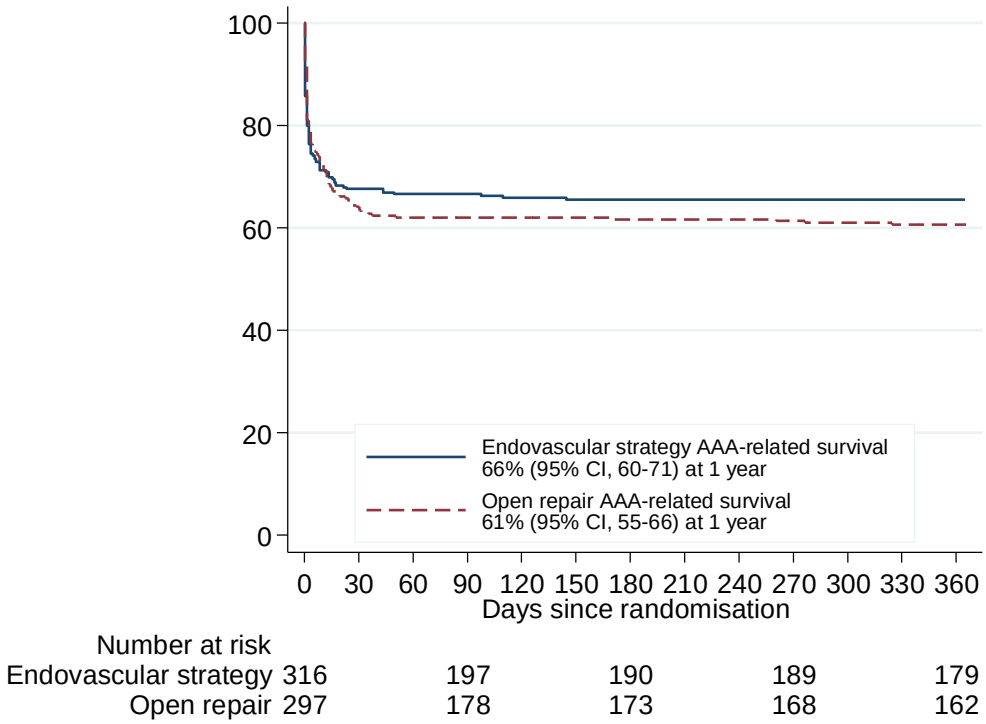
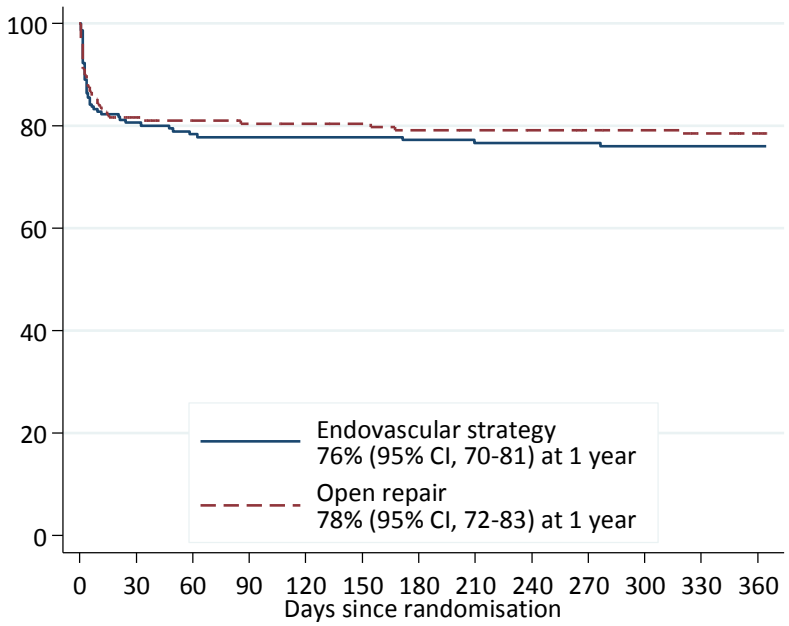


Figure S2 . Kaplan-Meier estimates for time to first re-intervention, by randomised group, across all patients randomised.



Number at risk					
Endovascular strategy	316	135	129	127	114
Open repair	297	129	123	118	109

Figure S3: Mean [95% Confidence Interval] Incremental Net Benefit (£ GBP), overall and by subgroup, across all randomised patients.

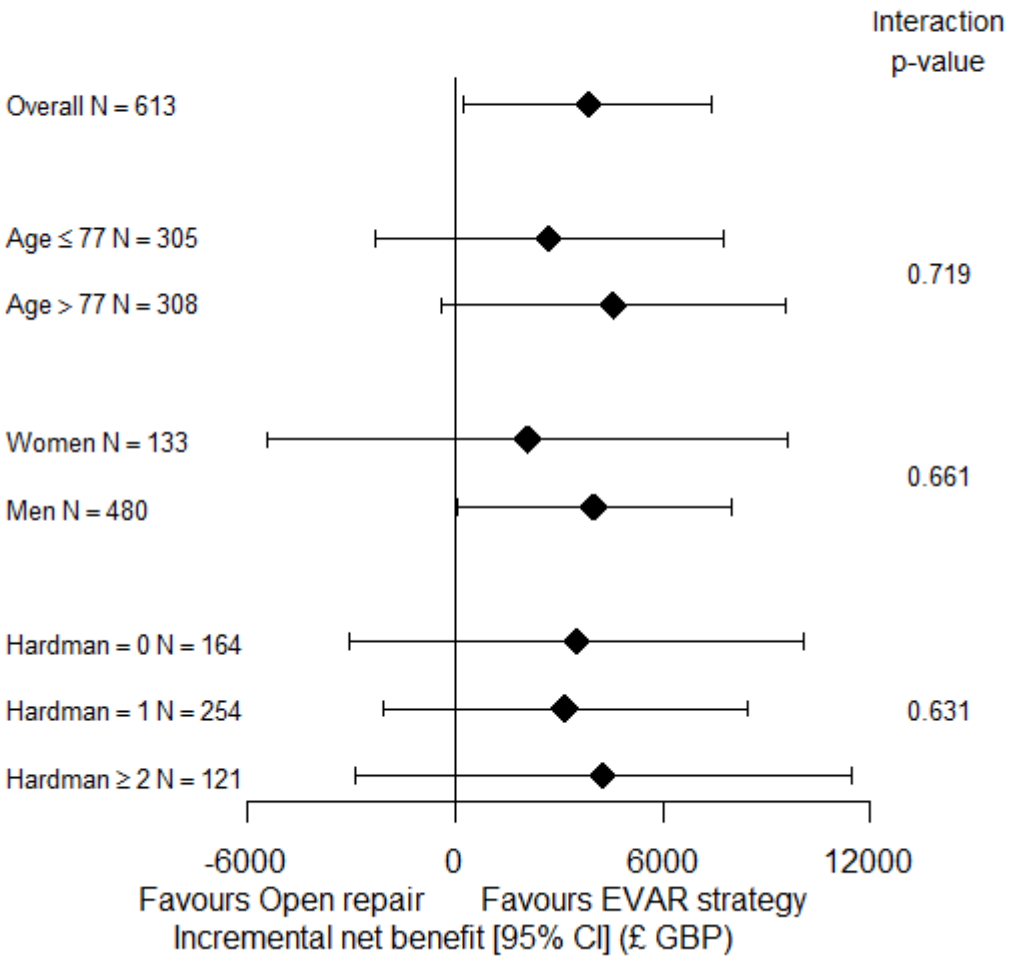


Figure S4: Cost-effectiveness acceptability curve, reporting the probability that the endovascular strategy is cost-effective at alternative levels of willingness to pay for a QALY gain.

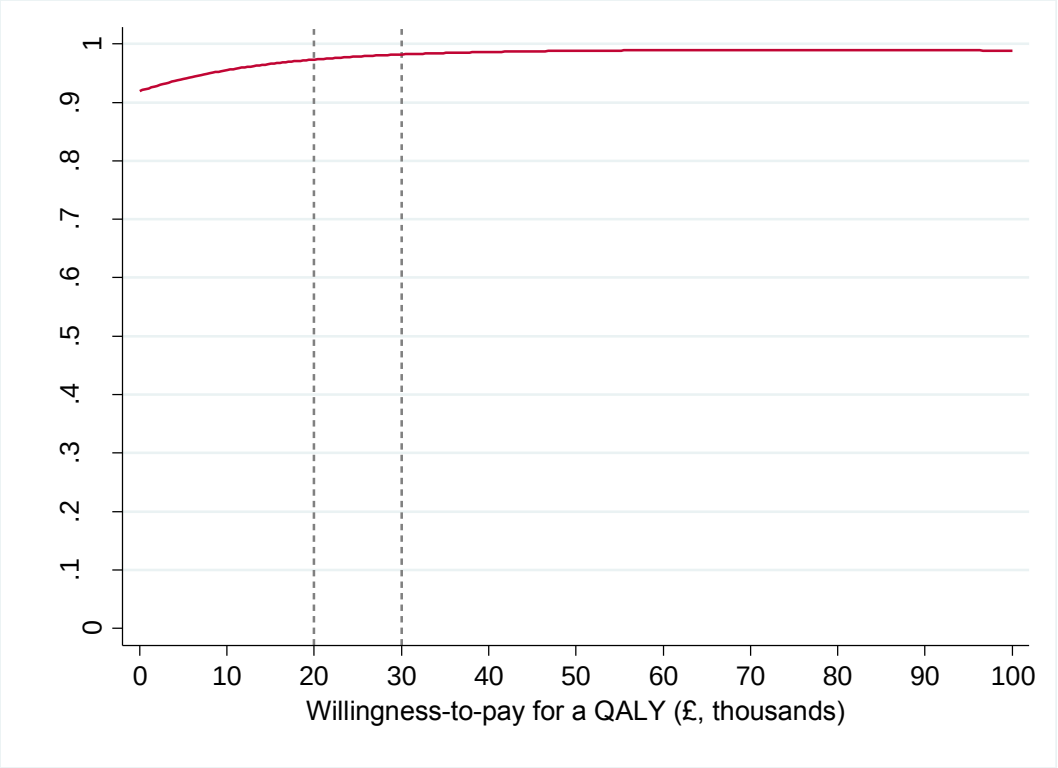
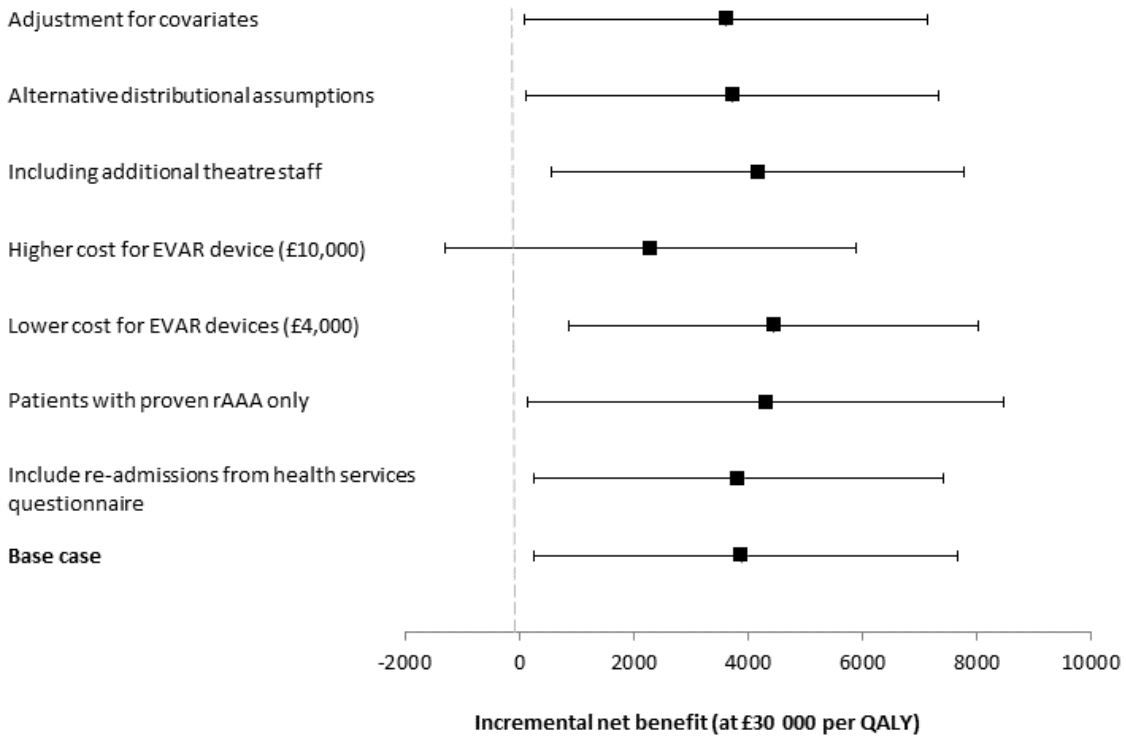


Figure S5: Sensitivity analysis that considers the effect on the Incremental Net Benefit (at £30 000 per QALY) of alternative assumptions, compared to the base case.



References:

1. National Institute for Health and Care Excellence. Guide to the methods of technology appraisals. National Institute for Health and Care Excellence, London 2013.
2. NHS Information Standard Board. Critical Care Minimum Data Set. Health and Social Care Information Centre; 2012.
3. Curtis L. Unit costs of health and social care: University of Kent, UK (Personal Social Services Research Unit). 2012.
4. Department of Health. National Schedule of Reference Costs for NHS Trusts, 2011-2012. London: Department of Health; 2012.
5. Dolan P, Gudex C, Kind P, Williams A. A Social Tariff for EuroQoL: Results from a UK General Population Survey. CHE Discussion Paper 138. Centre for Health Economics, University of York, York. 1999.
6. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005;14(5):487-96.
7. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.
8. Brown LC, Powell JT, Thompson SG, Epstein DM, Sculpher MJ, Greenhalgh RM. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy. Health Technol Assess. 2012;16(9):1-218.
9. OECD. Purchasing Power Parities and Exchange Rates for all OECD countries. Organisation for Economic and Cooperation and Development, Paris, France. 2012 http://www.oecd.org/std/prices-ppp/purchasingpowerparitiespppsdata.htm. Accessed 14th October 2014
10. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health Econ. 2004;13(5):461-75.
11. Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. Health Technol Assess. 2006;10(44):iii-iv, ix-x, 1-210.
12. British National Formulary Number 63. Joint Formulary Committee. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain.2012.
13. NHSBT. NHS Blood and Transplant. National blood and blood products price list 2011-2012. London2012.
14. Dixon S, Mason S, Knowles E, Colwell B, Wardrope J, Snooks H, et al. Is it cost effective to introduce paramedic practitioners for older people to the ambulance service? Results of a cluster randomised controlled trial. Emerg Med J. 2009;26(6):446-51.
15. IMPROVE Trial website: www.imperial.ac.uk/medicine/improvetrial. Accessed 14th October 2014