NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

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

Sponsor: JOTEC GmbH

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Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Figure 1	Incidence of thoracic aortic diseases in the Swedish population (men and women), 1987–2002 (cases per million) [3]
Figure 2	Operations for thoracic aortic aneurysms and dissection in the Swedish population (men and women), 1987–2002 (operations per million) [3]
Figure 3	Survival rates for patients with an occluded false lumen are 90% at 10 years and with a patent false lumen 60% at 10 years [30]
Figure 4	Freedom from re-treatment on the descending aorta for patients with an occluded false lumen are 94% at 10 years and with a patent false lumen 64% at 10 years [30]

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Glossary of terms

Term	Definition
E-vita open plus method	One-stage elephant trunk procedure for treating complex aneurysms and dissections of the thoracic aorta
Classical ET	Two stage open surgical repair with vascular graft placement
ET modern approach	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
IEOR	International E-vita open Registry with anonymous registration and calculation at Essen University Hospital.
AAD	Acute aortic dissection
CAD	Chronic aortic dissection
TAA	Thoracic aortic aneurysm

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Aneurysms: 5-10 / 100,000 people Dissection: 3-4 / 100,000 people	Aneurysms: No variation Dissection: 0.5-3.5 / 100,000 people	See [2, 6]
Intervention	E-vita open plus	No variation	-
Comparator(s)	See scope, p 6	No variation	-
Outcomes	See scope, p 6	The total length of stay was not considered	Data were not available in the published literature
Cost analysis	See scope, p 6	-	-
Subgroups to be considered	See scope, p 7	No variation	-
Special considerations, including issues related to equality	See scope, p 7	No variation	-

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

E-vita open plus

<table>
<tr><td rowspan="9">Product Nomenclature

(Catalogue numbers)</td><td><u>71AC2424S15-PL</u></td><td>Product group
71 = E-vita open plus</td></tr>
<tr><td><u>71AC2424S15-PL</u></td><td>Proximal configuration
AC = Aortic Cuff
SO = Straight Open
ST = Twin Stent</td></tr>
<tr><td><u>71AC2424S15-PL</u></td><td>Proximal diameter [mm]</td></tr>
<tr><td><u>71AC2424S15-PL</u></td><td>Distal diameter [mm]</td></tr>
<tr><td><u>71AC2424S15-PL</u></td><td>Distal configuration
S = Straight Cut
ST = Twin Stent
SO = Straight open</td></tr>
<tr><td><u>71AC2424S15-PL</u></td><td>Covered stent length [cm]</td></tr>
<tr><td><u>71AC2424S15-PL</u></td><td>Product identification</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Variations</td><td colspan="2">E-vita open plus stent graft can be manufactured with different stent graft dimensions, cuff dimensions and stent graft configurations.

Following the possible variations:

<u>71ACXXYYSZZ-PL</u> (drawing)
<u>71ACXXYYSOZZ-PL</u>
<u>71ACXXYYSTZZ-PL</u>

<u>71SOXXYYSZZ-00</u>
<u>71SOXXYYSOZZ-00</u>
<u>71SOXXYYSTZZ-00</u>

<u>71STXXYYSZZ-00</u>
<u>71STXXYYSOZZ-00</u>
<u>71STXXYYSTZZ-00</u>

YY = Distal diameter: 24mm – 40mm
ZZ = Covered length: 80mm – 240mm

Diameter cuff: 24mm – 40mm
Length cuff: 10mm – 150mm</td></tr>
</table>

2.2 What is the principal mechanism of action of the technology?

E-vita open plus is specifically designed for one-stage surgical repair in complex thoracic aortic diseases through median sternotomy in an elephant trunk like fashion.

It´s means an exclusion of blood circulation trough a targeted diseased section of the transverse and proximal descending aorta via a vascular graft implanting surgery combined, in the same stage, with an antegrade endoluminal stentgrafting of the proximal part of the descending thoracic aorta.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

The E-vita open plus vascular graft prosthesis is used for repair or replacement of damaged or diseased vessels of the thoracic aorta in cases of **aneurysms or dissections**. The device is intended only for use in hospital settings.

Thoracic Aortic Aneurysm

A Thoracic Aortic Aneurysm (TAA) is a localized, blood-filled dilatation of the thoracic aorta. Patients with thoracic aneurysms are often asymptomatic until the aneurysm expands. Their most common presenting symptom is pain. Pain may be acute, implying impending rupture or dissection, or chronic, from compression or distension. TAA is a serious life threatening condition because it can burst or rupture. A ruptured aneurysm can cause severe internal bleeding, which can rapidly lead to shock or death.
The life expectancy of untreated patients with aortic aneurysms is limited, with death occurring within 5 years from rupture and/or associated diseases in more than 75% of the cases [1]. The incidence of TAA rupture is 3.5 per 100,000 persons per year [2]. 22% of patients with a ruptured thoracic aorta do not reach the hospital alive [3]. For this reason, it is crucial to treat aneurysms early, in order to prevent their rupture. Aneurysms of the descending thoracic

aorta account for approximately 30% to 40% of all TAAs that are now estimated to affect 10 of every 100’000 elderly adults [4].

The overall prevalence of aortic aneurysms has increased significantly over the last 30 years. This is partly due to an increase in diagnosis based on the widespread use of imaging techniques. However, the prevalence of fatal and nonfatal rupture has also increased, suggesting a true increase in prevalence, probably due to an aging patient population [5,4, 3]. Figure 1 and Figure 2 show the increasing trend in incidence for thoracic aortic diseases and the number of operations per million people over the past year for the Swedish population. The increasing trend is basically the same for the other European population.

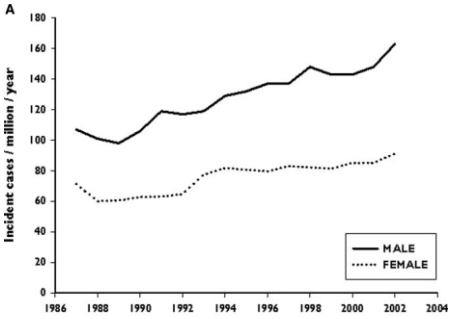


Figure 1: Incidence of thoracic aortic diseases in the Swedish population (men and women), 1987–2002 (cases per million) [3]

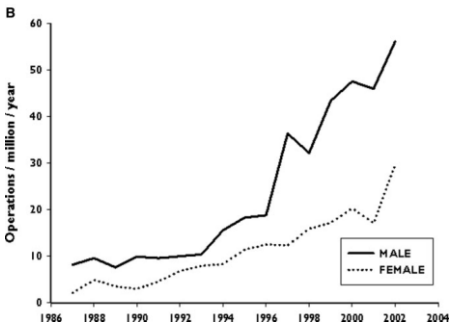


Figure 2: Operations for thoracic aortic aneurysms and dissection in the Swedish population (men and women), 1987–2002 (operations per million) [3]

Thoracic Aortic Dissection

A Thoracic Aortic Dissection is a separation of the walls of the thoracic aorta caused by an intimal tear. A false passage for blood develops between the layers of the aorta. This false lumen may extend into branches of the aorta in the chest or abdomen, causing malperfusion, ischemia, or occlusion with resultant complications. The dissection can also progress proximally, to involve the aortic sinus, aortic valve, and coronary arteries. Dissection can lead to aneurysmal change and early rupture, which represents a life-threatening emergency.

Population-based studies suggest an incidence of aortic dissection of at least 0.5 to 3.5 per 100,000 persons [2, 6]. The estimated rate of increase in incidence was 1.26 per 100’000 persons per 5 years [2] (over 15 years).

Moreover, 21% to 26% of aortic dissections die prior to hospital admission and up to 58% to 68% of acute dissection cases die prior to definitive operative intervention [7,8]. If not treated about 74% of patients die within the first two weeks [9]. Less than 10% of untreated patients with proximal aortic dissections live for one year, and almost all patients die within 10 years [6 ,7].

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

The state ‘of the art method for the treatment of complex thoracic aortic diseases is the two steps classical ET as described in 3.3.
Stent-graft placement in thoracic aneurysms is described in IPG 127: Endovascular stent-graft placement in thoracic aortic aneurysms and dissections (IPG127). A systematic review of the recent evidence for the efficacy and safety relating to the use of endovascular stent-graft (ESG) placement in the treatment of thoracic aortic disease. But this guideline does not include ascending aorta and aortic arch.

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

Treatment of complex thoracic aortic diseases involves surgical repair in good-risk patients who are at increased risk for rupture. Complex thoracic aortic diseases involving large aneurysms and dissections of the ascending aorta, the aortic arch and the descending aorta represent a challenge in cardiothoracic surgery.

Two-stage classical ET

The classic approach for the treatment of complex thoracic aortic diseases is the two-stage elephant trunk (ET) procedure. The introduction of the classical

ET by Borst et al. in 1983 was an important step to facilitate surgical repair of complex thoracic aortic diseases and is a well-established method [10]. Nevertheless, this surgical procedure is a highly invasive approach associated with a high mortality and morbidity for the patient.

The classic surgical strategy is a two-stage operation. In the first operation, the ascending aorta and the aortic arch are replaced with vascular graft prosthesis via a midline sternotomy. In the second operation, the descending aorta is replaced via a lateral thoracotomy.

The cumulative mortality of this surgical strategy remains substantial in that the two operations may sum up to a mortality of an estimated 30%; see also Table.13. Furthermore, the waiting period between the stages is associated with a mortality rate between 12% to 25% [11, 12, 13, 14] of its own since the descending aorta remains untreated after the first stage operation.

Importantly, a respected study by Etz et. al [11] showed an 89% mortality rate in patients who did not return for second stage completion at a median interval of only 4 months period. Moreover, the two-stage strategy has an inherent limitation, due to the co morbidity and advanced age of the majority of patients. Therefore, the second stage cannot be offered to up to 50% of patients [11,12]. New developments and improvements in aortic surgery were introduced to overcome these shortcomings and to simplify the surgical repair.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

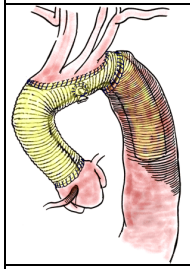
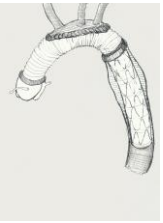
Response to question 3.3 is consistent with the relevant NICE clinical guideline.

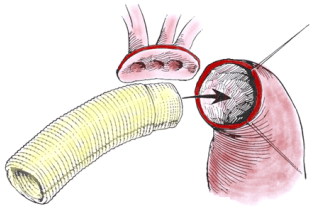
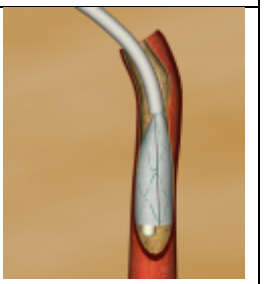
3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

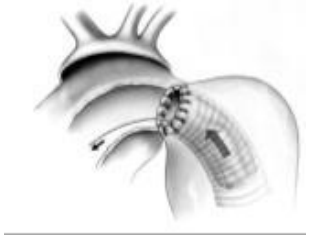
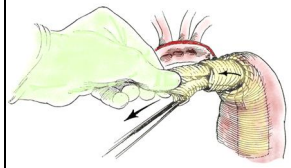
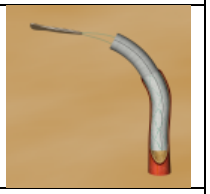
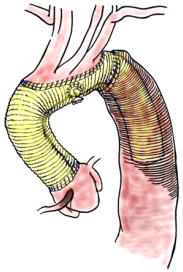
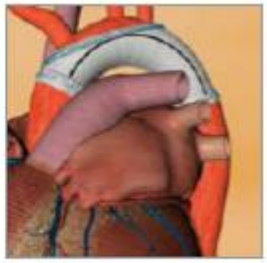
The surgical technique to implant E-vita open plus is basically the same as a first stage classic ET. The supported elephant trunk allows repair of the descending aorta during the first stage procedure and therefore a second

stage procedure can be avoided. This one stage approach allows for repair of complex thoracic aortic disease in patients who do not qualify or have a contraindication to a second stage repair. A detailed side by side comparison of the use of E-vita open plus compared to the classic elephant trunk technique is included in Table 1

Table 1: Overview surgical repair with classical ET two-stage procedure compared to one-stage surgical repair with E-vita open plus

Two stage classical ET	One stage elephant trunk like procedure with E-vita open plus
In 1983, Borst and colleagues introduced the classical ET . The classical ET is a two-stage procedure used to treat complex thoracic aortic diseases involving both the ascending aorta and aortic arch, and the descending thoracic or thoracoabdominal aorta.	The E-vita open plus vascular graft prosthesis is specifically designed for one-stage repair of complex thoracic aortic diseases, involving both the ascending aorta and aortic arch, and the descending thoracic aorta in an elephant trunk like fashion. The E-vita open plus vascular graft prosthesis was first introduced to the market in 2005. The device is CE-marked and approved for clinical use in Europe.
The first stage of this procedure involves the prosthetic replacement of the ascending aorta and the aortic arch with an elephant trunk extension of the arch graft into the descending aorta through a median sternotomy.	Same fundamental principle. The one-stage procedure involves the prosthetic replacement of the ascending aorta and the aortic arch with an elephant trunk extension of the arch graft into the descending aorta through a median sternotomy.
 The elephant trunk is a free-floating extension of the arch prosthesis, which is left behind in the proximal descending aorta. This free-floating extension does not have any apposition or sealing in the descending aorta. In a mandatory second-stage operation, the elephant trunk must be extended to the desired level through an additional lateral thoracotomy to replace the descending aorta.	The E-vita open plus is a modified vascular graft prosthesis in that the elephant trunk extension of the device is a supported segment with fixed nitinol springs. Due to this fixation the elephant trunk is not free-floating in the descending aorta. The supported elephant trunk covers the damaged section of the descending aorta right after its insertion, which avoids a second stage operation for the patients. 
With the classic elephant trunk surgical repair, there is a peri-operative in-hospital mortality and morbidity associated with the first stage procedure as well as added mortality and morbidity during both the second stage procedure and the interval between the two procedures. Up to 50% of patients (in particular elderly patients > 60 years) do not even qualify for a second stage in case co-morbidities exist [11, 15]. This means these patients are still subject to the significant risks imposed by the underlying thoracic aortic disease.	The one-stage procedure with the E-vita open plus vascular graft prosthesis is also associated with a peri-operative in-hospital mortality and morbidity. By avoiding the second stage surgical repair, the associated risks to the patient from interval and second stage mortality and morbidity is eliminated. In addition patients who do not qualify for a second stage operation can be offered with a complete surgical treatment.
An important advantage of leaving behind an elephant trunk is the avoidance of a difficult and hazardous dissection in the region of the distal aortic arch where arterial, venous, neural, bronchial, esophageal and lymphatic structures cross. Using this procedure, the risk of damage to one of these structures can be reduced.	Same principle; this important advantage of the classic ET is also achieved in surgical repair using the E-vita open plus vascular graft prosthesis.

<table>
<tr><th>Two stage classical ET</th><th>One stage elephant trunk like procedure with E-vita open plus</th></tr>
<tr><td colspan="2">Preparing the 1st stage surgical procedure</td></tr>
<tr><td>Prior to the procedure, the dimensions and properties of the diseased aortic section must be determined by means of suitable imaging techniques with the emphasis on vessel diameter and condition.</td><td>Same preparation as for the classical ET.</td></tr>
<tr><td colspan="2">Preparing the graft for implantation</td></tr>
<tr><td>The classical ET using a standard thoracic vascular graft (e.g. Hemashield platinum) requires invagination of the elephant trunk into the main body of the graft.
The main body of the graft is then pulled back for eventual proximal repair after completion of the distal anastomosis. This is done with a heavy retracting suture previously placed on the elephant trunk tip.
.</td><td>A preparation of the implant itself is not required.
The E-vita open plus vascular graft is preloaded in a delivery system and ready to use. The arch portion of the graft is already invaginated into the elephant trunk extension and a stay suture is already attached to the end of the future proximal arch portion during the manufacturing process.
Prior to surgical incision a transoesophageal echocardiography (TEE) guided stiff wire placement is required to allow for optimal tracking of device delivery.</td></tr>
<tr><td colspan="2">Antegrad insertion of the graft</td></tr>
<tr><td> 
After transection of the distal aortic arch, the whole graft is inserted into the descending aorta in an antegrad fashion.</td><td>After transection of the distal aortic arch, the delivery system with the preloaded graft is inserted into the descending aorta in an antegrad fashion.
After complete insertion of the supported elephant trunk segment into the descending aorta, a switch on the handle releases a lever which turns the delivery system to operating mode.
The self-expanding E-vita open plus supported elephant trunk section is released by retracting the outer sheath of the delivery system against the pusher handle.
 
After complete expansion of the supported elephant trunk section, the delivery system is removed from the vascular system.</td></tr>
</table>

Two stage classical ET	One stage elephant trunk like procedure with E-vita open plus
Fixation of the trunk on the descending aorta	
 For standard vascular grafts (e.g. Hemashield platinum) the anastomosis is created between the fold or crest in the invaginated prosthesis and the aortic wall. For the Siena graft the anastomosis is to the collar of the device. A variety of suture techniques can be used. Pre-clotting of the device is not required.	The invaginated aortic arch portion is retracted 5-10 mm proximally and the anastomosis is created between the E-vita open plus graft prosthesis and the aortic wall. A variety of suture techniques can be used. Pre-clotting of the device is not required.
Full retraction of the invaginated prosthesis	
 Upon completion of the distal anastomosis, the stay suture is retrieved via the lumen of the graft, retracting the total length of the invaginated portion.	Upon completion of the distal anastomosis, the total length of the invaginated portion is retracted by pulling the stay suture. 
Completion ascending and aortic arch repair	
 From that point the operation proceeds like conventional ascending and aortic arch replacement. At the completion of the thoracic aortic reconstruction, the unsupported elephant trunk segment is free-floating (dangling) in the descending aorta.	From that point the operation proceeds like conventional ascending and aortic arch replacement. The supported elephant trunk segment either excludes the aneurysmal portion of the descending aorta or expands the true lumen with obliteration of the false lumen in aortic dissection. The supported segment restores the dissected descending aorta to its optimal diameter. This avoids a second stage operation. 
2nd stage procedure	
At the second stage, via left thoracotomy, a completion descending aortic procedure must be performed if a definitive treatment is desired and patients qualify for a second stage operation.	A second stage procedure is not required.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

The classic approach for the treatment of complex thoracic aortic diseases is the classic two-stage elephant trunk (ET) procedure. At the second stage, via left thoracotomy, a completion descending aortic procedure must be performed.

By using E-vita open plus a second intervention procedure is not required.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

The following equipment is required for the implantation of an E®-vita open plus stent graft:

A radiographic image converter with digital angiography function (mobile C-arch device or stationary angiography system). Fluoroscopic visualization and facilities for recording and call-up of all images.

All patients must be carefully monitored and undergo regular check-ups to determine changes in their pathological status and the function and integrity of the stent graft.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

The following equipment is required for the implantation of an E-vita open plus stent graft:

A radiographic image converter with digital angiography function (mobile C-arch device or stationary angiography system). Fluoroscopic visualization and facilities for recording and call-up of all images.

Important: The implantation procedure must be carried out by a physician trained in endovascular techniques (cardiovascular, thoracic or vascular surgeon).

Materials required for the implantation procedure:

• Various guide wires with a length of 180cm
• A stiff coated guide wire measuring 0.035" (0.87mm) in diameter and 180cm in length, preferably the JOTEC E-wire
• Various angiography catheters
• Contrast medium
• Sterile syringes
•Heparin and heparinized physiological saline solution.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

The second stage surgery via left thoracotomy, is no longer necessary

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

By using E-vita open plus a second intervention procedure is not required.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use

- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- Quality systems (ISO 13485) certificate (if required).

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The E-vita open vascular graft prosthesis was first introduced to market in 2005. The E-vita open plus was launched in October 2008. The device is CE-marked and in clinical use in Europe.

One of the currently participating centres in International E-vita Open Registry is: Department of Cardiothoracic Surgery, University Hospital Birmingham, NHS Foundation Trust, Birmingham, UK

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The technology is described for the CE marked Stent Graft System E-vita open plus. The use of hybrid prosthesis for resection or interposition of the thoracic aorta is listed in the German-Diagnosis Related Groups (G-DRG) as F05Z.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Inapplicable

4.5 If the technology has been launched in the UK provide information on the use in England.

The technology is described for the CE marked Stent Graft System E-vita open plus. The product launch for the first generation E-vita

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Market and complaint history

The E-vita open vascular graft prosthesis was first introduced to the market in 2005. The device is CE-marked and in clinical use in Europe. As of end of 2012, 2695 devices are on the market and a total of 16 complaints have been received. The market and complaint history is summarized in Table 2 and 3 below.

Table 2. Market and complaint history

Year	2005	2006	2007	2008	2009	2010	2011	2012	Total
	86	187	229	328	438	426	505	496	2695
	1	1	0	2	4	4	2	2	16

Complaints were mainly related to problems with the release of the E-vita open/E-vita open plus vascular graft prosthesis. The results of investigation and corrective actions are summarized the complaint summary in Table 3

Table 3: Complaint Summary

Reason for complaint	No. complaints	Root causes(s)	Corrective actions
Problems with the release of the graft	1	Production error of a single device	Functional test implemented into routine production
	2	Guide wire not used	None, need for a guide wire described in the IFU and training materials
	2	Size of the aorta was too small to implant the device	None, IFU and device training contains detailed sizing instructions
	1	Lever broken	Protective wires inserted to increase the stiffness
	4	Unknown (3x product not returned for investigation) (1x release mechanism performed as intended during the investigation)	None
	1	The olive tip was caught in a fold of the	None

Reason for complaint	No. complaints	Root causes(s)	Corrective actions
		cuff (which was not pulled out yet). Therefore the whole system, including the Stent graft was pulled out of the aorta without harming the patient. Instead of the 40 mm implant a 36 mm E-vita open plus was implanted successfully.	
	1	Stent graft was pulled out of the aorta	None
	2	Squeeze to release mechanism did not work	None, failure could not be reproduced during investigation. Mechanism performed as intended and was within specification
Bleeding	1	Pre-clotting of the device not performed	Design improved, pre-clotting is no longer required
Death of the patient, seroma fluid developed after implantation	1	unknown	none

An International E-vita Open Registry (IEOR)

Another relevant clinical data is European multicentre registry. The IEOR is an **observational study** and is based upon data of eight European cardiovascular surgery departments (Barcelona, Birmingham, Bologna, Essen, Gratz, Leipzig, Prague and Vienna-Hietzing) and has been established to follow-up patients with the E-vita open vascular graft prosthesis [18].

In this observational study (open register) we don´t have:

- permission from an institutional review board (IRB), also known as an independent ethics committee (IEC)
- clinical trial protocol.
- trial design
- clinical monitoring - during registry
- primary safety endpoint
- primary effectiveness endpoint

Between January 2005 and December 2010 the data of 274 patients treated with the E-vita open vascular graft prosthesis were entered to the registry. The registry data are summarized in the following sections.

Patient characteristics

Table 4: Patient characteristics

	Dissections	Aneurysms	Total
Number of patients	N = 190	N = 84	N = 274
Age	58 ± 12	66 ± 9	60 ± 12
Male	150 (79%)	54 (64%)	204 (74%)
Emergency surgery	81 (43%)	5 (6%)	81 (30%)

Postoperative data

Table 5: Postoperative data

	Dissections	Aneurysms	Total
Number of patients	N = 190	N = 84	N = 274
Hospital stay, days	20	18	19
In-hospital mortality	29 (15%)	12 (14%)	41 (15%)
Reexploration for bleeding	54 (28%)	9 (11%)	38 (14%)
Dialysis permanent	5 (3%)	5 (6%)	10 (4%)
Stroke	8 (4%)	8 (10%)	16 (6%)
Spinal cord injury	13 (7%)	9 (11%)	22 (8%)

Follow-up data and survival rates

Actuarial survival rate after five years (all patients included) was 74%. Freedom from secondary endovascular intervention and secondary surgery distally was 82% and 95%.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

There are no limitations in the population. However, there are some contraindications.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

There are no limitations in the population. However, there are some contraindications.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

There are no limitations in the population. However, there are some contraindications.

Contraindications

The E-vita open plus stent graft system is contraindicated in the following situations:

- Patients whose vessel and/or aneurysm size is not suitable for treatment with the E-vita open plus stent graft system.
- Patients whose aneurysm or vascular disease includes vitally important vessel branches (visceral and renal arteries).
- Patients whose aorta features a pronounced curve in the distal landing zone of the E-vita open plus stent graft.
- Patients in whom materials required for this kind of implantation cannot be used (see below).

The therapeutic indications must be very carefully considered in the following case:

- Patients with systemic or local infections and the potential for a bacterial infection of the stent graft

Important: The final decision must be made by the treating physician.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

The literature search was restricted to the period of the last seven years, which corresponds to the period for E-vita open on the market. Basically all types of publications, including case reports were used. Literature in other languages than English and German were covered by their English summaries.

Search terms	Items found	Relevant items
e-vita open	18	13

Not relevant publications, rationale:

- Initial experience with abdominal aneurysm repair using the E-vita abdominal stent-graft: a single-centre study." Relates to another product – E-vita abdominal.
- Management of postdissection thoracoabdominal aneurysm after previous frozen classical ET with the E-vita Open Plus stent-graft." - PubMed – publication in process, only abstract available
- Treatment of chronic aortic type A dissection with new designed hybrid prosthesis" Case report - (Marfan Syndrom), low level of evidence.
- The frozen elephant trunk: an interesting hybrid endovascular-surgical technique to treat complex pathologies of the thoracic aorta." Case report, low level of evidence.
- Repair of multiple aneurysms of the thoracic aorta with a hybrid prosthesis" – Case report, low level of evidence

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Not applicable

7.2 Study selection

Published studies

Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table 6 Selection criteria used for published studies

Inclusion criteria	
Population	Adults only
Interventions	Treatment of complex pathologies of the thoracic aorta as aneurysms and dissections with E-vita open plus, method
Outcomes	In-hospital mortality, 30 day mortality, 1,3 or/and 5 years survival rate
Study design	Retrospective study, observative registry data
Language restrictions	English, German
Search dates	2005-2012
Exclusion criteria	
Population	Children and contraindications for E-vita open
Interventions	Abdominal aorta
Outcomes	Not defined
Study design	Case reports
Language restrictions	Other than English, German
Search dates	Older than 2005

7.2.1 Report the numbers of published studies included and excluded at each stage in an appropriate format.

14 studies are included

Unpublished studies

7.2.2 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Unpublished studies aren't available.

Table 7 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Not applicable
Interventions	Not applicable
Outcomes	Not applicable
Study design	Not applicable
Language restrictions	Not applicable
Search dates	Not applicable
Exclusion criteria	
Population	Not applicable
Interventions	Not applicable
Outcomes	Not applicable
Study design	Not applicable
Language restrictions	Not applicable
Search dates	Not applicable

7.2.3 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Not applicable

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

As there are no clinical studies available for JOTEC, we used as main data source publications of results based on the International E-vita open Registry with anonymous registration and calculation at Essen University Hospital. (IEOR).
As second data source published observations studies of single centers were used.

Some authors: Lifftman K. or EVAR trial participants. (Lancet 2005; 365: 2187–92) claim that open registers provide comparable data such as randomized trials but with much less effort. It is true under the special condition, that only the data of reliable centres are included.

The publications are listed according to their date of publication. Articles based on IEOR are highlighted in green.

Table 8 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
[17]	*Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance*	77 patients The mean age 59 years, 75% male	complex thoracic aortic disease	Not available
[18]	*The International E-vita Open Registry: data sets of 274 patients*	274 patients The mean age 60; 74% males	complex thoracic aortic disease	Classic elephant trunk technique [24] [25] and frozen elephant trunk technique
[19]	*Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection*	32 patients	acute type A aortic dissection	Not available
[20]	*Repair of stent graft-induced retrograde type A aortic dissection using the E-vita open prosthesis.*	29 patients	Retrograde aortic dissection type A	Not available
[21]	*The frozen elephant trunk for the treatment of chronic dissection of the thoracic aorta: a multicenter experience.*	90 patients The mean age was 57 ± 12 years, 80% of the patients were male.	Chronic dissection of the aorta	Not available

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
[22]	*Multicenter early experience with extended aortic repair in acute aortic dissection: is simultaneous descending stent grafting justified?*	68 patients The mean age 58±12 77% males	Acute aortic dissection	Standard surgery of proximal aorta
[23]	*DeBakey type I dissection: when hybrid stent-grafting is indicated?*	29 patient The mean age 60±12 66% males 16 patient The mean age 54±14 100% males	Acute AD Chronic AD	Classic surgical treatment of acute type I aortic dissection
[24]	*Arch replacement and downstream stent grafting in complex aortic dissection: first results of an international registry.*	106 patients The mean age 57±13 77% male	Acute type I AD in downstream aorta	Conventional surgical repair and frozen elephant trunk
[25]	*Impermeability to blood of the E-vita open plus hybrid stent-graft: experimental and clinical evaluation.*	animal experiments	To evaluate the impermeability to blood of the modified E-vita open plus	Not available
[26]	*Treatment of complex disease of the thoracic aorta: the frozen elephant trunk technique with the E-vita open prosthesis.*	34 patients The mean age 61,7±9,6 85% male	complex pathologies of the thoracic aorta	Classic elephant trunk technique [24]
[27]	*Complex repair of the thoracic aorta with the E-vita open prosthesis.*	24 patients the mean age 62.4+/-9.9 87.5% male	complex aortic pathologies	Classic elephant trunk technique [24], and frozen elephant trunk technique
[28]	*Combined surgical and endovascular repair of complex aortic pathologies with a new hybrid prosthesis.*	7 patients the mean age 62 +/- 11 years 71% male	Complex thoracic aortic aneurysms and dissections	Not available
[29]	*Change of paradigms in the surgical treatment of complex thoracic aortic disease.*	16 patients the mean age 62 +/- 11 years 71% male	Complex thoracic aortic aneurysms and dissections	14 patienten Medtronic Talent

Table 9 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
n.a.	n.a.	n.a.	n.a.	n.a.
n.a.	n.a.	n.a.	n.a.	n.a.

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

"The International E-vita Open Registry: data sets of 274 patients" [18] is the most actual publication based on the IEOR includes the results from several studies published earlier. Therefore, we decided to focus on the results published in this article. We excluded from our analysis articles published before as:

- [20] "Repair of stent graft-induced retrograde type A aortic dissection using the E-vita open prosthesis."
- [21] "The frozen elephant trunk for the treatment of chronic dissection of the thoracic aorta: a multicenter experience"
- [22] "Multicenter early experience with extended aortic repair in acute aortic dissection: is simultaneous descending stent grafting justified?"
- [23] "DeBakey type I dissection: when hybrid stent-grafting is indicated?"
- [24] "Arch replacement and downstream stent grafting in complex aortic dissection: first results of an international registry"
- [26] "Treatment of complex disease of the thoracic aorta: the frozen elephant trunk technique with the E-vita open prosthesis"
- [27] "Complex repair of the thoracic aorta with the E-vita open prosthesis"
- [29] "Change of paradigms in the surgical treatment of complex thoracic aortic disease

Further excluded article:

- [25] "Impermeability to blood of the E-vita open plus hybrid stent-graft: experimental and clinical evaluation." - animal experiments
- [28] "Combined surgical and endovascular repair of complex aortic pathologies with a new hybrid prosthesis." Only very few patients (7 patients), low level of evidence.

In the following, we summarized the results of three published articles, two based on the data of the IEOR and one observational single center study [17,18,19,]

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table 10 Summary of methodology for randomised controlled trials

Randomised controlled trials aren't available.

Study name	n.a.
Objectives	n.a.
Location	n.a.
Design	n.a.
Duration of study	n.a.
Sample size	n.a.
Inclusion criteria	n.a.
Exclusion criteria	n.a.
Method of randomisation	n.a.
Method of blinding	n.a.
Intervention(s) (n =) and comparator(s) (n =)	n.a.
Baseline differences	n.a.
Duration of follow-up, lost to follow-up information	n.a.
Statistical tests	n.a.
Primary outcomes (including scoring methods and timings of assessments)	n.a.
Secondary outcomes (including scoring methods and timings of assessments)	n.a.

Table 11 Summary of methodology for observational studies

Study name	Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance [17]
Objective	Treatment of the ascending, arch and descending aortas, relying proximally on a surgical suture line with an integrated distal stent graft for downstream splinting.
Location	Department of Thoracic and Cardiovascular Surgery, West-German Heart Center Essen, University Hospital Essen, Germany
Design	Data collected in the International E-vita Open Registry Mid-term single-centre experience.
Duration of study	January 2005 and March 2011
Patient population	mean age 59 years, male 75%,
Sample size	77 patients, patients with acute (AAD, n = 39) or chronic aortic dissection (CAD, n = 23) and extensive thoracic aortic aneurysm (TAA, n = 15)
Inclusion criteria	acute aortic dissection, chronic aortic dissection and extensive thoracic aortic aneurysm
Exclusion criteria	Children
Intervention(s) (n = 77 and comparator(s) (n =)	E-vita open plus procedure compared with classical ET-procedure. Comparision are descriptive only, and not quantitative
Baseline differences	Higher rate of morbidity and mortality associatied with classical ET
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	The follow-up was 100% over a mean period of 29 months (2–66 months)
Statistical tests	SPSS 19.0 package for statistical analysis Kaplan-Meier analysis
Primary outcomes (including scoring methods and timings of assessments)	30 days mortality – 10% in AAD and 4% in chronic AD and 7% inTAA The late mortality was 16%
Secondary outcomes (including scoring methods and timings of assessments)	According to the CT examination of the aorta, the complete thrombosis of the FL was achieved in 92% (36/39) and 91% (21/23) in patients with AAD and CAD, respectively. In TAA cases,100% exclusion of the aneurysm was achieved

Study name	The International E-vita Open Registry: data sets of 274 patients [18]
Objective	E-vita open Registry was founded in 2008 to study the principles of this treatment algorithm and to control reported favorable single center results on a large patient data set basis up to six years after the first clinical implant.
Location	Eight European referral centers: Barcelona, Birmingham, Bologna, Essen, Graz, Leipzig, Prague and Vienna-Hietzing
Design	Multicenter observational studie
Duration of study	From January 2005 to December 2010
Patient population	The mean age 60; 74% males
Sample size	274 patients
Inclusion criteria	complex aortic disease: acute AD, chronic AD, expanded aortic aneurysm and Marfan Syndrom
Exclusion criteria	Children
Intervention(s) (n = 274) and comparator(s) (n =)	E-vita open plus procedure Comparision with other products and methods (off-label-use frozen elephant trunk) are descriptive only, and not quantitative
Baseline differences	Avoidance of secondary surgical procedure by left lateral thoracotomy
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow-up using CT- or MRI technology. At six month, one year and annually thereafter.
Statistical tests	SPSS 18.0 package for statistical analysis Kaplan-Meier analysis
Primary outcomes (including scoring methods and timings of assessments)	30 days mortality –Total 12% Survival rate after five years 74%
Secondary outcomes (including scoring methods and timings of assessments)	Fate of the false lumen: First CT – Acute AD 83%, Chronic AD 72% Last CT – Acute AD 93%, Chronic AD 92%

Study name	Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection [19]
Objective	The present study explored the safety and effectiveness of sizing the stent graft of the hybrid prosthesis in relation to the total aortic diameter and landing zone
Location	Department of Cardiothoracic and Vascular Surgery, Department of Anesthesiology, and Department of Diagnostic and Interventional Radiology, University Hospital RWTH Aachen, Aachen, Germany
Design	Observational study
Duration of study	November 2009 to September 2011
Patient population	mean age 58±9 years, 81% male
Sample size	32 patients
Inclusion criteria	acute type A aortic dissection
Exclusion criteria	Not described
Intervention(s) (n =) and comparator(s) (n =)	E-vita open plus procedure. Comparision with off-label-use frozen elephant trunk but only descriptive.
Baseline differences	Not described
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	The follow-up was 100% over a period of 17±4 months
Statistical tests	Standart devation
Primary outcomes (including scoring methods and timings of assessments)	The 30-day survival was 100%. The late mortality was 3.1%(1/32)
Secondary outcomes (including scoring methods and timings of assessments)	During follow-up, no endoleaks or false lumen patency developed.

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Not applicable

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

There are no relevant differences in patient populations and methodology. The mean age of Patients in all included studies is about 60 and more then 2/3 of these patients are male. All this studies are either retrospective studies or open register studies. The data were collected in 8 European centres specialised for thoracic and cardiovascular interventions and surgery.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

In general 2 subgroups can be determined: Complex dissection and complex aneurysm of thoracic aorta.

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Not applicable. Randomised studies aren’t available.

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Not applicable. We don’t’ have access to data of single patients

7.5 Critical appraisal of relevant studies.

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables 12 and 13.

Randomised controlled trials aren't available

Table 12 Critical appraisal of randomised control trials

Study name		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	n.a.	n.a.
Was the concealment of treatment allocation adequate?	n.a.	n.a.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	n.a.	n.a.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	n.a.	n.a.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	n.a.	n.a.
Is there any evidence to suggest that the authors measured more	n.a.	n.a.

outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	n.a.	n.a.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table 13 Critical appraisal of observational studies

In section B, clinical evidence, we analysed published data summarizing the data emerged from IEOR. In addition, further publications dealing with E-vita open plus have been considered.

The IEOR observational studies don't have:

- permission from an institutional review board (IRB), also known as an independent ethics committee (IEC)
- clinical trial protocol.
- clear trial design
- clinical monitoring

Therefore, JOTEC does not have access to individual data of IEOR.

Study name	IEOR **Publication: „The International E-vita Open Registry: data sets of 274 patients" [18]**	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	NOT CLEAR	The IEOR was startet in January 2005 to December 2010 at Essen University Hospital, compiling anonymously data from 8 european centers. JOTEC has no access to the data.
Was the exposure accurately measured to minimise bias?	NOT CLEAR	Follow-up time was five years.
Was the outcome accurately measured to	NOT CLEAR	Outcome was shown according to Kaplan Meier analysis. SPSS 18.0 package for statistical analysis was used.

Study name	IEOR **Publication: „The International E-vita Open Registry: data sets of 274 patients“ [18]**	
minimise bias?		
Have the authors identified all important confounding factors?	NOT CLEAR	Distinction between complex aortic dissection (acute and chronic) and complex aneurysm.
Have the authors taken account of the confounding factors in the design and/or analysis?	NOT CLEAR	The E-vita open plus procedure was compared to classical ET procedure, but descriptive only, and not quantitative.
Was the follow-up of patients complete?	NO	The IEOR is a registry with anonymous registration and calculation, therefore the follow-up data are not complete in this publication.
How precise (for example, in terms of confidence interval and p values) are the results?	NOT CLEAR	Statistical analysis of survival and freedom of secondary intervations was performed by using Kaplan-Meier analysis. Confidence interval and p-values are not given.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Control groups aren’t available. Results were compared with existing literature data –see below Table 14.

Table 14 Comparison of different options for surgical treatment of complex thoracic aortic disease

Procedure	Literature source	Mortality after completed surgical treatment*	5y survival	Complications		
				stroke	paraplegia	renal failure
Classical ET procedure						
139 patients	Etz [11]	24.3%	55%	4%	2%	11%
94 patients	Svensson [14]	24,6%	68%	5,3% (stage one)	4.5%	n.a
254 patients	Safi [12]	31,9%	65%	2% (stage one)	9%	n.a
148 patients	LeMaire [13]	41%	52%	5%	9%	n.a
635 patients	**Summary**	**24 to 41% (31.2%)**	**52 to 68%**	**2 to 6%**	**2 to 9%**	**11%**
E-vita open plus procedure						
274 patients	**IEOR [18]**	**15%**	**74%**	**6%**	**8%**	**4%**

Table 15 Outcomes from published and unpublished studies

Study name		**Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance [17]**
Size of study groups	**Treatment**	77 patients
	Control	Not available
Study duration	**Time unit**	January 2005 to March 2011
Type of analysis	**Intention-to-treat/per protocol**	Extensive thoracic aortic disease
Outcome	**Name**	In-hospital mortality
	Unit	77 patients
Effect size	**Value**	10%
	95% CI	Not determined
Other outcome	**Name**	Fate of the false lumen. Last CT, complete thrombosis in patient with **AAD**
	Unit	39 patients
Effect size	**Value**	92%
	95% CI	Not determined
Other outcome	**Name**	Fate of the false lumen. Last CT, complete thrombosis in patient with **CAD**
	Unit	23 patients
Effect size	**Value**	91%
	95% CI	Not determined
Other outcome	**Name**	Exclusion of the aneurysm in **TAA** cases
	Unit	13 patients
Effect size	**Value**	100%
	95% CI	Not determined

Type of analysis	**Intention-to-treat/per protocol**	**Complex thoracic AAD, CAD, TAA**
Other outcome	**Name**	Actuarial survival rate after 5 years
	Unit	77 patients
Effect size	**Value**	79% (AAD-69%; CAD-93%; TAA-85%)
	95% CI	Not determined

Type of analysis	**Intention-to-treat/per protocol**	**Complex thoracic AAD, CAD, TAA**
Other outcome	**Name**	Freedom from secondary endovascular intervention and secondary surgery distaly
	Unit	69 patients
Effect size	**Value**	84% and 96%
	95% CI	Not determined

Comments	Data sampling was prospectively achieved by physicians using database for aortic disease and the SPSS 19.0 package was used for statistical analysis. Continuous variables are presented as the mean ± SD. Categorical variables are presented as a percentage.The Kaplan–Meier analysis was used for the evaluation of survival, freedom from aortic-related death and secondary interventions.

Study name		The International E-vita Open Registry: data sets of 274 patients [18]
Size of study groups	Treatment	274 patients
	Control	Not available
Study duration	Time unit	January 2005 to December 2010
Type of analysis	Intention-to-treat/per protocol	Complex thoracic aortic acute dissection AAD, (88 patients)
Outcome	Name	In-hospital mortality
	Unit	88 patients
Effect size	Value	18%
	95% CI	Not determined
Other outcome	Name	Fate of the false lumen. First CT, complete thrombosis
	Unit	75 patients
Effect size	Value	83%
	95% CI	Not determined
Other outcome	Name	Fate of the false lumen. Last CT (30d follow-up), complete thrombosis
	Unit	56 patients
Effect size	Value	93%
	95% CI	Not determined

Type of analysis	Intention-to-treat/per protocol	Complex thoracic aortic chronic dissection CAD,
Outcome	Name	In-hospital mortality
	Unit	102 patients
Effect size	Value	13%
	95% CI	Not determined
Other outcome	Name	Fate of the false lumen. First CT, complete thrombosis
	Unit	94 patients
Effect size	Value	72%
	95% CI	Not determined
Other outcome	Name	Fate of the false lumen. Last CT (30d follow-up), complete thrombosis
	Unit	67 patients
Effect size	Value	92%
	95% CI	Not determined

Type of analysis	Intention-to-treat/per protocol	Complex thoracic aortic aneurysm TAA
Outcome	Name	In-hospital mortality
	Unit	84 patients
Effect size	Value	14%
	95% CI	Not determined

Type of analysis	Intention-to-treat/per protocol	Complex thoracic AAD, CAD, TAA
Other outcome	Name	Actuarial survival rate after 5 years
	Unit	274 patients
Effect size	Value	74%
	95% CI	Not determined

Type of analysis	Intention-to-treat/per protocol	Complex thoracic AAD, CAD, TAA
Other outcome	Name	Freedom from secondary endovascular intervention and secondary surgery distally
	Unit	274 patients
Effect size	Value	82% and 95%
	95% CI	Not determined

Comments	Continuous values are expressed as mean ± standard deviation or median and interquartile range (range from 25th to 75th percentile). Survival was analysed by Kaplan-Meier analysis and was used for presentation of the survival and freedom of secondary intervention.

Study name		Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection [19]
Size of study groups	**Treatment**	32 patients
	Control	-
Study duration	**Time unit**	Since November 2009 – September 2011
Type of analysis	**Intention-to-treat/per protocol**	Acute type A aortic dissection- AAD
Outcome	**Name**	In-hospital mortality
	Unit	32 patients
Effect size	**Value**	0%
	95% CI	Not determined
Other outcome	**Name**	Fate of the false lumen. Last CT (30d follow-up), complete thrombosis
	Unit	32 patients
Effect size	**Value**	100%
	95% CI	Not determined
Other outcome	**Name**	Freedom from secondary endovascular intervention distally
	Unit	32 patients
Effect size	**Value**	75%
	95% CI	Not determined

Comments	The follow-up was 100% over a period of 17±4 months

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

In-hospital mortality: Fundamental criteria indicating the success of a treatment.

Actuarial survival rate after 5 years

Treatment of complex and extensive thoracic aortic diseases currently has high mortality and morbidity.

Complex and extensive aneurysms of the thoracic aorta are classically treated with a two-stage surgical procedure using a commercially available vascular graft with subsequent distal completion aortic surgery. Full review of this surgical strategy reveals an overall mortality consisting of first stage mortality, interval mortality between procedures and second stage mortality of 24.3% to 41 %(average 31,2%), see Table.

Based on the clinical experience as presented in „**The International E-vita Open Registry: data sets of 274 patients**“[18] in comparison to published literature it can be demonstrated that the concept of one-stage surgical repair reveals an improvement in mortality rates for extensive thoracic aortic diseases from 31,2% to 15% and for actuarial survival rate after 5 years from 60% to 75% respectively.

Freedom from secondary intervention which is strongly correlated with mortality rate

Fate of false lumen

Studies demonstrated that a persistent false lumen in the descending aorta after surgical repair of an acute aortic dissection is a predisposing factor to late downstream aortic mortality [30, 31, 32, 33]. With classic surgical repair, free flow in both the true and false lumen still occurs in over 70% to 89% of cases [31, 32, 33].

New concepts in surgical treatment of the downstream aorta at the time of initial Type A dissection repair, of which the E-vita open plus vascular graft prosthesis is one option presently used in Europe, show remodeling of the downstream aorta with obliteration, thrombus and normalization of the

downstream thoracic aorta in 77% to 100% of cases [32, 34, 33]. A recent review of this operative concept demonstrates a decrease in the serious clinical endpoints of thoracic aneurysm formation, re-operations [35] and long-term mortality [30], see also Figue 3 and Figure 4.

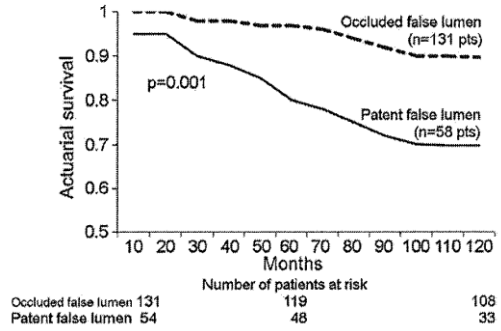


Figure 3: Survival rates for patients with an occluded false lumen are 90% at 10 years and with a patent false lumen 60% at 10 years [30]

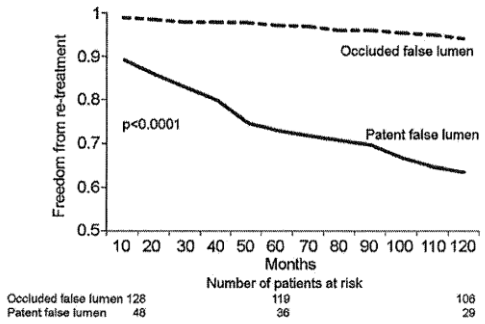


Figure 4: Freedom from re-treatment on the descending aorta for patients with an occluded false lumen are 94% at 10 years and with a patent false lumen 64% at 10 years [30]

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical apprasial and results.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table 16.

Table 16 Adverse events across patient groups

[18] N (%)	Total N=274	AAD N=88	CAD N=102	TAA N=84
Intubation >72h	91(33)	33 (38)	32 (32)	26 (31)
Stroke	16 (6)	5 (6)	3(3)	8 (10)
Spinalcord injury	22 (8)	5 (6)	8 (8)	9 (11)
Dialysis permanent	10 (4)	31 (35)	14 (14)	15 (18)
Re-exploration for bleeding	38 (14)	16 (18)	13 (13)	9 (11)

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

There are no data associated with E-vita open plus stent graft or similar technology in national regulatory databases

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

Risk-benefit discussion

The two-stage classical ET is a highly invasive surgical approach associated with a high mortality and morbidity for the patient. The treatment of the underlying disease is incomplete after the first-stage operation. Moreover, the two-stage strategy has an inherent limitation, because the second-stage cannot be offered to up to 50% of patients due to existing co-morbidities after the first-stage operation and advanced age of the majority of patients.

Therefore, new developments and improvements in aortic surgery were introduced to overcome these shortcomings and to simplify the surgical repair procedure. For example, ET modern approach with stent grafts (TEVAR) implanted in the second-stage is a new emerging therapeutic concept for the treatment of descending thoracic aneurysms.

ET modern approach procedures have an incidence of proximal aortic complications such as serious type 1a endoleaks.These complications are lethal unless addressed through re-intervention. Therefore, continued vigilant surveillance of patients treated with stent grafts is important; however it subjects patients to life-long CTA radiation exposure.

The E-vita open plus stent graft is an improvement over currently marketed stents to achieve one-stage treatment of the thoracic aorta in cases of complex thoracic aortic diseases. The device has been designed to overcome shortcomings of the currently existing surgical approaches. In the following the risks and benefits of using this device compared to elephant trunk and ET modern approach

Benefits:

The one-stage surgical approach (E-vita open plus procedure) allows for a complete and definite treatment at one stage. The descending aorta is treated at the same time as for the ascending aorta and the aortic arch.

The in-hospital mortality rates for the E-vita open plus stent graft are decreased compared to classical ET procedures because the risk of intermediate and second stage mortality is conceptually eliminated. Kaplan-Meier analysis based upon multicenter European registry data reveals comparable 5 year survival rates for the E-vita open plus procedure -74% [18].

Patients who do not qualify for a second-stage classical ET procedure may be provided with a treatment option using one-stage approach with the E-vita open plus procedure. This means that more patients would have access to a surgical treatment option.

Complications associated with ET modern approach procedures such as proximal type 1a endoleaks are conceptually eliminated with the E-vita open plus procedure because the prosthesis is designed as a one-piece polyester tube with a stent graft section.

The E-vita open plus procedure promotes the thrombosis of the false lumen in cases of acute aortic dissections. This operative concept demonstrates a decrease in the serious clinical endpoints of thoracic aneurysm formation, re-operations and long-term mortality. The rational and indication for the use of the E-vita open plus procedure in acute dissections is to allow for a standard classic definitive open proximal procedure, with all of its proven benefits, in addition to providing a new and desirable treatment of the presently residual dissection and diseased downstream aorta.

The device is specifically designed for antegrad insertion into the thoracic descending aorta.

The surgical technique to implant the device is very similar to the first-stage of a classical ET procedure, i.e. there is no big change in the overall surgical procedure.

No gelatine or collagen coating is used in the E-vita open plus procedure to avoid the need for pre-clotting of the device during surgery. The materials used for the E-vita open plus procedure do not bear inherent BSE/TSE risks.

Risks:

The surgical technique to implant the device is very similar to the first-stage of a classical ET procedure, i.e. there is no big change in the overall surgical procedure.

Long-term reliability of the E-vita open plus procedure is not yet established. Until now, 5Y data are available.

The duration of surgical intervention might be extended.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

meta-analysis data isn't available. See 7.6

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

See 7.6.1, Table 14 and Table 15

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Clinical benefit and risk as listed in 7.7.4 are:

- Low mortality rates after completed surgical treatment – 15%
- 5 year survival rates -74%
- Complications associated with modern ET procedures such as proximal type 1a endoleaks are conceptually eliminated with the E-vita open plus
- Almost 100% thrombosis of the false lumen in cases of acute aortic dissections.

- Pernament or regressive stroke in 6% patients
- The incidence of paraplegia or paraparesis – 8%
- Spinal cord injury is about 8%
- The rate of a permanent dialysis is 4%

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

	Stroke	**Paraplegia/ Paraplasia**	**permanent dialysis**	**1a endoleaks**	**5-years survive**
E-vita open plus [18]	6%	8%	4%	0%	74
ET (Table 14)	2-6%	2-9%	11	-	** [14]

**Five-years survive was 34% without a second stage procedure versus 75% 3-years survive with it

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The evidence is based on published data originating from IEOR (a systematic collection of data) and other published data only. A randomized study would violate ethical standards

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The IEOR is a systematic and comprehensive collection of data without precisely defined study design. Therefore, we cannot define any factors that may influence the external validity of the study except for the indications and contraindications mentioned in the indications for use. The results are published in peer reviewed journals.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

The E-vita open plus stentgrafts from JOTEC GmbH have been specifically developed for the treatment of aneurysms, dissections and specific lesions of the thoracic aorta. The indications for the use of the E-vita open plus stentgraft from JOTEC GmbH primarily involve acutely life-threatening patient conditions due to:

- aortic dissections (type Stanford A) extending deep into the descending aorta,
- extensive aortic aneurysms of the ascending aorta or of the aortic arch extending to the descending aorta

The E-vita open plus stentgraft system is contraindicated for Patients:

- Patients whose vessel and/or aneurysm size is not suitable for treatment with the E-vita open plus stentgraft system.
- Patients whose aneurysm or vascular disease includes vitally important vessel branches (visceral and renal arteries).
- Patients whose aorta features a pronounced curve in the distal landing zone of the E-vita open plus stentgraft
- Patients in whom materials required for this kind of implantation can not be used
- Patients with systemic or local infections and the potential for a bacterial infection of the stentgraft

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

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.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studiesis not applicable in the absence of published economic assessments.

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Not applicable.

8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Not applicable**.**

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Not applicable.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

E-vita open plus is a single operation for a complex procedure that currently requires two distinct and separate stages for patients who are seriously ill, with improved morbidity and mortality. The level of potential cost savings appears to be strong and requires quantification.
A problem with the current procedure is the frequency of endo-leaks requiring further surgery. The construction of the E-vita open plus Stent Graft system minimises that and will again reduce costs through less surgery.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

The product is used for the treatment of aneurysms, dissections and specific lesions of the thoracic aorta. The device is intended only for use in hospital settings and used by Cardiovascular, Vascular and Thoracic surgeons.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

The major current method is to perform a 2-stage procedure that is called the "elephant trunk procedure" as detailed in Section A.

- Repair of ascending aorta & arch by median sternotomy.
- Replacement of descending aorta.

In the first stage a free floating extension of the arch prosthesis is left behind- the Elephant Trunk.

Classical Elephant Trunk procedure requires a woven graft to be used in Stage 2 whilst a modern approach is to use an Endovascular Stent. The latter is a faster procedure with higher stent cost but reduced hospital stay. There is limited long term outcome data at this time for the Stent approach but it is included in the economic comparison as its use is a significant part of modern treatment.

Model structure

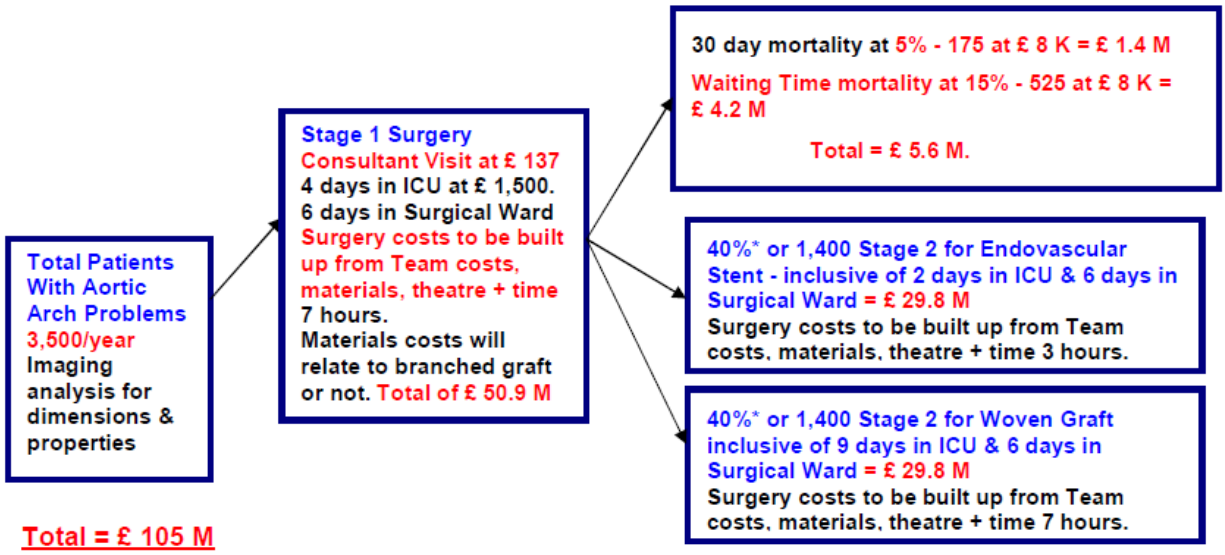
9.1.4 Provide a diagram of the model structure you have chosen.

A decision tree approach has been used and the comparison is between the patient pathway for the current procedure and that if the E-vita open plus device is used. The patient pathways are shown below and the decision tree model allows for variable levels of uptake by the potential surgeon users for their patients.

The Patient Pathways chart includes variables that are built into the model and varied in the sensitivity testing.

The Patient Pathways given here are the basis for the economic model and demonstrate the procedures as currently performed and as would be performed if all were replaced by E-vita open plus.

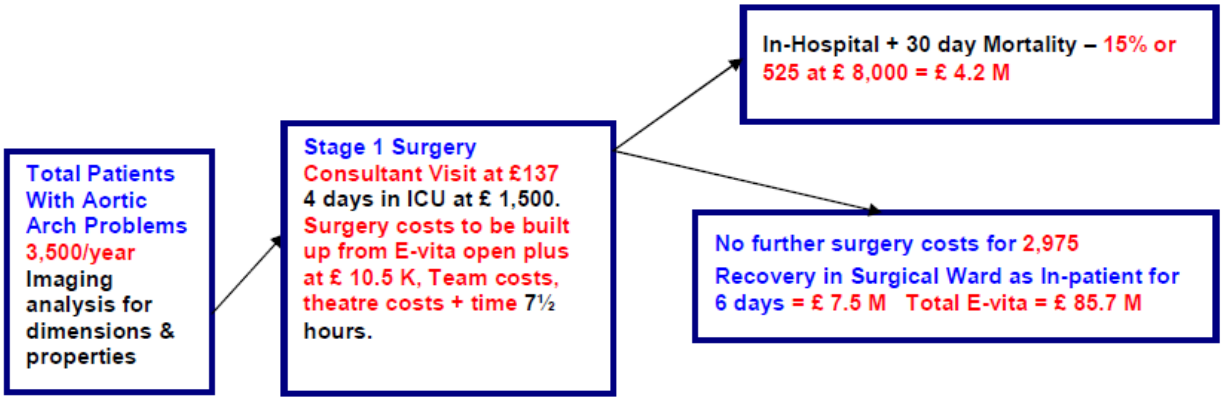
Current Pathway



Total = £ 105 M

* The 80% figure for Stage 2 takes into account all reasons patients do not make the 2nd stage. In the core Model use of Woven Graft or Endovascular Stent is split equally. Variations are assessed in Sensitivity Testing.

E-vita open plus Pathway

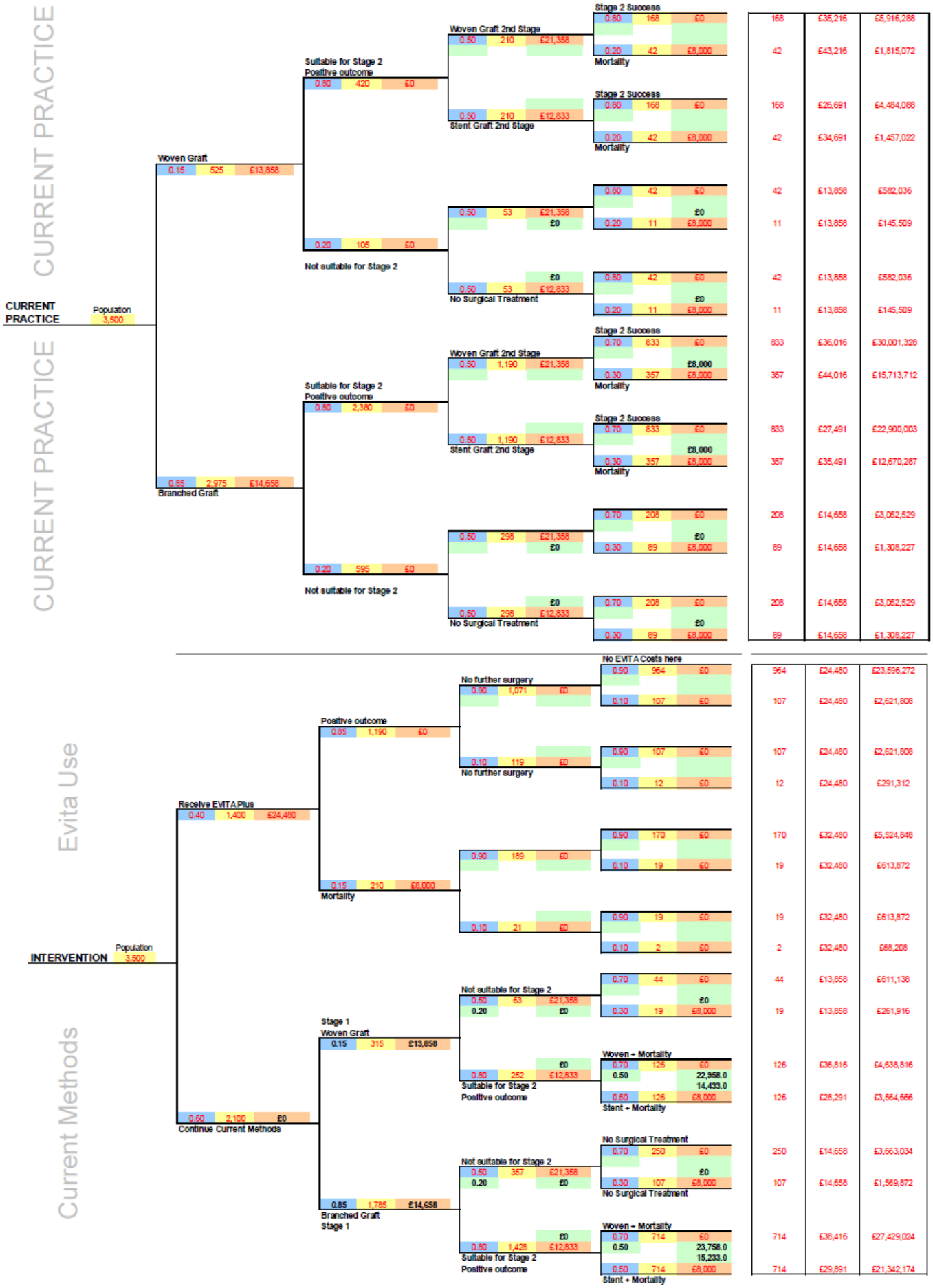


Total = £ 89.9 M

[Cost figures given here are rough indicators before Decision Tree Model & Sensitivity Testing.]

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

With E-vita open plus the two stages seen with the current Elephant Trunk method are performed as a single procedure through median sternotomy. The technology uses an endovascular stent attached to a conventional vascular graft permanently fixed by surgical suture material to a woven polyester covering. It is crimped so that it is like a traditional vascular graft. Within this part of the device is an inverted woven graft extension that once in position can be pulled out to allow surgical repair of the aortic arch. An important feature is that the extension is of low porosity so that no pre-clotting is necessary and requires no further sealing or special sealants.
The decision tree model is shown below for 40% adoption of the E-vita open plus technology. Usage of E-vita open plus is shown with parallel use of current procedures in Chart 2.
The economic model examines the procedural changes for the various cost and time elements as detailed below together with the consequential changes on outcomes.


CURRENT PRACTICE
CURRENT PRACTICE
CURRENT PRACTICE
Population 3,500
Woven Graft
0.15 525 £13,858
Branched Graft
0.85 2,975 £14,658
Suitable for Stage 2
Positive outcome
0.80 420 £0
Not suitable for Stage 2
0.20 105 £0
Suitable for Stage 2
Positive outcome
0.80 2,380 £0
Not suitable for Stage 2
0.20 595 £0
Woven Graft 2nd Stage
0.50 210 £21,358
Stent Graft 2nd Stage
0.50 210 £12,833
No Surgical Treatment
0.50 53 £12,833
Woven Graft 2nd Stage
0.50 1,190 £21,358
Stent Graft 2nd Stage
0.50 1,190 £12,833
No Surgical Treatment
0.50 298 £12,833
Stage 2 Success
0.80 168 £0
Mortality
0.20 42 £8,000
Stage 2 Success
0.80 168 £0
Mortality
0.20 42 £8,000
0.80 42 £0
£0
0.20 11 £8,000
0.80 42 £0
£0
0.20 11 £8,000
Stage 2 Success
0.70 833 £0
£8,000
Mortality
0.30 357 £8,000
Stage 2 Success
0.70 833 £0
£8,000
Mortality
0.30 357 £8,000
0.70 208 £0
£0
0.30 89 £8,000
0.70 208 £0
£0
0.30 89 £8,000
168 £35,216 £5,916,288
42 £43,216 £1,815,072
168 £26,691 £4,484,088
42 £34,691 £1,457,022
42 £13,858 £582,036
11 £13,858 £145,509
42 £13,858 £582,036
11 £13,858 £145,509
833 £36,016 £30,001,328
357 £44,016 £15,713,712
833 £27,491 £22,900,003
357 £35,491 £12,670,287
208 £14,658 £3,052,529
89 £14,658 £1,308,227
208 £14,658 £3,052,529
89 £14,658 £1,308,227
Evita Use
Current Methods
INTERVENTION
Population 3,500
Receive EVITA Plus
0.40 1,400 £24,480
Continue Current Methods
0.60 2,100 £0
Positive outcome
0.85 1,190 £0
Mortality
0.15 210 £8,000
No further surgery
0.10 119 £0
No further surgery
0.90 1,071 £0
0.90 189 £0
0.10 21 £0
Stage 1
Woven Graft
0.15 315 £13,858
Branched Graft
Stage 1
0.85 1,785 £14,658
Not suitable for Stage 2
0.50 63 £21,358
0.20 £0
Suitable for Stage 2
Positive outcome
0.80 252 £12,833
Not suitable for Stage 2
0.50 357 £21,358
0.20 £0
Suitable for Stage 2
Positive outcome
0.80 1,428 £12,833
No Evita Costs here
0.90 964 £0
0.10 107 £0
0.90 107 £0
0.10 12 £0
0.90 170 £0
0.10 19 £0
0.90 19 £0
0.10 2 £0
0.70 44 £0
£0
0.30 19 £8,000
Woven + Mortality
0.70 126 £0
0.50 22,958.0
14,433.0
Stent + Mortality
0.50 126 £8,000
No Surgical Treatment
0.70 250 £0
£0
0.30 107 £8,000
No Surgical Treatment
Woven + Mortality
0.70 714 £0
0.50 23,758.0
15,233.0
Stent + Mortality
0.50 714 £8,000
964 £24,480 £23,596,272
107 £24,480 £2,621,808
107 £24,480 £2,621,808
12 £24,480 £291,312
170 £32,480 £5,524,848
19 £32,480 £613,872
19 £32,480 £613,872
2 £32,480 £68,208
44 £13,858 £611,136
19 £13,858 £261,916
126 £36,816 £4,638,816
126 £28,291 £3,564,666
250 £14,658 £3,663,034
107 £14,658 £1,569,872
714 £38,416 £27,429,024
714 £29,891 £21,342,174

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Item	Unit
Initial consultant visit – cost neutral as required for current & Evita	£ 137 [1]
Surgeon Cost	£ 399/hr. [1]
Assistant Surgeon	£ 131/hr. [1]
Perfusionist & Anaesthetist at Registrar Rate	£ 87/hr. each [1]
Theatre cost inclusive of Nursing & Consumables	£ 24/hr. [2]
Theatre cost inclusive of Nursing & Consumables for ICU	£ 30/hr. [3]
ICU ward In-Patient daily costs	£ 1,500 [4]
Surgical ward In-Patient daily costs	£ 420/day [5]
Number of operations /year = No. of Patient Procedures	3,500 [6,7,8,9]
Proportion of patients receiving Woven Graft at Stage 1	15% [10]
Cost of Woven Graft for Stage 1 & Stage 2 in Classical ET	£ 200 [11]
Cost of Branched Graft at Stage 1	£ 1,000 [11]
Cost of covered Stent Endograph at Stage 2 in modern procedure	£ 5,000 [11]
Cost of E-vita open plus	£ 10,500 [12]
Patient Days - Classical ET Procedures for Stage 1 & Stage 2	10 + 15 days [6]
Patient Days – Endovascular Graft Procedure – Stage 1 & 2	10 + 8 days [13]
Patient Days with E-vita open plus: ICU & Surgical ward	4 + 6 days [13]
ICU Theatre Time for Current Procedures – Stage 1.	7 hrs. [9]
ICU Theatre Time for Current Procedure – Stage 2: Woven & Stent.	7 hrs. or 3 hrs.[9]
Surgical Ward Theatre Time for E-vita open plus	7½ hrs. [13]
Percentage of current patients unsuitable for Stage 2	20% [14]
In-Hospital & Waiting Time mortality rate with current procedure	20% average [15]
In-Hospital mortality rate with E-vita open plus procedure	15% [16]
Cost of Death within NHS	£ 8,000 [17]

The list of references for these parameters and their sources that justifies the figures used is given in 9.2.6.

9.1.7 Define what the model's health states are intended to capture.

The primary health state is related to clinical outcome success for use of E-vita open plus compared with the general options for the current procedure. The elements that are included and addressed in the economic model are:

- Use of woven graft or branched graft at Stage 1 in the current procedure.
- Savings due to loss when patients do not reach Stage 2 for the current procedure.
- Comparison of In-Hospital deaths for the current and E-vita open plus procedures.
- Overall success rates of the different procedures.

Need for pre-surgery and recovery times in ICU and Surgical wards.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

The impact matrix below addresses this item with only Hospital In-Patient elements important. There will be an impact on PCT or CCG budgets under the new NHS system.

Element / Segment	Hospital In Patients
Are there resource savings?	Yes
Will these rely on Patient Nos?	Individual cost benefits
Are there added value savings?	Yes – Reduced treatment savings for those patients not reaching Stage 2 with current methods.
Are there savings on other purchases?	Yes: reduced treatment savings for those patients not reaching Stage 2 with current methods.
Is there Life Extension or Saving?	Almost certainly: morbidity also
Is it Hospital saving?	Yes – plus reduced ICU costs.
Is it PCT or Other NHS saving?	Bed days as In-Patient rather than ICU costs during recovery.
Is it 3rd Level saving? Carer, Social Services, etc	Indirect and not quantified.
Are there reductions in other costs? H&S, QC, etc	Subsequent social care might be less.
Are there Training or Education Costs or Savings?	For surgeons – to be provided by company.

The Time Horizon of the economic model is the current one year period. This is appropriate since the main focus of the economic model is to determine if there are immediate savings potential for the NHS for the extra costs of the E-vita open plus product. For this reason the model is cash based.

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

The elements elements of the decision tree used in the Economic Model are detailed below. The probabilities were used based on best average levels and varied in the sensitivity testing described in 9.4 below.

Product	Jotec E-vita open plusPlus Open

The detailed components of Cost items are given in the Assumptions sheet of

the main Product Positioning section of this report. a Selection Decision has no cost but is allowed for in the pathway probabilities.

Cell Change (C/C) means that the Input Data item for that cell has been over ridden although it remains in another cell within the decision tree layout. Such changes are indicated by C/C and are highlighted in bold on the decision tree. Titles of boxes have been changed to fit this analysis.

Current Pathway

Colum Number	Factors (Blue Cell)	Pathway Item with Unit costs (Yellow Cell for Patient Nos.)	Element Costs	Total Cost (Pink Cell)
Start point	3,500	The Total target population is as recorded in the HES data for 2011.		
Col.1 **Selection for Woven or Branched Graft** **Stage 1**	15%	4 days in ICU @ £ 1,500	£ 6,000	
		6 days in Surgical @ £ 420	£ 4,520	
		7 hr. Theatre at £ 30	£ 210	
		7 hr. Surgery Team at £ 704	£ 4,928	
	85%	Woven Graft	£ 200	£ 13,858
		Branched Graft	£ 1,000	£ 14,658
Col.2 - **Woven Graft Arm**	80% Yes	Suitable for Stage 2	No Cost	£ 0
	20% No	Decision Point		£ 0
Col.2 - **Branched Graft Arm**	80% Yes	Suitable for Stage 2	No Cost	£ 0
	20% No	Decision Point		£ 0
Col. 3: **Woven Graft Arm**	50%	2nd Stage – Woven Graft	£ 200	
		9 days in ICU at £ 1,500	£ 13,500	
		6 days in Surgical at £ 420	£ 2,520	
		7 hr. Theatre at £ 30	£ 210	
		7hr. Surgery team at £ 704	£ 4,928	£ 21,358
	50%	2nd Stage – Stent Endograph	£ 5,000	
		2 days in ICU at £ 1,500	£ 3,000	
		6 days in Surgical at £ 420	£ 2,520	
		3 hr. Theatre at £ 30	£ 90	
		3hr. Surgery team at £ 741	£ 2,223	£ 12,833

Col. 3 **Branched Graft Arm**	50%	2nd Stage – Woven Graft 9 days in ICU at £ 1,500 6 days in Surgical at £ 420 7 hr. Theatre at £ 30 7hr. Surgery team at £ 704	£ 200 £ 13,500 £ 2,520 £ 210 £ 4,928	£ 21,358
	50%	2nd Stage – Stent Endograph 2 days in ICU at £ 1,500 6 days in Surgical at £ 420 3 hr. Theatre at £ 30 3hr. Surgery team at £ 741	£ 5,000 £ 3,000 £ 2,520 £ 90 £ 2,223	£ 12,833
Col. 4: **Woven Graft Woven Graft Arm for Stage 2**	80% 20%	Success - No further costs. In-Hospital Death	£ 0 £ 8,000	£ 0 £ 8,000
Col. 4: **Woven Graft Endovascular Stent for Stage 2**	80% 20%	Success - No further costs. In-Hospital Death	£ 0 £ 8,000	£ 0 £ 8,000
Col. 4: **Branched Graft Arm Woven Graft Arm for Stage 2**	80% 20%	Success - No further costs. In-Hospital Death	£ 0 £ 8,000	£ 0 £ 8,000 c/c
Col. 4: **Branched Graft Arm Endovascular Stent for Stage 2**	80% 20%	Success - No further costs. In-Hospital Death	£ 0 £ 8,000	£ 0 £ 8,000 c/c

There are Cell Changes for the “2nd Stage Unsuitable” Arms to give zero costs for these.

Current Pathway Reteined

Colum Number	Factors (Blue Cell)	Pathway Item with Unit Costs (Yellow Cell for Patient Nos.)	Element Costs	Total Cost (Pink Cell)
Start point	3,500	The Total target population is as recorded in the HES data for 2011.		
Col 1. Selection	40% 60%	Adoption level of E-vita open plus Continue with Current Methods	Decisions – No cost	£ 0 £ 0 c/c
Col.2 – Selection for Woven or Branched Graft Stage 1	15% c/c 85% c/c	4 days in ICU @ £ 1,500 6 days in Surgical @ £ 420 7 hr. Theatre at £ 30 7 hr. Surgery Team at £ 704 Woven Graft Branched Graft	£ 6,000 £ 4,520 £ 210 £ 4,928 £ 200 £ 1,000	 £ 13,858 c/c £ 14,658 c/c
Col.3 - Woven Graft Arm	20% No c/c 80% Yes	Suitable for Stage 2 Decision Point	No Cost	£ 0 c/c £ 0 c/c
Col.3 - Branched Arm	20% No c/c 80% Yes	Suitable for Stage 2 Decision Point	No Cost	£ 0 c/c £ 0 c/c
Col. 4: Woven Graft – No Stage 2	Factor not used & not changed	**Not** Suitable for Stage 2	No costs	£ 0 £ 0 c/c
Col. 4: Woven Graft Arm – 2nd Stage & Mortality	50% 50%	2nd Stage – Woven Graft 9 days in ICU at £ 1,500 6 days in Surgical at £ 420 7 hr. Theatre at £ 30 7hr. Surgery team at £ 704 + 20% of Mortality cost of £ 8,000 2nd Stage – Stent Endograph 2 days in ICU at £ 1,500 6 days in Surgical at £ 420 3 hr. Theatre at £ 30 3hr. Surgery team at £ 741 + 20% of Mortality Cost at £ 8,000	£ 200 £ 13,500 £ 2,520 £ 210 £ 4,928 £ 1,600 £ 5,000 £ 3,000 £ 2,520 £ 90 £ 2,223 £ 1,600	 £ 22,958 £ 14,433
Col. 4: Branched Graft Arm – NO 2nd Stage	Factor not used & not changed	**Not** Suitable for Stage 2	No costs	£ 0 £ 0 c/c
Col. 4: Branched Graft Arm Stage 2 & Mortality	50%	2nd Stage – Woven Graft 9 days in ICU at £ 1,500 6 days in Surgical at £ 420 7 hr. Theatre at £ 30	£ 200 £ 13,500 £ 2,520 £ 210	
	50%	7hr. Surgery team at £ 704 + 30% of Mortality cost of £ 8,000 2nd Stage – Stent Endograph 2 days in ICU at £ 1,500 6 days in Surgical at £ 420 3 hr. Theatre at £ 30 3hr. Surgery team at £ 741 + 30% of Mortality Cost at £ 8,000	£ 4,928 £ 1,600 £ 5,000 £ 3,000 £ 2,520 £ 90 £ 2,223 £ 1,600	 £ 23,758 £ 15,233

Pathways with New Device

E-vita open plus Adopted Pathways

Colum Number	Factors (Blue Cell)	Pathway Item (Yellow Cell for Patient Nos.)	Element Costs	
Start point	3,500	The Total target population is as recorded in the HES data for 2011.		
Col 1. **Selection & E-vita open plus Treatment**	40%	Adoption level of E-vita open plus 4 days in ICU at £ 1,500 6 days in Surgical Ward at £ 420 3 hr. Theatre at £ 24 3 hr. Surgery team at £ 704 E-vita open plus Stent Endograph	 £ 6,000 £ 2,520 £ 180 £ 5,280 £ 10,500	£ 24,480
	60%	Continue with Current Methods	Decision No cost	£ 0 C/C
Col.2 – **E-vita open plus Use Arm**	85% 15%	Success In-Hospital Death	No cost £ 8,000	£ 0 £ 8,000
Col. 3: **E-vita open plus Use Arm**		No further costs after success		£ 0
Col. 4: **E-vita open plus Use Arm**		In-Hospital death incurs no further costs		£ 0

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The economic analysis is focussed on In-Hospital outcomes and the success of the procedure itself without quantifying the longer term benefits. There is only limited information on the longer term mortality rate benefits for E-vita and for Endovascular Stents but there are indications of further improved patient outcomes with a reduction in 30 day mortality. The impact of this element is much smaller than the In-Hospital Death element.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The important element in this respect is treatment of all patients by the E-vita open plus device, whereas a significant proportion of patients (30%) in the current procedure do not reach Stage 2 for completion of the whole treatment process because of their unsuitability or death during the time between the two stages. These measures were based on clinical evidence on both current and E-vita open plus procedures.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The common adverse event in both E-vita open plus and comparator methods is In-Hospital death and the incidence and costs for this are included in the economic model.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The clinical information on both the current procedures and that with E-vita open plus has been assessed based on published and peer reviewed information. These are cited in both the clinical sections and in 9.1.6 above & 9.2.6 below for those used directly in the economic model.
The economic model was developed and applied independently for the company by Dr David Huckle, Chief Executive of Adams Business associates. He is a Chartered Chemist with 25 years commercial experience in healthcare sectors of Pharmaceuticals, Diagnostics and Medical Devices.
He was selected for this process because of an established record in independent economic analysis for assessment of medical devices for potential use in the NHS. This HTA experience was obtained in developing

economic models for the NIC technology assessment programme and since then applying these techniques to a range of medical devices including a number of submissions to various NICE approval and Guideline programmes. An important aspect to this work was the totally independent identification of clinical and resource information used in developing the economic model and its use in the analysis.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

This is the same as given in 9.1.6 and is repeated here for completeness**.**

Item	Unit
Initial consultant visit – cost neutral as required for current & Evita	£ 137 [1]
Surgeon Cost	399/hr. [1]
Assistant Surgeon	131/hr. [1]
Perfusionist & Anaesthetist at Registrar Rate	£ 87/hr. each [1]
Theatre cost inclusive of Nursing & Consumables	£ 24/hr. [2]
Theatre cost inclusive of Nursing & Consumables for ICU	£ 30/hr. [3]
ICU ward In-Patient daily costs	£ 1,500 [4]
Surgical ward In-Patient daily costs	£ 420/day [5]
Number of operations /year = No. of Patient Procedures	3,500 [6,7,8,9]
Proportion of patients receiving Woven Graft at Stage 1	1 15% [10]
Cost of Woven Graft for Stage 1 & Stage 2 in Classical ET	£ 200 [11]
Cost of Branched Graft at Stage 1	£ 1,000 [11]
Cost of covered Stent Endograph at Stage 2 in modern procedure	£ 5,000 [11]
Cost of E-vita open plus	£ 10,500 [12]
Patient Days - Classical ET Procedures for Stage 1 & Stage 2	10 + 15 days [6]
Patient Days – Endovascular Graft Procedure – Stage 1 & 2	10 + 8 days [13]
Patient Days with E-vita open plus: ICU & Surgical ward	4 + 6 days [13]
ICU Theatre Time for Current Procedures – Stage 1.	7 hrs. [9]
ICU Theatre Time for Current Procedure – Stage 2: Woven & Stent.	7 hrs. or 3 hrs.[9]
Surgical Ward Theatre Time for E-vita open plus	7½ hrs. [13]
Percentage of current patients unsuitable for Stage 2	20% [14]
In-Hospital & Waiting Time mortality rate with current procedure	20% average [15]
In-Hospital mortality rate with E-vita open plus procedure	15% [16]

Cost of Death within NHS	£ 8,000 17

The listing of sources of data and clinical information together with actual usage of both current and E-vita open plus procedures is given below.

Sources of Information:

1. PSSU Unit costs of Health & Social Care.
2. NHS Tariff for Admitted Patient Cases & Out-Patient Procedures
3. 25% increase over normal surgical theatre costs.
4. Learning from Experience (NHS Scotland), www.bbc.co.uk/new/health - 11503873, Oxford

Journals, Medicine: on line ISSN 1743-1824.

5. NHS Tariff figure.
6. Health Economics Statistics (HES) at L27.3
7. Bavaria, *J Thorac Cardivasc Surg 2007;**133**:369-77. [4]*
8. Clouse, *Mayo Clin Proc 2004:**79**: 176-180 [2]*
9. NICE Guidelines IPG 127 on Endovascular Stentgraft placement for aortic aneurysms. [36]
10. *Typified by* da Volta Ferreira, J Vascular Brasileiro, 2006;**5**(3):220-4.[37]
11. Commercial figures from current suppliers.
12. Company target price.
13. Company clinical studies.
14. IPG 127 & Jakob review.
15. 4 references in Jakob [17] review paper. Fann [9], Safi [38] and LeMaire [13] also.
16. Company registry data on 274 patients. Jakob et al International E-vita Open Registry JCardiovasc. Surg 2011;**52**:717-723. [18]
17. Scottish Cancer Therapy Network Newsletter Autumn 2003

Other References:

*Tsagakis et al, Avoidance of Proximal Endoleak Using a Hybrid Stent Graft in Arch Replacment and descending Aorta Stenting, . Ann Thorac Surgery, 2009;**88**, 773-780*

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The general HRG codes are QZ01A and QZOIB for Aortic or Abdominal Surgery with or without Clinical Complications respectively. The Tariff figures are £ 6,667 for QZ01A and £ 3,965 for QZ01B respectively. The implantable stent graft is on the Exclusion List and is additional to the Tariff and there are Elective Long Stay and Specialist top ups where appropriate.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

The description is “Transluminal insertion of stent graft for aneurysmal segment of aorta” and is listed under L27 in HES data and as per the HRG codes noted in 9.3.1.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

The Health Economic Statistics (HES) data provided information on frequency of the procedure and importantly the average length of stay in hospital per patient. Other NHS data was obtained from NHS sources as indicated by the items in 9.2.6 above. Clinical information on UK use of the current procedures was made and references are included in the listing for section 9.2.6 above.

The applicability of the resource data used in the economic model was assessed from the whole range of peer reviewed publications and the published NHS figures of the latest date available, 2011. Comparisons were

made between the identified publications for commonality and differences of findings to determine a strong consensus of the clinical and cost data. The uncertainty around the various parameters is addressed in the sensitivity analysis. An indicative price to the customer of £ 10,500 was used based on information provided by the company. Consumables and the extra costs (£ 130) for a “stiff guide wire” were common to current and E-vita technologies and taken to be cost neutral in assessing potential NHS costs or savings. The product price was as defined by the company and no changes or direct sensitivity testing of this price is made in the economic analysis.

The economic model considers the overall costs and potential savings to the NHS based on the definitive product price as above and the costs of all procedures for surgery costs, In-Patient costs at ICU or Surgical ward and outcomes, notably in-hospital deaths as the primary adverse event cost. The sources and values for all of these costs are given in 9.2.6 above. The table below compares the overall costs and cost areas for current and E-vita open plus procedures. Savings will depend upon the relative adoption level of the new procedure and the typical new technology adoption level of 40% is used in which the costs compared are those of the current procedure versus the parallel use of the current procedure and 40% with the E-vita open plus technology.

Cost Item	**Current Costs/Year for 3,500 patients**	**E-vita open plus Cost/Year at 40% adoption [1,400 patients by E-vita & 2,100 as Current]**
Total Costs	**£ 105.13 M**	**£ 99.03 M**
Complete Surgery Costs*	£ 28.4 M	£ 24.70 M
In-Hospital Stay Costs	£ 59.9 M	£ 47.92 M
In-Hospital Costs of Death	£ 6.4 M	£ 5.04 M
Graft Product Costs – Stage 1 **Stage 2 & Total**	£ 3.08 M £ 6.22 M **= £ 10.36 M**	**£ 14.7 M for E-vita** + Retained Current £ £ 6.79 M **= £ 21.49 M**
There are small rounding differences within the sub-groups and the totals. *The specific cost of E-vita open plus at 40% adoption is £ 14.7 M to generate savings of £ 6.1 M.*		

Notes: * For current methods this is Stage 1 & Stage 2 where completed and is for resources and theatre time.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

The applicability of the resource data used in the economic model was assessed from the whole range of peer reviewed publications and the published NHS figures of the latest date available, 2011. Comparisons were made between the identified publications for commonality and differences of findings to determine a strong consensus of the clinical and cost data. The uncertainty around the various parameters is addressed in the sensitivity analysis.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

An indicative price to the customer of £ 10,500 was used based on information provided by the company. Consumables and the extra costs (£ 130) for a "stiff guide wire" were common to current and E-vita technologies and taken to be cost neutral in assessing potential NHS costs or savings.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The product price was as defined by the company and no changes or direct sensitivity testing of this price is made in the economic analysis.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The economic model considers the overall costs and potential savings to the NHS based on the definitive product price as above and the costs of all procedures for surgery costs, In-Patient costs at ICU or Surgical ward and outcomes, notably in-hospital deaths as the primary adverse event cost.

The sources and values for all of these costs are given in 9.2.6 above. The table below compares the overall costs and cost areas for current and E-vita open plus procedures. Savings will depend upon the relative adoption level of the new procedure and the typical new technology adoption level of 40% is used in which the costs compared are those of the current procedure versus the parallel use of the current procedure and 40% with the E-vita open plus technology.

Cost Item	**Current Costs/Year for 3,500 patients**	**E-vita open plus Cost/Year at 40% adoption [1,400 patients by E-vita & 2,100 as Current]**
Total Costs	**£ 105.13 M**	**£ 99.03 M**
Complete Surgery Costs*	£ 28.4 M	£ 24.70 M
In-Hospital Stay Costs	£ 59.9 M	£ 47.92 M
In-Hospital Costs of Death	£ 6.4 M	£ 5.04 M
Graft Product Costs – Stage 1 **Stage 2 & Total**	£ 3.08 M £ 6.22 M = **£ 10.36 M**	**£ 14.7 M for E-vita** + Retained Current £ £ 6.79 M **= £ 21.49 M**
There are small rounding differences within the sub-groups and the totals. *The specific cost of E-vita open plus at 40% adoption is £ 14.7 M to generate savings of £ 6.1 M.*		

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

We have no knowledge of any additional costs.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not to our knowledge, we cannot provide any data.

Include a justification as to why it has not possible to quantify the resource use and/or costs.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

Response to 9.4.1, 9.4.2, 9.4.3, 9.4.4

All of these items (9.4.1, 9.4.2, 9.4.3, 9.4.4) are addressed in the Sensitivity Analysis detailed below. In practice each facility would have different patient incidence, costs, approaches to In-Patient care and start with specific outcomes parameters so multi-dimensional analysis was not appropriate and more important was determining which elements had most impact on the economic outcomes.

The key variables considered in the sensitivity analysis are:

- Adoption Level of E-vita open plus from 20% to 100%: 40% as core.
- Variables related to different options at Stages 1 and 2 and Mortality

E-vita open plus Adoption Level	Total Current Costs	Total E-vita open plus Costs	Total Savings	Number of Patients for E-vita open plus	Savings per Patient
Adoption level for E-vita open plus use – Core model at 40%					
40% core base	£ 105.13 M	£ 99.0 M	£ 6.1 M	1,400	£ 4,358
20%		£ 102.1M	£ 3.05 M	700	£ 4,358
100%		£ 89.9 M	£ 15.25 M	3,500	£ 4,358

- The average savings per patient under the implementation assumptions used in the Core Model are about £ 4,358 per patient.
- An important feature is the additional number of patients that would be treated to the equivalent of Stage 2 if E-vita was used since it would be a single stage procedure. At the different adoption levels as in the table above the extra patients that would be treated would be: @ 40% adoption = 280 @ 20% adoption = 140 @ 100% adoption = 700.

This is the number of patients that would otherwise be receiving continued treatment for the disease with significant costs.

A difficult figure to define rigidly, and one that would change in each specific facility, is the use of Woven Graft (at a cost of £ 200) and Branched Graft (at a cost of £ 1,000) at Stage 1. These are lower cost products than the final Stage 2 Stent graft (at a cost of £ 5,000) but the impact of the variable is addressed below where the core figure of 85% for Branched Graft is varied from 60% to 95%.

Woven or Branched Graft Proportions at Stage 1 at 40% adoption level.					
Branched Graft Proportion	Total Current Costs	Total E-vita open plus Costs	Total Savings	Number of Patients	Savings per Patient
85% core figure	£ 105.13 M	£ 99.0 M	£ 6.1 M	1,400	£ 4,358
60% share	£ 103.9 M	£ 98.3 M	£ 5.6 M	1,400	£ 3,998
70% share	£ 104.4 M	£ 99.6 M	£ 5.8 M	1,400	£ 4,142
90% share	£ 105.4 M	£ 99.2 M	£ 6.2 M	1,400	£ 4,430
95% share	£ 105.6 M	£ 99.3 M	£ 6.3 M	1,400	£ 4,502

Important outcome variables are those concerned with:

- Suitability of patients for the 2nd Stage operation to complete the repair work.

E-vita open plus Adoption Level 40% as baseline	Total Current Costs	Total E-vita open plus Costs	Total Savings	Number of Patients for E-vita open plus	Savings per Patient
Core Consideration of Suitability for 2nd Stage at 90%					
80% Suitable	£ 105.13 M	£ 99.0 M	£ 6.1 M	1,400	£ 4,358
90%	£ 111.9 M	£ 103.1 M	£ 8.8 M	1,400	£ 6,296
65%	£ 94.96 M	£ 92.9 M	£ 2.0 M	1,400	£ 1,452

- Reduction in In-Hospital death rates. The core model is based on current methods having 20% mortality if Woven Graft at Stage 1 and 30% if Branched Graft at Stage 1 with E-vita plus open at 15%. Variations are addressed below.

Consideration of In-Hospital Death Rates with Core figure at 30% for current & 15% for E-vita open plus.					
E-vita open plus Adoption Level 40% as baseline	Total Current Costs	Total E-vita open plus Costs	Total Savings	Number of Patients for E-vita open plus	Savings per Patient
30% core death & 15% for E-Vita	£ 105.13 M	£ 99.0 M	£ 6.1 M	1,400	£ 4,358
20% core death & 15% for E-vita	£ 103.1 M	£ 97.8 M	£ 5.27 M	1,400	£ 3,766
30% core death & 20% for E-vita	£ 105.13 M	£ 99.16 M	£ 5.54 M	1,400	£ 3,958
20% core death & 20% for E-vita	£ 103.06 M	£ 98.3 M	£ 4.71 M	1,400	£ 3,366

All Stage 2 there are options of the classical Woven Graft or the more modern Endovascular Graft.

Variations in overall use of the two options currently and the impact if E-vita was used are given in the table below. The core model is based on a 50/50 use of the two options.

Consideration of Stage 2 Options - Core figure at 50%/50% for Woven Graft & Endovascular Graft versus E-vita open plus.					
E-vita open plus Adoption Level 40% as baseline	Total Current Costs	Total E-vita open plus Costs	Total Savings	Number of Patients for E-vita open plus	Savings per Patient
50% Woven Graft & 50% Endovascular	£ 105.13 M	£ 99.0 M	£ 6.1 M	1,400	£ 4,358
60% Woven Graft & 40% Endovascular	£ 107.5 M	£ 100.5 M	£ 7.1 M	1,400	£ 5,040
40% Woven Graft & 60% Endovascular	£ 102.75 M	£ 97.6 M	£ 5.15 M	1,400	£ 3,676
100% Endovascular	£ 93.2 M	£ 91.9 M	£ 1.33 M	1,400	£ 948.4
100% Woven Graft	£ 117.1 M	£ 106.2 M	£ 10.88 M	1,400	£ 7,768

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

9.5.2 Report the total difference in costs between the technology and comparator(s).

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Response to 9.5.1, 9.5.2, 9.5.3, 9.5.4, 9.5.5:

The suggested format is used and provides in a single table the costs per patient in total, for treatment, for administration (hospital stay) and total adverse event (death) for complete (100% adoption).

Table C12 - At 100% adoption level summary of average costs by category of cost per patient

Item	Cost *intervention* *(3,500 Patients with E-vita open plus)*	Cost *comparator* *(3,500 Patients with current methods)*	Change/Patient [Saving or (Cost)]	Total Change for 3,500 patient cohort	% absolute Saving or (Cost)
Technology cost	£ 10,500	£ 2,960	(£ 7,540)	(£ 26.39 M)	(> 200%)
Mean total treatment cost	£ 5,468.5	£ 8,114	£ 2,646.5	£ 9.26 M	32.6 %
Administration cost (Hospital Stay)	£ 8,520	£ 17,114	£ 8,594	£ 30.08 M	50.2 %
Cost of Death average/patient	£ 1,200	£ 2,053	£ 853	£ 1.36 M	34.4 %
Total	**£ 25.68 K**	**£ 30.04 K**	**£ 4,553.5**	***£ 15.25 M***	***14.5%***

These figures are confirmed by the economic model and conclusions from the Decision Tree as shown below. Numbers are rounded.

OVERALL EXPECTED COSTS	E-vita open plus at 100% Use	Standard care
Total costs	£89,880,000	£105,134,400
Cost savings	£15,254,400	

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

9.5.9 What were the main findings of each of the sensitivity analyses?

Response to 9.5.6, 9.5.7, 9.5.8, 9.5.9

All the 40% adoption level for use of the E-vita open plus Open Plus technology it was found that:

- The average savings per patient under the implementation assumptions used in the Core Model are about £ 4,358 per patient.
- In-Hospital death is a key clinical factor and a contribution to failure to reach Stage 2 treatment in the current methods. E-vita open plus is superior clinically to current methods even if incidence was the same with E-vita individual patient savings would be above £ 3 K.
- Introduction of Endovascular Stent graft is an easier procedure for Stage 2 and even with a device cost of £ 5-6 K. provides cost savings. E-vita plus open provides superior cost economy over the current woven graft and over the Endovascular Stent approach.

The conclusions are that each of the parameters of 2nd Stage Suitability and In-Hospital Death rates has an impact on the total savings and the average savings per patient. However these changes are relatively small despite large relative changes and maintain the average savings close to or above the £ 4,000/patient mark.

9.5.10 What are the key drivers of the cost results?

The major savings arise from the reduced need for in-patient stay in hospital because the E-vita open plus is a single stage surgical procedure with good outcomes. There are equally important savings from the overall Surgery (Treatment) costs and the reduction in Death costs from both In-Hospital and waiting time between stages. These three areas contribute together to off-set the increased costs for the device over current products.
The savings achieved are with an increased patient population since all those suitable are treated without losses during waiting for the 2nd Stage. At the different adoption levels the extra patients that would be treated would be:

@ 40% adoption = 280 @ 20% adoption = 140 @ 100% adoption = 700

This is the number of patients that would in the current situation be receiving continued treatment for the disease with significant costs.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

None

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

This whole item is not applicable.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The input parameters were all justified as detailed above. An important aspect of the model is that it allows for different levels of technology adoption as well as the plausible use of current and E-vita open plus technologies alongside each other. The model was first checked so that at 0% adoption the Current

and Retained Current Technology parts of the tree matched to give the same total costs.
Secondly at 100% adoption the match with the Patient Pathway shown above was checked.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published literature having an economic content comparing the current and new procedures. The current costs were found to be higher than indicated in anecdotal assessments but this was due to inclusion of all costs including undesirable outcomes (death) and full procedure costs not just the products and/or surgery costs.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

There are different conditions with individual patients and their suitability for current procedures. Those patients with less clinical damage will be suitable for the less expensive Woven Graft at Stage 1 of the current method. The relative proportions that are used of the Woven Graft and the Branched Graft at Stage 1 need to be factored in to the economic model but actually has limited impact as these product costs are small relative to the Administrative (In-Patient) costs and the product costs at Stage 2. The biggest change assessed of 25% only affected current costs by 1.3% and the final outcome savings with use of E-vita open plus by 7%, with all figures within the £ 5,000-6,000/patient mark.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

See 9.8.4.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The economic model includes all the immediate surgery and recovery costs together with the immediate consequential outcomes, which are effectively In-Hospital Death. This gives extreme flexibility to the model to deal with all the likely variables particularly the level of adoption and the main assumptions of actual clinical practice. The input parameters for frequency, variations and costs can quickly be changed for further sensitivity testing or modification from a global NHS assessment, as used, to an individual Trust and its patient population to a generalised single patient cost. This covers use of the model for multivariate analysis if required, although not carried out here because of the key driver from savings from the single stage procedure. This might be an area for further sensitivity analysis to show robustness. There are inputs in the decision tree model that have to be changed by the user and this requires an understanding of the patient pathway models and also the links within the model, as given in 9.2.1. A suitable user tool for use within an individual Trust can be developed from the economic model taking into account the specific patient cohort, clinical make up and the local costs but this would be a commercial action.

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Pubmed was the databased searched.

10.1.2 The date on which the search was conducted.

The last search was conducted on 30th September 2012.

10.1.3 The date span of the search.

1st January 2005 to 30th September 2012

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

(e-vita[All Fields] AND open[All Fields]) OR (e-vita[All Fields] AND ("aortic aneurysm"[MeSH Terms] OR ("aortic"[All Fields] AND "aneurysm"[All Fields]) OR "aortic aneurysm"[All Fields]) AND ("dissection"[MeSH Terms] OR "dissection"[All Fields]))

In addition, the latest publication of Prof. Jakob [17] was included in the analysis. This publication was provided by Prof. Jakob who is responsible for the IEOR.

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Pubmed - http://www.ncbi.nlm.nih.gov/entrez/

10.1.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria were taken as published.

10.1.7 The data abstraction strategy.

Published data were processed according to Table 15.

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Pubmed was the databased searched.

10.2.2 The date on which the search was conducted.

September 30, 2012.

10.2.3 The date span of the search.

The span of the search was January 01, 2005 to September 30, 2012.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

(e-vita[All Fields] AND open[All Fields]) OR (e-vita[All Fields] AND ("aortic aneurysm"[MeSH Terms] OR ("aortic"[All Fields] AND "aneurysm"[All Fields]) OR "aortic aneurysm"[All Fields]) AND ("dissection"[MeSH Terms] OR "dissection"[All Fields]))

In addition, the latest publication of Prof. Jakob [17] was included in the analysis. This publication was provided by Prof. Jakob who is responsible for the IEOR.

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

In addition, the latest publication of Prof. Jakob [17] was included in the analysis. This publication was provided by Prof. Jakob who is responsible for the IEOR.

10.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria were taken as published.

10.2.7 The data abstraction strategy.

Published data were processed according to Table 15.

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The search for data for economic evidence was performed by an external company Adams Business Associates, Dr David Huckle. See 9.2.6, sources of information.

ADAMS BUSINESS ASSOCIATES (ABA) has been established for 25 years and is a global strategic marketing and business development operation with an established position in Europe and North America. ABA has worked mainly on multi-national projects in different aspects of the Life Science sectors with particular emphasis on Healthcare. An important element in achieving this strong market position has been maintaining a close awareness of user needs with the impact of innovative new technologies and their development in commercial cycles. The focus of ABA has been on the international markets globally, not just that of the UK or Europe.

The Chief Executive of ABA (Dr David Huckle) has extensive technical and commercial experience in the Diagnostic, Pharmaceutical and Medical Device markets. The significant management positions held in development and marketing of commercial Pharmaceutical and Diagnostic products have been extended with wider activities in the overall Healthcare sectors. He was a Member of the Biotechnology & Pharmaceutical Advisory Group (BPSAG) on strategic business developments for UKTI.

This extensive experience in many Healthcare areas led to involvement in Healthcare Economics procedures to demonstrate financial benefits of new products and technologies. Participation as an Industrial Partner in the MATCH [Multidisciplinary Assessment of Technology Centre for Healthcare]

group has provided the health economics experience for development of methods for effective assessment of value and the economic impact of advances made for Healthcare technologies. This combined experience was used in development of an NIC Suite of Economic Models that was used routinely by ABA on behalf of NIC for assessment of new innovations.
This suite of economic tools, including the Decision Tree based economic Model was used by ABA in its support of the NIC in its evaluation of innovations to be added to the NIC Showcase. More than thirty (30+) collaborations with Medical Device companies have now been made using these analytical tools to determine the economic value arguments for access to the NHS.
ABA has been ISO 9001:2008 (and its predecessor) approved for the last eight years.

10.3.2 The date on which the search was conducted.

See 10.3.1

10.3.3 The date span of the search.

See 10.3.1

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See 10.3.1

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See 10.3.1

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

See 10.3.1

10.4.2 The date on which the search was conducted.

See 10.3.1

10.4.3 The date span of the search.

See 10.3.1

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See 10.3.1

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See 10.3.1

10.4.6 The inclusion and exclusion criteria.

See 10.3.1

10.4.7 The data abstraction strategy.

See 10.3.1

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).