External Assessment Centre report

Title: E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta

Produced by: KITEC - King's Imaging Technology Evaluation Centre

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Erratum: section 3.0, page 27.

‘The review of comparators found 1929 abstracts, which were screened and finally resulted in ten relevant studies (Etz et al 2008,Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004, Kim et al 2009, Kawaharada et al 2009, Lee et al 2011, Antoniou et al 2010a, Antoniou et al 2010b), which also included five studies cited by the sponsor (Etz et al 2008,Safi et al 2007, LeMaire et al 2006,Svensson et al 2004, Safi et al 2004)’.

This should read:

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Contents

1 Summary 4
2 Background 8
2.1 Overview and critique of sponsor's description of clinical context 8
2.2 Overview of sponsor's description of ongoing studies 9
2.3 Critique of sponsor's definition of the decision problem 9
3 Clinical evidence 12
3.1 Critique of the sponsor's search strategy 12
3.2 Critique of the sponsor's study selection 12
3.3 Included and excluded studies 12
3.4 Overview of methodologies of all included studies 22
3.5 Overview and critique of the sponsor's critical appraisal 22
3.6 Results 24
3.7 Description of the adverse events reported by the sponsor 26
3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor 26
3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence 26
3.10 Conclusions on the clinical evidence 33
4 Economic evidence 34
4.1 Published economic evidence 34
4.2 De novo cost analysis 35
4.3 Results of de novo cost analysis 43
4.4 Interpretation of economic evidence 44
4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence 45
4.6 Conclusions on the economic evidence 55
5 Conclusions 65
6 Implications for research ..... **Error! Bookmark not defined.**
References 66
Appendix 70

1 Summary

Scope of the sponsor's submission

The sponsor has submitted clinical and economic evidence related to E-vita open plus. The sponsor claims clinical benefits over the current 2-stage procedures. The scope of the evidence was to compare E-vita with three two-stage procedures (two-stage with vascular graft, two-stage with endovascular stent graft, open debranching with endoluminal stent graft). The sponsor has submitted most of the relevant evidence related to E-vita open plus and that related to one comparator (two-stage with vascular graft). However, in the economic evidence, a de novo cost model has been submitted for all the comparators listed in the scope. The cost model included only varied levels of adoption, suitability for second stage, and in-hospital mortality but did not include complications occurring at each stage.

Summary of clinical evidence submitted by the sponsor

The sponsor has submitted all available evidence related to E-vita open plus. The paper by Jakob et al (2011) provided a summary of evidence from January 2005 to December 2010 based on the International E-vita Open Registry. The EAC reviewed the other studies cited and found that they were either subsets of the registry data or too small to provided additional information, therefore only the Jakob et all (2011) data were used in the calculation of outcome estimates. For the comparators, the sponsor submitted papers related to only one comparator: two-stage with vascular graft (Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004). Clinical evidence on other comparators listed in the scope was not included.

Summary critique of clinical evidence submitted by the sponsor

The EAC considers that the sponsor has included most of the relevant evidence related to E-vita open plus but has included only one comparator. The EAC therefore conducted a systematic review and meta-analysis of all comparators to supplement the limited information provided in the sponsor's submission. Data presented by the sponsor were largely descriptive and contained no measures of precision such as confidence intervals. Since numbers were commonly quite small, the lack of confidence intervals limited the interpretation that could be drawn from the data presented.

Summary of economic evidence submitted by the sponsor

The sponsor reports that 'health economics studies are not known and certainly would not have been widely carried out prior to the analysis reported here for this new and innovative product'. However, the sponsor has not made clear whether this conclusion was reached based on a systematic search. In the absence of published economic evidence, the sponsor has presented a de novo cost model. Unlike the clinical evidence, the cost model includes all the comparators listed in the scope. The cost model includes only varied levels of adoption, suitability for second stage, and in-hospital mortality and uses many assumptions to arrive at the cost estimates.

The sponsor concludes that currently there is no published literature comparing the technology and comparators and the cost model analysis shows that E-vita open plus has cost savings compared to the comparators. The sensitivity analysis also reveals that E-vita open plus has only one stage and has cost savings, even with varied levels of adoption, suitability for second stage, and in-hospital death rates. The sponsor concludes that E-vita is superior over the comparators.

Summary critique of economic evidence submitted by the sponsor

The EAC felt that the search strategy and databases included for the economic evidence could be improved. The sponsor has submitted a short term cost model, but has used different adoption rates for the technology and comparators. The EAC felt that it is better to present the per patient cost model based on probabilities of clinical outcome measures. The model submitted by the sponsor includes four comparators compared to the technology. One extra comparator has been included in addition to the three comparators listed in the scope. The additional comparator refers to Open surgical 'debranching' of the head and neck vessels with woven graft, instead of endoluminal stent graft. However, the model does not include complications such as stroke, paraplegia, renal failure and bleeding during each stage of the procedure. Once the complications were included, a long term model with the lifetime cost of some of the complications also needed to be modelled. Further, some of the assumptions used in the cost model needed to be revised.

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

Most of the clinical evidence related to E-vita open plus and one of the comparators was based on published evidence. The cost model has also incorporated data based

on the published evidence. Where published evidence was missing, data were taken from either manufacturers' studies or registry data. The EAC considered that the sponsor might have decided to use published evidence to inform the required assumptions on costing of the interventions and comparators. The EAC was able to source most of the parameters from the literature for the revised costing model.

Summary of any additional work carried out by the External Assessment Centre

The EAC conducted a systematic review and meta-analysis of comparators as these were not included in the sponsor's submission. The systemic review of comparators identified 1929 abstracts. The review included aneurysms (aortic/aortic thoracic degenerative, dissecting aneurysm), dissection (chronic/acute type A) with two-stage vascular graft using classical elephant trunk procedure, two-stage with endovascular stent graft, and open debranching with endoluminal stent graft. The following outcomes were included: mortality/hospital mortatlity, survival, stroke, bleeding, paraplegia, renal failure. Studies not including these outcomes and case reports were excluded. The search terms and strategy are provided in the Appendix 1. The review resulted in 10 studies; Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004, Kim et al 2009, Kawaharada et al 2009, Lee et al 2011, Antoniou et al 2010a, Antoniou et al 2010b. Of these, five studies were cited by the sponsor; Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004. Outcome estimates from these studies were incorporated into a meta-analysis to provide pooled estimates for six outcomes for the four comparators, some at each of 2-stages where data were available, providing an additional 30 outcome estimates with 95% confidence intervals.

The EAC also undertook an additional systematic review related to economic evidence and did not find any published economic evidence related to the technology and comparators. The EAC revised the cost model, with updated assumptions based on literature that was sourced from the additional systematic review of clinical evidence, as described in section 3 of this report. A short term decision model was first constructed with complications and in-hospital mortality modelled. The technology (E-vita open plus) was compared with three comparators (two-stage with vascular graft, two-stage with endovascular stent graft, open debranching with endoluminal stent graft). Some of the complications, for example stroke, paraplegia and renal failure were expected to accrue lifetime costs. These estimated lifetime costs of complications were added to the decision model and a long-term model was

estimated. The models estimated the expected cost in the short-term and long-term. The results of the revised model indicated that E-vita open plus might not provide cost saving when compared to some of the comparators in the short-term, but would have high cost savings in the long term.

2 Background

2.1 Overview and critique of sponsor's description of clinical context

The device is intended to treat aortic disease involving the aortic arch. The sponsor specifically describes its use in aneurysm and dissection. The sponsor's description does not define separately the incidence and natural history of aneurysms affecting the ascending aorta, arch and descending thoracic aorta. The statement 'The increasing trend is basically the same for the other European population' should have been referenced.

NICE IPG 127 refers to descending thoracic pathology as stated by the sponsor. To our knowledge and that of clinical experts contacted by the EAC, there are no guidelines available (UK or other) specifically for treatment of the aortic arch.

Clinical expert advice indicates that the clinical pathway described by the sponsor is probably the 'gold standard' option for treatment of aortic disease involving the arch. Experts also indicate that repair for aortic disease involving the ascending aorta, arch and descending aorta probably involves techniques using endovascular technology such as second stage with thoracic endovascular repair, arch hybrid repair and total endovascular repair (either with chimney, fenestrated, or branched devices). Many cardiovascular centres now offer treatment involving these endovascular techniques.

There are some further issues in the clinical pathway of care presented on the technology and comparator.

The description of the use of the technology should mention that the stent graft should be deployed over a guide wire and under image (usually X-ray) guidance. The latter would be associated with a small dose of ionising radiation.

Use of hybrid technology such as the E-vita open plus may necessitate reorganisation and costs associated with the use of radiographic equipment, radiographers, radiologists and so on as per expert advice. Furthermore, it is not certain that a second stage completion endovascular procedure will be avoided because the stent graft component of the E-vita open plus may not be long enough to treat all descending aortic pathology.

The second stage completion procedure could be endovascular stent graft placement and does not necessarily require a left thoracotomy. It is not certain that a second interventional procedure will be avoided in all cases.

The sponsor has included E-vita open plus as a one stage procedure and compared it with two-stage vascular grafting using a classical elephant trunk procedure. There is limited discussion of other comparators in the submission, in particular regarding two of the comparators listed in the final scope: two-stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta; and open surgical debranching of the head and neck vessels with endoluminal stent graft placement in the aortic arch and descending aorta.

In the decision problem in the final scope, three comparators are described but these are not adequately described in the sponsor's submission of the clinical context (Section 3). There is very little information regarding the outcomes listed, cost, subgroups to be considered (acute and chronic Type A dissection, degenerative aneurysm) and special considerations (patients with connective tissue disorders, in particular Marfan's and Ehlers-Danlos syndromes.

2.2 Overview of sponsor's description of ongoing studies

The sponsor's description of on-going studies related to the E-vita device is reasonable but there is limited information presented regarding the comparators. The clinical experts which were contacted by the EAC stated that there are no randomised controlled trials being performed in this area at the current time. NIHR Health Technology Assessment board minutes of 5-6 March 2013 indicate that provisional funding has been allocated to a trial of the management of thoracic aortic aneurysm. No further details are available to the EAC but as this study is yet to start, the results will not be available for several years.

2.3 Critique of sponsor's definition of the decision problem

Population

The patient population described in the scope issued by NICE was patients with aneurysms or aortic dissection involving the ascending aorta, arch and descending thoracic aorta. The sponsor chose to reduce the incidence of aortic dissection from 3-

4 per 100,000 people in the scope issued by NICE to 0.5-3.5 per 100,000 people based on published evidence (Khan & Nair, 2002, Clouse et al 2004). The clinical evidence that has been submitted is relevant to the population described in the final scope, although the characteristics of the populations described in the various manuscripts may not necessarily reflect that in England.

The ratio of dissection to aneurysmal disease may be worth considering as dissection can be more challenging to treat, and therefore may affect the data regarding the technical success of the procedure.

Intervention

There is a good association between the technology described in the sponsor's submission and the technology described in the final scope. The technology described is the E-vita open plus device which is a combination of a proximal polyester fabric tube attached to a distal nitinol stent graft.

The E-vita open plus device received a CE mark in October 2008 for repair or replacement of the thoracic aorta in cases of complex aneurysms or dissection which involve the ascending aorta, the arch and the descending aorta.

Comparator(s)

The sponsor has included only one comparator (two-stage vascular graft using classical elephant trunk procedure). There is limited discussion of other comparators in the submission, in particular regarding two of the comparators listed in the final scope: two-stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta; and open surgical debranching of the head and neck vessels with endoluminal stent graft placement in the aortic arch and descending aorta.

The sponsors do not appear to have carried out a systematic review of comparator studies so the EAC conducted one (described below).

Outcomes

Important outcomes such as technical success, length of intensive care unit stay, and incidence of endoleak have not been included. The consensus view of expert advisors was that the outcome measures used by the sponsor were reasonable but that clear definitions of the outcomes were needed.

Cost analysis

The cost analysis in the sponsor's submission included all the comparators and technology listed in the scope. However, only a short term model with in-hospital mortality modelled has been presented. The EAC considers that this cost model does not match the cost analysis specified in the final scope, since complications have not been modelled. Further, if complications are modelled, there could be lifetime costs associated with these complications and a longer term model needs to be estimated.

Subgroups

Acute and chronic Type A dissection and degenerative aneurysm were identified in the scope as separate subgroups but in the sponsor's submission this has not been specifically addressed. Review of clinical evidence from the sponsor supplemented by the systtematic review carried out by the EAC revealed that data are available for technology subgroups only (Jakob et al, 2011) and are not available for the comparators. This is an area for future research.

Special considerations, including issues related to equality

Expert opinion was that connective tissue disease is a difficult area and that the Clinical Reference Group for Vascular Surgery has specifically excluded these patients from the commissioning of complex endovascular procedures. Endovascular procedures may therefore be the best treatment option in selected patients (for example those requiring repeat surgery) but these patients needed to be dealt with on a case-by-case basis due to the paucity of the data available.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

The search strategy provided by the sponsor for E-vita open plus was considered by the EAC to be adequately comprehensive at the time it was conducted. The search was verified by the EAC search. The sponsor's search located 18 papers of which 13 were considered relevant by the sponsor. A conference abstract was identified (Mestres et al 2012), which was a subset of the E-vita open registry dataset. This provided only one relevant outcome, in-hospital mortaility, and in addition the data largely overlapped with the Jakob et al (2011) paper so was not useable. The sponsor has not included any comparators in the search strategy as stated above in section 2.3. The EAC therefore conducted a systemic review of comparators. The details of this are described in section 3.8.

3.2 Critique of the sponsor's study selection

The sponsor has only included published studies from the E-vita open plus register on 274 patients in total. These are reported in the 2011 publication and relate to patients added between January 2005 and December 2010. There are therefore more data potentially available that are not reported on and these might have been included as an update to the published figures. Another two years' data would have provided useful information on approximately 90 new patients and would also have provided longer term follow up on those already in the register. These data were not available to the EAC and so could not be incorporated into the summary of clinical evidence.

3.3 Included and excluded studies

Table 1 provides a summary of all 13 included studies with their key findings. The EAC agreed with the sponsor's decision regarding inclusion and exclusion of each study described below with one query: the sponsor's excluded paper 'Management of postdissection thoracoabdominal aneurysm after previous frozen classical ET with the E-vita Open Plus stent-graft' ('PubMed – publication in process'), was not uncovered in the EAC's search and could not be found. While 13 papers were considered to be relevant, the sponsor only included evidence for the International E-vita Open Registry paper by Jakob et al (2011) in the summary of evidence. The EAC agrees with this decision since as the descriptions below and table 1 indicate, Jakob et al (2011) covers all the relevant published information.

All studies reported by the sponsor are descriptive and none had comparators (table 1). Jakob et al (2011) reports on the International E-vita Open Registry and provides data from January 2005 to December 2010. This includes 274 patients with complex aortic disease who were enrolled into the registry. The majority were male (74%) and mean age was 60 years. At the time of publication of this study, the registry included eight referral centres in Europe: Barcelona, Birmingham, Bologna, Essen, Graz, Leipzig, Prague, and Vienna. This is the most comprehensive paper as it includes the best quality evidence available (discussed below). A further set of publications were on a subset of the register population and include patients treated at: Essen (Jakob et al (2012), N=77; Jakob et al (2010), N=45), and six of the eight centres (Pacini et al (2011), N=90). The paper by Hoffman et al (2012) describes a cohort study in 32 subjects, who were predominantly male, mean age 58, who received E-vita open plus and were followed for 33 months. Gorlitzer et al (2012) had a very short follow up with only three eligible patients and so provided no robust useable data. Similarly, two further small papers from Gorlitzer et al (2007), in seven patients, and Tsagakis et al (2010c), in nine patients. Bartolomeo's two papers (2008a, 2008b) reported on cohorts of 34 and 24 patients from Italy and these were not included by the sponsor because their data was collected before the published registry paper (Jakob et al 2011). These might have been included but the EAC considers that as they were small, estimates of mortality are unreliable. Similarly, Herold's paper (2006) on a cohort of 30 patients that were excluded by the sponsor, might have been excluded but the EAC considers the data to be of limited usefulness Tsagakis (2010a, N=68), reported on five centres participating in the registry but the outcomes reported in this paper were not those specified in the scope of the present work and so provided no useable data. The sponsor included very limited comparator data (table 1b). There was no evidence that a systematic review had been conducted. The four comparator studies only described outcomes in patients who had undergone two-stage open surgical repair with vascular graft replacement. These studies were observational, and all were from the USA. They were all conducted between 1990 and 2006, therefore most of the evidence preceded the E-vita open plus registry. As described above and reported in detail below, the EAC conducted a systematic review on comparators and have conducted a thorough meta-analysis of outcomes.

Table 1: Summary of key points from sponsor-included E-Vita open plus studies

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Jakob et al., 2011 INCLUDED BY SPONSOR AS RELEVANT ****NOTE THIS STUDY ONLY WAS USED BY EAC FOR EVIDENCE**	The International E-vita Open Registry: data sets of 274 patients.	Jan 2005 to Dec 2010. Patients with complex aortic disease underwent arch replacement combined with open antegrade stent-grafting using the E-vita open hybrid stent-graft and have enrolled to the international E-vita Open Registry (IEOR).	E-vita open	International E-vita Open Registry (IEOR). 8 referral centres: Barcelona, Birmingham, Bologna, Essen, Graz, Leipzig, Prague, Vienna	Mean age= 60; 74% males	Multi-centre cohort study with up to 6 years follow-ups	n=274 (AAD=88, CAD=102, TAA=84)	• Multi-centre study using register data • No CIs for estimates • No comparator in paper • Numbers in some subgroups are very small • Any centre effect? • Large data set with data collected in uniform manner
Jakob et al., 2012 INCLUDED BY SPONSOR AS RELEVANT	Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance.	Jan 2005 to Mar 2011. Patients with complex thoracic aortic disease underwent arch replacement combined with antegrade stent grafting of the descending aorta using the E-vita open hybrid stent graft in West-German Heart Centre, University of Duisburg-Essen, Essen, Germany.	E-vita open	Essen, Germany	Mean age= 59; 75% males	Cohort study with up to 66 months follow-ups	n=77 (AAD=39, CAD=23, TAA=15)	• Single-centre study • Subset of the register • No CIs for estimates • No comparator

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Hoffman et al., 2012 INCLUDED BY SPONSOR AS RELEVANT	Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection.	Nov 2009 to Sep 2011. Patients with acute Stanford type A aortic dissection underwent the frozen elephant trunk procedure (E-vita open plus) for replacement of the aortic arch and stenting of the descending aorta, at University Hospital RWTH Aachen, Aachen, Germany.	E-vita open plus	Aachen, Germany	Mean age= 58; 81% males	Cohort study with up to 33 months follow-ups	n=32	• Singe-centre study • Short follow-ups • Descriptive statistics only • No comparator
Gorlitzer et al.,2012 INCLUDED BY SPONSOR AS RELEVANT	Repair of stent graft-induced retrograde type A aortic dissection using the E-vita open prosthesis	Aug 2005 to Feb 2011. Consecutive patients who underwent Thoracic endovascular aortic repair (E-vita open) for acute complicated aortic dissection type B, at Department of Cardiovascular Surgery, Hospital Hietzing, Vienna, Austria.	E-vita open	Vienna, Austria	Mean age= 58; 33% males	Retrospective cohort study with up to 14 days follow-ups.	n=3 (E-vita open was used)	• Single-centre study • Only 3 patients who used E-vita open • Very short follow-ups (<14 days)

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Pacini et al., 2011 INCLUDED BY SPONSOR AS RELEVANT	The Frozen Elephant Trunk for the Treatment of Chronic Dissection of the Thoracic Aorta: A Multicenter Experience	Jan 2005 to May 2010. Patients underwent complex repair of the thoracic aorta with the frozen elephant trunk (FET) technique and were enrolled in the International E-vita Open Registry.	E-vita open	International E-vita Open Registry. 6 European centres (Barcelona; Bologna; Essen; Birmingham; Hietzing-Vienna, and Leipzig).	Mean age=57; 80% males	Multi-centre cohort study with up to 5 years follow-ups	n=90	• Subset of the register data • No CIs for estimates • No comparator • Only univariate analysis for survival • Any centre effect?
Tsagakis et al., 2010a INCLUDED BY SPONSOR AS RELEVANT	Multicentre early experience with extended aortic repair in acute aortic dissection: is simultaneous descending stent grafting justified?	Jan 2005 to Jan 2010.Patients underwent surgery for acute aortic dissection using the E-vita open stent graft (Jotec GmbH, Hechingen, Germany) from the International E-vita Open Registry (5 European centres)	E-vita open	5 European centres (Barcelona, Spain; Bologna, Italy; Essen, Germany; Hietzing, Vienna, Austria; and Prague, Czech Republic).	Mean age=58; 77% males	Multi-centre cohort study. Mean Follow-ups: 23+/-17 months.	n=68	• Subset of the register data • No CIs for estimates • No comparator • Any centre effect?

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Jakob and Tsagakis, 2010 INCLUDED BY SPONSOR AS RELEVANT	DeBakey type I dissection: when hybrid stent-grafting is indicated?	Jan 2001 to Jan 2010. Patients underwent surgery of the thoracic aorta and received an E-vita open Hybrid stent-graft prosthesis implanted at Department of Thoracic and Cardiovascular Surgery, West German Heart Centre, University Hospital of Essen, Essen, Germany.	E-vita open	Essen, Germany	Mean age (AAD=29):60; 66% males. Mean age (CAD=16): 54; 100% males.	cohort study with up to 4 years follow-ups	n=45 (AAD=29; CAD=16)	• Single-centre study • Subset of the register data • No CIs for estimates • No comparator • Numbers in some subgroups are very small

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Tsagakis et al., 2010b INCLUDED BY SPONSOR AS RELEVANT	Arch replacement and downstream stent grafting in complex aortic dissection: first results of an international registry	Patients with complex aortic disease enrolled in the International E-vita Open Registry (IEOR) from Jan 2005 to March 2009. 106 operated on for aortic dissection (AD) and 22 for extended aortic aneurysm (EAA). Males: 82%,	E-vita open	Barcelona Spain, Bologna Italy, Essen Germany, Prague Czech Republic, Vienna Austria	Mean(SD): 57(13) years	Multicentre retrospective cohort; Follow up: 4 years 2 months	128 (AD: N=106, EAA: N=22)	• Outcomes not pre-specified in methods section • Aims of study are not clearly outlined. • No comparison group • Confidence intervals needed for rate of aortic-related death and actuarial survival rate • Standard deviations for mean time for CBP SACP , HCA and myocardial ischemia are needed • Outcomes were reported for patients operated for AD (n=106) but not for patients operated for EAA (n=22) • Subset of the register data • Variations between centres was not accounted for in the analysis
Tsagakis et al., 2010c INCLUDED BY SPONSOR AS RELEVANT	Impermeability to blood of the E-vita open plus hybrid stent-graft	Patients had single-stage thoracic aortic repair between Oct 2008 and Oct 2009. Six treated with DeBakey type I aortic dissection and 3 with extensive TAA. Males : 78% (N=7)	E-vita open plus	Germany	Mean(SD): 55(13)	Prospective cohort; Follow up time : 1 year	9	• No comparison group • Not clear why the section on the animal study has been included • Sample size is quite small so results are not conclusive • Eligibility criteria not stated

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Bartolomeo et al., 2008a	Treatment of complex disease of the thoracic aorta: the frozen elephant trunk technique with the E-vita open prosthesis.	Patients operated on consecutively between Jan 2007- July 2008 for complex pathologies of the thoracic aorta using the frozen elephant trunk technique. Data from Italian Society of Cardiac Surgery dataset. Males: 85.3%;	E-vita open	Italy	Mean (SD): 61.7(9.6)(Range : 35-78 years)	Prospective cohort; Follow up : 19 months	34	• No comparison group. • Results are purely descriptive. • Eligibility criteria not stated • Methods section does not include statistical procedures performed • Sample is small and no comparator so inferences on mortality rate(6%) with E-vita is inconclusive • Confidence intervals needed for mortality rate
Bartolomeo et al., 2008b	Complex repair of the thoracic aorta with the E-vita open prosthesis.	Patients operated on consecutively between Jan 2007- Jan 2008 for complex pathologies of the thoracic aorta using the frozen elephant trunk technique. Data from Italian Society of Cardiac Surgery dataset. Males: 87.5%	E-vita open	Italy	Mean(SD): 62.4(9.9) (Range: 37-74 years)	Prospective cohort; Follow up: 1 year	24	• No comparison group • No details of stats for patient follow up time • Methods section does not include statistical procedures performed • Study outcomes were not clearly defined • Typo error in abstract: 'None' patient had postoperative stroke'. Is this 1 or none? • Mortality rate needs confidence interval • No detailed table of patients' characteristics at baseline

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size	Comments
Gorlitzer et al., 2007	Combined surgical and endovascular repair of complex aortic pathologies with a new hybrid prosthesis	Patients with aortic pathologies (5 dissections and 2 aneurysms) monitored by computed tomography angiography and had replacement of the ascending aortic arch and simultaneous implantation of a stent graft into the descending aorta between August 2005 and December 2006. Males: 71%(n=5)	E-vita open	Austria	Median (SD): 62(10.8) years(range: 40-74 years)	Prospective cohort; Follow up: 16 months	7	• No comparison group • Mean (SD) follow up time: 11(3.8) months, range: 8-16 months • No table showing detailed characteristics of patients at baseline
Herold et al., 2006	Change of paradigms in the surgical treatment of complex thoracic aortic disease	June 2001 – March 2006	E-vita open	Germany	Mean(SD): 60.5(12)	cohort	30	• Descriptive data only

AAD: Acute aortic dissection, CAD: Chronic aortic dissection, TAA: Thoracic aortic aneurysm, AD: aortic dissection, EAA: Extended aortic aneurysm, SD: Standard deviation, CI: Confidence interval, CPB: Cardiopulmonary bypass, SACP: Selective antegrade cerebral perfusion, HCA: Hypothermic circulatory arrest.

Table 1b **Summary of key points from sponsor-reported comparator studies**

Reference	Study	Patient population	Intervention	Country	Age	Study design	Sample size
Etz et al 2008	Staged repair of thoracic and thoraco-abdominal aortic aneurisms	Consecutive patients who underwent total arch replacement February 1990 to September 2006	Two-stage open surgical repair with vascular graft replacement	USA	Median 68yrs Range: 20 to 87 59% male	Observational study	215
Svensson et al 2004	Elephant trunk procedure: newer indications and uses	Consecutive patients who underwent total arch replacement November 1990 to February2003	Two-stage open surgical repair with vascular graft replacement	USA	Mean 67 (SD 10.5) yrs 47% male	Retrospective observational	94
Safi et al 2001	Staged repair of extensive aortic aneurysms	Patients who underwent total arch replacement February 1991 to December 2003	Two-stage open surgical repair with vascular graft replacement	USA	16-57yrs: 23% 58-66yrs: 25% 67-73yrs: 26% 73-81yrs: 26% 54% male	Observational study	218
LeMaire et al 2006	The elephant trunk technique for staged repair of complex aneurysms of the entire thoracic aorta	Consecutive patients with e extensive aneurysms 1990 to 2005	Two-stage open surgical repair with vascular graft replacement	USA	Mean 66yrs (SD10.3) 48% male	Observational study	205

3.4 Overview of methodologies of all included studies

The studies are all observational, single group studies that have followed up patients who have received E-vita open plus or its comparators. There are no studies that include a direct comparison of E-vita open plus with a comparator. The statistical analyses are descriptive and typically include the presentation of proportions of patients who experienced a particular event or adverse effect. In addition, survival analysis was performed in some studies to provide the probabilities of longer-term survival. However, almost all results in the published papers are given without confidence intervals, which make the proportions very difficult to interpret since they are inevitably based on small numbers. For example the proportion 8/77 quoted in Jakob 2012 is 10% but has a 95% confidence interval that spans 5.4 to 19.2%. This is wide and shows that there is a lot of uncertainty about the true value. In addition, many papers did not state the aims of the study at the outset, nor state the outcomes to be reported. Details of patient characteristics were generally poorly reported which makes it harder to interpret or generalise the findings with confidence.

3.5 Overview and critique of the sponsor's critical appraisal

The critical appraisal reported by the sponsor was very limited with answers to questions in a tick box format and no discussion of the strengths or weaknesses of the studies. For many of the questions, such as 'was the cohort recruited in an acceptable way', the response was 'not clear' suggesting that the evidence reported was of questionable quality. This relates to patient characteristics, outcome measurement, confounding, loss to follow-up, statistical analysis and presentation of results. The critique while highlighting some omissions in papers, does not discuss the importance and consequences of these problems. In its review of the papers the EAC has highlighted the strengths and weaknesses and described the consequences of these. The summary given by the EAC lists the main shortcomings, principally the observational nature of the studies, the lack of detail about patient groups, differences and similarities between centres, and the lack of presentation of measures of precison for estimates. Therefore data have been presented without clear consideration of the strengths and weakness of the underlying studies and so the interpretation is difficult.

We give specific comments on the sponsor's comparison of different options for surgical treatment of complex thoracic aortic aneurysm (sponsor submission table 14), below:

- A summary of outcomes (mortality, 5-year survival, and complications) reported for the comparators (Etz et al., 2008; Safi et al., 2007; Lemaire et al., 2006; Svensson et al., 2004) included in the sponsor's submission using classical elephant trunk procedure have been compared with outcomes on E-vita open plus procedure using only data from study by Jakob et al., 2011. It is not very clear why summary data of the other papers included in the review (Jakob et al., 2012; Hoffman et al., 2012) were not included.
- The time period for three of the comparators included in the sponsor's submission (Etz et al., 2008; Safi et al., 2007; Svensson et al., 2004) ranged from 1990-2006 while that of the studies included in the sponsor's submission on evidence for E-vita open plus procedure ranged from 2005-2011.
- The studies included in the E-vita open plus review were carried out in European countries while all the comparators (Etz et al., 2008; Safi et al., 2007; Lemaire et al., 2006; Svensson et al., 2004) were based in the US.
- The sponsors did not compare the baseline characteristics for the patients in the included studies for E-vita open plus (Jakob et al.,2012; Jakob et al.,2011; Hoffman et al., 2012) with those in the studies on the comparators (Etz et al., 2008; Safi et al., 2007; Lemaire et al., 2006; Svensson et al., 2004).
  Tables 1 and 1b show that the mean age was 60 for the patients included in the E-vita open plus registry and 74% were male. This compares to a very slightly higher mean age in the comparator studies: around 67 (table 1b), with around 48% male.
- Detailed baseline characteristics were not reported (Safi et al., 2007).
- Percentage of patients with post-operative paraplegia (Safi et al., 2007) should be 0.9% and not 9%.
- Reference section 7.6.2 of the sponsor's submission: It is not clear how summary mortality rate (31.2%) was calculated for the comparators (Etz et al., 2008; Safi et al., 2007; Lemaire et al., 2006; Svensson et al., 2004).

3.6 Results

In table 2, the EAC provides a summary of the outcomes reported in Jakob 2011 as cited by the sponsor. As discussed earlier in section 3.3, the EAC considers that this paper provides a comprehensive summary of the data available. Jakob 2012 provides some additional patients as it spans a longer time but since there is considerable overlap in the patients included with Jakob 2011, these data could not be included for any outcome. Hoffman 2012 as described above in section 3.3 is small and contains limited outcome data as the follow-up was short. For this reason this study is not useable. Hence table 2 contains only one study which provides the totality of outcome data for E-vita open plus.

One potential problem with the registry data is that it relates to E-vita open rather than E-vita open plus. The main difference between the 'open' and the 'open plus' devices is that the open plus fabric is impermeable to blood, whereas with the open device pre sealing the device with fibrin glue was required. It is difficult to know exactly how this will affect the performance of the device, as presumably if the open device was adequately pre-sealed with fibrin glue then they should have approximately the same performance.

The outcome data in Jakob 2011 were presented without confidence intervals and so the precision of the estimates is not apparent. In-hospital mortality, the main outcome, is 15% (40/274). The exact binomial 95% confidence interval calculated by the EAC is 10.6 to 19.3% which is quite wide and provides a better base from which to interpret the (understandable) uncertainty in these data. Thirty day mortality was 12% (33/274). Five-year survival was 74% and no confidence interval was given. This cannot be calculated without the individual patient data so the uncertainty around this estimate is unknown, making interpretation less straightforward. The EAC noted that the confidence interval are very likely to be wide as the Kaplan –Meier plots in the Jakob (2011) paper show that only 7 patients were followed for the full five years.

Table 2: Summary of outcomes from studies

Reference	Study	Outcome 1 mortality	Outcome 2 Adverse Outcomes	Outcome 3 Survival	Outcome 4 Other outcomes	Outcome 5
Jakob et al., 2011	The international E-vita Open Registry: data sets of 274 patients.	In-hospital mortality: 15% (40/274) (18% for AAD, 13% for CAD, 14% for TAA). 30-day mortality: 12% (33/274) 81 out of 274 (30%) patients underwent emergency surgery.	Emergency surgery: 30% (81/274) Stroke: 6% (16/274) Spinal cord injury: 8% (22/274) Renal failure: 4% (10/274) Bleeding: 14% (38/274)	5-year survival: 74% Freedom from secondary endovascular intervention and secondary surgery distally: 82% and 95%, respectively	Incidence of secondary endovascular intervention or surgery downstream among survivors (233/274): 13% (29/233), 3% (6/233), respectively. Full exclusion of the aneurysmal disease during primary hospital stay: 77% (61/79) From the first follow up CT-examination to the last, thoracic complete FL thrombosis increased from 83% to 93% in AAD, from 72% to 92% in CAD	

AAD: Acute aortic dissection, CAD: Chronic aortic dissection, TAA: Thoracic aortic aneurysm, AD: aortic dissection, EAA: Extended aortic aneurysm

The paper that was therefore used for the main outcomes and thus used to populate the economic model was Jakob et al (2011). The paper has some omissions, namely: technical procedure success, incidence of junctional endoleak, and length of intensive care unit stay.

Comparators, as discussed previously, are not covered in sufficient detail and so the EAC has conducted a systematic review and meta-analysis (reported below).

It is noted that there are no head to head trials comparing E-vita open plus with any comparator. Further, there is heterogeneity among the comparator studies. Given these caveats, an indirect comparison will be made, but we note that clinical expert advice has cautioned that the comparison of results from cohort series from different centres is potentially problematic as it will include different patient groups, surgeons and post-operative care regimes.

3.7 Description of the adverse events reported by the sponsor

The EAC believe that the adverse events rates reported by the sponsor, namely bleeding (14%), stroke (6%), paraplegia (8%) and renal failure (4%) are as expected and therefore do not raise any safety concerns for the technology being evaluated.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

No meta-analysis was carried out. The data have been described and ranges of values for outcomes have been taken directly from papers without any consideration of precision or study quality. Further, no consideration has been given to the precision of estimates presented, with event rates given as percentages of whole numbers and no confidence intervals (CIs). The EAC was able to calculate 95% CIs for the proportions as the raw data were given. However, CIs could not be calculated for the survival estimates without access to the individual patients' data, which we do not have.

In addition there are some minor inconsistencies in the sponsor's submission tables 4 and 5, namely: emergency surgery total should be 86 not 81, and the total for re-exploration for bleeding should be 63 not 38.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

Registry data

The EAC contacted the E-vita Open Registry team to ascertain more details about the register in order to form an opinion about the data quantity and quality. A teleconference took place on 17th May 2013 with the E-vita Open Registry team which revealed that there have been changes since the Jakob et al (2011) paper on the International E-vita Open Registry paper. There are now 11 participating centres, an increase on the original eight, now with 470 patients, an increase from the 274 published in 2011 (Jakob 2011). The registry data was not available to the EAC and so we cannot say with certainty whether or not the clinical conclousions would be different. However, the longer follow-up time together with the greater numbers of patients included would naturally provide more precise estimates of all outcomes.

The EAC ascertained that the registry collects data for patients with aortic dissection or aneurysm for the preoperative, intraoperative, postoperative and follow up stages. Safety data were collected at the various stages. Patients are followed up in six monthly intervals for two years and then annually for three years, and this mandatory for all centres. At the teleconference the EAC team were told that the registry had follow up data for about 70 to 80% of patients. The registry is coordinated at the University Hospital Essen (West German Heart Center) and there is regular cooperation and feedback between the participating clinics for data validity. Furthermore, all follow up is carried out under the supervision of the attending surgeon. At the teleconference the evaluation team were told that there was no standard procedure for surgery but that the outcomes did not differ with the different procedures.

The EAC considered that the registry data was robust as far as could be discerned without more information.

POSTSCRIPT: the E-vita open registry sent their 26-page data collection manual on 2 June 2013. This was received as this report was close to press and so a thorough review and interaction with the senders to ask further questions was not possible, but review shows the document to be detailed and so supports the quality of the data from the registry. No actual registry data has been made available to the EAC and so no further comment on the registry is possible at this point in time.

Systematic review of comparators

The EAC conducted a systematic review and meta-analysis of comparators as these were not included in the sponsor's submission. The review included aneurysms

(aortic/aortic thoracic degenerative, dissecting aneurysm), dissection (chronic/acute type A) with two-stage vascular graft using classical elephant trunk procedure, two-stage with endovascular stent graft, and open debranching with endoluminal stent graft. The following outcomes were included: mortality/hospital mortatlity, survival, stroke, bleeding, paraplegia, renal failure. Studies not including these outcomes and case reports were excluded. The search terms and strategy are provided in the Appendix 1. The review of comparators found 1929 abstracts, which were screened and finally resulted in ten relevant studies (Etz et al 2008,Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004, Kim et al 2009, Kawaharada et al 2009, Lee et al 2011, Antoniou et al 2010a, Antoniou et al 2010b), which also included five studies cited by the sponsor (Etz et al 2008,Safi et al 2007, LeMaire et al 2006,Svensson et al 2004, Safi et al 2004).The full texts were retrieved and assessed for relevance to this decision problem. All studies were observational. No explicit assessment of quality was undertaken. The five studies cited by the sponsor plus five newly identified papers (one was a systematic review (Antoniou 2010a) were subject to detailed review and meta-analysis. The inclusion of the five extra papers uncovered by the EAC filled the gaps for the three other comparators not included in the sponsor's submission, namely: two-stage repair with endovascular stent graft placement, open surgical 'debranching' with endoluminal stent graft placement (hybrid procedure) and open surgical 'debranching' with endoluminal stent graft placement (two-stage procedure). Table 3a provides a summary of the patient characteristics for the reviewed studies and includeds the Jakob (2011) paper for comparison. This shows that the age distribution varied somewhat among studies from a mean of 60 to a mean of 70. Not all studies gave a clear description of patient characheristics as table 3a shows. For example Safi (2004) did not report age data for stage one, stating that 77.1% were aged 58+. Most studies had a higher proportion of males with the overall proportions ranging from 47% to 79%. Outcome data by subgroups were available for the E-vita open registry paper (Jakob 2011) but not for for the comparator papers (table 3b).

Table 3a summary characteristics of ten studies included in EAC meta-analysis

Paper/Reference	Study size and period.	Overall age and gender.

Jakob, H., et al. (2011). "The International E-vita open Registry: Data sets of 274 patients."	274 patients. Jan 2005 to Dec 2010.	Mean (SD) age 60(12). 74% males.
Safi, H. J., et al. (2004). "Staged repair of extensive aortic aneurysms: long-term experience with the elephant trunk technique.".	Stage One 218 patients. Stage Two 103 patients. Feb 1991 to Dec 2003.	Stage one: No mean/median values given. 77% aged 58+. 54% males.
LeMaire, S. A., et al. (2006). "The elephant trunk technique for staged repair of complex aneurysms of the entire thoracic aorta."	205 patients. 15 ½ year period. From 1983 onwards?	Mean (SD) 66 (10). 48% males.
Svensson, L. G., et al. (2004). "Elephant trunk procedure: newer indications and uses."	94 patients. Nov 1990 and Feb 2003.	Mean (SD) 67 (11). 47% males.
Antoniou, G. A., et al. (2010a). "Hybrid treatment of complex aortic arch disease with supra-aortic debranching and endovascular stent graft repair."	Systemic review resulting in analysing 11 published studies. 195 patients. Study size range (n=6 to 27). 2004-2009.	Range of mean age (65 to 74 years). 60% to 87% males.
Antoniou, G. A., et al. (2010b). "Hybrid repair of the aortic arch in patients with extensive aortic disease."	33 patients. Aug 2003 to Dec 2009.	Total hybrid procedure: Mean age 63 (range, 31-87). 79% males.
Kawaharada, N., et al. (2009). "Hybrid treatment for aortic arch and proximal descending thoracic aneurysm: experience with stent grafting for second-stage elephant trunk repair."	31 patients. Feb 2001 to Jun 2008.	Mean age 70 (range, 39-83, SD 9). 77% males.
Safi, H. J., et al. (2007). "Optimization of aortic arch replacement: two-stage approach.".	2120 patients. Feb 1991 to Dec 2005.	Mean age 68 (range, 16 to 87). 51% males.
Lee, C. W., et al. (2011). "Arch debranching versus elephant trunk procedures for hybrid repair of thoracic aortic pathologies."	58 patients. 2005 to 2009.	Mean (SD) for elephant trunk 68 (14). 62% males.
Kim, T., et al. (2009). "Evolution in the management of the total thoracic aorta."	103 patients. 1992-2007.	Total mean (SD): age 65 (13). 45% males.

Etz, C. D., et al. (2008). "Staged repair of thoracic and thoracoabdominal aortic aneurysms using the elephant trunk technique: a consecutive series of 215 first stage and 120 complete repairs."	215 patients. 1990 to 2006.	Overall: Median age 68 (range, 20-87). 59% males.

Methods for meta-analysis

The included studies were reviewed and outcome data were extracted (Table 3b). Where only a single estimate was available, the proportion with the event plus an exact 95% binomial confidence interval was calculated. Where there were two or more estimates available for an outcome, meta-analysis was used to provide a pooled estimate with its 95% confidence interval.

Conventional meta-analyses of proportions assume that the proportions follow a Normal distribution when calculating the 95% confidence interval but this is not so with very small proportions and/or small numbers. To overcome this difficulty, the logit transform of each proportion, log{p/(1-p)} was used in the meta-analysis as a normalising transformation. Results have been back-transformed to the natural scale for presentation. A test of statistical heterogeneity was performed for each meta-analysis and where the p value was less than 0.10, a random effects model was fitted. Otherwise, a fixed effects estimate was obtained. All meta-analyses were conducted using the Metan procedure in Stata v 11.0.

The meta-analysis provided estimates with 95% CIs for in-hospital mortality, 30-day mortality, bleeding, stroke, paraplegia, and renal failure for the comparators. In all, 30 additional comparator pooled outcome estimates were calculated. For the E-vita open plus, all estimates are now reported with 95% CIs (Table 4). It was not possible to conduct any analyses on the survival rates because they are given without any measure of precision.

Table 3b Summary of outcome data for meta-analysis

Table 1 - Summary outcomes from Included Studies								
References	**Hospital Stay(Median days)**	**In-hospital Mortality**	**30 Days Mortality**	**Bleeding**	**Stroke**	**Paraplegia**	**Renal Failure**	**5 Yr Survival Rate**
E-vita Open Plus								
Jakob et al,2011	All- 19	All- 41/274(15%)	All-33/274(12%)	All- 38/274(14%)	All-16/274(6%)	All-22/274(8%)	All-10/274(4%)	
	AAD-23	AAD-16/88(18%)	AAD-11/88(13%)	AAD-16/88(18%)	AAD-5/88(6%)	AAD-5/88(6%)	AAD-1/88(1%)	74%
	CAD- 17	CAD-13/102(13%)	CAD-10/102(10%)	CAD-13/102(13%)	CAD-3/102(3%)	CAD-8/102(8%)	CAD-4/102(4%)	
	TAA-18	TAA-12/84(14%)	TAA-12/84(14%)	TAA-9/84(11%)	TAA-8/84(10%)	TAA-9/84(11%)	TAA-5/84(6%)	
Two stage open surgical repair with vascular graft placement								
Etz et al 2008		Stage 1- 9/139(6.5%)		Stage 1-7/139(5%)	Stage 1-4/139(3%)		Stage 1-4/139(3%)	55%
		Stage 2-9/120(7.5%)		Stage 2-1/120(0.8%)	Stage 2-1/120(0.8%)	Stage 2-2/120(1.6%)	Stage 2-2/120(1.6%)	
Safi et al 2007	Stage 1-16,6(ICU)	Stage 1-16/254(6.3%)			Stage 1-5/254(2%)			
	Stage 2-15,4(ICU)	Stage 2-11/115(9.6%)				Stage 2-1/115(0.9%)		
LeMaire et al 2006		Stage 1-18/148(12%)	Stage 1-11/148(7%)	Stage 1-5/148(3%)	Stage 1-7/148(5%)		Stage 1-14/148(9%)	70%
		Stage 2-3/76(4%)	Stage 2-2/76(3%)	Stage 2-3/76(4%)	Stage 2-2/76(3%)	Stage 2-2/76(3%)	Stage 2-3/76(4%)	
Svensson et al 2004		Stage 2-4/47(8.5%)	Stage 1-2/94(2%)		Stage 1-5/94(5.3%)			75%
						Stage 2-2/47(4%)		
Safi et al 2004			Stage 1-19/218(8.7%)		Stage 1-3/218(2.7%)			71%
			Stage 2-10/103(9.7%)					
Kim et al 2009*	Stage 1-12.5	Stage 1-5/50(10%)		Stage 1-3/50(6%)	Stage 1-3/50(6%)		Stage 1-9/50(18%)	
	Stage 2-17	Stage 2-2/20(10%)		Stage 2-1/20(5%)	Stage 2-2/20(10%)	Stage 2-3/20(15%)	Stage 2-5/20(25%)	
Two stage repair with endovascular stent graft placement								
Kawaharada et al 2009		Stage 2- 2/31(6.4)	Stage 2- 1/31(3.2)		Stage 1- 1/31(3.2)	Stage 2- 2/31(6.4)		73%
Kim et al 2009*	Stage 1-15.5	Stage 1-2/24(8%)		Stage 1-1/24(4%)	Stage 1-1/24(4%)	Stage 1-1/24(4%)	Stage 1-3/24(13%)	
	Stage 2-6	Stage 2-2/18(11%)		Stage 2-1/18(6%)		Stage 2-1/18(6%)		
Lee et al 2011*	Stage 1-18	Stage 1-2/21(9.5%)			Stage 1-2/21(9.5%),			
	Stage 2-8	Stage 2-2/16(12.5%)						
Open surgical 'debranching' with endoluminal stent graft placement(Hybrid Procedure)								
Antoniou et al 2010a		18/195(9%)	11/169(7%)		14/195(7%)	1/195(0.5%)		
Antoniou et al 2010b			7/33(21%)		4/33(12%)	2/33(6%)	6/33(18%)	
Open surgical 'debranching' with endoluminal stent graft placement(2 Stage procedure)								
Lee et al 2011*	Stage 1-14	Stage 1-5/37(13.5%)		Stage 1-3/37(8%)	Stage 1-3/37(8.1%)			
	Stage 2-6	Stage 2-1/27(3.7%)			Stage 2-1/27(3.7%)			
* Comparative studies								

Table 4 Pooled estimates with 95% confidence interval for the proportion of patients experiencing key outcomes for E-VITA and its comparators

		E-vita Open plus	2-stage open surgical repair with vascular graft placement	2-stage repair with endovascular stent graft placement	Open surgical 'debranching' with endoluminal stent graft placement (Hybrid Procedure)	Open surgical 'debranching' with endoluminal stent graft placement (2 Stage procedure)
In-hospital Mortality	**Stage 1**	15.0%(11.0-19.7%)	8.5%(6.4-11.1%)	8.9%(3.4-21.4%)	9.2%(5.6-14.2%)	13.5%(4.5-28.8%)
	Stage 2		8.0%(5.6-11.2%)	9.6%(4.4-19.8%)		3.7%(0.1-19.0%)
30 Days Mortality	**Stage 1**	12.0%(8.4-16.5%)	7.5%(5.4-10.5%)		11.7%(3.4-33.3%)	
	Stage 2		5.9%(1.6-19.0%)	3.2%(0.08-16.7%)		
Bleeding	**Stage 1**	13.9%(10.0-18.5%)	4.6%(2.8-7.4%)	4.2%(0.1-21.1%)		8.1%(1.7-21.9%)
	Stage 2		3.7%(1.7-7.8%)	5.6%(0.1-27.3%)		
Stroke	**Stage 1**	5.8%(3.4-9.3%)	3.4%(2.3-4.9%)	7.4%(3.3-16.1%)	8.0%(5.1-12.4%)	8.1%(1.7-21.9%)
	Stage 2		3.9%(1.1-13.0%)			3.7%(0.1-19.0%)
Paraplegia	**Stage 1**	8.0%(5.1- 11.9%)		4.2%(0.1-21.1%)	2.5%(0.3-20.3%)	
	Stage 2		4.1%(1.6-9.8%)	7.8%(3.0-19.1%)		
Renal Failure	**Stage 1**	3.6%(1.8-6.6%)	8.5%(3.4-19.6%)	12.5%(2.7-32.4%)	18.2%(7.0-35.5%)	
	Stage 2		6.0%(1.1-27.6%)			

3.10 Conclusions on the clinical evidence

The EAC considered that most of the available evidence for E-vita open plus was included by the sponsor. The paper by Jakob et al 2011 was a comprehensive paper based on the International E-vita Open Registry. All other studies were either based on subsets of the registry data or included very small numbers of patients. The EAC considered that the evidence provided from the paper by Jakob et al 2011 is comprehensive and is appropriate for use as the main evidence for E-vita open plus.

The meta analysis of the two-stage comparators carried out by the EAC filled the gaps in the evidence base by providing 30 additional pooled outcome estimates with 95% confidence intervals. These have used outcome data for the two-stages separately for two reasons: first these were the parameters required for the economic modelling. Second estimates of 'total surgery mortality' or 'treatment mortality' are provided in some papers but the EAC was unable to reproduce all of the calculations, presumably because there is uncertainty/ambiguity about which patients went forward to stage two and what happended to those who did not. For example Etz (2008) table 6 gives treatment mortality across several studies but the EAC was unable to repeat the calculation for LeMaire (2006) and Safi (2004). For these reasons direct comparsion of outcomes for E-vita open plus and its comparators from the outcome data in table 4 is difficult. As an example, bleeding looks more common for E-vita open plus than the comparators but this simple comparision does not take account of survival from stage one to two or offset the risk of bleeding against death. Added to this, direct comparisions of outcome rates are potentially confounded by differences between the patients groups, surgeons, settings etc. Hence the economic modelling which provides a synthesis of outcomes is able to account for different scenarios and provide a more reliable comparsion of outcomes.

Long-term survival could not be incorporated into the clinical review because the data provided did not include any measures of precision as discussed in section 3.6. Unlike with simple proportions, survival estimates are calculated using a life table approach and so confidence intervals cannot be calculated from the proportions and totals alone, the individual patient data are needed. Hence this outcome could not be reliably explored further than simply reporting survival proportions.

4 Economic evidence

4.1 Published economic evidence

Critique of the sponsor's search strategy

The sponsor reports that 'health economics studies are not known and certainly would not have been widely carried out prior to the analysis reported here for this new and innovative product'. However, the sponsor has not made clear whether this conclusion was reached based on the search strategy provided. Further, no conclusions on the economic evidence related to the comparator are reported. The search strategy document provided separately (included in the correspondence table) has the following issues:

- The purpose of the search is not specified– was it to answer section 8 (economic evidence) or section 9.3 (resource identification, measurement and valuation)?

- The date of search strategy is between August 3rd and September 15th 2012. This means the search was performed well before the scope was issued and needs updating.

- Databases included in the search are not specified in the submission. Following a query raised by the EAC regarding the databases included, the sponsor clarified that Embase and Cochrane Database of Systematic Reviews were the databases included.

The EAC felt that the search strategy and databases included could be improved. The EAC undertook a new search for economic evidence related to the technology and comparators. The search was conducted on Medline, Embase, Medline(R), ECONLIT, NHS EED and HTA databases and was limited to the time period 1990 - 2013. The detailed search strategies are included in Appendix 1. Briefly, the search strategy included the following:

(((((Aortic Aneurysm) OR (Thoracic Aorta) OR (Thoracic Aortic Aneurysm) OR (Degenerative Aneurysm) OR (Dissecting Aneurysm)) OR ((chronic type A dissection) OR (acute type A dissection) OR (Dissecting Aneurysm)))))

AND

((E-vita open) or (hybrid stent graft$)) OR ((elephant trunk) OR (elephant trunk procedure) OR (elephant trunk technique)) OR ((aortic arch replacement) OR

(thoracic stent graft) OR ((open stent graft$) or (open surgical debranch$) or (branched graft$)) OR ((endovascular stent graft$) or (endovascular stent)))

AND

(cost$ OR economic$)

The search returned no results for the technology (E-vita open plus) but returned 47 abstracts, which were reviewed and 3 full texts were retrieved. However, the 3 studies that were found did not specifically relate to aneurysms or dissections of the thoracic aorta involving the ascending aorta, arch and descending aorta, and were excluded. Thus the EAC concludes that there is no published economic evidence related to the technology and comparators.

Critique of the sponsor's study selection

Not applicable as the sponsor has not included any economic studies. The new searches that were conducted by the EAC also did not find any further economic evidence.

Included and excluded studies

Not applicable as the sponsor has not included any economic studies. The new searches that were conducted by the EAC also did not find any economic evidence.

Overview of methodologies of all included economic studies

Not applicable as the sponsor has not included any economic studies. The new searches conducted by the EAC also did not find any economic evidence.

Overview and critique of the sponsor's critical appraisal for each study

Not applicable as the sponsor has not included any economic studies. The new searches conducted by the EAC also did not find any economic evidence.

Does the sponsor's review of economic evidence draw conclusions from the data available?

Not applicable as the sponsor has not included any economic studies. The new searches conducted by the EAC also did not find any economic evidence.

4.2 De novo cost analysis

The sponsor has submitted a short term cost model, but has used different adoption rates for the technology and comparators. In a cost consequence analysis, it is better

to present the per patient cost model based on probabilities of clinical outcome measures. The model presented has 4 comparators compared to the technology. However, the modelling approach has some issues to be addressed before results can be used to draw firm conclusions. The following sections provide some of the critical issues to be addressed.

Patients

The patient group used in the cost analysis includes those with aneurysms, dissections and specific lesions of the thoracic aorta. The scope had specifically stated the patient group of interest is those with aneurysms or dissections of the thoracic aorta involving the ascending aorta, arch and descending aorta (Stanford Type A). From the sponsor's description it is not clear whether the cost analysis refers broadly to all aneurysms, dissections and specific lesions of the thoracic aorta. Given that E-vita open plus is used in patients with aneurysms or dissections of the thoracic aorta involving the ascending aorta, arch and descending aorta, the sponsor's description of the patient group could have been more specific. Further, the sponsor in their cost model assumes that there are around 3500 patients with aortic arch problems, who could benefit from the technology. However, this number could be an overestimate since experts foresee (see scope page 3) that only 50-100 people per year in England would be suitable for treatment with E-vita open plus.

Technology & Comparator(s)

The technology included by the sponsor for the cost analysis is E-vita open plus. The comparators include a 2-stage procedure called the 'elephant trunk procedure'. The ascending aorta and arch are repaired by a median sternotomy during the first stage. The descending aorta is replaced by either a woven graft or by an endovascular stent during the second stage. Further, in the decision tree, there are two options for the first stage, namely 'woven graft' and 'branched graft'. The sponsor has not defined the comparators in relation to those listed in the scope and this makes it difficult to understand which appropriate comparator listed in the scope (that is: two-stage open surgical repair with vascular graft placement, or two-stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta, or open surgical 'debranching' of the head and neck vessels with endoluminal stent graft placement in the aortic arch and descending aorta) they are applicable to. The EAC clarified this with the sponsor, and

they have confirmed the comparators to be used in the economic analysis are as follows:

- Two-stage open surgical repair with vascular graft placement –This is the Woven Graft (in Col 1) followed by a further Woven Graft (Col. 3).

- Two-stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta –This is the Woven Graft (in Col. 1) followed by Stent Graft at second stage (Col.3).

- Open surgical 'debranching' of the head and neck vessels with endoluminal stent graft - placement in the aortic arch and descending aorta - This is the Branched Graft (in Col. 1) followed by Woven or Stent Graft at second stage (Col.3).

In which case, it is assumed that the 'woven graft' refers to 2-stageopen surgical repair and 'debranched graft' refers to open surgical 'debranching' of the head and neck vessels with endoluminal stent graft placement in the aortic arch. The descending aorta is replaced by a woven graft or by an endovascular stent. Thus the total number of comparators included in the cost analysis is four.

Model structure

The sponsor provided a decision tree model from the NHS and personal social services perspective, for estimating the cost for E-Vita open plus along with the comparators ('woven graft' and 'branched graft' during first stage followed by 'woven graft' or 'endovascular stent' during the second stage). If this is so, the sponsor has included all the comparators and interventions listed in the scope, in the costing model. The structure of the model includes mortality at the completion of the procedure, using a cohort approach. It is estimated that there would be 3500 patients every year with aortic arch problems, and there would be a 40% adoption for E-vita open plus. The remaining 60% would either receive a 'woven graft' (15%) or a 'branched graft' (85%). The basis of the estimation of 3500 patients every year is not clear from the materials submitted by the sponsor. The sources for this estimation listed are HES (2011), Bavaria et al (2007), Clouse et al (2004), NICE (2005). Bavaria et al (2007) and Clouse et al (2004) are US-based estimates and might not

be appropriate for the UK context. HES (2011) is referred to as 'Health Economics Statistics at L27.3', which should have been 'Hospital Episode Statistics' (this was later rectified by the sponsor). We investigated the code L27.3 in the Hospital Episode Statistics for England Inpatient statistics, 2011-12, and found the number of admissions was only 183. Expert estimates (see scope page 3) that 50-100 people per year in England would be suitable for treatment with E-vita open plus thus seems reasonable. Thus the population size of 3500 considered for the cost model is an overestimation. The decision model does not have to take a cohort approach, but should use probabilities to estimate per person/treatment costs associated with the technology and each comparator.

The decision arm for E-vita open plus models in-hospital and 30 day mortality at 15% and assumes the remaining 85% to have a positive outcome. This may not be appropriate, as patients could have major complications such as stroke, paraplegia and renal failure. The cost model needs to incorporate these complications as they will have cost implications, particularly in the longer term. The decision arm for the comparators also models only those suitable for stage 2 procedure, but has not incorporated complications like stroke, paraplegia and renal failures during stage 1. There is thus a need for additional work to substantially revise the cost models.

Clinical parameters and variables

The sponsor has undertaken a bottom-up approach for costing the technology and comparators. Since there are differences in operating times and ICU stay, it is reasonable to have undertaken a bottom-up costing approach. The important data source for cost includes the annual Personal Social Services Research Unit (PSSRU) unit cost compendium, NHS Reference Costs and other literature. The cost of the stents has been sourced from current suppliers and the cost of E-vita open plus is the company's target price.

Mortality rates with E-vita open plus and the comparators are based on the studies identified in the clinical section. Mortality rates (15%) for E-vita open plus were based on the International E-vita Open Registry publication (Jakob et al, 2011),and is reasonable. It is not clear which of the papers on comparators were used, since the sponsor mentions that "4 references in Jakob et al (2011) review paper, Fann & Miller(1995),Safi et al. (2004) and LeMaire et al. (2006) also". The mortality rates for stage 1 for the comparators are not modelled. Only stage 2 mortality rates of 20%(woven graft option) and 30%(branched graft option) are assumed. From the

presentation of the clinical evidence from the sponsor, it is difficult to ascertain the basis of the assumption on stage 2 mortality rates. The time horizon of the economic model is one year. This is quite reasonable given that most of the literature reports short term outcomes, and the second stage surgery is expected to be completed in 6 months' time for the majority of the cases (Etz et al. 2008, Safi et al. 2007, Svensson et al. 2004, LeMaire et al. 2006). The sponsor did not include any long term outcomes, citing limited information on long term mortality rates for E-vita open plus and the comparators. However, most of the papers included by the sponsor report 5 years survival rates and the sponsor has included a table on the 5 years survival rates in the clinical evidence submitted. The reason cited for not including a long term model is not reasonable. However, 5 year survival rates from studies identified from the new systematic review done by the EAC reveals that 5 years survival rates for the 2-stagerepair ranges from 70-75% (Kawaharada, et al. 2009, Safi et al. 2004, Svensson et al. 2004, LeMaire et al. 2006) and is comparable to 74% for E-vita open (Jakob et al, 2011). This creates a much stronger case for not including a long term modelling of costs if only mortality is considered, as done by the sponsor. However, the short term model does not include complications occurring as a result of the surgery. This needs to be incorporated into the cost models. Once the complications are incorporated into the model, a long term model of the complications might be required. For instance, stroke, paraplegia and renal failure can accrue a lifetime cost and therefore it might be appropriate to model them.

Resource identification, measurement and valuation

Cost estimates included in the calculations are sourced from the PSSRU compendium, NHS Reference Costs and literature. These have the following issues and needs to be revised:

- Surgeon cost (Consultant-Surgical), as given in the PSSRU document, is only £172/hr and not £399 (Curtis 2012).

- It is reasonable to assume that a perfusionist can be costed at a registrar's rate but an anaesthetist cannot. This is due to the fact that major cardiac surgery requires an anaesthetist at a consultant rather than registrar level. Using a Consultant-Surgical cost of £172/hr seems therefore more appropriate (Curtis 2012).

- Theatre cost inclusive of nursing and consumables at £24/hr and £30/hr for ICU is sourced from 'NHS Tariff for Admitted Patient Cases & Out-Patient Procedures' without specifying the tariff codes, which makes it difficult to validate this figure. The EAC recommends using hourly rates for 2 nurses @ £100/hr (Curtis 2012) to construct a new bottom-up estimate. The sponsor indicates that consumables cost £130 per procedure, and that such cost is common for E-vita open plus and the comparators. This could be added to the cost model along with nursing costs.

- From the sponsor's submission, there are assumed differences in ICU stay between procedures and it is reasonable to use a daily cost for ICU. The reference for the £1500 estimate is based on a BBC news item that appeared in 2010, which in turn is based on a report in the Lancet. The EAC considers that the appropriate NHS tariff for adult critical care (Code XC01Z- XC07Z) should have been used. As the number of organs supported during the critical care in the ICU is uncertain, the EAC recommends using a mid-range of 3 organs with a minimum of 1 organ and a maximum of 6 organs supported for, in the sensitivity analysis.

- The daily surgical ward in-patient cost is cited as £420/day and is referenced to have been sourced from 'NHS Tariff Figure'. The appropriate tariff code is not given, making the validation of the estimate more difficult. The sponsor has responded to this query by stating that the tariff codes are QZ01A and QZ01B. However, the EAC was not able to reconcile the given estimates with the NHS Reference Costs 2011. The EAC recommends using tariffs that are closely related to the procedure. For instance - Elective Inpatient Excess Bed Day cost from the NHS reference cost for Aortic or Abdominal Surgery with CC (QZ01A) and Aortic or Abdominal Surgery without CC (QZ01B).

- The cost of death within the NHS of £8,000 is sourced from 'Scottish Cancer Therapy Network Newsletter Autumn 2003'. The newsletter reports 'those dying of cancer had a higher acute care NHS mean cost per person (£7079) than those dying of any other cause'. The cost refers to cancer death and might not be appropriate for the technology and comparators. Moreover, the outcome of interest is 'in hospital death' due to the procedure, and the cost of the procedure until the death occurred would be the 'cost of death' to NHS. It could be assumed that 'death' could incur complications and the extra cost of

managing the complications along with procedure can reflect the cost of 'death' in the hospital.

For the purpose of costing, some assumptions have been made on the number of patient days, which has the following issues:

- The patient days required for the classical ET procedure for stage 1 is 10 days (4 days ICU and 6 days surgical ward) and for stage 2 is 15 days (9 days ICU and 6 days surgical ward). The reference for this assumption is 'Hospital Episode Statistics', code L27.3 - Endovascular insertion of stent graft for thoracic aortic aneurysm. Scrutiny of this code reveals that the mean length of stay for this code is 12.2 days. It is not clear why the sponsors made the assumption of 15 days for stage 2 patient days.

- For the Endovascular procedure done at stage 2, the EAC could locate the code L28.3 Endovascular stenting for thoracic aortic aneurysm with a length of stay of 8.1 days, which is similar to what the sponsor has assumed from the 'company clinical studies'(not referenced).

- The assumption to split patient days between the ICU and surgical ward days is also not clear.

Given these issues, the assumptions need to be confirmed from further literature search and the model has to be revised accordingly.

Technology and comparators' costs

An indicative price of £10,500 for E-vita open plus is based on the information from the company and is reasonable to be used in the model. The comparator costs are cited as £200 for woven graft for stages 1 & 2, £1000 for branched graft, and £5000 for stent endograft. These figures are based on commercial prices from current suppliers and are reasonable values to use in the model. Consumables and extra costs of £130 for a "stiff guide wire" are common for the technology and comparator and need to be included in the cost models.

Sensitivity analysis

It is estimated that there would be 3500 patients every year with aortic arch problems, and a 40% adoption for E-vita open plus. The remaining 60% would either receive a 'woven graft' (15%) or a 'branched graft' (85%). One way sensitivity analysis was undertaken with different levels of adoption of E-vita open plus, with a base case value of 40% varied from 20% to 100%. The proportion of woven or branched graft was also varied from 60% to 95% with a base case estimate of 85%. The basis of the estimation of 3500 patients every year is not clear from the materials submitted by the sponsor. The sources for this estimation listed are HES (2011), Bavaria et al (2007), Clouse et al (2004), and NICE (2005). Bavaria et al (2007) and Clouse et al (2004) are US-based estimates and might not be appropriate for the UK context. As stated earlier, we investigated the code L27.3 in the Hospital Episode Statistics for England Inpatient statistics, HES (2011), and found the number of admissions to be only 183. Expert's estimates (see scope page 3) that 50-100 people per year in England would be suitable for treatment with E-vita open plus appears reasonable. Thus the population size of 3500 considered for the cost model is an overestimate. The decision model need not take a cohort approach, but could use probabilities to estimate per person/treatment costs associated with the technology and each comparator. Hence a sensitivity analysis on adoption and proportion levels may not be appropriate.

Sensitivity analyses were also performed by varying some of the outcome variables:

- The suitability of patients for second stage operation was varied in a one way sensitivity analysis from a base case estimate of 80%, to between 65% and 90%. This seems to be an appropriate variable to be tested for uncertainty.

- A two way sensitivity analysis including In-Hospital Death Rates at stage 1 for the comparators and E-vita open was considered. It is not clear why these two variables were varied in a two way sensitivity analysis. More appropriate would have been to vary the in-hospital death rates in a one way sensitivity analysis.

- Stage 2 procedures (woven graft and endovascular graft) proportions were varied from a 50% base case, to between 40% and 100%. This is

appropriate as it could indicate potential cost-savings options for the stage 2 procedure.

4.3 Results of de novo cost analysis

Base-case analysis results

The sponsor has reported the average cost per patient for E-vita open plus (£25,688.5) and for all comparators combined (£30,241), resulting in a saving of £4552.5 (please notes the totalling errors in the sponsor's submission). They have arrived at these figures by assuming a 100% adoption for the technology and comparators combined and averaged it across the 3500 patients. This approach has shown differences when the individual procedure costs are considered. For example, E-vita open plus shows a cost of £24,480, woven graft (stage 1) with woven graft (stage 2) shows a cost of £35,216, woven graft (stage 1) with endovascular stent (stage 2) shows a cost of £26,691, branched graft (stage 1) with woven graft (stage 2) shows a cost of £36,016 and branched graft (stage 1) with endovascular stent (stage 2) shows a cost of £27,491. As stated earlier, it is not necessary for the decision analysis to take a cohort approach, but probabilities can be used instead to estimate the cost per treatment/patient for the technology and the comparators. All the earlier issues mentioned need to be addressed in the revised cost models.

Sensitivity analysis results

The adoption level for E-vita open plus use was varied and the average saving per patient was about £4,358 which remained the same for any level of use. For reasons mentioned earlier, sensitivity analysis on adoption levels may not be appropriate.

Suitability of patients for a second stage operation was varied and the results showed that for a higher probability of suitability, the savings per patient are also higher.

The saving per patient is more than £3,000 for the different in-hospital death rates. The sponsor concludes that E-vita open plus is clinically superior over the comparators, as there are no significant differences in savings per patient even with similar levels of in-hospital death rates.

The sponsor also concludes that endovascular stent graft might be clinically an easier stage 2 procedure to perform and has a potential for cost savings as a stage 2

procedure. However, since E-vita open plus has only one stage and has cost savings, even with varied levels of adoption, suitability for second stage, and in-hospital death rates, the sponsor concludes that E-vita open plus is superior over the comparators.

The EAC considers the sensitivity analyses to be reasonable but with the cost models requiring revision to incorporate outcomes such as complications, the sensitivity analyses need to revised before any firm conclusions are reached.

Subgroup analysis

Though the scope mentioned consideration of Acute Type A dissection, Chronic Type A dissection and Degenerative aneurysm as subgroups, the sponsor has not considered them in the cost models. Systematic review of clinical evidence taken further by the EAC has revealed that data is available for the subgroups only for the technology (Jakob et al, 2011). Outcomes data for subgroups are not presented for the comparators in the included studies. Hence any cost analysis on the subgroups was not possible in this assessment.

Model validation

The model presents internal validity despite some typographical errors in the presentation of the economic evidence (e.g. page 66, 6 days in surgical wards with an - incorrect - £4,520 cost rather than £2,520). Nevertheless, the electronic version of the model presented (the Microsoft Excel file) seems to be accurate.

4.4 Interpretation of economic evidence

The sponsor concludes that currently there is no published literature comparing the technology and comparators and the cost model analysis shows that E-vita open plus has cost savings compared to the comparators. The sensitivity analysis also reveals that E-vita open plus has only one stage and cost savings, even with varied levels of adoption, suitability for second stage, and in-hospital death rates. The sponsor concludes that E-vita is superior over the comparators. The EAC agrees with the search strategy conclusions but the cost models need to be revised in terms of their structure and data inputs before firm conclusions can be reached.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

Since the short term model has not incorporated outcomes such as complications, the model needs to be revised. Further, some of the variables in the model need to be changed. Though there is evidence to show the technology and comparators might be comparable in terms of long term survival rates, if complications are included in the short term model, a long term model to incorporate costs accrued due to complications will have to be included.

Given these issues, the EAC revised the cost model, with updated assumptions based on literature that was sourced from an additional systematic review of clinical evidence. A short term decision model was first constructed with complications and in-hospital mortality modelled. The technology (E-vita open plus) was compared with 3 comparators (two-stage with vascular graft, two-stage with endovascular stent graft, open debranching with endoluminal stent graft). Some of the complications like stroke, paraplegia and renal failure were expected to accrue lifetime cost. This estimated lifetime cost of complications was added to the decision model, and a long term model was estimated. The models estimated the expected cost in the short-term and long-term.

Model Structure

Short term Model

The revised model incorporated complications and in-hospital mortality at each stage of the procedure for the technology and comparators, from the NHS and personal social services perspective. The important complications modelled were stroke, paraplegia, renal failure and bleeding along with in-hospital mortality. This was based on the results of the systematic review of clinical evidence performed by the EAC (Table 3). The technology (E-vita open plus) only has one stage and hence the short-term model terminated after outcomes of stage 1 had occurred. The comparators were all two stage procedures, and outcomes were modelled at each stage. Those with 'No Complications' and 'Bleeding' in stage 1 were assumed to move on to stage 2 for all the comparators. All the other outcomes like stroke, paraplegia, renal failure and in-hospital mortality terminated at stage 1. The time horizon for the short term model was 1 year, since most of the 2 stage procedures are expected to be completed within 6 months' time (Etz et al. 2008, Safi et al. 2007, Svensson et al. 2004, LeMaire et al. 2006). The decision trees for the technology and comparators are presented in Figure 1 -8.

Long term Model

In the long term model, the lifetime cost of stroke, paraplegia and renal failure was modelled separately and added to the decision model to estimate the expected cost (Figures 1 -8). The time horizon for the lifetime cost was 20 years. This was based on the average age of 65 years of patients in the included studies (Jakob et al, 2011, Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Kim et al 2009, Kawaharada et al 2009, Kim et al 2009,Lee et al 2011, Antoniou et al 2010a, Antoniou et al 2010b) and the life expectancy at 65 years for the UK population, which is around 20 years (ONS, 2011). Annual cost of care for stroke, paraplegia and renal failure were sourced from published literature (NICE, 2006, French et al., 2007, NICE, 2010) and discounted at 3.5%. The discounted annual cost was multiplied with a survival probability for 65 to 85 years, estimated using background mortality rate from UK life tables multiplied with a standard mortality ratio of 2 for stroke, paraplegia and renal failure (Brønnum-Hansen et al 2001, Yeo et al 1998, Hobson et al 2009). The weighted annual costs were summed to estimate the lifetime cost of the complications.

Figure 1 – Short term model for E-vita Open plus

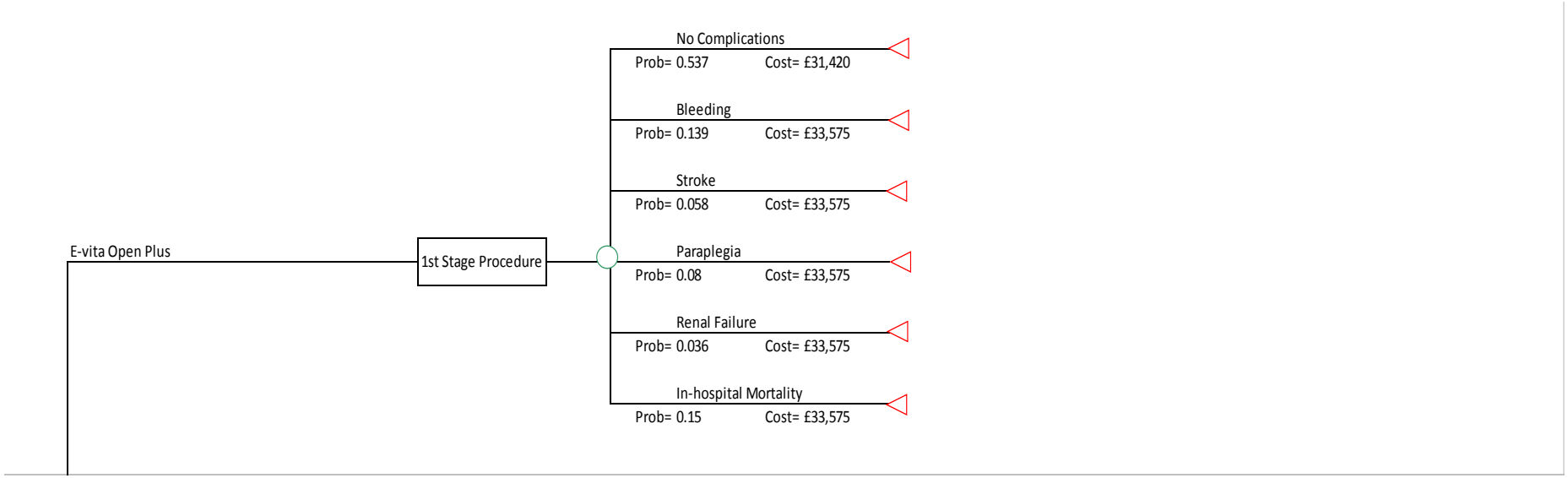


Figure 2 – Long term model for E-vita Open plus

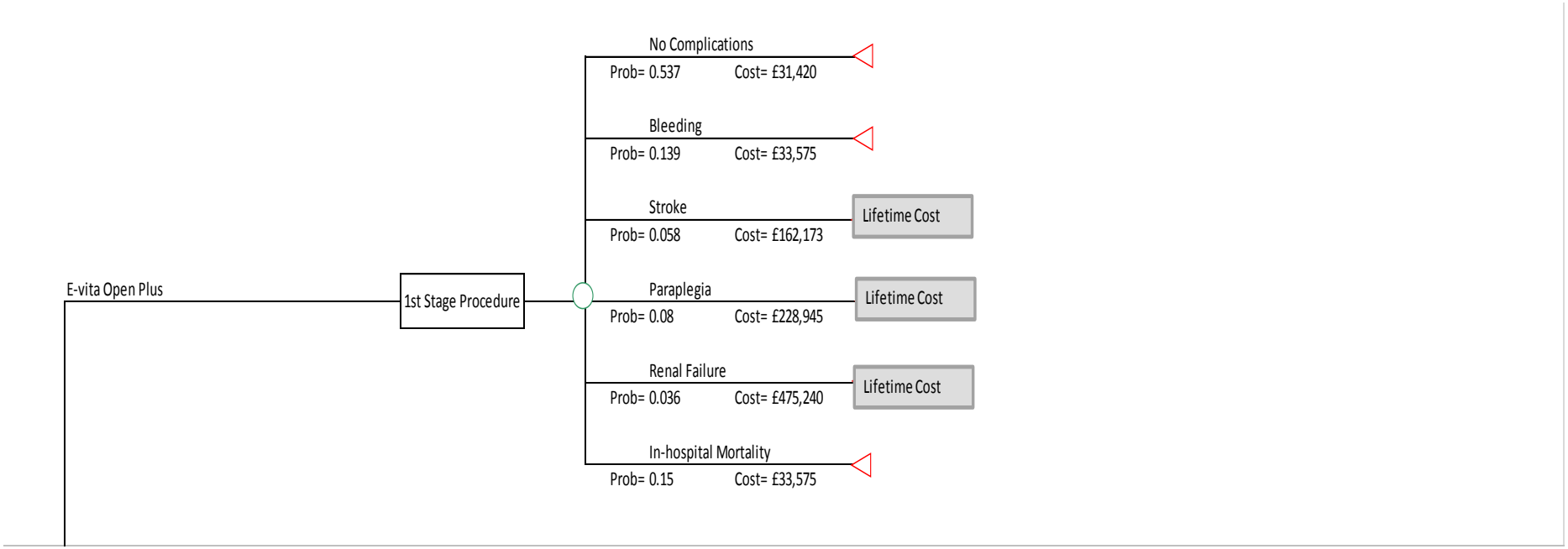


Figure 3 – Short term model for 2-stageprocedure with vascular graft

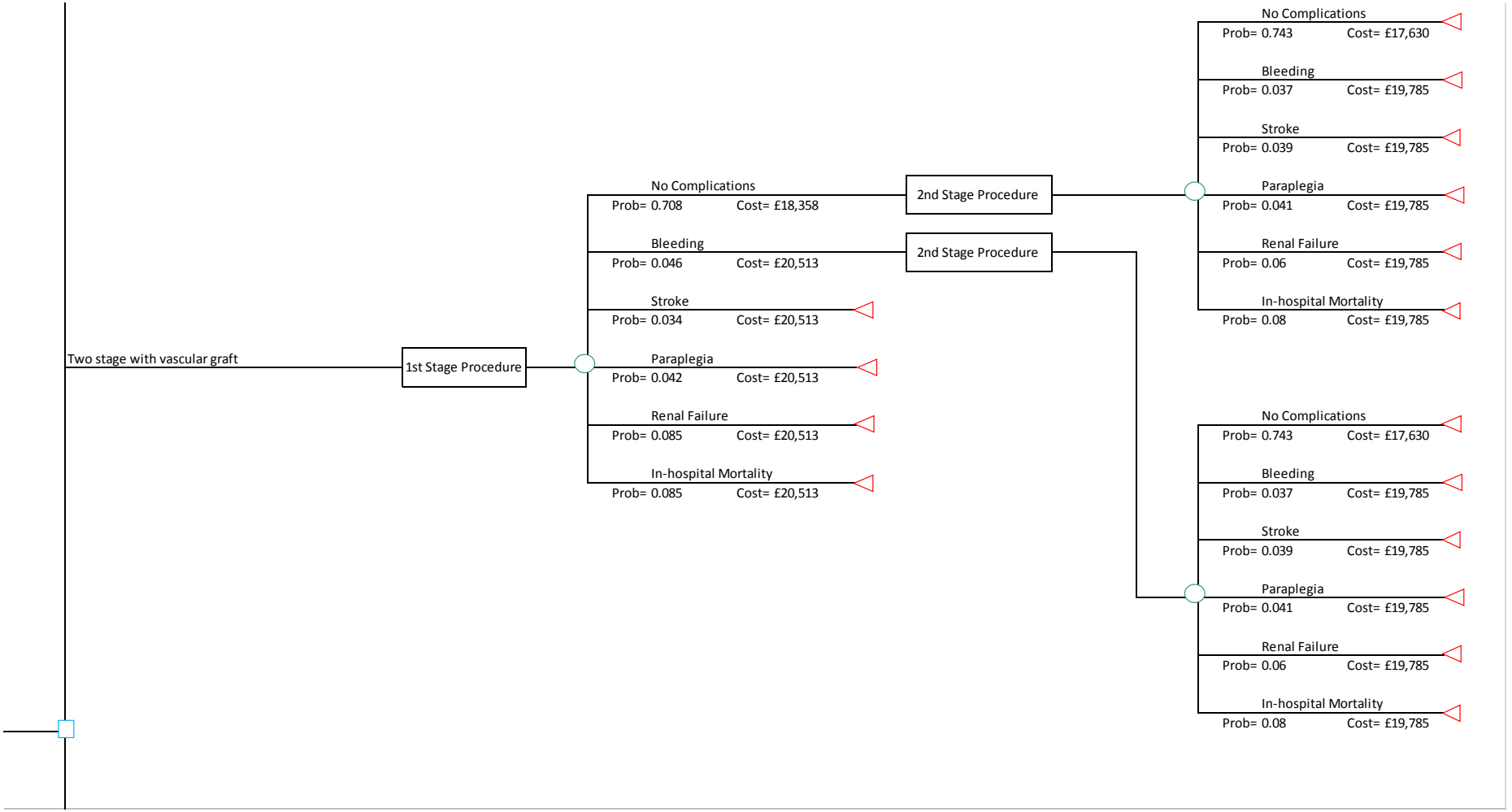


Figure 4 – Long term model for 2-stageprocedure with vascular graft

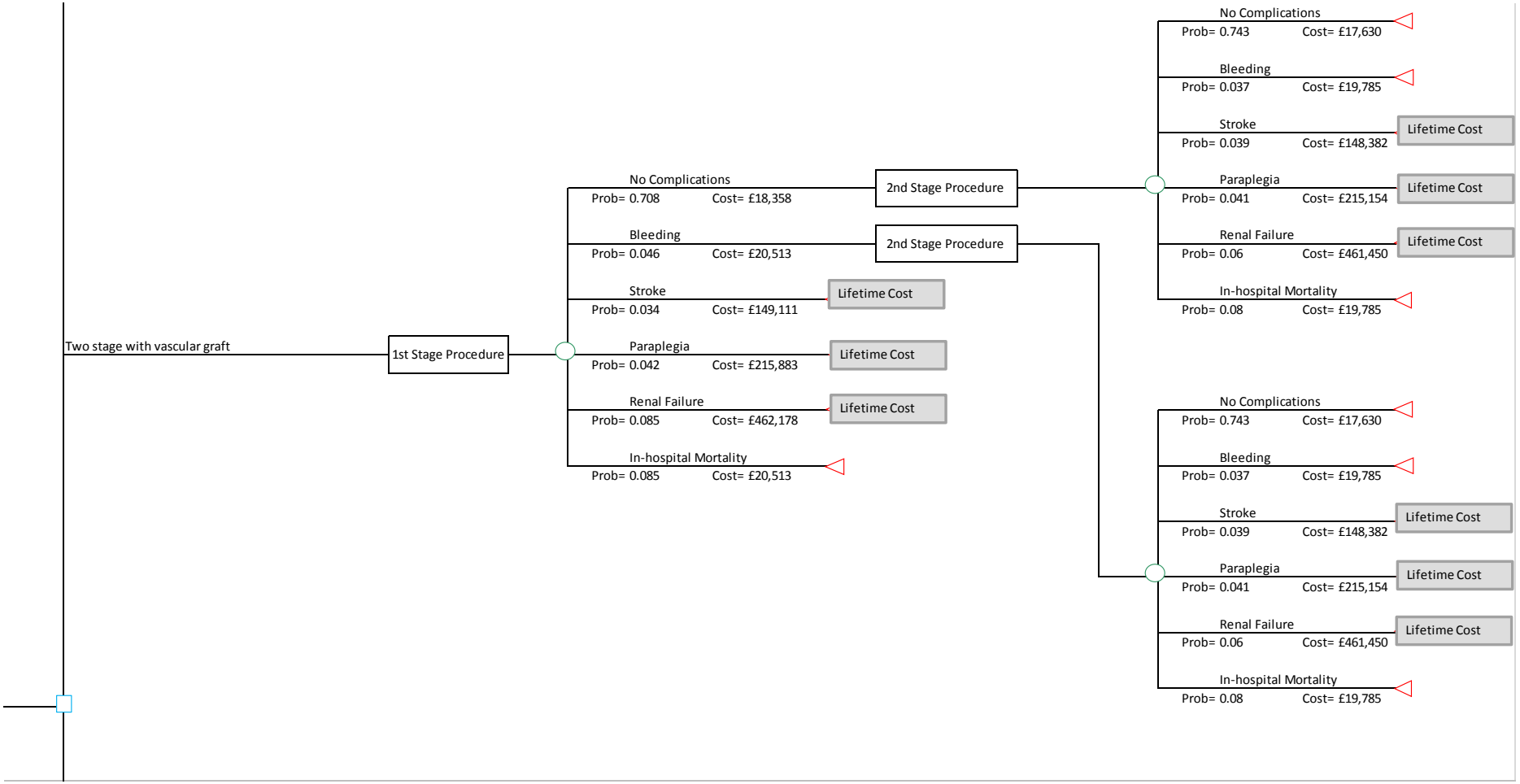


Figure 5– Short term model for 2-stageprocedure with endovascular stent graft

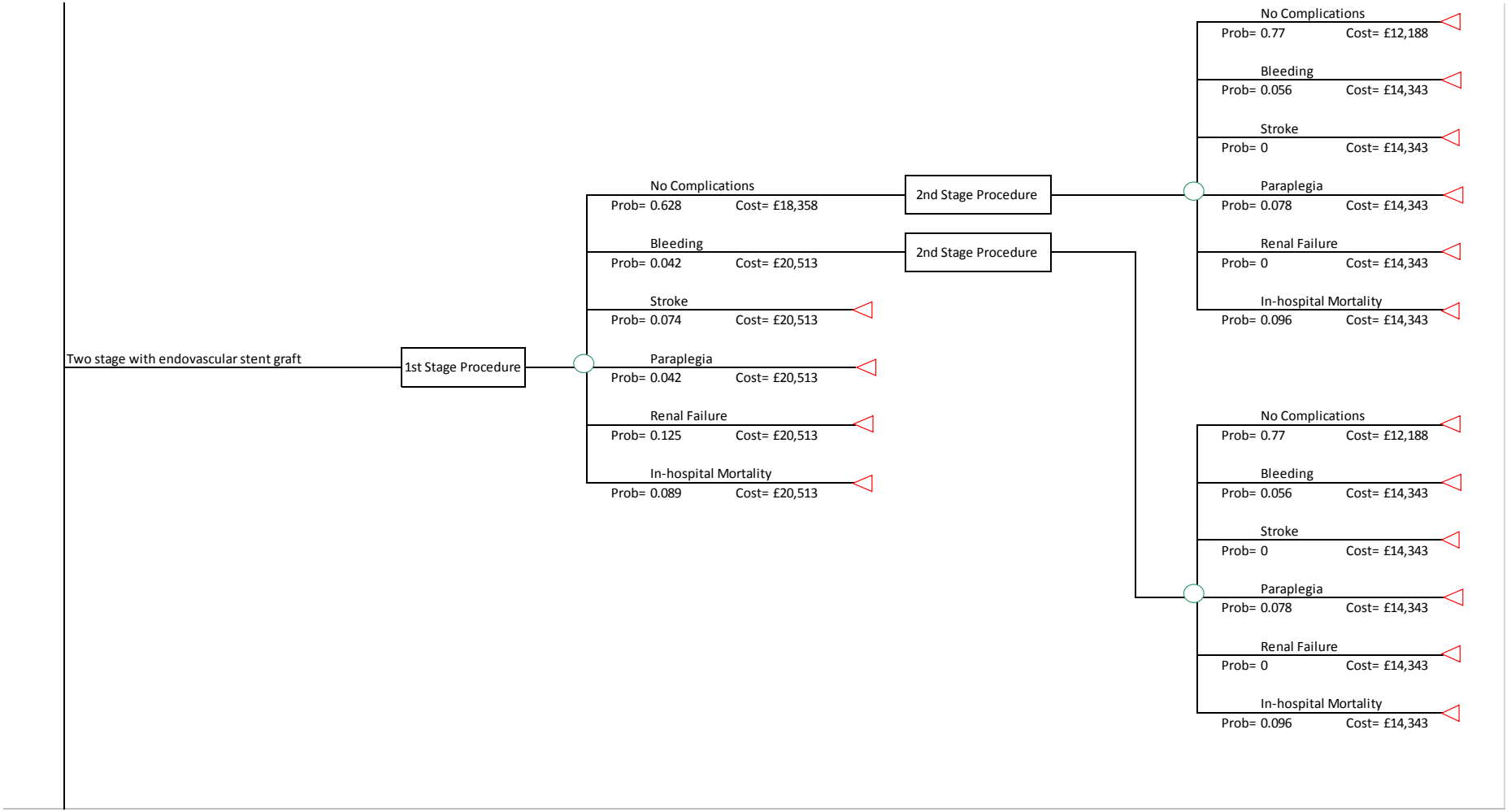


Figure 6 – Long term model for 2-stageprocedure with endovascular stent graft

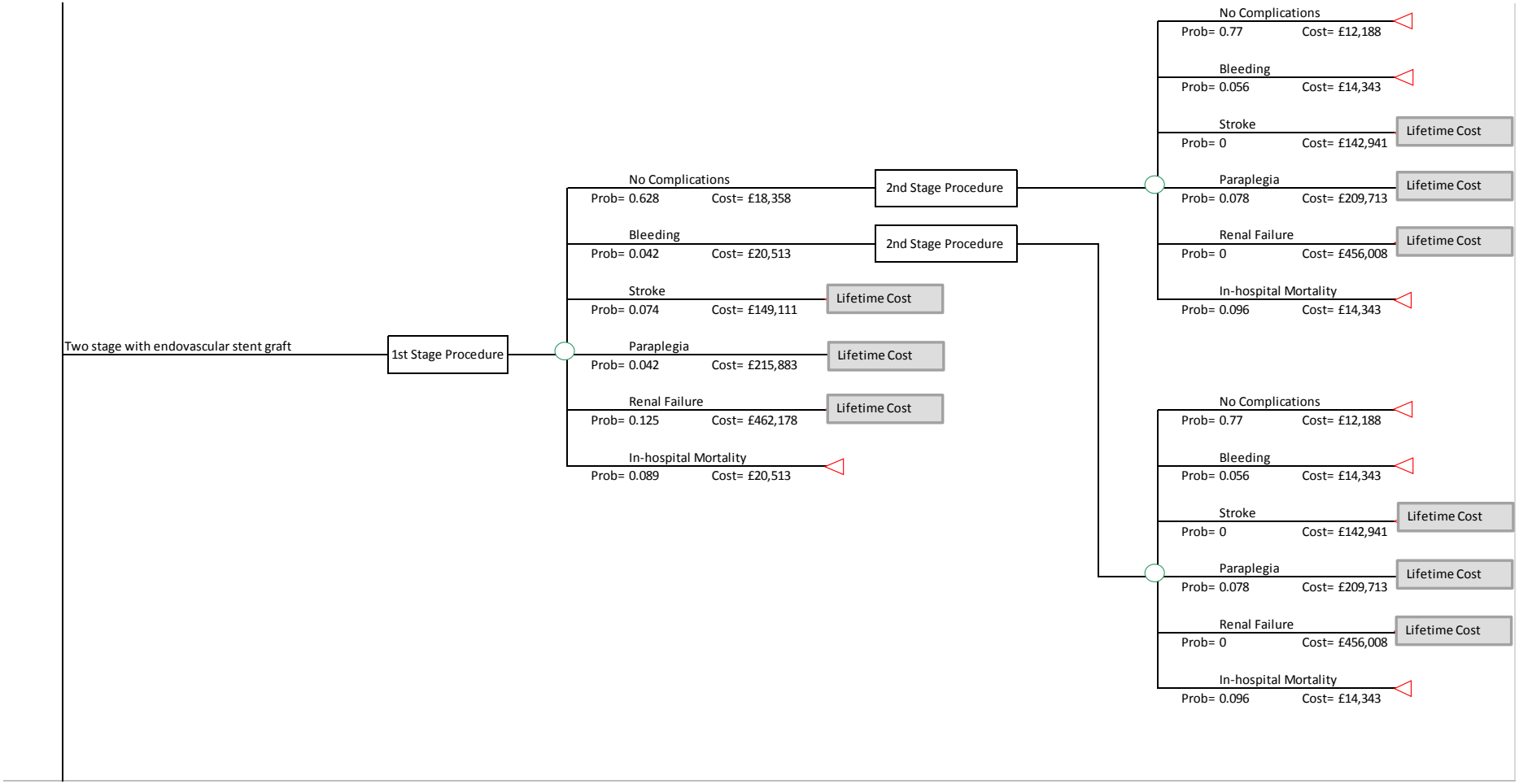


Figure 7 – Short term model for open debranching with endoluminal stent graft

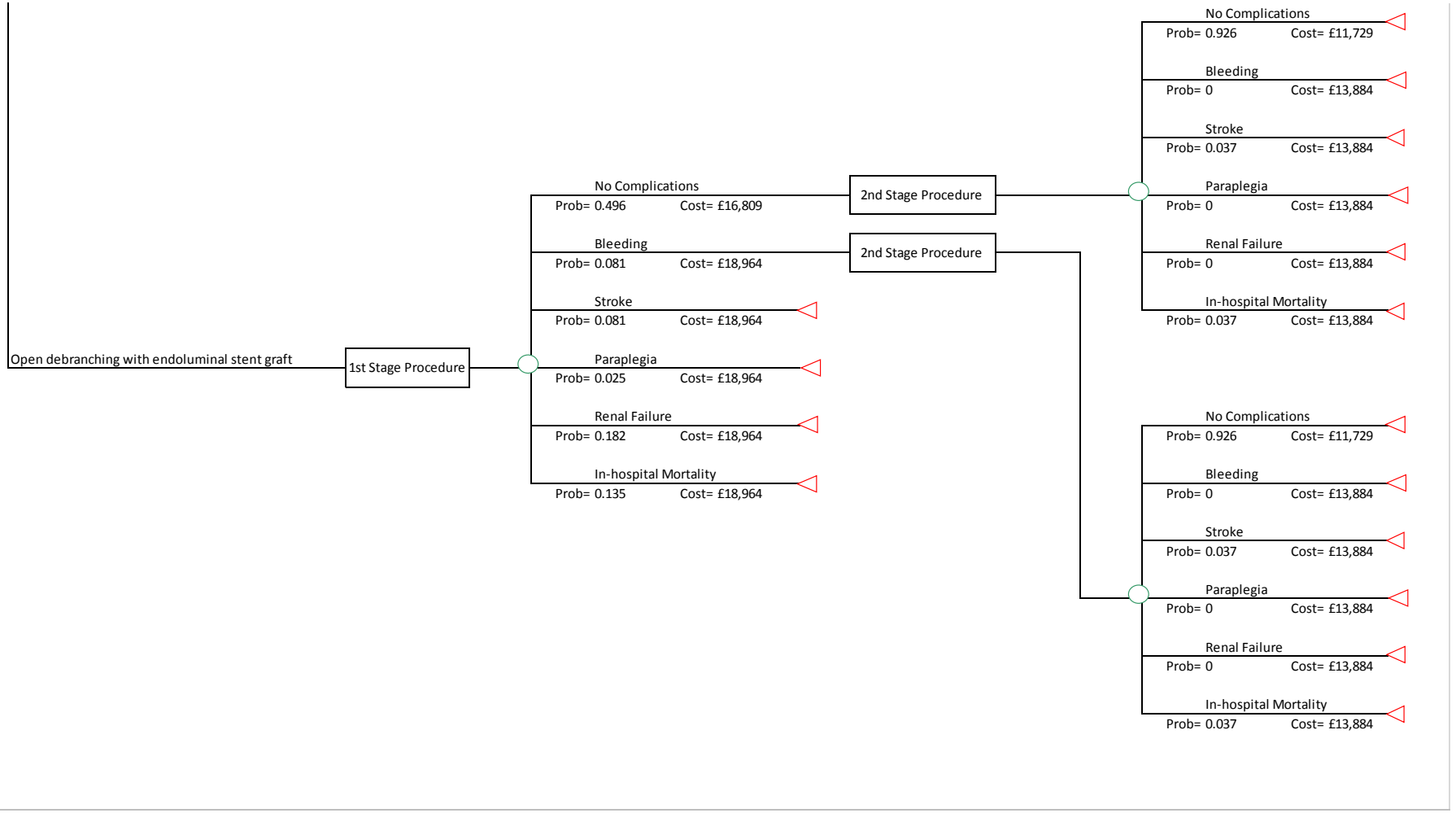
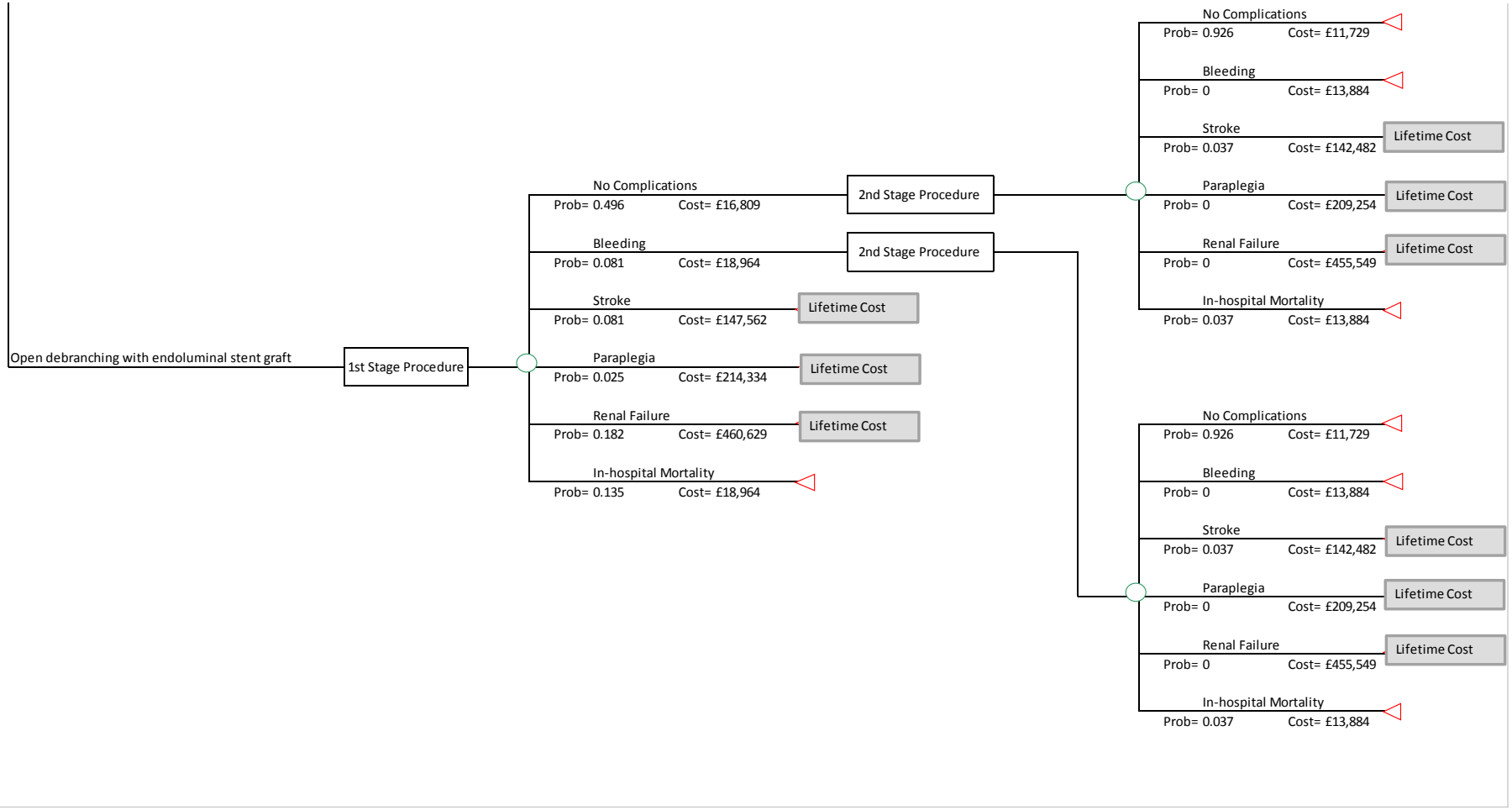


Figure 8 – Long term model for open debranching with endoluminal stent graft



Assumptions

The assumptions on probabilities and costing used in the models are presented in Table 5.

Probabilities were estimated from the meta-analysis (Table 4) on the studies included from the systematic review performed by the EAC. Some of the missing probabilities were based on the following assumptions:

- Probability of Paraplegia (Stage 1) for two stage with vascular graft was assumed to be same as two stage with endovascular stent graft.

- Probability of Paraplegia (Stage 1) and Renal Failure (Stage 1) for open debranching with endoluminal stent graft was based on hybrid procedure estimates.

These might be simplistic assumptions that might benefit from further clinical expert validation, which was not sought during the preparation of the report. Assumptions for costing the technology and comparators were based on the literature and sponsor's submission. Uncertain parameters were varied in the sensitivity analysis. The major assumptions for costing include the following.

- Operating time for all the comparators were sourced from literature (Lee at al., 2011; Kim et al., 2009). Operating time for technology was based on sponsor's submission which was retrieved from company studies).

- Total length of stay for the technology and comparator procedures were sourced from literature (Jakob et al., 2011; Safi et al., 2007; Kim et al., 2009; Lee et al., 2011).

- The proportion of ICU stay within the total length of stay was assumed to be 40% for the base case estimate. This assumption was based in one study (Safi et al., 2007). As there was uncertainty surrounding this assumption, the ICU stay proportion was varied from 20% to 60% in the sensitivity analysis arbitrarily.

- The surgical team for the procedures was assumed based on the information in the sponsor's submission. It comprised of a Consultant Surgeon (1) @ £172/hr, Consultant Anaesthetist (1) @ £172/hr, Associate Specialist (1) @ £131/hr, Perfusionist (1) at Registrar's rate £86/hr. Additionally, two

Specialist Nurses @ £100/hr were also included as a part of the surgical team. A Consultant Radiologist (Medical) @157/hr was also included in stage 2 of two-stage with endovascular stent graft and open debranching with endoluminal stent graft procedures. The hourly cost of the team was sourced from PSSRU compendium (Curtis 2012).

- Cost of E-vita open plus, Cost of Woven Graft, Cost of Branched Graft, Cost of Endovascular stent Graft and other Consumables were sourced from the sponsor's submission.

- Complications like bleeding, stroke, paraplegia, renal failure during procedures and in-hospital death will incur extra cost to manage the complications in the hospital. This was assumed to be £ 2155, estimated from the NHS Reference Cost 2011-12 (DOH, 2012). This figure is the difference between QZ01A (Aortic or Abdominal Surgery, with CC) (£8292) and QZ01B (Aortic or Abdominal Surgery, without CC) (£6137). There was uncertainty regarding this assumption, since the same cost of managing complications was assumed for all complications. Hence, the variable was varied in a sensitivity analysis by 50 % (£1075 to £3235), which was rather arbitrary due to the lack of information.

- Cost of ICU/day was assumed to be £ 1410/day, which was sourced from NHS Reference Cost 2011-12 (DOH, 2012), for Code XC04Z (Adult Critical Care, 3 Organs Supported). A range of £870 - £ 2000 was considered for sensitivity analysis, essentially reflecting XC06Z (Adult Critical Care, 1 Organ Supported) and XC01Z (Adult Critical Care, 6 or more Organs Supported).

- Cost of a surgical ward day was £383/day, which was sourced from NHS Reference Cost 2011-12 (DOH, 2012), for Elective Inpatient Excess Bed Day HRG Data for Code QZ01B (Aortic or Abdominal Surgery, without CC).

- Annual cost of stroke care was sourced from NICE Clinical Guidance on Atrial fibrillation (NICE, 2006). This was estimated at £9,597 (min – max, £3,691 - £14,396) at 2012 prices.

- Annual cost of paraplegia was sourced from literature (French et al., 2007). Since the cost was US based, the estimate was converted to UK pounds and

inflated to 2012 prices. This was estimated at £14,580 (min – max, £11,320 to £19,256).

- Annual cost of renal failure care was sourced from a NICE economic assessment of Peritoneal Dialysis (NICE, 2010). At 2008 prices, automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) had an average annual cost of £21,655 and £15 570, respectively. Assuming that 75% had CAPD and 25% had APD, the weighted average was £17,091. The average for haemodialysis (hospital and satellite unit haemodialysis) was £33,846. Assuming that 25% of the patients with permanent renal failure are managed with peritoneal dialysis techniques and 75% of the patients are managed with haemodialysis, either in a hospital or satellite units (NICE, 2010), the annual cost of renal failure care was estimated using a weighted average. This was estimated at £32,961 (min – max, £24,724 - £41,210) at 2012 prices.

Table 5 – Probabilities and costing for technology and comparators

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	Stage 1	*Stage 1*	*Stage 2*	*Stage 1*	*Stage 2*	*Stage 1*	*Stage 2*
Probabilities							
Complications(Bleeding)	0.139	0.046	0.037	0.042	0.056	0.081	0
Complications(Stroke)	0.058	0.034	0.039	0.074	0	0.081	0.037
Complications(Paraplegia)	0.08	0.042	0.041	0.042	0.078	0.025	0
Complications(Renal Failure)	0.036	0.085	0.06	0.125	0	0.182	0
Mortality(In-hospital)	0.15	0.085	0.08	0.089	0.096	0.135	0.037
Costs							
Operating time (hrs)	7.5	7	5	7	2.5	6	2
Operating time(range, hrs)	(4.5-13.5)	(4-13)	(3-7)	(4-13)	(1.2-4.5)	(3-10)	(1.2-5)
Total Length of Stay(days)	19	16	17	16	6	14	6
Total length of stay(range, days)	(12-29)	(9-20)	(12-25)	(9-20)	(4-10)	(9-20)	(4-10)
ICU Days(40%)	8	6	7	6	2	6	2
Surgical Ward Days(60%)	11	10	10	10	4	8	4
Cost of Surgery							
Consultant Surgeon(1) @ £172/hr	£1,290	£1,204	£860	£1,204	£430	£1,032	£344
Consultant Anaesthetist(1) @ £172/hr	£1,290	£1,204	£860	£1,204	£430	£1,032	£344
Associate Specialist(1) @ £131/hr	£983	£917	£655	£917	£328	£786	£262
Perfusionist(1) at Registrar's rate £86/hr	£645	£602	£430	£602	£215	£516	£172
Specialist Nurse(2) @ £100/hr	£1,500	£1,400	£1,000	£1,400	£500	£1,200	£400
Consultant Radiologist(Medical) @157/hr					£393		£314
Cost of E-vita open plus	£10,500						
Cost of Woven Graft		£200	£200	£200			
Cost of Branched Graft						£1,000	
Cost of Endovascular stent Graft					£5,000		£5,000
Other Consumables	£130	£130	£130	£130	£130	£130	£130
Cost of Complications Management @ £2155	£2,155	£2,155	£2,155	£2,155	£2,155	£2,155	£2,155
Cost of ICU @ £ 1410/day (Range £870 - £ 2000)	£10,716	£9,024	£9,588	£9,024	£3,384	£7,896	£3,384
Cost of Surgical Ward @ £ 383/day	£4,366	£3,677	£3,907	£3,677	£1,379	£3,217	£1,379
Total Cost(With Complication)	£33,575	£20,513	£19,785	£20,513	£14,343	£18,964	£13,884
Total Cost(Without Complication)	£31,420	£18,358	£17,630	£18,358	£12,188	£16,809	£11,729

Sensitivity Analysis :

As there was uncertainty surrounding some of the key variables used in the cost model, deterministic sensitivity analysis was performed to check for robustness of results. The variables varied in the sensitivity analysis were:

- The E-vita open plus in-hospital mortality probability was varied from 10% to 20%, a range chosen to reflect the 95% confidence intervals for the meta-analysis estimates for in-hospital mortality (Table 4).

- The E-vita open plus paraplegia probability was varied from 3% to 10%, the range reflecting the 95% confidence intervals for the meta-analysis estimates for paraplegia (Table 4).

- Proportion of ICU Stay varied from 20% to 60%. Due to the lack of information, the range was arbitrarily chosen to reflect a 50% change from the base case.

- Cost of ICU varied from £870 to £2,000. The range of £870 - £ 2000 essentially reflects the tariff codes XC06Z (Adult Critical Care, 1 Organ Supported) and XC01Z (Adult Critical Care, 6 or more Organs Supported).

- Cost of complications management varied from £1,075 to £ 3,235. Due to the lack of information, the range was arbitrarily chosen to reflect a 50% change from the base case.

- Multiple stents are used for the two stage procedures and are included in the cost analysis and these were sourced from the sponsor's submission. Multiple stents may also be used during each procedures due to technical reasons. The implications of using multiple stents during each procedure has not been included in the cost analysis, because of the lack of evidence available on the utilization of multiple stents.

- Annual Cost for stroke varied from £3,691 to £14,396. The range was essentially the minimum and maximum costs reported in the literature (NICE, 2006).

- Annual Cost for paraplegia varied from £11,320 to £19,256. The range was essentially the minimum and maximum costs reported in the literature (French et al., 2007)

- Annual Cost for renal failure varied from £24,724 to £41,210. As minimum and maximum amounts could not be estimated from literature (NICE, 2010), the range was arbitrarily chosen to reflect a 25% change from base-case.

Results

Base-case estimate

The expected cost in the short term and long term are presented in Table 6. In the short term, E-vita open plus showed little cost savings (£280) compared to two-stage with vascular graft. However, E-vita open plus was cost-incurring in the short term when compared to two-stage with endovascular stent graft (£4,760) and open debranching with endoluminal stent graft (£7,663). When lifetime cost of complications were modelled into the long term model, the expected cost of E-vita open plus was much lower than all the comparators, providing high cost savings for E-vita open plus in the long term. There were savings of £41,213 when compared to two-stage with vascular graft, £39,392 when compared to 2-stage with endovascular stent graft and £51,778 when compared to open debranching with endoluminal stent graft.

Table 6: Expected cost and savings of technology and comparators

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Short term)	£32,417	£32,697	-£280	£27,657	£4,760	£24,755	£7,663
Expected Cost(Long term)	£71,406	£112,619	-£41,213	£110,797	-£39,392	£123,184	-£51,778

Sensitivity Analysis

In the deterministic sensitivity analysis, a number of variables with uncertainty were varied. The variables included in the sensitivity analysis included In-hospital mortality and paraplegia probability of E-vita open plus, proportion of ICU stay, cost of ICU, cost of complications management and annual cost of stroke, paraplegia and renal failure. The results are presented in Table 7-14.

Table 7: Sensitivity Analysis – Probability of In-hospital mortality of E-vita open plus varied from 10% to 20%

	E-vita Open	Two stage with vascular		Two stage with		Open debranching with	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Short term)@10%	£32,310	£32,697	-£388	£27,657	£4,652	£24,755	£7,555
Expected Cost(Long term)@10%	£71,298	£112,619	-£41,321	£110,797	-£39,499	£123,184	-£51,886
Expected Cost(Short term)@20%	£32,525	£32,697	-£172	£27,657	£4,868	£24,755	£7,770
Expected Cost(Long term)@20%	£71,513	£112,619	-£41,105	£110,797	-£39,284	£123,184	-£51,671

Table 8: Sensitivity Analysis – Probability of paraplegia of E-vita open plus varied from 3% to 10%

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Short term)@3%	£32,310	£32,697	-£388	£27,657	£4,652	£24,755	£7,555
Expected Cost(Long term)@3%	£61,529	£112,619	-£51,089	£110,797	-£49,268	£123,184	-£61,655
Expected Cost(Short term)@10%	£32,461	£32,697	-£237	£27,657	£4,803	£24,755	£7,706
Expected Cost(Long term)@10%	£75,356	£112,619	-£37,263	£110,797	-£35,441	£123,184	-£47,828

Table 9: Sensitivity Analysis – Proportion of ICU stay varied from 20% to 60%

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Short term)@20%	£28,515	£26,778	£1,737	£23,545	£4,970	£21,168	£7,347
Expected Cost(Long term)@20%	£67,503	£106,700	-£39,197	£106,685	-£39,182	£119,597	-£52,094
Expected Cost(Short term)@60%	£36,320	£38,617	-£2,297	£31,769	£4,551	£28,342	£7,979
Expected Cost(Long term)@60%	£75,308	£118,538	-£43,230	£114,909	-£39,601	£126,771	-£51,462

Table 10: Sensitivity Analysis – Cost of managing complications varied from £1,075 to £ 3,235

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Short term)@£1,075	£31,917	£32,173	-£255	£27,089	£4,828	£24,164	£7,753
Expected Cost(Long term)@£1,075	£70,906	£112,094	-£41,189	£110,229	-£39,323	£122,594	-£51,688
Expected Cost(Short term)@£3,235	£32,918	£33,222	-£305	£28,226	£4,692	£25,345	£7,572
Expected Cost(Long term)@£3,235	£71,906	£113,144	-£41,238	£111,365	-£39,460	£123,774	-£51,869

Table 11: Sensitivity Analysis – Cost of ICU varied from £870 to £ 2,000

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Short term)@£870	£28,313	£26,473	£1,841	£23,333	£4,980	£20,983	£7,330
Expected Cost(Long term)@£870	£67,302	£106,394	-£39,093	£106,473	-£39,171	£119,412	-£52,111
Expected Cost(Short term)@£2,000	£36,901	£39,498	-£2,597	£32,382	£4,519	£28,876	£8,026
Expected Cost(Long term)@£2,000	£75,890	£119,420	-£43,530	£115,522	-£39,632	£127,305	-£51,415

Table 12: Sensitivity Analysis – Annual Cost for Stroke varied from £3,691 to £14,396

	E-vita Open	Two stage with vascular		Two stage with		Open debranching with	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Long term)@£3,691	£66,816	£107,601	-£40,785	£104,941	-£38,125	£115,084	-£48,269
Expected Cost(Long term)@£14,396	£75,135	£116,696	-£41,561	£115,555	-£40,420	£129,765	-£54,630

Table 13: Sensitivity Analysis – Annual Cost for Paraplegia varied from £11,320 to £19,256

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Long term)@£11,320	£67,910	£109,433	-£41,523	£106,679	-£38,769	£122,092	-£54,181
Expected Cost(Long term)@£19,256	£76,418	£117,187	-£40,769	£116,703	-£40,285	£124,750	-£48,333

Table 14: Sensitivity Analysis – Annual Cost for Renal Failure varied from £24,724 to £41,210

	E-vita Open Plus	Two stage with vascular graft		Two stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	(Comparator 1)	(Savings)	(Comparator 2)	(Savings)	(Comparator 3)	(Savings)
Expected Cost(Long term)@£24,724	£67,432	£98,243	-£30,811	£97,000	-£29,568	£103,095	-£35,663
Expected Cost(Long term)@£41,210	£75,385	£127,014	-£51,629	£124,613	-£49,229	£143,300	-£67,915

Sensitivity analysis results on probability of in-hospital mortality and paraplegia of E-vita open plus does not alter the cost savings conclusions in the base-case estimate. The proportion of ICU stay seems to affect the result in the short term. At the 20% level, two-stage with vascular graft along with other comparators have cost savings,

compared to E-vita open plus. At 60% levels, the conclusions are same as base-case estimates but with higher cost savings of £2,297 compared to two-stage with vascular graft procedure. The cost of ICU also seems to affect the results in similar way as the proportion of ICU stay in the short term. However, both the proportion of ICU stay and associated cost of ICU do not affect the cost-saving conclusions from the base case estimate for E-vita open plus in the long term. Varying the cost of managing complications does not change the conclusions from the base-case estimate. Further, varying the annual cost of stroke, paraplegia and renal failure does not change the conclusions of cost savings of E-vita open plus in the long term. E-vita open plus remains as a cost saving procedure, when compared to all comparators in the long term.

Limitations

There are limitations associated with the revised cost model. Firstly, long term data on complications and health states were not available from the literature. In the current model, all complications are assumed to occur in the short term, i.e. shortly after the procedure. Complications occurring in the longer term are likely to be rare but will still have cost implications. Secondly, decision analytic models were used in the analysis. This was considered appropriate given the questions we were addressing and the data availability, but more sophisticated models (e.g. Markov models, discrete event simulations) may allow for more refined analyses of the cost consequences of the intervention. Thirdly, we relied on deterministic rather than probabilistic sensitivity analyses, again largely as result of data limitations to inform parameter distributions. Finally, all complications were assumed to be occurring separately but this does not exclude the possibility that in some individuals multiple complications may occur and the implications of using multiple stents during procedures have not been included in the cost analysis due to the lack of evidence.

4.6 Conclusions on the economic evidence

The sponsor's search strategy to look for economic evidence was not complete. The EAC conducted a search and arrived at the conclusion that there were no published economic evidence and hence a de novo cost model was required. The sponsor's cost model had included the technology and comparators listed in the scope, but only varied levels of adoption, suitability for second stage, and in-hospital mortality were modelled to arrive at conclusions. The EAC felt that complications also need to be

included in the short term model and lifetime cost of some complications needs to be modelled to arrive at firm conclusions. The EAC revised the model structure and parameters and estimated the expected cost of E-vita open plus and the comparators. The results of the revised model suggests that E-vita open plus might not provide significant cost savings when compared to some of the comparators in the short term, but will have high cost savings in the long run. In the short term, the indicative price of the technology (E-vita open plus) and the total length of stay (which is high for the technology) seems to be the main driver for this cost difference. In the long run, the lifetime costs of complications are less than the comparators, since E-vita open plus is a single stage procedure and the occurrence of complications is only once, when compared to the occurrence of complications two times for the comparators. This reduces the lifetime cost and has implications on the cost saving of E-vita open plus in the long term.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

Table 15 presents the differences in estimated expected cost by the EAC and those estimated by the sponsor. The EAC estimated cost of the E-vita open plus is higher than that was estimated by the sponsor. For the two-stage with vascular graft, the EAC estimated cost was lower than the sponsor's estimate. For the two-stage with endovascular stent graft, the EAC estimated cost was higher that the sponsor's estimate. For the open debranching with endoluminal stent graft, the EAC's estimate was lower than the sponsor's estimate.

Table 15: Differences in estimated expected cost

	E-vita Open Plus	Two stage with vascular graft	Two stage with endovascular stent graft	Open debranching with endoluminal stent graft
	(Technology)	(Comparator 1)	(Comparator 2)	(Comparator 3)
Expected Cost(Short term)- EAC	£32,417	£32,697	£27,657	£24,755
Expected Cost(Short term)-Sponsor	£24,480	£35,216	£26,691	£27,491
Difference	£7,937	-£2,519	£966	-£2,736

5 Conclusions

The sponsor submitted clinical evidence regarding the E-vita open plus. All of the published evidence on E-vita open plus was included. In terms of the evidence related to the comparator, the sponsor submitted clinical evidence related to only one comparator – two-stage vascular graft using classical elephant trunk procedure. Two other comparators (two-stage with endovascular stent graft and open debranching with endoluminal stent graft) that were listed in scope were not included. The EAC performed a new systematic review and found studies that reported the other two comparators. A meta-analysis was performed with outcomes from the included studies.

The EAC also performed a new search and agrees with the sponsor that there are no published economic evidence related to E-vita open plus and the comparators. In the de novo cost model submitted by the sponsor, only varied levels of adoption, suitability for second stage, and in-hospital mortality was modelled. The EAC felt that other complications like stroke, paraplegia, renal failure and bleeding should be included in the model and the lifetime costs of some of the complications should also be modelled. Further, some of the assumptions used also needed change. With the results and probabilities from the meta-analysis, the EAC revised the cost models with some changes in the assumptions. The results of the revised model points out that E-vita open plus might not provide significant cost savings when compared to some of the comparators in the short term, but will nonetheless have high cost savings in the longer run (20 years). The cost difference in the short term is driven by the high technology costs and higher length of stay. Since the occurrence of complications is only once for E-vita open plus when compared to the two times occurrence for the comparators, it has implications on the lifetime costs and provides cost-savings in the longer term.

6 Implications for research

All the clinical evidence on E-vita Open plus is based on an international registry and the comparator evidence was obtained from separate observational studies in different patient groups. It would seem prudent to consider undertaking randomised studies to directly compare E-vita open plus and the two-stage comparators in order to achieve robust clinical evidence, possibly including subgroups too. Economic evaluations shouldalso be performed alongside the randomised trials.

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Appendix1 – Search Strategy for Clinical and Economic Evidence

Ovid MEDLINE(R) 1946 to May Week 1 2013

Embase 1980 to 2013 Week 19

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 10, 2013

1. exp Aortic Aneurysm/ or exp Aorta, Thoracic/ or exp Aortic Aneurysm, Thoracic/ or degenerative aneurysm.mp. or exp Aneurysm, Dissecting/

2. exp Aneurysm, Dissecting/ or chronic type A dissection.mp.

3. exp Aneurysm, Dissecting/ or acute type A dissection.mp.

4. 1 or 2 or 3

5. E-vita open.mp.

6. (E-vita adj3 open).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

7. Evita open.mp.

8. (Evita adj3 open).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

9. Evita.mp.

10. (hybrid adj3 stent adj3 graft$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

11. hybrid stent graft$.mp.

12. hybrid stent.mp.

13. (elephant adj3 trunk).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol

supplementary concept, rare disease supplementary concept, unique identifier]

14. (elephant adj3 trunk adj3 procedure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

15. (elephant adj3 trunk adj3 technique).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

16. (aortic adj3 arch adj3 replacement).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

17. aortic arch replace$.mp.

18. (aortic adj3 arch adj3 repair).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

19. (thoracic adj3 stent adj3 graft$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

20. thoracic stent graft$.mp.

21. thoracic stent.mp.

22. (open adj3 stent adj3 graft$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

23. (open adj3 surgical adj3 debranch$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

24. branched graft$.mp.

25. (endovascular adj3 stent adj3 graft$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

26. endovascular stent.mp.

27. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

29. mortality.mp. or exp Hospital Mortality/ or exp Mortality/

30. exp Stroke/ or stroke.mp.

31. exp Paraplegia/ or paraplegia.mp.

32. Renal Failure$.mp. or exp Renal Insufficiency/

33. endoleaks.mp. or exp Endoleak/

34. exp Long-Term Care/ or long$ term.mp.

35. exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ or survival.mp.

36. 29 or 30 or 31 or 32 or 33 or 34 or 35

37. 4 and 27 and 36

38. limit 37 to (english language and humans and yr="1990 -Current")

39. 4 and 28 and 36

40. limit 39 to (english language and humans and yr="1990 -Current")

41. cost$.mp.

42. economic$.mp.

43. 41 or 42

44. 4 and 27 and 43

45. 4 and 28 and 43

46. limit 45 to (english language and humans and yr="1990 -Current")

Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2013

#1 (Aortic Aneurysm) or (Thoracic Aorta) or (Thoracic Aortic Aneurysm) or (Degenerative Aneurysm) or (Dissecting Aneurysm) or (chronic type A dissection) or (acute type A dissection) or (Dissecting Aneurysm)

#2 (E-vita open) or (hybrid stent graft$)

#3 (elephant trunk) or (elephant trunk procedure) or (elephant trunk technique) or (aortic arch replacement) or (thoracic stent graft) or (open stent graft$)

#4 (open surgical debranch$) or (branched graft$)

#5 (endovascular stent graft$) or (endovascular stent)

#6 (mortality) or (stroke) or (paraplegia) or (Renal Failure$) or (endoleaks) or (Long$ term) or (Survival Rate$)

#1 and #2 and #6

#1 and #3 and #6

#1 and #4 and #6

#1 and #5 and #6

ECONLIT (13 May 2013)

(E-vita adj3 open) AND (aortic aneurysm OR type a aortic dissection) AND (cost$ OR economic$)

(elephant adj3 trunk) AND (aortic aneurysm OR type a aortic dissection) AND (cost$ OR economic$)

((branched graft$) OR (open surgical debranch$)) AND (aortic aneurysm OR type a aortic dissection) AND (cost$ OR economic$)

((endovascular stent graft$) or (endovascular stent)) AND (aortic aneurysm OR type a aortic dissection) AND (cost$ OR economic$)

NHS EED and HTA Databases (13 May 2013)

1 ((E-vita adj3 open) or (hybrid adj3 stent adj3 graft$)) OR ((elephant adj3 trunk) OR (elephant adj3 trunk adj3 procedure) OR (elephant adj3 trunk adj3 technique)) OR ((aortic adj3 arch adj3 replacement) OR (thoracic adj3 stent adj3 graft) OR ((open surgical debranch$) or (branched graft$)) OR ((endovascular stent graft$) or (endovascular stent))) IN NHSEED, HTA FROM 1990 TO 2013

2 (((((Aortic Aneurysm) OR (Thoracic Aorta) OR (Thoracic Aortic Aneurysm) OR (Degenerative Aneurysm) OR (Dissecting Aneurysm)) OR ((chronic type A dissection) OR (acute type A dissection) OR (Dissecting Aneurysm))))) IN NHSEED, HTA FROM 1990 TO 2013

3 #1 AND #2