NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

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

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Additional analyses carried out by External Assessment Centre
- Appendix E: External Assessment Centre correspondence
- Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

1 The technology

The E-vita open plus (JOTEC GmbH) is an endoluminal stent graft system designed for treating aneurysms and dissections of the thoracic aorta. The device is a 1-piece polyester fabric tube which combines a conventional vascular graft attached to an endovascular stent graft that allows treatment of the ascending aorta at the same time as the arch and descending aorta. The E-vita open, which was also available in the UK, is the immediate predecessor device and has been superseded by the E-vita open plus. The 2 devices are similar in design but the E-vita open plus is blood-tight and fibrin glue is not needed to seal the stent graft.

The E-vita open plus is used in a single stage procedure known as a 'frozen elephant trunk'. The thoracic aorta is surgically opened with access through a median sternotomy approach. The stent graft is deployed distally in the descending aorta and the vascular graft is surgically anastomosed (joined) to the ascending aorta. The distal stent graft is a self-expanding device that incorporates nitinol springs into the fabric and is used to treat the descending aorta. The distal stent graft is deployed by retracting a retaining sheath. The proximal vascular graft is then used to repair the ascending aorta and arch in a standard surgical fashion. The aortic branch vessels are re-attached to the graft using a patch. Radiopaque markers are integrated into the fabric of the graft to permit radiological imaging.

The E-vita open plus is a single-use device with a shelf life of 2 years. It is supplied sterile and is pre-loaded in its delivery system. The device is available in a range of sizes with varying diameters and lengths. The delivery system consists of a release handle, nested catheters and a positioning aid. A luer connector is also incorporated to permit flushing of the inner guide catheter. A stiff guide wire, placed by transoesophogeal echocardiography (TEE), is needed to aid tracking of the device delivery.

The E-vita open plus received a CE mark in October 2008 for the repair or replacement of the thoracic aorta in cases of complex aneurysms or

dissections which involve the ascending aorta, the aortic arch and the descending aorta.

2 Proposed use of the technology

2.1 Disease or condition

Thoracic aortic aneurysms result from weakening of the aortic wall leading to localised dilatation. If left untreated, the aneurysm may continue to enlarge and result in rupture and death.

Aortic dissection results from a tear in the inner layer of the aorta leading to blood entering and separating the layers of the wall. It can be acute or chronic and is classified according to the region of the aorta affected. Stanford type A dissections affect the ascending thoracic aorta. They may be more extensive and also include the arch and descending thoracic aorta. Stanford type B dissections do not affect the ascending aorta and typically involve the descending thoracic aorta. If left untreated acute type A dissection has a 75% mortality rate in the first 2 weeks. People with chronic dissections can present with pain but can also be asymptomatic.

2.2 Patient group

The E-vita open plus is intended for treating complex aneurysms and dissections of the thoracic aorta which involve the ascending aorta, aortic arch and descending aorta (Stanford type A). Both conditions are associated with increasing age and are most common in people aged over 50 years. The incidence of thoracic aortic aneurysm is estimated to be approximately 5–10 per 100,000 person-years and aortic dissection is estimated to occur in approximately 3–4 per 100,000 people. People with connective tissue disorders, in particular people with Marfan’s syndrome and Ehlers-Danlos syndrome, are at an increased risk of developing an aortic aneurysm or dissection and may present at a younger age.

Based on expert advice, it is estimated that the E-vita open plus would be suitable for treating approximately 50–100 people per year in England.

People with acute or chronic type A dissections, or those with degenerative aneurysms, were identified as subgroups for consideration.

2.3 Current management

The management of thoracic aortic aneurysms and dissections is determined by the location, severity and rate of change of the disease, as well as the clinical circumstances. People with thoracic aneurysms are often observed carefully with clinical and imaging surveillance. Invasive treatment may be offered depending upon the size and rate of enlargement of the aneurysm. In patients with type A aortic dissection, emergency surgery is usually offered, whereas patients with type B dissections are often managed with conservative medical treatment, although elective surgical repair is sometimes undertaken.

There are 3 main current methods of surgically treating complex disease of the thoracic aorta. Two of these methods involve a 2-stage ‘elephant trunk’ procedure. Both approaches are similar in their first stage but use alternative repair techniques to complete the second stage. During the first stage, the ascending aorta and arch are repaired with a vascular graft through a median sternotomy. This is often combined with aortic root or other cardiac interventions. During this procedure a free-floating extension of the arch graft prosthesis (the elephant trunk) is left dangling in the descending aorta. In one approach, the second stage of the procedure may be undertaken as an endovascular procedure during which a stent graft is inserted into the descending aorta with arterial access via the femoral artery (endovascular aortic vascular repair – EVAR). In an alternative approach, a second surgical procedure may be scheduled some weeks or months later during which the descending aorta is repaired by extending the ‘elephant trunk’ through a lateral thoracotomy approach.

The third method involves ‘debranching’ of the head and neck vessels from the aortic arch with the creation of a surgical anastomosis between the ascending aorta and the head and neck vessels using a vascular graft. This then allows the insertion of an endoluminal stent graft into the aortic arch and descending aorta either as a hybrid or second stage procedure.

2.4 Proposed management with new technology

The E-vita open plus allows the ascending aorta, arch and descending aorta to be repaired in a single stage procedure, potentially avoiding the need for a second stage procedure to repair the descending aorta. Both the vascular graft portion of the device and the self-expanding stent graft can be deployed through median sternotomy. The procedure requires imaging (usually X-ray or TEE) to guide the placement of the stent graft and therefore radiological equipment and staff are needed.

2.5 Equality issues

Patients with connective tissue disorders were included in the special considerations section of the scope. No evidence was presented about this specific group. The EAC has stated that the NHS England Specialised Commissioning Clinical Reference Group for Vascular Surgery has specifically excluded patients with connective tissue disorders from the commissioning of complex endovascular procedures. The EAC concluded that decisions on whether endovascular procedures would be the best treatment option for these patients would have to be made on a case-by-case basis due to the limited evidence available on patient outcomes.

3 Issues for consideration by the Committee

3.1 Claimed benefits

The benefits to patients claimed by the sponsor are that the E-vita open plus permits the ascending aorta, arch and descending aorta to be repaired in a single stage procedure which can lead to:

- reduced pain and discomfort
- elimination of the psychological distress associated with the anticipation of a second procedure
- a reduction in total end organ ischaemia
- a reduction in incisional complications and infections

- a reduction in anaesthetic use and the elimination of the need for additional epidural pain management
- a reduction in both total length of stay and intensive care unit (ICU) length of stay
- a reduction in rehabilitation time
- an earlier return to normal activities and work.

The benefits to the health system claimed by the sponsor are:

- a reduction in treatment times and costs due to the elimination of a second procedure
- a reduction in total length of stay
- a reduction in ICU stay
- reduced rehabilitation time
- fewer wound complications.

4 The evidence

4.1 Summary of evidence of clinical benefit

Note: to provide further clarification of the overlap issues between clinical studies of Evita open plus, NICE asked the EAC to revise section 3.3 (and tables 1 and 1b) of the assessment report after the main report had been submitted. The revised section is shown in Appendix D of this assessment report overview.

The sponsor identified 13 papers relevant to the E-vita open plus. The majority of these were derived from the International E-vita Open Registry, which is reported to contain data on 70–80% of patients with complex aortic disease who have received the E-vita open (predecessor device) or open plus devices. The registry is coordinated by the University Hospital Essen, Germany and was founded in 2008. In May 2013, it contained data on 470 patients from 11 participating centres.

The sponsor excluded 8 (of the 13) papers from further consideration because the data were already included in a more recent report on the entire registry dataset (Jakob et al. 2011), which became the focus of the sponsor's clinical evidence submission. Two further papers were excluded as 1 reported on animal studies and the other on only 7 patients. The remaining 2 papers (Jakob et al. 2012; Hoffman et al. 2012) were included in the sponsor's summary of clinical evidence. No critical appraisal was presented and they were not included in the sponsor's evidence synthesis. All 13 studies identified by the sponsor were descriptive and were noncomparative.

The EAC's literature search identified an additional study by Mestres et al. (2012), published as a conference abstract. This study described a series of patients treated in Barcelona, one of the registry centres. The EAC reviewed a pre-publication copy of this paper and, as it reported on a subset of the registry data, concluded that it contained no additional relevant information.

The EAC considered that the sponsor's literature search had identified all relevant evidence on the technology and confirmed that no comparative studies were available. The EAC particularly examined for relevance the studies by Jakob et al. (2012) and Hoffman et al. (2012). Jakob et al. (2012) reported on a subset of the International E-vita Open Registry data, evaluating outcomes for 77 patients undergoing surgery between January 2005 and March 2011 at the Essen centre. The study by Hoffman et al. (2012) was a single centre study, outside the registry, carried out in Aachen, Germany. The study included data on 32 patients with acute Stanford type A aortic dissection who received the E-vita open plus between November 2009 and September 2011 with a maximum follow-up of 33 months. Overall, the EAC concluded that the study by Jakob et al. (2011) was sufficiently comprehensive to form the sole clinical evidence base for the E-vita open plus, as the study by Jakob et al. (2012) reported on a subset of the same registry data and the study by Hoffman et al. (2012) reported on a small number of patients with a short follow-up period.

Details of the paper by Jakob et al. (2011) are shown below in table 1 (adapted from tables 1 and 2 of the assessment report). The authors reported observational data, gathered between January 2005 and December 2010, for 274 patients with complex aortic disease enrolled in the E-vita Open Registry, from 8 European centres. This comprised the entire dataset at the time of publication. The mean age was 60 years and 74% patients (204) were male. Of the 274 patients treated, 32% (88) had acute aortic dissection, 37% (102) had chronic aortic dissection and 31% (84) had extended aortic aneurysm. 5% of patients (12) were being treated for complications of Marfan's syndrome. Emergency surgery was performed in 88% of patients (77/84) with acute aortic dissection. Of those with chronic aortic dissection, 70% of patients (71/84) had already received proximal aortic repair. Outcomes were presented as proportions and survival analysis was carried out using the Kaplan-Meier technique. Stent-graft deployment and arch replacement was carried out under selective antegrade cerebral perfusion for a mean time of 75 minutes. Arch replacement was carried out with the integrated E-vita open prosthesis in 55% (151) cases or with branched or simple tubular prostheses in the remaining cases. Additional coronary artery bypass graft (CABG) was carried out in 16% (43) of cases. Median length of hospital stay was 19 days (range 12–29). In-hospital mortality was 15% and 30-day mortality was 12%. The false lumen was assessed postoperatively and at a median time of 59 months (range 28–99) after surgery in 248 cases. The false lumen thrombosed fully in 83% (62/75) of patients with acute aortic dissection, and 72% (68/94) of patients with chronic aortic dissection. After follow-up these figures rose to 93% and 92% respectively. For aneurysm, complete exclusion of the aneurysm was achieved in 77% of cases (61/79). The 5-year survival rate was 74%. Of the 233 patients surviving the procedure initially, secondary endovascular intervention was required in 13% (29) and surgery downstream in 3% (6).

The sponsor provided details (table 16 in the sponsor's submission) of the adverse events associated with the E-vita open plus when used to repair acute aortic dissection, chronic aortic dissection and thoracic aortic aneurysm.

The event rates were presented as proportions taken from the study by Jakob et al. (2011). The adverse events considered were intubation for longer than 72 hours (33%), re-exploration for bleeding (14%; this was 18% in those with acute aortic dissection), spinal cord injury (8%), stroke (6%) and permanent dialysis (4%). The EAC considered that the reported rates for adverse events were not unexpected for this type of procedure and did not raise any significant safety concerns.

The sponsor included 4 additional papers relating to interventions, defined as comparators in the scope, for complex thoracic aortic disease (Etz et al., 2008; Safi et al., 2007; Lemaire et al., 2006; Svensson et al., 2004). The sponsor included a summary of the mortality, 5-year survival and complications (stroke, renal failure and paraplegia) outcomes for the 4 comparator studies and compared the rates to those reported for Evita open plus in Jakob et al. (2011; table 14 of the sponsor's submission). No confidence intervals were reported. The EAC was able to calculate 95% confidence intervals for the reported proportions but not for the survival rates, citing insufficient data. Baseline characteristics were not described in the submission, however details of these papers are included in table 1b of the assessment report (an updated version of this table is included at Appendix D of this assessment report overview). The EAC noted that the 4 studies selected by the sponsor included data for only 1 comparator (of the 3 defined in the scope) – 2-stage repair with vascular graft, using a classical elephant trunk method – and that no assessment of quality for these studies was described in the submission. The EAC therefore conducted a further review and meta-analysis to evaluate all comparators listed in the scope.

Table 1: Study methodology and key points (adapted from tables 1 and 2 in the assessment report)

Study	Design	Intervention	Patient population	Country	Outcomes	EAC comments
Jakob et al., 2011	Multi-centre cohort study with up to 6 years follow-up	E-vita open	• Patients with complex aortic disease undergoing arch replacement combined with open antegrade stent-grafting using the E-vita open hybrid stent-graft between Jan 2005 and Dec 2010. • Enrolled to the international E-vita Open Registry. • Mean age= 60; 74% men • n=274 (AAD=88, CAD=102, TAA=84)	International E-vita Open Registry (IEOR). 8 referral centres: Barcelona (Spain), Birmingham (UK), Bologna (Italy), Essen (Germany), Graz (Austria), Leipzig (Germany), Prague (Czech Republic), Vienna (Austria)	• In-hospital mortality: 15% (40/274) (18% for AAD, 13% for CAD, 14% for TAA). • 30-day mortality: 12% (33/274) • Emergency surgery: 30% (81/274) • Stroke: 6% (16/274) • Spinal cord injury: 8% (22/274) • Renal failure: 4% (10/274) • Bleeding: 14% (38/274) • 5-year survival: 74% • Freedom from secondary endovascular intervention and secondary surgery distally: 82% and 95%, respectively • Incidence of secondary endovascular intervention or surgery downstream among survivors (233/274): 13% (29/233), 3% (6/233), respectively. • Full exclusion of the aneurysmal disease during primary hospital stay: 77% (61/79) • From the first follow up CT-examination to the last, thoracic complete false lumen thrombosis increased from 83% to 93% in AAD, from 72% to 92% in CAD downstream among survivors (233/274): 13% (29/233), 3% (6/233), respectively.	• Multi-centre study using register data • No CIs for estimates • No comparator in paper • Numbers in some subgroups are very small • Any centre effect? • Large data set with data collected in uniform manner • Included in sponsor's evidence synthesis

AAD, acute aortic dissection; CAD, chronic aortic dissection; TAA, thoracic aortic aneurysm.

Evidence synthesis

The sponsor did not carry out a formal evidence synthesis or meta-analysis. Results of the intervention and comparator studies were presented as proportions and ranges, without confidence intervals, for comparison as previously described (table 14 of the sponsor's submission).

Additional analyses by the External Assessment Centre

Registry data quality

The EAC assessed the quality of the International E-vita Open Registry based on discussions with the registry team and on the data collection manual provided by the registry owners (a copy of the manual is included with this assessment report overview). The EAC was informed that the registry now contains data on 470 patients from 11 centres (as of May 2013). Data is collected at preoperative, intraoperative and postoperative stages and patients are followed up every 6 months for the first 2 years and then annually. Data are validated by inter-centre communication. The EAC was not able to examine individual patient registry data, but concluded that the registry arrangements appeared robust as far as could be ascertained.

Comparator studies

The EAC carried out a systematic review and meta-analysis of data for the comparators defined in the scope, to address the gaps in the sponsor's submission. The EAC included data on open surgical debranching with endoluminal stent graft placement as a 2-stage or hybrid procedure. The review resulted in 10 relevant studies, including the 4 included in the sponsor's submission. Details of the studies are provided in table 3a of the assessment report. The EAC did not carry out a formal critical appraisal, but the studies were reviewed in detail to extract outcome data for inclusion in the meta-analysis. Table 4 of the assessment report contains all available pooled estimates of outcome rates for the E-vita open plus and the comparators.

The meta-analysis generated pooled outcome estimates with 95% confidence intervals for in-hospital and 30 day mortality, stroke, bleeding, paraplegia and

renal failure. Survival rates could not be included in the meta-analysis as data were limited. Results of the meta-analysis are shown in table 4 of the assessment report.

Conclusions about the clinical evidence

The EAC considered that the study by Jakob et al. (2011) was sufficiently comprehensive to form the clinical evidence base for the technology but noted that details of patient characteristics were poorly reported in the study, limiting its generalisability. Confidence intervals were not included in the reported outcomes, leading to uncertainty around the precision of the findings, therefore the EAC calculated confidence intervals as part of its additional analysis. The mortality rate reported in the study was 15% (n=40) and the 95% confidence interval ranged from 10.6% to 19.3%, indicating a degree of uncertainty in the data. The EAC was unable to calculate a confidence interval for 5-year survival, which was reported as 74%, but noted that this was based on 7 patients and therefore could also be subject to uncertainty. The EAC also noted that technical success, incidence of junctional endoleak and length of intensive care unit stay were not reported.

The EAC's meta-analysis generated pooled outcome estimates with 95% confidence intervals for outcomes at each stage of the comparator procedures. The EAC was unable to calculate single outcome estimates for the 2-stage procedures as this data was not available across all the comparator studies. The EAC felt that this made direct comparisons between the E-vita open plus and other techniques difficult. Several adverse outcomes appeared to be more common for the E-vita open plus than for the comparators, but the EAC concluded that the figures did not take into account factors such as survival from stage 1 to 2 or the impact of the combined outcomes for each procedure. Long-term survival rates could not be included in the meta-analysis because no confidence intervals were reported and individual patient data were not available. The EAC also considered that the heterogeneity of the studies in terms of patient group, setting, surgical team and postoperative care regime could be potentially confounding. The EAC

concluded that findings from economic modelling could provide a more accurate comparison of outcomes.

4.2 Summary of economic evidence

The sponsor did not submit any published economic evidence relating to the E-vita open plus, stating that no studies had been carried out. Although its search strategy was provided, the EAC noted that it was unclear whether the search had been carried out to identify published economic evidence or resource parameters for de novo analysis. The sponsor did not comment on the availability of economic studies for the comparators, but no evidence was submitted. The EAC considered that the sponsor's search strategy was flawed and devised a revised strategy, searching a wider range of databases. The search identified 47 abstracts, of which 3 were initially considered relevant, but where the full text revealed that the studies did not relate to the population defined in the scope, and so these were excluded from further consideration. The EAC concluded that no relevant economic studies were available for either the technology or the comparators.

Sponsor's de novo analysis

The sponsor submitted a de novo cost analysis comparing the use of the E-vita open plus to a 2-stage classical 'elephant trunk' procedure in terms of overall costs, in-hospital mortality and positive outcome rates. Costs were modelled from an NHS and personal social services perspective. The population included in the model was a cohort of 3500 people with aneurysms, dissections and specific lesions of the thoracic aorta. The model consisted of 2 decision trees over a 1-year time horizon: a current practice model using the classical 'elephant trunk' procedure and an intervention model, comparing current practice and use of the E-vita open plus, and assuming a 40% adoption rate. The first stage of the current practice arm was divided into 2 options; woven graft or branched graft. For patients undergoing stage 2, the options were woven graft or endovascular stent. A diagram of the model is included in section 9.1.5 of the sponsor's submission.

The sponsor carried out 1- and 2-way sensitivity analyses on several of the clinical parameters. The assumptions, costs and clinical parameters used in the model are listed in sections 9.1.6 and 9.2.1 of the sponsor's submission.

The EAC identified several limitations with the selected model structure, population and clinical parameters. The EAC considered that the model should have employed a per-patient approach using probabilities for each clinical state to estimate the cost for the technology and comparators. The sponsor did not clearly define the patient group as including those with aneurysms or dissections of the thoracic aorta involving the ascending aorta, arch and descending aorta, as in the scope. The estimated cohort of 3500 patients treated annually was taken from published sources including hospital episode statistics (HES); however on further examination the EAC considered that the number of admissions had been overestimated and that the population defined in the scope (50–100 people per year) was a more realistic estimate.

The 2 options considered in the model for the first stage of the elephant trunk procedure were 'woven graft' or 'branched graft', which were not clearly defined in relation to the comparators outlined in the scope. The EAC clarified this with the sponsor to confirm that:

- woven graft at stages 1 and 2 referred to 2-stage open surgical repair with vascular graft placement
- woven graft followed by stent graft at stage 2 referred to 2-stage repair with open surgical graft placement in the ascending aorta and arch and endovascular stent graft placement in the descending aorta
- branched graft followed by woven or stent graft at stage 2 referred to open surgical 'debranching' of the head and neck vessels with endoluminal stent graft placement in the aortic arch and either a vascular graft or endovascular stent graft in the descending aorta.

As the descending aorta would be repaired by either a woven graft or a stent graft at stage 2, the EAC concluded that 4 comparators were included in the model.

The sponsor assumed that in-hospital and 30 day mortality was 15% for the E-vita open plus. This was taken from registry data in the paper by Jakob et al. (2011) and the EAC considered this to be a reasonable assumption. The EAC commented that the assumption that the remaining 85% would have a positive outcome was flawed, as complications such as stroke, paraplegia or renal failure were not included. For the comparators, stage 1 mortality was not included and the EAC felt that the basis for the assumed mortality rates of 20% (woven graft) and 30% (branched graft) at stage 2 was not clear.

The EAC considered the 1 year time horizon for the model to be reasonable to cover short term outcomes. The sponsor did not include modelling of longer term outcomes, citing limited availability of mortality information. The EAC felt that the availability of literature including 5 year survival rates meant that longer term outcomes could have been modelled. The EAC also concluded that a longer term model would be more appropriate to assess the costs of complications such as stroke or paraplegia.

The number of inpatient days needed for the classical elephant trunk procedure was assumed by the sponsor to be 10 at stage 1 and 15 at stage 2. These figures were taken from HES code L27.3. The EAC felt that this was incorrect as the mean length of stay for HES code L27.3 is 12.2. The EAC agreed with the sponsor's estimate of the patient days taken for the endovascular stent procedure carried out at stage 2, but noted that this had been taken from an unreferenced source rather than HES. The EAC queried the sponsor's assumption that patient days would be split between the ICU and surgical ward.

Costs and benefits

The costs used in the sponsor's model are listed in sections 9.1.6 and 9.2.1 of its submission. The cost estimates for clinical time and resource use were

sourced from published literature, Personal Social Services Research Unit (PSSRU) unit costs of health and social care manual (Curtis, 2012) and NHS reference costs (DH, 2012). The cost of the E-vita open plus provided by the sponsor was £10,500 and the comparator costs were £200 for a woven graft for stages 1 & 2, £1000 for a branched graft, and £5000 for a endovascular stent graft. These figures were based on commercial prices which the EAC considered to be reasonable.

The EAC considered several of the sponsor's cost estimates to be flawed. The cost of a surgeon was estimated to be £399 per hour, when the PSSRU figure is £172 per hour. The cost of a perfusionist and anaesthetist was estimated to be £87 per hour (at registrar rate). The EAC's view was that a consultant anaesthetist would be needed for complex cardiac surgery and the cost would therefore be £172 per hour.

The cost for theatre time, including nursing and consumables, was estimated to be £24 per hour, and £30 per hour for ICU. These were derived from the 'NHS tariff for admitted patient case and outpatient procedures', but no codes were specified, making these figures hard to verify. The EAC felt that using hourly rates for 2 nurses at £100 per hour would be more appropriate. The EAC noted that consumable costs, estimated to be £130, had not been included, as the sponsor considered these to be equivalent for both the technology and comparators.

The EAC considered that the sponsor's use of a daily cost for ICU was reasonable, as this varied between procedures, although it felt that the figure used (£1500) should have been taken from an NHS tariff code and not indirectly from a report in the Lancet. The EAC was unable to reconcile the costs for a surgical ward inpatient stay (£420 per day) with the NHS reference costs and suggested using more appropriate cost codes.

The cost of death cited by the sponsor (£8000) was taken from a cancer network publication. The EAC felt that as this related to cancer death, a more appropriate figure could have been used, relating to in-hospital death from the procedure and including any associated complications.

The sponsor carried out 1-way sensitivity analyses varying the adoption rate (from the base case assumption of 40%) of the E-vita open plus from 20% and 100%. The proportion of woven or branched grafts at stage 1 was varied from 60% to 95% from a base-case estimate of 85%. The suitability of a second stage operation was varied from a base-case of 80% to 60% and 95%, and the proportion of patients having each stage 2 procedure was varied from a 50% base-case to 40% and 100%.

The sponsor carried out a 2-way sensitivity analysis varying the in-hospital death rate at stage 1 of the classical elephant trunk procedure and for E-vita open plus. The EAC considered that a 1-way sensitivity analysis would have been more appropriate for this outcome.

Results

The EAC was able to validate the model despite some typographic errors. The sponsor presented the results of their de novo analysis as an average cost per patient, assuming a 100% adoption level for the E-vita open plus compared with current practice. Costs for the technology, treatment, administration and death were totalled for the E-vita open plus and for all comparators (table C12 in the sponsor's submission). The cost for E-vita open plus was £25,688 and the cost for the comparators was £30,241, a cost saving per patient of £4552. The EAC examined the costs for each comparator and found variation across the totalled figures, ranging from £26,691 for woven graft (stage 1) with endovascular stent (stage 2) to £36,016 for branched graft (stage 1) with woven graft (stage 2). The EAC was of the opinion that a probability approach, rather than a cohort approach, would have been more appropriate to calculate per-patient costs.

The sponsor's sensitivity analysis showed little variation in the cost savings generated for the E-vita open plus at different adoption levels, with an average of around £4358. The sponsor reported that varying the parameters for second-stage suitability and in-hospital death had an impact on the cost savings, but that this was relatively small. Varying the patient suitability for a second stage operation produced higher cost savings per patient if the level of

suitability was raised. The sponsor concluded that the E-vita open plus was clinically superior to the comparators, as there were no significant differences in savings per patient even with similar levels of in-hospital death rates. The sponsor noted that endovascular stent graft might be an easier procedure to perform at stage 2, with potential for cost savings; however it maintained the clinical superiority of the E-vita open plus as it has only 1 stage and could generate the claimed cost savings.

The EAC noted that the sponsor did not consider the specific subgroups defined in the scope in their de novo analysis, but concluded that data for these groups were not available for the comparators and so could not have been included in the cost analysis.

The EAC considered that the sensitivity analyses were reasonable, but felt that the cost model would need revisions in terms of structure and parameters in order to draw robust conclusions about the cost consequences of the technology.

Additional cost analysis by the External Assessment Centre

The EAC carried out additional analysis to include the costs of complications (stroke, paraplegia, renal failure and bleeding) and in-hospital mortality at each stage of each procedure. The complications were chosen based on the EAC's review of the clinical evidence. The EAC constructed short and long term models. Both models compared expected per-patient costs for the E-vita open plus and the 3 comparators defined in the scope (2-stage repair with vascular graft, 2-stage repair with endovascular stent graft and open debranching with endoluminal stent graft). The time horizon for the short term model was 1 year, as the EAC considered that stage 2 procedures were likely to be carried out within 6 months of stage 1. The long term model had a 20 year time horizon, based on the UK life expectancy of the average age (65 years) of the population receiving treatment described in the literature (Jakob et al. 2011). The model included the lifetime costs of complications. A decision tree was constructed for each procedure in the short and long term and these are presented in figures 1 to 8 of the assessment report.

In the short term model for the comparators, patients with no complications or bleeding at stage 1 were assumed to proceed to the second stage procedure, whereas those who had a stroke, renal failure or paraplegia would not.

In the long term model, the annual costs of care for stroke, paraplegia and renal failure were taken from published literature and discounted at 3.5%. The discounted annual cost was multiplied by a survival probability for 65 to 85 years and the weighted annual costs were summed to estimate the lifetime cost of the complications.

A detailed list of the EAC's assumptions, probabilities and costs used in the model are in table 5 of the assessment report. Probabilities for the outcomes at each stage were taken from the EAC's meta-analysis of the clinical evidence (table 4 of the assessment report). The probability of paraplegia at stage 1 was assumed to be the same for 2-stage repair with vascular graft and 2-stage repair with endovascular stent graft. For open debranching, this probability and that of renal failure at stage 1 was taken from hybrid procedure estimates.

The EAC estimated operating time for the comparators and total length of stay from the literature. Operating time for the E-vita open plus was taken from the sponsor's submission. Details of the surgical team involved for each procedure were taken from the sponsor's submission and included a consultant surgeon, consultant anaesthetist, associate specialist, perfusionist and 2 specialist nurses. A consultant radiologist was included for stage 2 procedures involving stent grafts.

Costs and benefits

Costs for each professional in the surgical team were taken from the PSSRU unit costs of health and social care manual (Curtis 2012). The costs of the technology and comparators were taken from the sponsor's submission. The costs for an ICU and surgical ward stay were sourced from NHS reference costs at £1410 per day and £383 per day respectively.

Complications were assumed to incur additional in-hospital management costs and a single cost figure was applied across all procedures (£2155). The annual cost for stroke care was estimated to be £9,597 at 2012 prices, from Atrial fibrillation (NICE clinical guideline 36). The annual cost of paraplegia was estimated to be £14,580, based on the literature and inflated to 2012 prices. The annual cost for renal failure used was £32,961. This was taken from Peritoneal dialysis (NICE clinical guideline 125), using proportional estimates for automated peritoneal dialysis, continuous ambulatory peritoneal dialysis and haemodialysis to calculate a weighted average, inflated to 2012 prices.

The cost of using multiple stents, a consideration in the scope, was included in the analysis and sourced from the sponsor's submission. However the EAC was not able to model the implications of using multiple stents, citing a lack of available clinical evidence.

Sensitivity analysis

The EAC felt that there was uncertainty around many of the assumed costs and therefore carried out deterministic sensitivity analysis on several variables. The probabilities for E-vita open plus in-hospital mortality and paraplegia were varied from 10% to 20% and 3% to 10% respectively, based on 95% confidence intervals form the EAC's meta-analysis. The proportion of days in ICU was varied from 20% to 60% (40% base-case) and the cost of an ICU day was varied from £870 to £2000 to reflect the uncertainty in the number of organs needing support (range 1–6, base-case 3).

The management cost for complications was varied from £1,075 to £ 3,235, to allow a 50% variation from base-case. The annual costs for stroke and paraplegia were varied to reflect the minimum and maximum ranges identified in the literature (from £3,691 to £14,396 and from £11,320 to £19,256 respectively), and the annual cost for renal failure was varied from £24,724 to £41,210 to reflect a 25% variation from base-case.

Results

The results of the EAC's base case for both short and long term models are shown in table 2. The short term model showed that treatment with the E-vita open plus could generate a cost saving of £280 per patient when compared to 2-stage repair with vascular graft. The technology was cost-incurring when compared to 2-stage repair with endovascular stent graft and also when compared to open debranching with endoluminal stent graft.

The long term model, considering the lifetime costs of complications, showed that treatment with the E-vita open plus could generate significant cost savings when compared to all three comparator procedures. The savings per patient were £41,213 when compared to 2-stage repair with vascular graft, £39,392 when compared to 2-stage repair with endovascular stent graft and £51,778 when compared to open debranching with endoluminal stent graft.

Table 2: Base-case results (cost savings are shown as negative values)

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

Results of the EAC's sensitivity analysis are presented in tables 7–14 of the assessment report. Varying the probability of in-hospital mortality and paraplegia for the E-vita open plus, or the management or annual costs of complications, did not significantly alter the expected cost savings in the base-case estimate. In the short term model, varying the proportion of ICU stays did alter the observed cost savings. At the 20% level, the E-vita open plus was cost incurring when compared with all 3 comparators. At the 60% level, there were greater cost savings for the E-vita open plus compared against 2-stage repair with vascular graft. Varying the cost of ICU stay affected the short term results in a similar way, however neither variable significantly altered the cost savings in the long term.

The EAC acknowledged some limitations in its model. Complications were assumed to occur only in the short term, as data were not available for the longer term. The EAC used a decision analytical model and considered this to be a reasonable approach, but recognised that a more complex model (such as Markov or discrete event simulation) may have facilitated a more refined analysis. The EAC also noted that using deterministic sensitivity analysis did not account for the possibility of multiple complications occurring in individual patients.

The EAC concluded that results of the revised model indicated that the E-vita open plus could generate significant cost savings in the long term, but not in the short term. The indicative cost and total length of stay for the E-vita open plus were the main drivers for the cost differences in the short term. In the long term (over 20 years), the lifetime costs of complications were lower for the E-vita open plus because it is a single stage procedure and therefore the risk of complications would only apply once. This was considered to be the main driver for the observed cost savings.

4.3 Main issues

Clinical evidence

The evidence for the E-vita open plus is limited to studies based on the International E-vita Open Registry, mainly 1 observational study reporting on the registry dataset in 2011. Neither the sponsor nor the EAC identified any evidence directly comparing the E-vita open plus to any other treatments for complex aortic disease, so only an indirect comparison could be made by reviewing evidence on the comparators. The EAC was advised by clinical experts that the heterogeneity of the studies originating from different centres necessitated caution when making comparisons. Table 4 of the assessment report contains all available pooled estimates of outcome rates for the E-vita open plus and comparators.

The pooled estimates from the EAC's meta-analysis of the comparator studies provide an indication of outcome measures for the 2 stages of treatment

individually. The EAC could not provide overall estimates of mortality or complications owing to a lack of data and urged caution in directly comparing outcomes across different stages. This was because of the possibility of confounding factors such as survival to second stage and the overall impact of combined outcomes. The EAC concluded that its revised economic model could provide a more accurate comparison of outcomes as it included outcome synthesis.

Despite the limitations in the published evidence, the EAC considered that the E-vita Open Registry was robust and the data collection manual sufficiently detailed. The EAC was informed that the registry currently included data on 470 patients from 11 centres. The EAC were not able to obtain the registry data and so could not comment on the impact this additional patient data would have on the clinical conclusions, other than to point out that the data from the additional 196 patients and longer overall follow-up time could provide more accurate outcome data.

The EAC commented that the included registry data related to the E-vita open, the predecessor device to the open plus. The E-vita open needed pre-sealing with fibrin glue, but the EAC stated that if the device was adequately pre-sealed, performance should be comparable to the open plus device, which is impermeable to blood.

The EAC pointed out that aortic dissection can be more difficult to treat and therefore the ratio of dissection to aneurysm should be taken into account when evaluating the technical success of the E-vita open plus. The EAC found clinical evidence relating to the subgroups of aneurysm and dissection listed in the scope for the E-vita open plus, but not for the comparators and so a comparison could not be made.

In terms of future possible research, the EAC's view was that randomised clinical studies should be considered in order to make direct comparisons between the E-vita open plus and the comparator techniques. It suggested that studies could also include consideration of the subgroups defined in the scope as well as economic evaluation.

Economic evidence

Neither the sponsor nor the EAC identified any published economic evidence. The economic evidence for the E-vita open plus therefore comprised the sponsor's de novo cost analysis and the additional cost analysis carried out by the EAC. The EAC considered that the information on parameters and outcomes described in the published clinical evidence was sufficient to be able to model short and long term costs of the technology and comparators.

The sponsor submitted a model comparing the E-vita open plus to the comparators defined in the scope, varying adoption levels, suitability for a second stage procedure and in-hospital mortality. The EAC considered that it would be more appropriate to use probabilities for each outcome and that the costs of complications would need to be modelled in the short and long term in order to best address the outcomes defined in the scope.

The EAC's additional analysis found that the E-vita open plus would be cost saving in the short term only when compared to 2-stage surgical repair with vascular graft placement, and would be cost incurring if the proportion of length of stay in the ICU and ICU costs were lowered from the base-case figure. The EAC concluded that costs were incurred as a result of the indicative price of the E-vita open plus and the total length of stay needed. Over a 20 year period, however, the EAC concluded that significant cost savings could be made by using the E-vita open plus in place of the comparators. The observed cost savings were driven by the lifetime costs of stroke, paraplegia and renal failure as a consequence of the procedures, which were lower for the single-stage E-vita open plus, as potential complications would only be encountered once.

The EAC noted that in some cases further stent placement procedures may be necessary if the stent graft component of the E-vita open plus is not long enough to repair all areas of damage in the descending aorta. This was not specifically addressed in the cost modelling because of a lack of available evidence.

5 Ongoing research

Recruitment to the International E-vita Open Registry is ongoing.

NIHR Health Technology Assessment board minutes of 5–6 March 2013 indicate that provisional funding has been allocated to a trial of the management of thoracic aortic aneurysm. No further details were available to the EAC.

6 Authors

Joanne Higgins, Technical Analyst

Mark Campbell, Associate Director

NICE Medical Technologies Evaluation Programme

July 2013

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Clough R, Keevil S, Lewis C et al. E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta. June 2013 – King's Imaging Technology Evaluation Centre (KITEC)

B Submissions from the following sponsors:

- JOTEC GmbH

C Related NICE guidance

Published

- Endovascular stent-graft placement in thoracic aortic aneurysms and dissections. NICE interventional procedure guidance 127 (2005). Available from www.nice.org.uk/guidance/IPG127

D References

Curtis L (2012) Unit Costs of Health and Social Care 2012. Personal Social Services Research Unit. University of Kent. Kent.

Department of Health (2012) NHS Reference Costs 2012 accessed from https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012

Etz CD, Plestis KA, Kari FA et al. (2008) Staged repair of thoracic and thoracoabdominal aortic aneurysms using the elephant trunk technique: a consecutive series of 215 first stage and 120 complete repairs. European Journal of Cardio-Thoracic Surgery 34(3): 605-615.

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Hoffman A, Damberg AL, Schälte G et al. (2012) Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection. J Thorac Cardiovasc Surg 145(4):964-9.

Jakob H, Dohle DS, Piotrowski J et al. (2012) Six- year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance. Eur J Cardiothorac Surg 42(6):1018-25.

Jakob H, Tsagakis K, Pacini D et al. (2011) The International E-vita open Registry: Data sets of 274 patients. Journal of Cardiovascular Surgery 52(5): 717-723.

LeMaire SA, Carter SA, Coselli JS et al. (2006) The elephant trunk technique for staged repair of complex aneurysms of the entire thoracic aorta. The Annals of thoracic surgery 81(5): 1561-1569; discussion 1569.

Mestres CA, Tsagakis K, Pacini D et al. (2012) One-stage repair in complex multisegmental thoracic aneurysmal disease: Results of a multicentre study. Interactive Cardiovascular and Thoracic Surgery 15: S97.

Safi HJ, Miller CC 3rd, Estrera AL et al. (2007) Optimization of aortic arch replacement: two-stage approach. Annals of Thoracic Surgery 83(2): S815-818; discussion S824-831.

Svensson LG, Kim KH, Blackstone EH et al. (2004) Elephant trunk procedure: newer indications and uses. Annals of Thoracic Surgery 78(1): 109-116; discussion 109-116.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Prof John Brennan
Consultant Vascular and Endovascular Surgeon, Vascular Society of Great Britain and Ireland

Mr Marcus Brooks
General and Vascular Surgeon, Vascular Society of Great Britain and Ireland

Mr Graham Cooper
Consultant Cardiothoracic Surgeon, Society of Cardiothoracic Surgery of Great Britain and Ireland

Dr Mo Hamady
Consultant Interventional Radiologist, British Society of Interventional Radiology

Mr Michael Jenkins
Consultant Vascular Surgeon, Vascular Society of Great Britain and Ireland

Mr Stephen Large
Consultant Surgeon, Society of Cardiothoracic Surgery of Great Britain and Ireland

Professor Matt Thompson
Professor of Vascular Surgery, British Society for Endovascular Therapy

Prof Olaf Wendler
Professor of Cardiac Surgery, Royal College of Surgeons

- 1 expert has had direct involvement with the technology, and 4 have referred patients for its use or managed patients in whom it has been used. 2 experts would like to use the technology if it were available to them.

- 6 experts considered the E-vita open plus to be a significant modification of an existing technology.
- There was general consensus amongst the experts concerning the scenario for use. This was in the management of patients with thoracic aneurysms or dissections involving the arch and descending aorta, who would be suitable for open surgical repair.
- The majority of experts thought that the main comparator would be the staged elephant trunk procedure via open sternotomy, followed by thoracotomy or endovascular stent graft placement for repair of the descending aorta. Surgical debranching was also considered.
- The majority of experts (7) were not aware of any competitor devices, however 1 expert identified the Thoraflex Hybrid as a competitor.
- The benefits for patients were thought to be the opportunity to manage complex thoracic aortic disease in a single procedure, the potential reduction in morbidity, mortality and length of stay compared to 2-stage repair, the ability to repair the aortic arch more quickly and the avoidance of late dilatation of the descending aorta with its associated complications. Half the experts believed that the benefits to patients would be realised in practice; 2 felt that more evidence would be needed.
- The potential benefits to the healthcare system were thought to be the resource savings from avoidance of a second stage procedure and the treatment of any associated long term morbidity. Reduced length of stay was also mentioned by several experts. 5 experts thought that the benefits to the healthcare system would be realised in practice.
- Suggested outcome measures included overall mortality and morbidity from complications, avoidance of a second stage procedure, length of stay and freedom from aortic disease. 1 expert suggested that cost-effectiveness analysis could be carried out, and another that clinical trials were needed. The registry data was also considered.
- The majority of experts thought that the evidence base was limited, other than the E-vita open plus registry data.
- All the experts were of the opinion that training would be required to use the device. Several experts stated that a hybrid operating theatre or

excellent imaging facilities in cardiac theatres would be required, as would a multidisciplinary team approach, possibly in a specialist centre.

- None of the experts expressed concerns about the costs of the E-vita open plus and the device was not considered to be controversial by the majority of experts. Some experts were concerned as to the longer term durability of the device and the need for careful patient selection was mentioned.
- The majority of experts thought that guidance on the E-vita open plus would be useful, although one expert thought that it would be limited by the small patient population. 2 experts felt that guidance would improve access to the technology.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient organisations were contacted and no response was received.

- Arrhythmia Alliance
- Action Heart
- British Cardiac Patients Association
- British Heart Foundation
- Cardiac Risk in the Young
- Cardiomyopathy Association
- Coronary Artery Disease Association (CORDA)
- Heartcare Partnership UK
- Marfan Association UK
- National Heart Forum (UK)
- Royal College of Surgeons Patient Liaison Group
- SADS UK
- The Somerville Foundation

Appendix D: Additional analyses carried out by the External Assessment Centre (EAC)

The EAC submitted an addendum after the External Assessment Report was initially submitted to NICE, in order to provide clarification on the clinical evidence submitted by the sponsor and to provide a brief erratum.

Addendum to report

The following pages include an addendum to clarify which studies were included by the sponsor, and to also provide textual description of those studies reported by the sponsors to be 'included'. Ten studies have been removed from table 1 that were described by the sponsor as 'relevant', but were subsequently described as 'excluded'. Details in table 1b for the reference 'Safi 2001' which should have read 'Safi 2007' have been amended. Further, the EAC has added a comment on a potentially relevant study that is now in press, and that the EAC received on 16 June 2013 from the sponsor, which was too late to be included in the body of the report.

Herewith we provide a revised section 3.3 and revised tables 1 and 1b.

KITEC EAC 27 June 2013

3.3 Included and excluded studies (section revised)

The sponsor initially reported finding 18 published studies of which 13/18 studies were reported as being 'relevant' (Jakob 2012, Jakob 2011, Hoffman 2012, Gorlitzer 2012, Pacini 2011, Tsagakis 2010a, Jakob 2010, Tsagakis 2011, Tsagakis 2010b, Di Bartolomeo 2009, Di Bartolomeo 2008, Gorlitzer 2007, Herold 2006). The sponsor subsequently excluded 10/13, leaving just three (Jakob 2012, Jakob 2011, and Hoffman 2012). Details of these three studies are given in table 1 and described below.

All three studies included by the sponsor are descriptive and none included comparators (table 1). Jakob et al (2011) reports on the International E-vita Open Registry and provides data from January 2005 to December 2010. This includes 274 patients with complex aortic disease who were enrolled into the registry. The majority were male (74%) and mean age was 60 years. At the time of publication of Jakob's study, the registry included eight referral centres in Europe: Barcelona, Birmingham, Bologna, Essen, Graz, Leipzig, Prague, and Vienna. The maximum follow-up was six years. This is the most comprehensive paper and includes the best quality evidence available (discussed below).

Jakob 2012 also reports on patients from the International E-vita Open Registry and included patients receiving surgery between January 2005 and March 2011, a three-month longer span than the Jakob 2011 paper. However, Jakob 2012 only included the 77 patients from the Essen (Germany) centre, and so the patients are a subset of the entire registry. Unsurprisingly, mean age and the proportion of males were similar to the whole registry reported in Jakob 2011 (mean 59 years, 75% males). The maximum follow-up was six years. Hoffman's 2012 study was small with just 32 patients treated in Aachen, Germany. Their mean age was 58 years and 81% were males. This was a single centre study but was not part of the International E-vita Open Registry. The study included patients with acute Stanford type A aortic dissection who underwent the frozen elephant trunk procedure (E-vita open

plus) for replacement of the aortic arch and stenting of the descending aorta, between November 2009 and September 2011. The maximum follow-up was 33 months.

The sponsor reported (in reference to Jakob 2011) that they:

‘decided to focus on the results published in this article. We excluded from our analysis articles published before as:’

This was followed by the list of the 10/13 studies to be excluded. The reason for exclusion was not totally clear but the EAC considers that for the papers that reported on subsets of the International E-vita Open Registry, their exclusion is appropriate as their data largely overlap with the data provided in the Jakob 2011 paper. Studies that this applies to are as follows: Pacini 2011, Tsagakis 2010a, Jakob 2010, Tsagakis 2011. For the other papers excluded, the EAC also considers this appropriate. Specifically Gorlitzer 2012 included just three patients from Vienna who received emergent E-vita open and so these data are appropriately excluded. Tsagakis 2010b is a two-part study in Essen: i) an animal study, and ii) the clinical use of E-vita open plus in nine (human) patients. This study provided limited outcomes in humans and no follow-up and so the EAC considers its data to be unusable here. Di Bartolomeo 2009 included 34 patients from Bologna, between January 2007 and July 2008. Bologna is one of the International E-vita Open Registry centres but it was not clear if this series of patients were included in the registry. Follow-up was short at 12 months maximum and a mean of 9 months. Given the doubt about overlap and the limited data, the EAC considers these data to be appropriately excluded. Di Bartolomeo 2008 reports on 24 patients receiving surgery between January 2007 and January 2008 from the same centre and it seems likely that these are a subset of the 34 patients described above. Hence the EAC considers that these data are appropriately excluded. Gorlitzer 2007 included seven patients receiving surgery in Vienna. This was also one of the International E-vita Open Registry centres and so the data may be included in the Jakob 2011 study report. The

EAC concludes that this, together with its small size and short follow-up, preclude its inclusion. Finally, Herold 2006 reports on a study in 30 patients from Essen, a registry centre and so as with other papers above, seems likely to overlap with the Jakob 2011 series. Hence the EAC agrees that this must be excluded.

One additional paper reported by the sponsor as unobtainable in its complete form: 'Management of postdissection thoracoabdominal aneurysm after previous frozen classical ET with the E-vita Open Plus stent-graft' was also excluded by the sponsor. The EAC was similarly unable to find this paper. However, the EAC did identify a different study published as a conference abstract by Mestres (2012) that was not cited by the sponsor. This study described a series of patients treated in Barcelona, one of the registry centres. The EAC received a pre-publication copy of this paper on 16 June 2013 and it is clear that this is a subset of the International E-vita Open Registry data and so the EAC considers it not appropriate for inclusion.

The sponsor chose to use only the data from Jakob 2011 and not to use data from Jakob 2012 or Hoffman 2012 in its evidence for E-vita open. The EAC considers that this is reasonable because Jakob 2012 overlaps considerably with Jakob 2011 and Hoffman's study was small, with 32 patients, and had a short follow-up.

However while the Jakob (2011) study provides a full and thorough account of the use of the device, it was confusing that the sponsor described Jakob 2012 and Hoffman 2012 as 'relevant' and did not explicitly say that they were excluding them.

The four comparator studies (table 1b) only described outcomes in patients who had undergone two-stage open surgical repair with vascular graft replacement. These studies were observational, and all were from the USA (New York, Cleveland Ohio, Houston Texas) while the E-vita open evidence was all from Europe. The comparator studies were all conducted between

1990 and 2006, therefore most of the evidence preceded the E-vita open plus registry. As described above and reported in detail below, the EAC conducted a systematic review on comparators and have conducted a thorough meta-analysis of outcomes.

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

Reference	Study used by sponsor in evidence synthesis?	Study	Patient population	Inter-vention	Country	Age/Sex	Study design	Sample size	Comments
Jakob et al., 2011	YES	The International E-vita Open Registry	Jan 2005 to Dec 2010. Patients with complex aortic disease underwent arch replacement combined with open antegrade stent-grafting using the E-vita open hybrid stent-graft and have enrolled to the international E-vita Open Registry (IEOR).	E-vita open	International E-vita Open Registry (IEOR). 8 referral centres: Barcelona (Spain), Birmingham (UK), Bologna (Italy), Essen (Germany), Graz (Austria), Leipzig (Germany), Prague (Czech Republic), Vienna (Austria)	Mean age= 60; 74% males	Multi-centre cohort study with up to 6 years follow-up	n=274 (AAD=88, CAD=102, TAA=84)	• Multi-centre study using register data • No CIs for estimates • No comparator in paper • Numbers in some subgroups are very small • Any centre effect? • Large data set with data collected in uniform manner

Reference	Study used by sponsor in evidence synthesis?	Study	Patient population	Inter-vention	Country	Age/Sex	Study design	Sample size	Comments
Jakob et al., 2012	NO	Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance.	Jan 2005 to Mar 2011. Patients with complex thoracic aortic disease underwent arch replacement combined with antegrade stent grafting of the descending aorta using the E-vita open hybrid stent graft in West German Heart Centre, University of Duisburg-Essen, Essen, Germany.	E-vita open	Essen, Germany	Mean age= 59; 75% males	Cohort study with up to 66 months follow-up	n=77 (AAD=39, CAD=23, TAA=15)	• Subset of the International E-vita Open Registry • Single-centre study • No CIs for estimates • No comparator

Reference	Study used by sponsor in evidence synthesis?	Study	Patient population	Inter-vention	Country	Age/Sex	Study design	Sample size	Comments
Hoffman et al., 2012	NO	Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection.	Nov 2009 to Sep 2011. Patients with acute Stanford type A aortic dissection underwent the frozen elephant trunk procedure (E-vita open plus) for replacement of the aortic arch and stenting of the descending aorta, at University Hospital RWTH Aachen, Aachen, Germany.	E-vita open plus	Aachen, Germany	Mean age= 58; 81% males	Cohort study with up to 33 months follow-up	n=32	• Singe-centre study • Short follow-up • Descriptive statistics only • No comparator

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

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

Reference	Study	Patient population	Intervention	Country	Age/Sex	Study design	Sample size
Etz et al 2008	Staged repair of thoracic and thoraco-abdominal aortic aneurisms	February 1990 to September 2006. Consecutive patients who underwent total arch replacement.	Two-stage open surgical repair with vascular graft replacement	New York, USA	Median 68 years Range: 20 to 87 59% male	Observational study	215
Svensson et al 2004	Elephant trunk procedure: newer indications and uses	November 1990 to February 2003 . Consecutive patients who underwent total arch replacement.	Two-stage open surgical repair with vascular graft replacement	Cleveland, Ohio, USA	Mean 67 years (SD 10.5) 47% male	Retrospective observational	94
Safi et al 2007	Optimisation of Aortic Arch Replacement: Two-Stage approach	February 1991 to December 2005. Patients who underwent repair for extensive aortic aneurysm.	Two-stage open surgical repair with vascular graft replacement	Houston, Texas, USA	Mean 68 years Range: 16 to 87 51% male	Observational study	254
LeMaire et al 2006	The elephant trunk technique for staged repair of complex aneurysms of the entire thoracic aorta	1990 to 2005. Consecutive patients with extensive aneurysms.	Two-stage open surgical repair with vascular graft replacement	Houston, Texas, USA	Mean 66 years (SD10.3) 48% male	Observational study	205

Appendix E: External Assessment Centre correspondence

National Institute for Health and Clinical Excellence
External Assessment Centre correspondence

E-vita open plus

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Editorial note: Responses to the EAC's questions are shown in italics. Citations provided by the sponsor in appendix 7 are detailed versions of those already in the sponsor's submission and are not new evidence.

Submission Document Section/Sub-section number	**Question / Request** *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	**Response** *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	**Action / Impact / Other comments**
3	**Expert Adviser – Stephen Large, Consultant Surgeon**	**Appendix 1**	**Questions clarifying clinical submission**
3	**Expert Adviser – Marcus Brooks, Consultant Vascular Surgeon**	**Appendix 2**	**Questions clarifying clinical submission**
3	**Expert Adviser – Matt Thompson, Professor of Vascular Surgery**	**Appendix 3**	**Questions clarifying clinical submission**
3	**Sponsor – JOTEC**	**Appendix 4**	**Questions clarifying clinical submission**
3	**Sponsor – JOTEC**	**Appendix 5**	**Further clarification over outcomes definitions**
3, 7	**Sponsor - JOTEC**	**Appendix 6**	**Further clarification on the reduction of second surgical procedures if E-vita is used**
C	**Sponsor - JOTEC**	**Appendix 7**	**Questions clarifying Economic Evidence submission**

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Other	**Dr. med. Konstantinos Tsagakis, Colleague of Professor Jakob who holds the registry**	**Appendix 8**	**Questions regarding the registry data and collection**
3	**Expert Adviser – Peter Taylor, Professor of Vascular Surgery**	**Appendix 9**	**Questions clarifying clinical submission**
Other	**Dr. med. Konstantinos Tsagakis, Colleague of Professor Jakob who holds the registry**	**Separate accompanying document, 'Appendix 10 Manual_registry.doc'** **ACADEMIC IN CONFIDENCE**	**Registry Manual** ***Editorial note: The Committee received this document for consideration, however it has not been included here as it was submitted as academic in confidence.***

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Other	**Dr. med. Konstantinos Tsagakis, Colleague of Professor Jakob who holds the registry**	**Appendix 11** **ACADEMIC IN CONFIDENCE**	**Unpublished paper, received 16/6/2013** ***Editorial note: The EAC have provided a commentary on this paper in the assessment report addendum, however it has not been included in this table as it was submitted as academic in confidence.***

Additionally, the expert advisers M Hamady, J Brennan and O Wendler were approached for clarifications of the clinical submission (same questions as in appendix 1), however no response was received.

Appendix 1

Our questions:

Dear All,

I am working with the group at King's Imaging Technology Assessment Centre (KITEC) and we have been asked by NICE to undertake an assessment of the E-vita open plus system.

The sponsor has submitted evidence relating to the device and we are currently preparing our report. As part of this, I am writing to you on behalf of the group to ask for your thoughts regarding the following:

1. Would you agree that the state-of-the-art clinical pathway for the treatment of complex thoracic aortic disease (aneurysm and dissection) involving the ascending aorta, arch and descending aorta is a two-stage operation, consisting of a first operation to replace the ascending aorta and the aortic arch with a vascular graft prosthesis via a midline sternotomy, and a second during which the descending aorta is replaced via a lateral thoracotomy?

2. Do you think that treatment using endovascular technology such as arch hybrid repair and total endovascular repair (either with chimney, fenestrated, or branched devices) should be included as a comparator to the E-vita open plus in the sponsor's submission?

3. Are you aware of any UK or other guidelines for the treatment of complex thoracic aortic disease? We were able to find the NICE IPG 127, which refers to descending thoracic pathology but not specifically to complex thoracic aortic disease.

4. Are you aware of any current trials evaluating the management of complex thoracic aortic disease?

5. The sponsor suggested the following as outcome measures to evaluate their device with reference to comparators: technical procedure(s) completion and success; mortality; major complications (stroke, paraplegia, renal failure, myocardial infarction and others that may delay discharge); length of intensive care unit stay; total length of hospital stay; freedom from further interventions; long-term survival rates; incidence

of junctional endoleak; device-related adverse events. Do you think that this list is adequate? Are there any others parameters which should be included? Do you think that any of the parameters should be more carefully defined? Should any of these outcome measures be changed when patients with connective tissue disease are treated?

6. Do you think that the sponsor should take into account issues regarding service re-organisation and associated cost in view of the fact that this device would require both radiological and surgical equipment and expertise to be available?

7. Are you aware of any trials directly comparing E-Vita with comparators? If not, do you consider the comparison of results from cohort series from different centres a valid approach as it will include different patients groups, surgeons and post-op care regimes?

Thank you for your help.

With best wishes,

Rachel

Response:

Dear Rachel and colleagues in answer to your questions: yes to all but add time for distal anastomosis/connection in aortic surgery and haemorrhage. I have a particular concern over use of self expanding stents in collagen-opathies. Hopefully well have a good conference on 15th. Best wishes Stephen large

Appendix 2

1. Would you agree that the state-of-the-art clinical pathway for the treatment of complex thoracic aortic disease (aneurysm and dissection) involving the ascending aorta, arch and descending aorta is a two-stage operation, consisting of a first operation to replace the ascending aorta and the aortic arch with a vascular graft prosthesis via a midline sternotomy, and a second during which the descending aorta is replaced via a lateral thoracotomy?
By state of the art I assume that you mean 'gold standard' open surgical approach - YES

2. Do you think that treatment using endovascular technology such as arch hybrid repair and total endovascular repair (either with chimney, fenestrated, or branched devices) should be included as a comparator to the E-vita open plus in the sponsor's submission?
NO, unnecessary to make this overtly complex – we know that the data on these procedures is difficult to interpret and follow up is short. The question to be answered first is should eVITA be routinely commissioned as an alternative to a 2 stage open procedure. It is of course likely over time that total endovascular solutions will advance. Currently these are experimental in the ascending aorta and none deal with the coronary ostia.

3. Are you aware of any UK or other guidelines for the treatment of complex thoracic aortic disease? We were able to find the NICE IPG 127, which refers to descending thoracic pathology but not specifically to complex thoracic aortic disease.
No, we drew up some local guidelines but nothing UK specific for reference.

4. Are you aware of any current trials evaluating the management of complex thoracic aortic disease?
No.

5. The sponsor suggested the following as outcome measures to evaluate their device with reference to comparators: technical procedure(s) completion and success; mortality; major complications (stroke, paraplegia, renal failure, myocardial infarction and

others that may delay discharge); length of intensive care unit stay; total length of hospital stay; freedom from further interventions; long-term survival rates; incidence of junctional endoleak; device-related adverse events. Do you think that this list is adequate? Are there any others parameters which should be included? Do you think that any of the parameters should be more carefully defined? Should any of these outcome measures be changed when patients with connective tissue disease are treated?
Adequate. Connective tissue disease is a difficult area, you will be aware that the Clinical Reference Group for vascular surgery have specifically excluded these patients from the commissioning of complex endovascular procedures. I have an issue with this as I do think that for some endovascular is the better option, particularly re-do surgery or complications in later life. As with the comparison with chimneys/branches the problem for an assessment is the paucity of comparable data. I suggest that you do not try to tackle this area!

6. Do you think that the sponsor should take into account issues regarding service re-organisation and associated cost in view of the fact that this device would require both radiological and surgical equipment and expertise to be available?
Yes, I think that it is important that the provider is considered alongside the procedure – I am thinking here of adequate population size, experience with endovascular thoracic procedures, multi-disciplinary team, robust follow up and submission of audit data.

7. Are you aware of any trials directly comparing E-Vita with comparators? If not, do you consider the comparison of results from cohort series from different centres a valid approach as it will include different patients groups, surgeons and post-op care regimes?
No

Appendix 3

Dear All,
I am working with the group at King's Imaging Technology Assessment Centre (KITEC) and we have been asked by NICE to undertake an assessment of the E-vita open plus system.
The sponsor has submitted evidence relating to the device and we are currently preparing our report. As part of this, I am writing to you on behalf of the group to ask for your thoughts regarding the following:
1. Would you agree that the state-of-the-art clinical pathway for the treatment of complex thoracic aortic disease (aneurysm and dissection) involving the ascending aorta, arch and descending aorta is a two-stage operation, consisting of a first operation to replace the ascending aorta and the aortic arch with a vascular graft prosthesis via a midline sternotomy, and a second during which the descending aorta is replaced via a lateral thoracotomy?
No, I think second part is now TEVR first option

2. Do you think that treatment using endovascular technology such as arch hybrid repair and total endovascular repair (either with chimney, fenestrated, or branched devices) should be included as a comparator to the E-vita open plus in the sponsor's submission?
Yes

3. Are you aware of any UK or other guidelines for the treatment of complex thoracic aortic disease? We were able to find the NICE IPG 127, which refers to descending thoracic pathology but not specifically to complex thoracic aortic disease.
No

4. Are you aware of any current trials evaluating the management of complex thoracic aortic disease?
No

5. The sponsor suggested the following as outcome measures to evaluate their device with reference to comparators: technical procedure(s) completion and success; mortality; major complications (stroke, paraplegia, renal failure, myocardial infarction and others that may delay discharge); length of intensive care unit stay; total length of hospital stay; freedom from further interventions; long-term survival rates; incidence of junctional endoleak; device-related adverse events. Do you think that this list is adequate? Are there any others parameters which should be included? Do you think that any of the parameters should be more carefully defined? Should any of these outcome measures be changed when patients with connective tissue disease are treated?
Seems reasonable but all need to be defined carefully

6. Do you think that the sponsor should take into account issues regarding service re-organisation and associated cost in view of the fact that this device would require both radiological and surgical equipment and expertise to be available?
No - that should be standard in any centre treating this sort of disease

7. Are you aware of any trials directly comparing E-Vita with comparators? If not, do you consider the comparison of results from cohort series from different centres a valid approach as it will include different patients groups, surgeons and post-op care regimes?
No. Its not really ideal but is about as good as you are going to get

Appendix 4

Please find below our answers to the questions that have been sent from the External Assessment Centre regarding the clinical evidence submission:

1. How were the outcomes measures included in the submission selected, specifically the outcome measures that are interim measures? Were they based solely on the data available in the published literature, or were other considerations taken into account? *The outcome measures included in the submission are based solely on the published literature.*

2. How do you consider that the device will reduce total end organ ischaemia? *In the literature mentioned in the submission total end organ ischemia is not stated. In our submission we did not consider total end organ ischaemia due to the lack of data. However, Jakob et al (2012) described one death caused by acute visceral ischaemia.*

3. How did you decide which parameters should be used to assess technical success? *We decided to use in-hospital survival to assess technical success because this criterion was described in all publications selected for the submission. Furthermore, the following secondary outcomes were also considered: fate of the false lumen, exclusion of the aneurysm, development of endoleaks. However, the secondary outcomes were slightly different described.*

4. What do you estimate the likely absolute reduction in the number of second surgical procedures will be if E-vita open plus were to be introduced as standard practice? *We expect an absolute reduction in the number of second surgical procedures of 100%. In some cases, secondary surgery or endovascular interventions are required due to proceeding of the symptoms or due to complications. But those secondary surgery or endovascular interventions are expected after treatment with classical two-steps elephant trunk procedure, too.*

5. Please can you provide an explanation of how the differences between the E-vita open and the E-vita open plus may affect the outcomes? Is this difference limited to an impact on junctional endoleak or are there other considerations to be taken into account?

The difference between E-vita open and E-vita open plus is limited to an impact on junctional endoleak due to the graft material permeability.

6. Section 10.2 has not been completed, please can you explain how you searched for studies reporting adverse events? *We applied the same criteria for the search for adverse events as for clinical evidence (10.1). Published data were processed according to table 16.*
Please find our answers below.
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.*

Response Pubmed
10.2.2 The date on which the search was conducted.
Response September 2012
10.2.3 The date span of the search.
Response January 2005 to December 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).
Response E-vita open plus, aortic thoracic aneurysm, dissection, e-vita
10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).
Response Pubmed - http://www.ncbi.nlm.nih.gov/entrez/
10.2.6 The inclusion and exclusion criteria.
Response The inclusion and exclusion criteria were taken as published.

10.2.7 The data abstraction strategy.

Response Published data were processed according to Table 16. Data were taken from Jakob et al. 2011 which includes all published data sets obtained of eight European centers participating in the International E-vita open Registry up to 2011.

Appendix 5

JOTEC response to EAC outcomes query

1. ***Endoleaks***

An endoleak is a leak into the aneurysm sac after endovascular repair. Five types of endoleaks exist:

- *Type I - Perigraft leakage at proximal or distal graft attachment sites*
- *Type II - Retrograde flow from collateral branches*
- *Type III - Leakage between overlapping parts of the stent or rupture through graft material.*
- *Type IV - Leakage through the graft wall due to the quality (porosity) of the graft material*
- *Type V - Leakage from unknown origin*

2. ***30 days mortality*** *-is the fraction of patients that died within 30 days from the date of the first surgery.*
3. ***False lumen -*** *blood travel through the media, creating a false lumen (the true lumen is the normal conduit of blood in the aorta).*
4. ***Survival rate -*** *indicating the percentage of people in a study or treatment group who are alive for a given period of time after diagnosis*

Appendix 6

Further information requested from JOTEC on the reduction in second surgical procedures

"A reference to where the anticipated reduction in second surgical procedures is cited in the clinical submission"

1. *Freedom from secondary endovascular intervention and secondary surgery distally was 82% and 95%. – Page 24 [18]*
2. *Freedom from secondary endovascular intervention and secondary surgery distaly - 84% and 96% – Page 44 [17]*
3. *Freedom from secondary endovascular intervention and secondary surgery distaly - 82% and 95% – Page 46 [18]*
4. *Freedom from secondary endovascular intervention distally - 75% – Page 47 [19]*
5. *Freedom from secondary intervention which is strongly correlated with mortality rate - Page 48,49 - References see text below*

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 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.

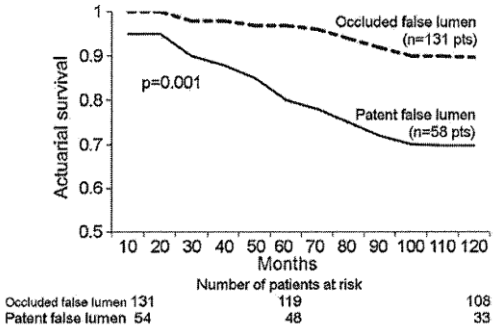

Figure 3: Survival rates for patients with an occluded false lumen are 90% at 10 years and with a patent false lumen 60% at 10 years [30]

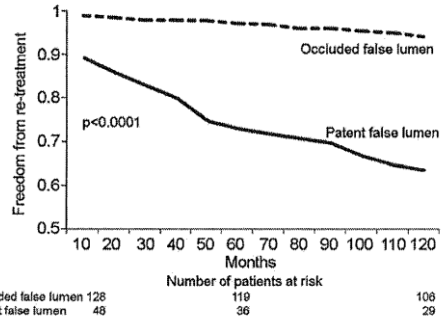

Figure 4: Freedom from re-treatment on the descending aorta for patients with an occluded false lumen are 94% at 10 years and with a patent false lumen 64% at 10 years [30]

Appendix 7

1) The search strategy document (submitted separately on 30.04.13) does not specify the purpose of the search – was it to identify studies for section 8 (economic evidence) or for section 9.3 (resource identification, measurement and valuation)? –

The purpose of the research was to support the development of the Economic Study. The objective was to secure independent data for use of the stent procedures in dissections and aneurysms of the Thoracic Aorta. This required objective quantification of usage and costs of the current procedures and how they might be changed through use of the E-vita open plus stent system.

2) Please confirm that the date of search was August 3rd to September 15th 2012, and that the last 6 month period (October 2012 – March/April 2013) has not been covered?

The date of search was confirmed as August 3rd to September 15th 2012.

3) Please confirm which specific databases were searched?

- *Databases were Embase and Cochrane Database of Systematic Reviews.*
- *Free Text and Intervention Terms were used including Economics and HTA*
- *Use was also made of the NICE Appraisal IPG 127 as a key source of independent information with its identification of the most relevant articles.*

With regards to the decision tree:

4) In the decision tree there are arms named Woven Graft and Branched Graft. Please specify which appropriate comparator listed in the scope (that is: Two stage open surgical repair with vascular graft placement, or Two stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta, or Open surgical 'debranching' of the head and neck vessels with endoluminal stent graft placement in the aortic arch and descending aorta) they are applicable to?

The different options as detailed for the Comparator alternatives are represented by the different options within the Decision Tree for the Current Methods.

- *Two stage open surgical repair with vascular graft placement –*
  This is the Woven Graft (in Col 1) followed by a further Woven Graft (Col. 3).
- *Two stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta –*
  This is the Woven Graft (in Col. 1) followed by Stent Graft at 2nd Stage (Col.3).
- *Open surgical 'debranching' of the head and neck vessels with endoluminal stent graft - placement in the aortic arch and descending aorta.*
  This is the Branched Graft (in Col. 1) followed by Woven or Stent Graft at 2nd Stage (Col.3).

5) In the sources for cost (page 72 of the submission document)– NHS Reference Costs and PSSRU Unit Costs are referenced. Please give the full reference along with the year that unit costs relate to. Please could you provide the full reference for each of the sources listed on page 72 (that is Authors, date, article title, journal title, volume no, issue number and page numbers).

1. *Unit costs of Health & Social Care,.2011. Personal Social Services Research Unit Cornwallis Building, University of Kent*
2. *2011-12 Tariff for Admitted Patient Care & Outpatient Procedures with 25% increase over normal surgical theatre costs, NHS Information Centre.*
3. *Learning from Experience (NHS Scotland), www.bbc.co.uk/new/health -11503873, Oxford Journals, Medicine: on line ISSN 1743-1824.*
4. *NHS Tariff figure for HRG4 codes at QZ01A and QZ01B 2012/13 from NHS Casemix Service.*
5. *Hospital Episode Statistics, HES 2010-11. NHS Information Centre at L27.2.*
6. *Bavaria, J Thorac Cardivasc Surg 2007;**133**:369-77. [**See below for full ref.**]*

7. *Clouse, Mayo Clin Proc 2004:**79**: 176-180 [**See below for full ref.**]*
8. *NICE Guidelines IPG 127 on Endovascular Stentgraft placement for aortic aneurysms.*
9. *Typified by da Volta Ferreira, J Vascular Brasileiro, 2006;**5**(3):220-4.*
10. *Commercial figures from current suppliers.*
11. *Company target price.*
12. *Company clinical studies.*
13. *IPG 127 & Heinz Jakob, Daniel-Sebastian Dohlea, Jarowit Piotrowskia, Jaroslav Benedika, Matthias Thielmanna, Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance, European Journal of Cardio-Thoracic Surgery Advance Access published May 25, 2012 European Journal of Cardio-Thoracic Surgery 0 (2012) 1–8 doi:10.1093/ejcts/ezs201*
14. *Guenter Marggrafa, Raimund Erbelb and Konstantinos TsagakisaJakob Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance, Eur J Cardiothorac Surg first published online May 25, 2012 review.*
15. *3 references in Jakob review paper. Fann and LeMaire also [**See below for refs**.].*
16. *Company registry data on 274 patients. Jakob et al International E-vita Open Registry J Cardiovasc. Surg 2011;**52**:717-723.*
17. *Cost of acute care & proximity to death in the UK, Barbara Graham, Yvonne Goodall, Ron Smith & Charles Norman, Scottish Cancer Therapy Network Newsletter - Autumn 2003.*

Other References:

- *Safi et al, Staged repair of extensive aortic aneurysms:morbidity and mortality in the elephant trunk technique, Circulation 2001: **104**,2938-2942*
- *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.*

- *Bavaria et al, Endovascular stent grafting versus open surgical repair of descending thoracic aortic aneurysms in low risk patients: A multicentre comparative trial J Thorac Cardivasc Surg 2007;**133**:369-77.*
- *Clouse et al, Acute Aortic Dissection: Population based incidence compared with degenerative Aortic Aneurysm Rupture, Mayo Clin Proc 2004:**79**: 176-180*
- *Fann & Miller, Aortic Dissection Annals of Vascular Surgery Volume 9 Number 3, 311-323. DOI:10.1007/BF02135293.*
- *Lemaire et al The Elephant Trunk Technique for Staged Repair of Complex Aneurysms of the Entire Thoracic Area Ann Thorac Surg. 2006:**81**:1561-9.*

6) Please could you clarify why the longer term outcomes listed in the scope are not included in the cost models.

In the economic analysis the costs/savings were considered for only one year as major savings were obtained in that single year. Further savings, enhanced quality of life and prolonged life in subsequent years would only add to the benefits from the product use. It was also considered that economic information for Commissioners affecting the immediate 12-month budget was key information to allow for decision making.

Additional Searches:

Further search of product and company data that were identified from the above search procedure for alternative or competitive treatments and companies that might be offering current or future products for similar of identical applications. These were obtained from the standard internet search engines.

Inclusion and Exclusion criteria

All items identified as relevant for describing the action, possible medical treatments and resources (human & financial) required to treat the medical condition for the Jotec device.

The exclusion criteria were anecdotal reports, on-line publications without peer review, those showing evidence of poor scientific quality, those before 2000 because of the major changes in the last ten years of treatment and sponsored reports by commercial companies.

Appendix 8

Our questions identified from the registry:

The international E-vita Open Registry: data sets of 274 patients, October 2011, H.Jakob et al

Hypothesis evaluated:
Evaluation of early and midterm results in regards to morbidity and mortality, and the fate of the false lumen in dissection cases (p718 of publication)

Centres
The registry includes eight centres. Are these the only ones using E-vita or are these eight randomly chosen from the centres?

Data collection
Was the data collection standardised. Did the variables have strict definitions? Were the data collected in real time or retrospectively? The data form, data dictionary and data collection guidelines will be helpful.

Patients
What are the eligibility criteria for a patient being part of the registry?

Data quality
What type of data management checks were performed on the centres? Such checks will include accuracy, completeness, and adherence to guidelines in completing the data collection forms. Are there missing data from the centres? Details of the missingness pattern of the data will be helpful.

Usage of EVITA
Did all centres follow the same surgical procedures in implementing EVITA?

Duration of register

First-in-man EVITA trial (single-centre) was in January 2005 and ‘after achieving favorable single centre results’ the registry started in September 2008. However, the cohort of 274 patients is from January 2005 to December 2010. How were results from the first-in-man trial patients and the post September 2008 patients combined? How many patients were analysed retrospectively?

Proportion of data reported
Both favourable and unfavourable data have been stated in the paper. However, is this all the data collected? Again, the data forms and data dictionary will be helpful.

Follow up
Were there any patients lost to follow up over the registry duration?

Ethics
The registry has no ethics approval (page 40 of Sponsor submission of evidence document).

Adverse events
Though adverse events such as in-hospital mortality, strokes and spinal cord injury were mentioned are these all. We need evidence that all data collected has been reported.

Withdrawals
Were there any withdrawals over the six years and, if so, what were the reasons.

Enrolment
What is the pattern of enrolment? For all 274 patients to be followed up for six years implies that they were all recruited in January 2005!

Notes from Teleconference

In summary though, the register now has 470 patients from data collected from 11 centres. Of these there is a complete collection of data from about 70 – 80% of patients. The register has an extensive list of fields about the disease as well as the device and Dr Tsagakis will forward the manual to Bola.

There is no standard surgical procedure for introducing the stent but, according to Dr Tsagakis, there is no significant difference in outcomes from the 11 centres.

Dr Tsagakis will also send Bola (for onward circulation) a paper that is not yet in the literature but has been accepted for publication.

Dr Tsagakis said he could make himself available for further communication should we have any more questions.

Has manual re registry and will send to Bola
Registry collects data for disease (aneurysm and dissection) as well as device

Now 11 active centres

How long in registry – no end for patients in trial – will be followed until die or leave registry
Difficult to get data from all users. Currently are concentrating on about 11 centres who are willing to provide data
Full follow up available for about 70 – 80% of patients in register

Will be more than 500 patients from centres

Active Register includes the following centres;

Barcelona

Birmingham,
Essen
Leipsig,
Grad
Stuttgart
Bologna
Poland
Finland (Tempere)
Vienna

Safety data;
Large amount of safety data collected – in registry

No data on cost

Is there a standard procedure for surgery – there is no standard. Every clinic has different standards – can include site of cannulation for example. Inspection suggests that no difference in outcomes from different procedures.

Dr Tsagakis will send Bola the registry manual with details of the data fields and also a paper** that has been accepted for publication but not yet published and was not in the data submission to NICE.*

**Registry manual is in appendix 10*
*** Paper not received by project submission date*

Appendix 9

Questions as in Appendix 1

Response:
Dear Rachel:
Thank you for your email. My answers to your questions are as follows:

1. *No state of the art clinical pathway is not an elephant trunk procedure as you describe. We have moved into hybrid repairs for these. In the end they may all be performed endovascularly.*
2. *Your suggestions of hybrid and total endovascular repair should be included as comparators for this analysis.*
3. *I do not think there are separate guidelines for the aortic arch. They are usually divided into ascending and descending aortic pathology. The arch remains very much neglected.*
4. *I know of no trials currently being performed on the management of complex thoracic aortic disease.*
5. *I think the list of measures is fine.*
6. *I think the reorganisation of services is not within the sponsors remit.*
7. *I do not know of any trials involving E-vita.*

Best wishes,
Peter Taylor

Appendix 10

International E-vita Open Plus registry manual – considered separately

Appendix 11

ACADEMIC IN CONFIDENCE paper – considered separately

[redacted]

Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

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

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from King's Imaging Technology Evaluation Centre (KITEC) to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 4pm on **7 June 2013** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

4 June 2013

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 6, Background The description of the use of the technology should mention that the stent graft should be deployed over a guide wire and under image (usually X-ray) guidance. The latter would be associated with a small dose of ionising radiation.	Usually, TEE is used. X-ray guidance is not possible because the procedure is done after exsanguination.	The description of the use of the technology should mention that the stent graft should be deployed over a guide wire using TEE guidance, especially in case of dissection	State-of-the-art cardiovascular centres usually have hybrid operating theatres which combine facilities for open surgery with either X-ray, transoesophageal (TEE) or other image guidance. The report has been amended.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20, 3.5. Reference section 7.6.2 of the sponsor's submission: It is not clear how summary mortality rate (31.2%) was calculated for the comparators (Etz et al., 2008; Safi et al., 2007; Lemaire et al., 2006; Svensson et al., 2004).	Summary mortality rate was determined as a sum of mortality after first, after second stage and during the time where patients are waiting for second stage surgery.	Summary mortality rate was determined as a sum of mortality after first, after second stage and during the time where patients are waiting for second stage surgery.	Thank you. Our query was that we were unclear how the overall estimate, 31.2%, was calculated. We now see that it was a simple summary of the estimates in the relevant studies. We have removed the comment from the report.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
There was criticism of the lack of a detailed search for comparative cost analysis publications. As this was a new product and such studies would be made known to the suppliers this was not required, had been checked from work in Germany and was confirmed by the EAC this seems to be a futile issue and only worth responding as an item known from company knowledge.			No response required

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The use of probabilities for outcomes relates to the EAC focus on a single patient cost and one that can lead to a patient QALY cost. The approach used to address incidences and the whole cost to the NHS was the primary objective and is why the level of adoption was included in the sensitivity analysis. This approach still leads to the cost per patient and if Utility Factors are known the QALY cost can be calculated.			No response required

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The long term outcomes was not an area that could be addressed in detail as there was limited information on the long term outcomes for the E-Vita even from the Registry at the time the economic analysis was put together. This was acknowledge in the report and only when they contacted the Registry team was it seen that now there is some data available.			No response required

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The focus on a short term economic analysis was recognised as appropriate within the EAC report and showed for the target group there were cost savings/patient. It was possible to establish a viable model based on available data for the short term analysis. The longer term model developed by the EAC group, as noted in the section devoted to this, included a range of outcome assumptions that could not be justified in our analysis and are largely hypothetical.			No response required

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC report also acknowledged that most of the post-operation impact outcomes were seen within the year after treatment.			No response required

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The use of probabilities and their confidence intervals, which was another constant issue in the report, were allowed for as was noted later in the sensitivity testing applied.			No response required

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
There was confusion over the comparators and this we resolved, as confirmed on page 38.			No response required

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It was stated that the model did not allow for patients with complications after Stage 1 not making it to Stage 2. This was allowed for in the model.			No response required

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It was suggested that Nursing Costs should be included – *these were within the Theatre Costs*, and that the cost of the "stiff guide wire" should be added – *in a comparison of costs this item would be added to all methods and was considered to be cost neutral.*			No response required

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It was acknowledged that sub-group analysis was not appropriate due to lack of information on other procedures.			No response required

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
As noted above there were issues on some of the data inputs the most important being the numbers of patients and the time in ICU care. The latter period used was 12 days as this was the 2011/12 figure not 15 days as cited (*this might have been in the Clinical part of the report*) and with actions within the NHS has been reduced to the 12.2 average quoted in the report. As regards cost an average was taken rather than a more complex level of care which will change with the population cohort and in any time period both of which are unknown.			No response required

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The Cost of Death was another item questioned but after some words it was concluded as not being unreasonable and was more likely to be a short term event. Careful reading of this item highlights the difficulty faced.			No response required

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The total patient cohort that would potentially be suitable for E-Vita plus was given as the 3,500 figure and the actual related to the adoption level. The L27 figure for 2011 was higher than this number – the EAC team looked at the specific L27.3 number which relates to the smaller number of only 348 patients treated with the directly comparable target group in 2011 that was acknowledged in the ABA figures.			No response required