Late aneurysm-related mortality up to 15 years, secondary endovascular repair late sac rupture risk and costs and cost-effectiveness implications in the United Kingdom EndoVascular Aneurysm Repair randomised controlled trials

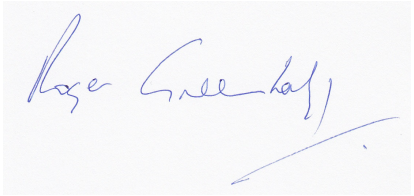
Version 2.0 – 01/12/2015

MAIN SPONSOR: Imperial College London

FUNDERS: National Institute of Health Research

STUDY COORDINATION CENTRE: Vascular Surgery Research Group, Imperial College

Protocol authorised by:

Roger Greenhalgh		5th February 2016
Name	Signature	Date

Study Management Group

Chief Investigator:	Professor Roger Greenhalgh
Co-investigator	Professor Janet Powell
Statistician:	Dr Michael Sweeting
Trial manager:	Dr Rajesh Patel
Data-base manager:	Murtaza Kaderbhai

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
5L10C, 5th Floor Lab Block
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Tel: +44-203 311 0204
Fax: +44203 311 0203

Funder
National Institute of Health Research

1. Introduction

1.1 Background

An abdominal aortic aneurysm (AAA) is defined as a localised enlargement of the abdominal aorta such that the diameter is greater than 3cm or more than 50% larger than the normal diameter at the level of the renal arteries. Once this aneurysm becomes larger than 5.5cm there is increased risk that it could burst open (rupture) [1]. A ruptured aneurysm can cause massive internal bleeding, which is usually fatal. Four out of five people with a ruptured aortic aneurysm will die as a result. The most commonly used surgical treatment for an abdominal aortic aneurysm is grafting. This involves replacing the affected section of the aorta with a piece of synthetic tubing known as a graft. There are two ways that grafting can be done:

1) Open surgery - a large incision is made in the abdomen to expose the aorta and insert the graft.

2) Endovascular surgery (EVAR) - this involves inserting a thin tube (a catheter) into one of the arteries of the legs and then guiding it in to the aorta. The graft is then moved through the catheter and used to reline the aorta wall.

Endografts for repair of abdominal aortic aneurysm were first reported in the late 1980s and commercially available grafts were developed rapidly during the 1990s. This prompted a head-to-head comparison of the new, less invasive, endovascular technology with the existing gold standard open repair (a major surgical procedure with approximately 5% operative mortality). The first (and largest) randomised trial of open versus endovascular repair for large aneurysms started in the UK in 1999, alongside a sister trial to evaluate the efficacy of endovascular repair in patients too frail to be considered for open repair [2,3]. Other trials comparing open and endovascular repair followed in the Netherlands [4], France [5] and the USA [6].

1.1.1 Operative mortality

The UK [7], Dutch [8] and US [6] trials all have shown that operative mortality is 3 times higher after open versus endovascular repair.

1.1.2 Two-year survival

After 2 years survival rates after open and endovascular repair were similar in the UK [9], Dutch [10] and French [5] trials. Although this was not shown in the US trial, the large US Medicare data-base [11] has shown that, by 3 years, the survival was similar after open or endovascular repair. Hence, there is a “catch-up” in all-cause mortality between 2 and 3 years after aneurysm repair.

1.1.3 Four-year survival

Four-year survival has only been reported from UK [9] and Dutch [10] trials and as at 2 years, survival was not statistically significantly different between the groups.

1.1.4 Aneurysm-related mortality

Aneurysm-related mortality has only been evaluated in the UK trial [2]. The early benefit of endovascular repair was lost after 6 years of follow up, principally because of secondary sac rupture after EVAR, which was fatal in 2/3 of cases [12]. A similar secondary sac rupture rate of ~0.7 per 100 patient-years was shown in the Dutch and French trials and even in large registries using newer generation endografts [5,13,14]. Only in a UK EVAR trials audit have specific underlying factors associated with secondary sac rupture been identified [12]. In this, 25 secondary sac ruptures were identified in EVAR trial 1 and another 2 in EVAR trial 2 and this contributed to the secondary sac rupture rate of 0.7% per 100 person years. The 27 EVAR sac ruptures were categorised into group A with 5 patients within the first 30 days, group B with 5 patients occurring in follow up without underlying endoleak and group C of 17 patients who had type 1 endoleak, type 2 endoleak or type 3, all with sac expansion, kinking or migration. These are referred to as the "cluster". In addition, increasing aneurysm neck diameter at the time of EVAR was associated with a 2-fold increase in risk of late sac rupture, although with only 27 ruptures this did not achieve statistical significance. This would benefit from further evaluation, particularly since there is accumulating evidence that when endografts are used outside "Instructions for Use", complication rates escalate [15]. No secondary aortic ruptures have been reported after open repair in the UK trial by 2009.

It is highly probable that "catch-up" of EVAR by open aortic repair in terms of aneurysm related mortality is a result of these EVAR late sac ruptures. On that account open repair (OR) will have a lower aneurysm-related mortality in later years follow up, if ruptures continue to occur at the present rates in the EVAR and open repair groups.

1.1.5 Aneurysm-related complications

All the trials have reported a higher and continuing occurrence of complications after endovascular repair including leaks around the endograft, failure of endograft components and sac rupture. This has led to a higher rate of reinterventions after endovascular repair to correct the problems.

1.1.6 Quality of Life

The UK and US trials reported no difference in quality of life, between open and endovascular repair, 1 year after repair. The Dutch trial reported that at 1 year, quality of life was better after open repair.

1.1.7 Costs and cost-effectiveness

Both the UK [9] and Dutch [16] trials have reported that there are higher costs associated with endovascular repair than open repair with endovascular repair being of doubtful cost-effectiveness. In contrast, NICE 2008 found endovascular repair to be cost-effective based on more favourable assumptions regarding costs, long term aneurysm-related mortality and need for reinterventions [17]. Prof RM Greenhalgh and Dr D Epstein were part of the 2008 NICE review.

1.1.8 Long-term follow-up

The UK trial has reported long-term follow up to 10 years. This again has shown no statistically significant difference in long-term survival after open or endovascular repair, the continuing occurrence of new leaks and complications and reinterventions after endovascular repair [18]. The proposed research will investigate long term aneurysm-related mortality and cost-effectiveness at 15 years between the randomised arms of both UK trials. This is the first time such long term follow up has been considered.

Only in the EVAR trials is aneurysm-related mortality used as an outcome measure. It was not adopted in the ACE, DREAM or OVER trials. ACE follows up for 5 years, DREAM has published to a mean of 6.4 years follow up and OVER is scheduled for 9 years. EVAR 1 and 2 are therefore the only trials with 10 year follow up so far and the only trials using aneurysm-related mortality

2. Study Objectives

2.1 Principal Objective

The principal objective is to follow the patients originally randomised in the EVAR trials out to 15 years and compare the rate of aneurysm-related mortality between the randomised arms in each trial (EVAR-1 and EVAR-2) separately. In follow up until December 2009, 25 sac ruptures have occurred after endovascular aortic aneurysm repair (EVAR) in EVAR-1 and 2 sac ruptures in EVAR-2, carrying a 67% mortality rate. By 2009 no secondary ruptures have occurred in late follow up with open aortic repair.

The initial EVAR trials patients were recruited from both sexes, aged 60 years and over and had an aortic aneurysm of ≥ 5.5cm, anatomically suitable for EVAR. EVAR trial 1 compared the novel EVAR with the standard, open surgical repair (OR) in patients fit for open repair.

If present trends continue, after 15 years, open repair will have a lower aneurysm-related mortality than endovascular repair, even with every attempt taken to intervene to correct known causes of sac expansion to reduce the risk of secondary rupture in EVAR patients, with possible future projections shown graphically below for the EVAR 1 trial (Figure 1). The additional follow-up to 15 years will allow us to test this hypothesis.

- Aneurysm-related mortality is the primary outcome measure for the 15-year follow up results.

- Secondary outcome measures will include all-cause mortality, complications and re-interventions.

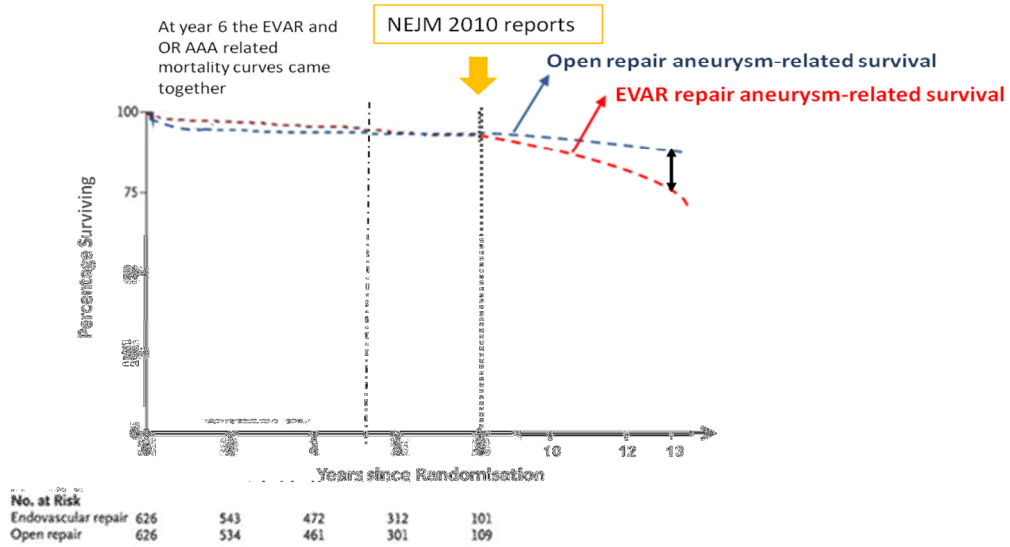


Figure 1. Possible aneurysm-related survival from 8 years of follow-up in the EVAR 1 trial if current trends continue.

2.2 Second Objective

The second objective is to re-evaluate the cost-effectiveness of open and endovascular repair after a 15-year time period. This is particularly pertinent because EVAR-related complications continue to occur many years after the original procedure [12]. This will require knowledge of continuing graft-related complications and use of hospital resources to the end of 2014.

- Further secondary outcomes will be costs and cost-effectiveness.

2.3 Third Objective

We hypothesise that sac growth after EVAR is associated with increased risk of rupture and the presence of a significant complication or endoleak: hence patterns of sac growth might predict the need for reintervention, even in the absence of a defined endoleak. Our third objective is therefore to investigate any association between sac growth (figure 2) and secondary rupture, complication, endoleak and reintervention correction.

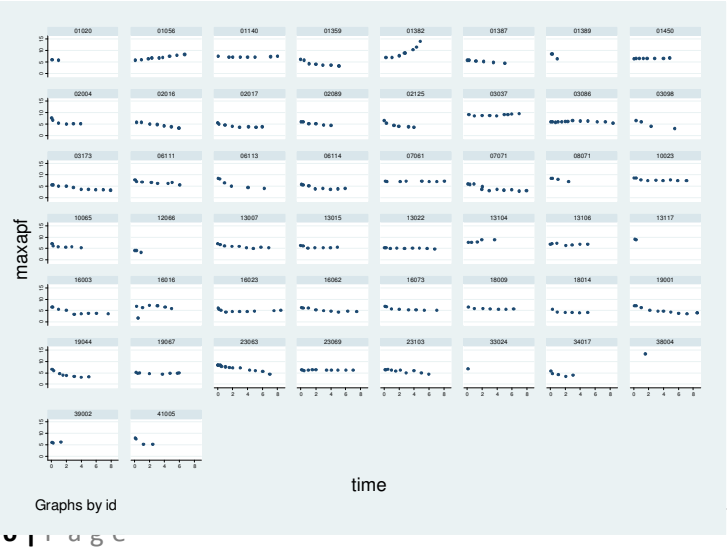


Figure 2: Change in sac diameter of a random selection of 50 patients (post EVAR measurements only, pre-op excluded)

- Further secondary outcomes will be the association between changes in aneurysm sac diameter and later re-interventions/mortality in those patients who received EVAR.

3 Study Design

1252 patients underwent randomisation from 1st September 1999 until 1st August 2004 in the EVAR trial 1. 626 patients were randomized to the EVAR arm of the study and 626 to the open repair (OR) arm. The numbers of patients still alive on 1st September 2009 were 366 EVAR and 362 OR. Similarly, 404 EVAR 2 patients underwent randomisation during the same time period. 197 patients were randomized to EVAR of which 52 were still alive in September 2009 and 207 were assigned to the no intervention arm of the study of which 47 were still alive in September 2009.

Upon checking, only 231 additional patients (not 235) were randomized between 1st September 2004 and 15th June 2005 and have not yet been reported. In EVAR trial 1 this included 88 patients who were randomized to the EVAR arm of the study of which 70 were alive in September 2009. 87 patients were also randomized to the OR arm of the study of which 66 were still alive in September 2009. For EVAR 2, 28 patients were randomized to EVAR of which 11 were alive in September 2009 and 28 patients were assigned to the no intervention arm of which 8 were alive in September 2009. Where available, details of the primary operation will be obtained for these additional patients. Retrospective follow-up data from the time of the primary procedure will also be obtained from hospital medical records. If the completeness of data relating to complications and reinterventions during follow-up is satisfactory these patients will be included in the data analysis. All of these additional 231 patients have been registered for reporting so it will be possible to include them in sensitivity analysis for all-cause mortality.

The follow up of the patients at the 34 UK EVAR trials centres will be conducted by local NHS staff, a lead clinician is identified at each of these centres and, in turn, the lead clinician will identify a member of staff to act as local coordinator. Due to the long delays in the signing of the collaboration agreement and obtaining local NHS Research & Development approval, data will be collected retrospectively up to December 2013. Data will be collected prospectively between 1st December 2013 and 31st March 2015. The single-page case record form, (CRF) shown in appendix 1 has been designed to capture all relevant information relating to complications and re-interventions during the current phase of follow-up (2010, 11, 12, 13, 14 & 15).

Wherever CT scans have been performed images will be copied for transfer to the trial centre. Sometimes duplex scan is preferred locally and infrarenal maximum outer-to-outer antero-posterior diameter recorded. For EVAR, crucially, maximum sac diameter is an essential finding. Endoleaks and type of endoleak will be noted on the basis of the opinion of the local NHS radiologist. All available CT scans will be examined in the trial centre core laboratory by a skilled and trained vascular fellow to note known factors associated with eventual secondary sac rupture.

Due to the majority of open repair patients and some EVAR patients no longer being followed up by the trial centres, and given the fact that nearly all of the EVAR 2 patients have died, the trial centre data will be supplemented by routine hospital administrative data for hospital readmissions and re-interventions for patients in the EVAR 1 trial only. Relevant readmissions and re-interventions will require verification by local trial coordinators/principal investigators. The source of information for all re-interventions and major adverse events will be documented. As there are so few EVAR-2 patients surviving, this option will not be pursued for EVAR-2. The added volume of data generated by using Hospital Episode Statistics necessitated the appointment of data-manager for the final few months before data base closure.

During the annual data collection, particular note will be taken of any reinterventions and endoleak corrections. Major adverse events will be noted, such as strokes, myocardial infarctions, renal replacement therapy and major lower limb amputation as these are vital for the cost effectiveness evaluation.

Due to the length of time involved in obtaining approval for our application for Hospital Episode Statistics data, the funders have agreed to the project end date being extended until 31st August 2016 and patient follow-up for reinterventions being extended to 31st March 2015 (and mortality flagging until 30th June 2015).

At the end of January 2016 the database will be locked and data checked and cleaned and made ready for the statistical and health economic analyses. A statistical analysis plan will be drawn up in late 2015.

3.1 Planned Interventions

There are no planned interventions for patients. All local principal investigators will be advised of the dangers of secondary sac rupture if particular complications, including late sac expansion, are not corrected, by circulation of the Wyss et al paper announcing factors associated with secondary sac rupture [12]. A documentation of reinterventions and outcomes at the 34 UK EVAR trial centres (as mentioned above) will be carried out.

3.2 Planned inclusion/exclusion criteria

There are no inclusion/exclusion criteria as these are additional follow up years up to 15 years of the world's first and longest follow up randomised controlled trials of the endovascular aneurysm repair technology.

3.3 Adjudication of mortality, re-interventions and adverse events.

The trial end-point committee adjudicates the cause of death based on information provided by the Office of National Statistics (date and cause of death), supplemented by clinical information about recent aneurysm-related readmissions or known aneurysm-related complications. All deaths within 30-days of either an aneurysm repair or an aneurysm-related re-intervention are considered as aneurysm-related. Death within 30-days of aneurysm rupture either before or after aneurysm repair is also considered as aneurysm-related. Other categories of cause of death included cardiac, other vascular disease, pulmonary, renal, lung cancer and other cancers. The endpoint committee also adjudicates on whether controversial

re-interventions are aneurysm-related. The major adverse events including myocardial infarction, stroke and amputation are not adjudicated.

3.4 Grading the Severity of Re-interventions and their resource use

There is no recognised reporting system for reinterventions or reintervention severity, to facilitate allocation of Resource use. We will therefore carry out a survey of all the trial site principal investigators to grade the severity of reinterventions along with the likely stay in HDU/ITU for these reinterventions. The survey will be completed by the 21st January 2016.

4 Statistics and Data Analysis

Final Statistical Analysis Plan (SAP) is attached in separate document.

5 Regulatory Issues

5.1 Ethical Arrangements for extended follow-up to 15-years

This proposal has ethical approval by the North West Multi-centre Research Ethics Committee (MREC, Ref Number 98/8/26 & 27) dated 16th February 2011.

- **Risks and anticipated benefits for trial participants and society, including how benefits justify risks**
  For this new endovascular aneurysm repair technology, it was considered essential to have annual follow up with CT scan as there were no data on satisfactory follow up of this technology. There is awareness of a potential increased risk of cancer but it was considered that the risk of complications requiring correction could more than offset the risk of cancer and so CT scan once per year was adopted. Several of the 34 UK EVAR trial centres have stepped down from CT scan annually to duplex ultrasound where local vascular technology using duplex is considered satisfactory. Accurate sac diameter using this method is considered to be achievable and wherever there is the suspicion of an endoleak and/or increase in diameter, CT scan is regarded as mandatory despite any theoretical but as yet unproven increased risk of cancer associated with CT scan EVAR follow up.

- **Informing potential trial participants of possible benefits and known risks**
  The lead applicant has informed the lead consultant at each centre of the results of trial outcomes. The EVAR trials were presented at the Charing Cross International Symposium in Imperial College in April 2010 to more than 3000 vascular specialists from all over the world. They were published in the New England Journal of Medicine and so reached a very high readership. It is said that in many countries of the world including the United States that knowledge of the UK Small Aneurysm trial

data and EVAR trials data are mandatory for every trainee in the subject. The publications stress all of the possible benefits and known risks of the new technology of EVAR.

Obtaining informed consent from participants whenever possible or proposed action where fully informed consent is not possible (e.g. emergency settings).
Informed consent was given at the beginning of the EVAR trials, before randomisation took place and included continued follow up via NHS resources. There was no specific consent for late follow-up from 2009 since this was deemed unnecessary by the MREC.

- **Proposed time period for retention of relevant trial documentation.**
  15 years

- **Proposed action to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004'.**
  Not relevant

5.2 Ethical Approval for the use of hospital administrative data

Since patients did not give consent for access to their routine hospital administrative data on enrolment (during 1999-2004) we have obtained ethics approval (Section 251) from the Confidentiality Advisory Group (CAG) to enable disclosure of confidential patient information. The CAG approval was given on 18th February 2015 (reference number 14/CAG/1024). Approval for Hospital Episode Statistics data was subsequently granted on 26th June 2015 and allowed the comprehensive reporting of hospital admissions until 31st March 2015.

5.3 Confidentiality, data security and data checks.

The trial manager at the trial centre in Imperial College will undergo a course of training in order to conduct data collection in a secure way according to good clinical trial practice with patient data confidentiality treated with proper due care. All data will be secured and only accessed by the trial manager or data-manager in the pre-existing database: double data entry will be performed on a randomly-selected 10% of patients surviving at the end of 2009. Additionally imaging data from annual follow up are also collected and transferred securely to the trial centre and stored with utmost patient confidentiality.

6 Trial Management

The trial will be conducted according to HTA guidelines, with oversight from a trial steering and data monitoring committees as well as benefiting from oversight and staff training from the Imperial Clinical Trials Unit. The principal role of these committees, in the late follow up phase, will be to ensure that data collection is complete. The trial management committee will meet on a regular basis to monitor progress and address problems which may arise.

Trial Management Committee

Professor RM Greenhalgh, Professor JT Powell, Dr M Sweeting, Dr D Epstein, Dr C Bicknell, Dr R Von-Allmen, Dr T Wyss, Dr N Burfitt

Trial Steering Committee

Professor RJ Lilford, Professor RM Greenhalgh (TMC), Mr M Wyatt, Professor S Thompson, Professor MJ Sculpher

Data Monitoring & Ethical Committee

Professor FGR Fowkes, Dr R Morgan, Professor B Campbell

Endpoints Committee

Professor JT Powell (Chair), Miss A Halliday, Dr S Gibbs.

Appendix 1 – Case Record Form (CRF)

EVAR Trials 10-15 year follow up to December 2014

Together we are collecting data for the NIHR for the world first 15 year follow-up of EVAR v OR. 34 centres with designated investigators and coordinators will be named authors of the publication. Below is a 2014 simplified data collection form to collect as much as possible in one go. The most important data for EVAR/OR follow-up are aneurysm-related complications and reinterventions for the original repair either in radiology department or theatre.

Patient ID number ☐☐☐☐☐☐ Date of Birth (DD/MM/YY) ☐☐ ☐☐ ☐☐ Date of Data Extraction (DD/MM/YY) ☐☐ ☐☐ ☐☐

Aneurysm Trial Patient Follow-up after 2009? Yes ☐ No ☐

If yes tick which years - 2010 ☐ 2011 ☐ 2012 ☐ 2013 ☐ 2014 ☐

If No Why: Lost to follow-up ☐ Too Frail ☐ Patient Refused ☐

Patient Died ☐ Date of Death _____ Discharged from follow-up ☐ Date last seen _____

Annual Follow-Up

Complications from Notes: None (0) Endoleak Type I (1) Type II (2) Type III (3) Migration (4) Kinking (5) Sac expansion from baseline (mm)(6)

Year	Scan	Scan Type*	Complications Detected (1-6)	Date Detected (DD/MM/YY)	Complications Detected (1-6)	Date Detected (DD/MM/YY)	Complications Detected (1-6)	Date Detected (DD/MM/YY)
2010	Yes / No	CT/Duplex						
2011	Yes / No	CT/Duplex						
2012	Yes / No	CT/Duplex						
2013	Yes / No	CT/Duplex						
2014	Yes / No	CT/Duplex						

***If Duplex please attach scan report**

Reinterventions 2010–2014 for complications listed above

List of Methods: Added Stent (1) Staple (2) Embolisation (3) Sclerosis (4) Conversion to open repair (5) Other (6)

Date	Type of complication (1-6)	Reintervention Method (1-6)
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

OTHER ANEURYSM-RELATED COMPLICATIONS REPORTED

7. Known aneurysmal extension above or below original graft? Yes ☐ No ☐ Date _____
8. Thrombosis of graft limb? Yes ☐ No ☐ Date _____
9. Graft Infection? Yes ☐ No ☐ Date _____
10. During follow-up - Incisional Hernia Yes ☐ No ☐ Date _____
11. During follow-up - False Femoral Aneurysm Yes ☐ No ☐ Date _____

Intervention/Repair for above? Event (7-11) ☐ Date _____ Open or Endovascular Repair _____

Intervention/Repair for above? Event (7-11) ☐ Date _____ Open or Endovascular Repair _____

Intervention/Repair for above? Event (7-11) ☐ Date _____ Open or Endovascular Repair _____

Other Major Adverse Events During EVAR Trial Follow-Up		Date 1	Date 2	Date 3
Stroke	Yes ☐ No ☐	_____	_____	_____
Myocardial Infarction	Yes ☐ No ☐	_____	_____	_____
Major Amputation	Yes ☐ No ☐	_____	_____	_____
Renal Failure	Yes ☐ No ☐	_____	_____	_____
New Cancer Diagnosed	Yes ☐ No ☐	_____	**ICD Code of cancer type** _____	

7. References

1. Powell JT, Brown LC, Greenhalgh RM and Thompson SG. The rupture rate of large abdominal aortic aneurysms: is this modified by anatomical suitability for endovascular repair?. *Ann Surg*. 2008;**247**:173-9

2. The United Kingdom Evar Trial Investigators, Greenhalgh, R.M., Brown, L.C., Powell, J.T., Thompson, S.G., Epstein, D., et al. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med* 2010;**362**: 1863-71.

3. The United Kingdom Evar Trial Investigators, Greenhalgh, R.M., Brown, L.C., Powell, J.T., Thompson, S.G., Epstein, D. Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. *N Engl J Med* 2010;**362**: 1872-80.

4. De Bruin, J.L., Baas, A.F., Buth, J., Prinssen, M., Verhoeven, E.L., Cuypers, P.W., et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. *N Engl J Med* 2010;**362**: 1881-9.

5. Becquemin, J.P., Pillet, J.C., Lescalie, F., Sapoval, M., Goueffic, Y., Lermusiaux, P., et al. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. *J Vasc Surg* 2011.

6. Lederle, F.A., Freischlag, J.A., Kyriakides, T.C., Padberg, F.T., Jr., Matsumura, J.S., Kohler, T.R., et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. *JAMA* 2009;**302**: 1535-42.

7. Greenhalgh, R.M., Brown, L.C., Kwong, G.P., Powell, J.T., Thompson, S.G. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. *Lancet* 2004;**364**: 843-8.

8. Prinssen, M., Verhoeven, E.L., Buth, J., Cuypers, P.W., van Sambeek, M.R., Balm, R., et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2004;**351**: 1607-18.

9. The United Kingdom Evar Trial Investigators. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet* 2005;**365**: 2179-86.

10. Blankensteijn, J.D., de Jong, S.E., Prinssen, M., van der Ham, A.C., Buth, J., van Sterkenburg, S.M., et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2005;**352**: 2398-405.

11. Schermerhorn, M.L., O'Malley, A.J., Jhaveri, A., Cotterill, P., Pomposelli, F., Landon, B.E. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. *N Engl J Med* 2008;**358**: 464-74.

12. Wyss, T.R., Brown, L.C., Powell, J.T., Greenhalgh, R.M. Rate and predictability of graft rupture after endovascular and open abdominal aortic aneurysm repair: data from the EVAR Trials. *Ann Surg* 2010;**252**: 805-12.

13. Schlosser, F.J., Gusberg, R.J., Dardik, A., Lin, P.H., Verhagen, H.J., Moll, F.L., et al. Aneurysm rupture after EVAR: can the ultimate failure be predicted? *Eur J Vasc Endovasc Surg* 2009;**37**: 15-22.

14. Mertens, J., Houthoofd, S., Daenens, K., Fourneau, I., Maleux, G., Lerut, P., et al. Long-term results after endovascular abdominal aortic aneurysm repair using the Cook Zenith endograft. *J Vasc Surg* 2011;**54**: 48-57 e2.

15. Schanzer, A., Greenberg, R.K., Hevelone, N., Robinson, W.P., Eslami, M.H., Goldberg, R.J., et al. Predictors of Abdominal Aortic Aneurysm Sac Enlargement After Endovascular Repair. *Circulation* 2011;**123**: 2848-55.

16. Prinssen, M., Buskens, E., de Jong, S.E., Buth, J., Mackaay, A.J., van Sambeek, M.R., et al. Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial. *J Vasc Surg* 2007;**46**: 883-90.

17. Endovascular stent–grafts for the treatment of abdominal aortic aneurysms. *National Institute for Health and Clinical Excellence (NICE)* 2009 http://www.nice.org.uk/TA167.

18. Brown, L.C., Greenhalgh, R.M., Powell, J.T., Thompson, S.G., Participants, E.T. Use of baseline factors to predict complications and reinterventions after endovascular repair of abdominal aortic aneurysm. *Br J Surg* 2010;**97**: 1207-17.

19. Brown, L.C., Brown, E.A., Greenhalgh, R.M., Powell, J.T., Thompson, S.G., Participants, U.E.T. Renal function and abdominal aortic aneurysm (AAA): the impact of different management strategies on long-term renal function in the UK EndoVascular Aneurysm Repair (EVAR) Trials. *Ann Surg* 2010;**251**: 966-75.

20. Epstein, D.M., Sculpher, M.J., Manca, A., Michaels, J., Thompson, S.G., Brown, L.C., et al. Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. *Br J Surg* 2008;**95**: 183-90.

21. Brown, L., Powell, J., Thompson, S., Epstein, D., Sculpher, M., Greenhalgh, R. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy. *Health Technol Assess* 2012;**16**: 1-218.

22. Curtis, L. Unit costs of health and social care. *Canterbury: PSSRU* 2009.

23. Anonymous. NHS Trust reference cost schedules 2007-08. *London: Department of Health* 2009.

24. Willan, A.R., Lin, D.Y., Manca, A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005;**24**: 131-45.

25. White, I.R., Royston, P., Wood, A.M. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;**30**: 377-99.

26. van Hout, B.A., Al, M.J., Gordon, G.S., Rutten, F.F. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ* 1994;**3**: 309-19.

27. Efron, B., Tibshirani, R. An introduction to the bootstrap. *New York: Chapman & Hall* 1993.

28. Harris, P.L., Buth, J., Mialhe, C., Myhre, H.O., Norgren, L. The need for clinical trials of endovascular abdominal aortic aneurysm stent-graft repair: The EUROSTAR Project. EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair. *J Endovasc Surg* 1997;**4**: 72-7; discussion 8-9.