Appl Health Econ Health Policy (2014) 12:485–495
DOI 10.1007/s40258-014-0114-9

REVIEW ARTICLE

E-Vita Open Plus for Treating Complex Aneurysms and Dissections of the Thoracic Aorta: A NICE Medical Technology Guidance

Muralikrishnan Radhakrishnan · Janet Peacock · Tiago Rua · Rachel E. Clough · Mercy Ofuya · Yanzhong Wang · Elizabeth Morris · Cornelius Lewis · Stephen Keevil

Published online: 24 July 2014

Abstract The E-vita open plus is a one-stage endoluminal stent graft system used for treating complex aneurysms and dissections of the thoracic aorta. The National Institute for Health and Care Excellence (NICE), as a part of its Medical Technologies Evaluation Programme (MTEP), selected this device for evaluation and invited the manufacturer, JOTEC GmbH, to submit clinical and economic evidence. King's Technology Evaluation Centre (KiTEC), an External Assessment Centre (EAC) commissioned by the NICE, independently critiqued the manufacturer's submissions. The EAC considered that the manufacturer had included most of the relevant evidence for the E-vita open plus, based on international E-vita open registry data for 274 patients, but had provided only limited evidence for the comparators. The EAC therefore conducted a systematic review and meta-analysis of all comparators to supplement the information, and found ten additional studies providing outcome data for the three two-stage comparators. The EAC noted that the cost model submitted by the manufacturer did not include key complications during the procedures. The EAC developed a new economic model incorporating data on complications along with their long-term costs. The revised model indicated that the E-vita open plus might not provide cost savings when compared with some of the comparators in the short-term (1 year), but would have high cost savings in the long-term, from the second year onwards. The NICE Medical Technologies Guidance MTG 16, issued in December 2013, recommended the adoption of the E-vita open plus in selected patients within the National Health Service in England.

M. Radhakrishnan · J. Peacock · T. Rua · E. Morris · C. Lewis · S. Keevil
King's Technology Evaluation Centre, London, UK

M. Radhakrishnan (✉)
Centre for the Economics of Mental and Physical Health, King's College London, Institute of Psychiatry, The David Goldberg Centre, De Crespigny Park, Denmark Hill, London SE5 8AF, UK
e-mail: muralikrishnan.radhakrishnan_kartha@kcl.ac.uk

J. Peacock · M. Ofuya · Y. Wang
Division of Health and Social Care Research, King's College London, London, UK

J. Peacock
NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK

T. Rua · R. E. Clough · E. Morris · S. Keevil
Division of Imaging Sciences and Biomedical Engineering, Department of Biomedical Engineering, King's College London, St Thomas' Hospital, London, UK

R. E. Clough
Department of Vascular Surgery, Guy's and St Thomas' NHS Foundation Trust, London, UK

C. Lewis
Medical Engineering and Physics, King's College Hospital, London, UK

S. Keevil
Department of Medical Physics, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Key Points for Decision Makers

Available evidence suggest that E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta could remove the need for a second procedure and the associated risk of serious complications.

The E-vita open plus is estimated to generate cost savings compared with current two-stage repair from about 2 years after the procedure.

The estimated cost savings ranged from around £21,850 to £28,160 across the two-stage repair comparators at 10 years after the procedure.

1 Introduction

The National Institute for Health and Care Excellence (NICE) promotes the adoption of cost- and clinically-effective medical devices and diagnostics by the National Health Service (NHS) in England through the work of the Medical Technologies Evaluation Programme (MTEP) and Diagnostics Assessment Programme (DAP), which were established in 2009. Manufacturers of medical devices and diagnostics notify the NICE when their product meets the eligibility criteria for entry to the programme. Technologies are selected for development of medical technologies guidance by the NICE's Medical Technologies Advisory Committee (MTAC) if they have the potential to offer a significant clinical benefit to patients and the NHS, at the same or reduced cost when compared with current practice. Once a technology has been selected, the NICE prepares a scope outlining the population and outcomes for which the manufacturer should submit clinical and economic evidence. A NICE-funded External Assessment Centre (EAC) independently critiques the submitted evidence and prepares an assessment report. The EAC is also required to provide additional evidence if there are gaps in evidence submitted by the manufacturer. The MTAC uses the EAC report, together with other sources of advice, to produce guidance on the proposed technology [1, 2].

This article presents a summary of the EAC report for the E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta and the development of the NICE guidance. The article is one among the series of NICE Medical Technology Guidance summaries published in *Applied Health Economics and Health Policy* [3–6].

2 Decision Problem

2.1 Disease Overview

Complex thoracic aortic disease encompasses acute (AAD) and chronic type A dissections (CAD), as well as aortic arch aneurysms (TAA) with or without involvement of the ascending and descending aorta [7].

Aortic dissection results from a tear in the inner layer of the wall of the aorta leading to blood entering and separating the layers of the wall. Acute aortic dissections are defined as those identified within the first 2 weeks after the initial tear, and chronic dissections as those identified at times greater than 2 weeks. Aortic dissection is classified by its location and the extent of involvement of the thoracic aorta. Stanford Type A dissection affects the ascending aorta and may extend to the arch and descending thoracic aorta. Stanford Type B dissection does not affect the ascending aorta and typically involves the descending thoracic aorta, distal to the origin of the left subclavian artery. Approximately two-thirds of aortic dissections are Stanford Type A. Patients with acute dissection typically present with pain and are classed as emergencies due to the risk of the dissection rupturing the wall of the aorta, affecting the integrity of the aortic valve and, through involvement of the origins of the coronary arteries, affecting perfusion of the myocardium. Population-based studies suggest an incidence of aortic dissection of at least 0.5–3.5 per 100,000 persons per year [8, 9]. Moreover, 21–26 % of patients with aortic dissections die prior to hospital admission, and up to 58–68 % die prior to definitive operative intervention [10, 11].

A thoracic aortic aneurysm results from weakening of the aortic wall, leading to localised dilatation, and is a life-threatening condition. Patients with thoracic aneurysms are often asymptomatic until the aneurysm expands. The most common presenting symptoms are pain and aortic rupture. A ruptured aneurysm can cause severe internal bleeding, which can rapidly lead to shock or death. The life expectancy of untreated patients with aortic aneurysms is limited, with death occurring within 5 years from rupture and/or associated diseases in more than 75 % of cases [12]. The incidence of TAA rupture is 3.5 per 100,000 persons per year [11]. TAAs that are now estimated to affect 10 of every 100,000 elderly adults, and aneurysms of the descending thoracic aorta account for approximately 30–40 % of these [13].

2.2 Current Treatment Options

The current treatment options are detailed on the NICE website [14] and are summarized briefly below. The size,

growth rate, location (including involvement of branch vessels) and the presence or absence of rupture determines the management of complex thoracic aortic disease. Patients can often be managed using clinical and imaging surveillance and best medical treatment, with surgery reserved for larger diameter aortas, rapid rates of enlargement and aortic rupture.

In order to treat complex disease of the thoracic aorta, three surgical methods can be used. Two of these methods involve a two stage 'elephant trunk' procedure; both approaches are similar in their first stage but use alternative repair techniques for 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 prosthesis (the elephant trunk) is positioned in the proximal descending thoracic 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 proximal descending aorta with arterial access via the femoral artery (thoracic endovascular aortic repair—TEVAR). 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 using a combination of vascular grafts. This then allows an endoluminal stent graft to be positioned in the aortic arch and descending aorta as either a single- or two-stage hybrid repair.

2.3 E-Vita Device

The E-vita open plus is an endoluminal stent graft system used for treating complex aneurysms and dissections of the thoracic aorta, and is manufactured by JOTEC GmbH (Hechingen, Germany). The device is a one-piece polyester fabric tube which combines a conventional vascular graft and an attached endovascular stent graft that allows simultaneous treatment of the ascending aorta, the arch and the descending aorta in one procedure. The E-vita open plus is a single-use device with a shelf life of 2 years. It is supplied sterile and pre-loaded in its delivery system. The device is available in a range of sizes with varying diameters and lengths. It is deployed using a delivery system which consists of catheters and a positioning aid. A luer connector is incorporated to permit flushing of the inner guide catheter.

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 proximal vascular graft is surgically anastomosed to the ascending aorta. The distal stent graft is a self-expanding device with nitinol springs incorporated into the fabric, and is used to treat the descending aorta. The deployment of the distal stent graft is achieved through retraction of a retaining sheath. The proximal vascular graft is then used to repair the ascending aorta and arch in a standard surgical fashion.

2.4 National Institute for Health and Care Excellence (NICE) Scope

The scope of the decision problem developed by the NICE for E-vita open plus defined the patient population as "patients with aneurysms or dissections of the thoracic aorta involving the ascending aorta, arch and descending aorta (Stanford Type A)". Three comparators were identified for consideration, corresponding to the current treatment options described above: two-stage open surgical repair with vascular graft placement; two-stage repair with open surgical graft placement in the ascending aorta and arch, and endovascular stent graft placement in the descending aorta; open surgical 'debranching' of the head and neck vessels with endoluminal stent graft placement in the aortic arch and descending aorta. The outcome measures specified for consideration were technical procedure(s) completion and success; mortality; major complications such as stroke, paraplegia, renal failure, myocardial infarction and others that may delay discharge; length of ICU stay; total length of stay; freedom from further interventions; long-term survival rates; incidence of junctional endoleak and device-related adverse events. The scope also requested cost analysis for the E-vita open plus compared with the three comparators from an NHS and personal social services perspective. It also requested consideration of certain subgroups: patients with acute Type A dissection, chronic Type A dissection and degenerative aneurysm. 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. This group was identified as being in need of special considerations, including issues of equality.

3 External Assessment Centre (EAC) Review

The first part of the manufacturer's submission included clinical evidence, comprising an overview of the disease and current treatment provision, and a systematic review of clinical evidence related to E-vita open plus and the comparators. The second part was a submission of the economic evidence comprising a systematic review of

economic evidence and a de novo economic model of E-vita open plus and the comparators. King's Technology Evaluation Centre (KiTEC), an EAC based in the King's Health Partners Academic Health Science Centre (KHP), was commissioned by the NICE to critique the manufacturer's submission of clinical and economic evidence. The EAC was required to produce a structured assessment report. Nominated expert advisers were available to provide advice to the EAC during the preparation of the report.

3.1 Clinical Effectiveness Evidence

The EAC considered that the sponsor's search strategy for clinical evidence relating to the E-vita open plus was comprehensive, but that not all available evidence relating to the comparators had been captured.

The sponsor reported finding 18 published studies on the E-vita open plus, of which 13/18 studies were initially reported as being relevant [7, 15–26]. The sponsor subsequently excluded 10/13 studies (for reasons discussed below), leaving just 3 for inclusion [7, 15, 16]. All 3 of these studies were descriptive, and none included comparators.

The paper by Jakob et al. [7] was the most comprehensive, and was based on predecessor technology known as the E-vita open stent. This was similar in design to E-vita open plus, except that the latter is blood-tight and does not require the addition of fibrin glue to seal the stent graft. This paper reported on the International E-vita open registry and provided data from January 2005 to December 2010 [7], including 274 patients with complex aortic disease who were enrolled in the registry. The majority were male (74 %) and mean age was 60 years. At the time of publication of Jakob's study [7], the registry included eight referral centres in Europe—Barcelona, Birmingham, Bologna, Essen, Graz, Leipzig, Prague and Vienna—and the maximum follow-up period was 6 years.

Jakob et al. [15] also reported on patients from the International E-vita open registry, including patients receiving surgery between January 2005 and March 2011, a 3-month longer time span than Jakob et al. [7]. However, Jakob et al. [15] only included patients from the Essen (Germany) centre (77 patients), a subset of the entire registry. The study by Hoffman et al. [16] was a small study with short follow-up and limited outcome data and therefore was not useable.

3.1.1 Critique of Clinical Effectiveness Evidence

In summarising clinical evidence for the E-vita open plus, the sponsor focussed on the results published in Jacob et al. [7]. The EAC agreed with this decision, since the majority of other articles were subsets of the International E-vita open registry, and so their data largely overlapped with the data in Jakob [18–21]. For other excluded papers it was unclear whether they overlapped with Jacob et al. [7] as reporting details were limited, but it was judged to be likely, and therefore the EAC considered that they had been correctly excluded [23–26]. One further paper was excluded because the patient group was very small (3 patients) [17], and another because it reported an animal study [25]. The EAC identified a conference abstract [27] that was not cited by the sponsor, but subsequent identification of the full paper revealed that it was a subset of the International E-vita open registry data and was therefore not included.

The comparator studies only described outcomes in patients who had undergone two-stage open surgical repair with vascular graft replacement [28–31]. These studies were observational, and all were from the US (New York; Cleveland, OH; and Houston, TX), while the E-vita open evidence was all from Europe. The comparator studies were all conducted between 1990 and 2006, and therefore most of the evidence preceded establishment of the E-vita open registry. The EAC conducted a systematic review on the three comparators to provide a complete picture of the evidence and and found 10 additional studies. These additional studies were then included in a meta-analysis of all relevant outcomes. Full details of the meta-analyses are given in the online report [32] but the EAC notes here that the descriptive nature of the published papers, without measures of precision such as confidence intervals, limited secondary analysis on outcomes, and specifically presented long-term survival data being pooled across studies.

3.2 Cost Evidence

The details of the cost evidence submitted by the manufacturer are presented in this section. The manufacturer provided details of the search strategy used to identify economic studies related to E-vita open plus and reported that "health economics studies are not known and certainly would not have been widely carried out prior to the analysis reported here for this new and innovative product". However, the manufacturer did not provide a search strategy related to the comparators.

The manufacturer provided a decision-tree model using 2012 prices, from the NHS and personal social services perspective, for estimating the cost of E-vita open plus along with four comparators ('woven graft' or 'branched graft' during the first stage, followed by 'woven graft' or 'endovascular stent' during the second stage). With the exception of 'branched graft' during first stage, followed by 'woven graft' during the second stage, these mapped with the three comparators listed in the scope. The 'woven

graft' referred to two-stage open surgical repair, and 'branched graft' referred to open surgical 'debranching' of the head and neck vessels with endoluminal stent graft placement in the aortic arch.

The structure of the model used a cohort approach. It was estimated that there would be 3,500 patients every year with aortic arch problems in the UK, and that there would be a 40 % adoption of E-vita open plus. The remaining 60 % of patients would either receive a 'woven graft' (15 %) or a 'branched graft' (85 %). The decision arm for E-vita open plus modelled in-hospital and 30-day mortality at 15 % and assumed the remaining 85 % of patients to have a positive outcome. Major complications such as stroke, paraplegia and renal failure, which has long-term cost implications, were not modelled for the E-vita open plus or the comparators.

Mortality rates with the E-vita open plus and the comparators were based on the studies identified in the clinical evidence section. Mortality rates for the E-vita open plus (15 %) were based on the international E-vita open registry publication [7]. The mortality rates for stage 1 for the comparators were not modelled. Stage 2 mortality rates of 20 % (woven graft option) and 30 % (branched graft option) were assumed. The time horizon of the economic model was 1 year. The manufacturer did not include any long-term outcomes, citing limited information on long-term mortality rates for the E-vita open plus and the comparators. No subgroup analysis was performed.

The manufacturer had undertaken a bottom-up approach for costing the technology and comparators. The important data sources for cost included the annual Personal Social Services Research Unit (PSSRU) unit cost compendium [33], NHS reference costs [34] and other literature. The cost of the stents was sourced from current suppliers, and the cost of the E-vita open plus was the company's target price.

The manufacturer reported the average cost per patient for the E-vita open plus (£25,688) and for all comparators combined (£30,241), resulting in a saving of £4,552 for the E-vita open plus. Adoption of the technology and comparators combined was assumed to be 100 %, and was averaged across the 3,500 patients. This approach showed differences when the individual procedure costs were considered. For example, E-vita open plus, woven graft (stage 1) with woven graft (stage 2), woven graft (stage 1) with endovascular stent (stage 2), branched graft (stage 1) with woven graft (stage 2) and branched graft (stage 1) with endovascular stent (stage 2) showed costs of £24,480, £35,216, £26,691, £36,016 and £27,491, respectively. Sensitivity analyses also revealed that the E-vita open plus has cost savings, even with varied levels of adoption, varied suitability for second stage in the comparator procedures, and varied in-hospital death rates. The manufacturer concluded that the E-vita open plus is superior to its comparators.

3.2.1 Critique of Cost Evidence

The EAC's critique of the cost evidence submitted by the manufacturer is presented in this section. The search strategy for economic evidence had a number of flaws: the search was performed well before the scope was issued and needed updating; only EMBASE and the Cochrane database of systematic reviews were included; no search was conducted on the comparators. The EAC undertook a new search for economic evidence related to the technology and comparators on MEDLINE, MEDLINE(R), EMBASE, Econlit, NHS Economic Evaluation Database (EED) and the Health Technology Assessment (HTA) database. The EAC did not find any relevant evidence related to the E-vita open plus or the comparators, and concluded that there is no published economic evidence.

The manufacturer assumed a cohort of around 3,500 patients with aortic arch problems, who could benefit from the technology. However, the EAC considered that this number could be an overestimate since NICE experts foresee that only 50–100 people per year in England would be suitable for treatment with the E-vita open plus. Furthermore, for a cost-consequence analysis, the per patient cost is more relevant than a cohort approach. The decision arm for the E-vita open plus modelled in-hospital and 30-day mortality at 15 % and assumed the remaining 85 % to have a positive outcome. The EAC considered that this was not appropriate as patients could develop major complications such as stroke, paraplegia and renal failure. The cost model needed to incorporate these complications as they will have cost implications, particularly in the longer term. The decision arm for the comparators also modelled only those patients suitable for a stage 2 procedure, but had not incorporated complications such as stroke, paraplegia and renal failure during stage 1. Only stage 2 mortality rates of 20 % (woven graft option) and 30 % (branched graft option) were assumed for the comparators. From the evidence presented by the manufacturer, it was difficult to ascertain the basis of the assumed stage 2 mortality rates.

In addition to the above concerns, there were issues with the cost estimates used in the model. The cost of the surgeon, as given in the PSSRU document, was only £172/h and not £399/h as used by the manufacturer [33]. The anaesthetist cost was valued at registrar level and should have been at consultant level. NHS reference costs [34] for adult critical care and elective inpatient excess bed day for aortic or abdominal surgery should have been used for ICU and surgical ward cost per day, respectively. The cost of cancer deaths within the NHS of £8,000 was assumed for

the technology and comparators, which the EAC considered was not appropriate.

Given these issues, the EAC revised the cost model using 2012 prices with updated assumptions based on literature sourced from the additional systematic review of clinical evidence. The E-vita open plus was compared with three comparators (two-stage with vascular graft, two-stage with endovascular stent graft, open 'debranching' with endoluminal stent graft), as specified in the scope. The revised decision model was created incorporating complications and in-hospital mortality at each stage of the procedure for the technology and comparators, from the NHS and personal social services perspective. The important complications modelled were stroke, paraplegia, renal failure and bleeding, along with in-hospital mortality. Probabilities were based on the results of the systematic review and meta-analysis of clinical evidence performed by the EAC (Table 1). Cost estimates included in the calculations were sourced from the PSSRU compendium, NHS reference costs and literature [7, 28, 33–36] (Table 1). E-vita open plus has only one stage and hence the short-term model terminated after outcomes of stage 1 had occurred. The comparators were all two-stage procedures, and outcomes were modelled at each stage. Those with 'no complications' and 'bleeding' in stage 1 were assumed to move on to stage 2 for all the comparators. All the other outcomes, such as stroke, paraplegia, renal failure and in-hospital mortality, terminated at stage 1. The time horizon for the short-term model was 1 year since most of the two-stage procedures were expected to be completed within 6 months [28–31].

In the long-term model, the lifetime cost of stroke, paraplegia and renal failure were modelled separately and added to the decision model to estimate the expected cost. The time horizon for the lifetime cost was 20 years. This was based on the average age of 65 years of patients in the included studies [7, 28–31, 35–39] and life expectancy at 65 years for the UK population, which is around 20 years [40]. Annual costs of care for stroke, paraplegia and renal failure were sourced from published literature [41–43] and discounted at 3.5 % per annum. The discounted annual cost was multiplied with survival probability for 65–85 years, estimated using background mortality rate from UK life tables multiplied with a standard mortality ratio of 2 for stroke, paraplegia and renal failure [44–46]. The weighted annual costs were summed to estimate the lifetime cost of the complications.

The base-case expected cost in the short-term and long-term is presented in Table 2. In the short-term, the E-vita open plus showed little cost savings (£280) compared with two-stage repair with vascular graft. However, the E-vita open plus was cost-incurring in the short-term when compared with two-stage repair with endovascular stent graft (£4,760) and open 'debranching' with endoluminal stent graft (£7,663). When lifetime costs of complications were modelled, the expected cost of the E-vita open plus was lower than all the comparators, providing high cost savings for the E-vita open plus in the long-term, from the second year after surgery onwards. After 20 years, there were savings of £41,213 when compared with two-stage repair with vascular graft, £39,392 when compared with two-stage repair with endovascular stent graft, and £51,778 when compared with open 'debranching' with endoluminal stent graft.

In a deterministic sensitivity analysis, a number of variables with uncertainty were varied. The variables included in the sensitivity analysis were in-hospital mortality; probability of paraplegia (for the E-vita open plus); length of ICU stay; cost of ICU; cost of managing complications; and annual cost of stroke, paraplegia and renal failure. Sensitivity analysis for the probability of in-hospital mortality and paraplegia (for the E-vita open plus) did not alter the cost savings conclusions from those in the base-case estimate. The length of ICU stay seemed to affect the result in the short-term. When the ICU stay was 20 % of the total length of stay, all the comparators were cost saving compared with the E-vita open plus. When it was 60 % of the total length of stay, the conclusions were the same as the base-case estimates but with higher cost savings of £2,297 compared with the two-stage repair with vascular graft procedure. The cost of ICU also affected the results in a similar way to the proportion of ICU stay in the short-term. However, neither the length of ICU stay nor the associated cost of ICU affected the cost saving found in the base-case estimate for the E-vita open plus in the long-term. Varying the cost of managing complications did not change the conclusions from the base-case estimate. Furthermore, varying the annual cost of stroke, paraplegia and renal failure did not change the conclusions on cost savings for the E-vita open plus in the long-term. Hence, the E-vita open plus remained a cost-saving procedure in the long-term when compared with all comparators.

3.3 Conclusion of the EAC

The manufacturer submitted clinical evidence regarding the E-vita open plus. All of the published evidence on the E-vita open plus was included. However, the manufacturer submitted clinical evidence related to only one comparator—two-stage vascular graft using classical elephant trunk procedure. Two other comparators (two-stage with endovascular stent graft and open 'debranching' with endoluminal stent graft) listed in the scope were not included. The EAC performed a new systematic review and found studies relating to the other two comparators. Meta-analyses were undertaken with outcomes from the included studies to

Table 1 Probabilities and costs for technology and comparators

	E-vita open plus	Two-stage with vascular graft		Two-stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	Stage 1	Stage 1	Stage 2	Stage 1	Stage 2	Stage 1	Stage 2
Probabilities							
Complications (bleeding)	0.139	0.046	0.037	0.042	0.056	0.081	0
Complications (stroke)	0.058	0.034	0.039	0.074	0	0.081	0.037
Complications (paraplegia)	0.08	0.042	0.041	0.042	0.078	0.025	0
Complications (renal failure)	0.036	0.085	0.06	0.125	0	0.182	0
Mortality (in-hospital)	0.15	0.085	0.08	0.089	0.096	0.135	0.037
Costs							
Operating time (h)	7.5	7	5	7	2.5	6	2
Operating time (range, h)	(4.5–13.5)	(4–13)	(3–7)	(4–13)	(1.2–4.5)	(3–10)	(1.2–5)
Total length of stay (days)	19	16	17	16	6	14	6
Total length of stay (range, days)	(12–29)	(9–20)	(12–25)	(9–20)	(4–10)	(9–20)	(4–10)
ICU days (40 %)	8	6	7	6	2	6	2
Surgical ward days (60 %)	11	10	10	10	4	8	4
Cost of surgery (£)							
Consultant surgeon (1) @ £172/h	1,290	1,204	860	1,204	430	1,032	344
Consultant anaesthetist (1) @ £172/h	1,290	1,204	860	1,204	430	1,032	344
Associate specialist (1) @ £131/h	983	917	655	917	328	786	262
Perfusionist (1) at registrar's rate £86/h	645	602	430	602	215	516	172
Specialist nurse (2) @ £100/h	1,500	1,400	1,000	1,400	500	1,200	400
Consultant radiologist (medical) @ £157/h					393		314
Cost of E-vita open plus[a]	10,500						
Cost of woven graft[a]		200	200	200			
Cost of branched graft[a]						1,000	
Cost of endovascular stent graft[a]					5,000		5,000
Other consumables[a]	130	130	130	130	130	130	130
Cost of complications management @ £2,155	2,155	2,155	2,155	2,155	2,155	2,155	2,155
Cost of ICU @ £1,410/day (range £870–£2,000)	10,716	9,024	9,588	9,024	3,384	7,896	3,384
Cost of surgical ward @ £383/day	4,366	3,677	3,907	3,677	1,379	3,217	1,379
Total cost (with complication) [£]	33,575	20,513	19,785	20,513	14,343	18,964	13,884
Total cost (without complication) [£]	31,420	18,358	17,630	18,358	12,188	16,809	11,729

ICU intensive care unit

[a] Source: JOTEC GmbH submission

provide pooled estimates of all key outcomes, including complications.

The EAC also performed a new search, which confirmed the manufacturer's finding that there was no published economic evidence related to the E-vita open plus and comparators. In the de novo cost model submitted by the manufacturer, only various levels of adoption, suitability for second-stage procedures, and in-hospital mortality were modelled by the manufacturer. The EAC considered that other complications (and their associated lifetime costs) such as stroke, paraplegia, renal failure and bleeding should be included in the model. Furthermore, the EAC felt that some of the manufacturer's assumptions could be improved upon. With the results and probabilities from the meta-analysis, the EAC revised the cost models with some changes in the assumptions. The results of the revised model shows that the E-vita open plus might not provide significant cost savings when compared with some of the comparators in the short-term, but will nonetheless have high cost savings in the long run. The cost difference in the short-term is driven by the high technology costs and longer stay in hospital. Since E-vita open plus is a single-stage procedure and the comparators are all two-stage procedures, the probability of complications is greater for

Table 2 Expected cost and savings of technology and comparators (£)

	E-vita open plus	Two-stage with vascular graft		Two-stage with endovascular stent graft		Open debranching with endoluminal stent graft	
	(Technology)	Comparator 1	Savings	Comparator 2	Savings	Comparator 3	Savings
Expected cost (short-term)	32,417	32,697	−280	27,657	4,760	24,755	7,663
Expected cost (long-term)							
Year 1	35,267	38,538	−3,271	33,733	1,534	31,948	3,319
Year 2	37,920	43,976	−6,057	39,391	−1,471	38,646	−726
Year 3	40,478	49,222	−8,743	44,847	−4,368	45,106	−4,627
Year 4	42,943	54,273	−11,331	50,102	−7,159	51,327	−8,384
Year 5	45,316	59,139	−13,822	55,164	−9,847	57,320	−12,003
Year 6	47,601	63,822	−16,221	60,036	−12,434	63,087	−15,486
Year 7	49,802	68,333	−18,531	64,728	−14,926	68,643	−18,841
Year 8	51,919	72,673	−20,754	69,243	−17,324	73,988	−22,069
Year 9	53,956	76,849	−22,893	73,587	−19,631	79,131	−25,175
Year 10	55,913	80,860	−24,948	77,760	−21,847	84,071	−28,158
Year 15	64,563	98,592	−34,029	96,206	−31,643	105,909	−41,346
Year 20	71,406	112,619	−41,213	110,797	−39,392	123,184	−51,778

the comparators, which has implications for lifetime costs and provides cost savings in the longer term for the E-vita open plus device.

4 NICE Guidance

In line with the MTEP process, the MTAC met to develop draft recommendations following which a medical technology consultation document was produced. Comments were accepted by the NICE on these draft recommendations as well as notification of inaccuracies and additional information. Following a consultation period, comments were collated and presented to the MTAC for discussion.

4.1 Draft Recommendations

The MTAC met in July 2013 and, following review of the manufacturer's submissions and the EAC report [32], together with evidence from expert advisers, the following provisional recommendations were made:

1. "The case for adopting the E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta, in a carefully selected group of people, is supported by the evidence.
2. Using the E-vita open plus could remove the need for a second procedure and the associated risk of serious complications, and it should therefore be considered for people:
   - who would otherwise need a two-stage repair procedure because their aortic disease extends into or beyond the distal part of their aortic arch (into the proximal descending aorta), but
   - who would not need additional intervention (such as stent grafting) in the descending aorta.
3. The E-vita open plus is estimated to generate cost savings compared with the current two-stage repair from about 2 years after the procedure. The estimated cost saving per patient at 5 years after the procedure is around £13,800 when compared with two-stage repair involving open insertion of a vascular graft, £9,850 when compared with two-stage repair involving endovascular stent grafting and £12,000 when compared with open surgical debranching followed by endoluminal stent grafting. At 10 years after the procedure, the estimated cost savings ranged from around £21,850 to £28,160 across the three comparators."

4.2 Consultation Response

The NICE received few (i.e. not many) comments during the public consultation period, the most important one being that new evidence on the E-vita open plus was identified [47]. The EAC reviewed this new paper to determine whether there were any substantive differences from the evidence provided in earlier literature. Jakob et al. [7] reported results from the E-vita open registry for the period January 2005 to December 2010, including 274 patients. The new evidence [47] reported results from the same registry for a longer period—January 2005 to October 2012, including 416 patients. Comparison of outcome data in the two papers revealed no important differences in the

overall estimates for in-hospital mortality, stroke and paraplegia, and therefore the EAC saw no necessity to change the assumptions in the cost model. In summary, the EAC considered that the original modelling, based on the 2011 outcomes, remained valid and appropriate.

4.3 Final Guidance

The MTAC considered the results of the consultation, and the final Medical Technology Guidance document for the E-vita open plus for treating complex aneurysms and dissections of the thoracic aorta was published by the NICE on 18 December 2013 [14]. There were no changes to the provisional recommendations, and the final guidance was substantially the same as the draft, except for some small changes to the description of the insertion procedure.

5 Challenges

Several challenges were encountered when reviewing and using the clinical evidence for this technology. First, the levels of statistical analysis and reporting in the published papers were quite basic, such that estimates were given without measures of precision or variability. This made it difficult to interpret estimates and, in some cases, impossible to incorporate them into meta-analyses; for example, when analysing long-term survival with estimates given as percentages without confidence intervals. A second challenge was the comparison of the single-stage outcomes for the E-vita open plus with the two-stage comparators. This was not straightforward as data for the two stages was not always clearly presented and not all subjects were accounted for. Therefore, it was difficult, if not impossible, to calculate a single estimate of, for example, mortality from the data that were reported in the literature. Other challenges to interpretation of clinical study data arise from the absence of randomised controlled trials making a direct comparison between the E-vita open plus and any of its comparators. Thus, all comparisons were of necessity indirect, which carries the risk of bias in the resultant estimates if the studies are not comparable. This difficulty is seen in this assessment by between-study differences in the time and place of the studies. The EAC noted that the comparator studies mostly preceded the E-vita open plus studies according to their date of publication and, furthermore, the comparator studies were all conducted in the US whereas the E-vita open plus studies were all conducted in Europe. In addition, data on the E-vita open plus were predominantly based on its predecessor technology, E-vita open stent. The two are similar in design but the E-vita open plus is blood-tight and does not require the addition of fibrin glue to seal the stent graft. From the baseline patient information presented in the papers, there was no reason to suspect that the patient populations in the E-vita open plus studies were markedly different from those included in the comparator studies. Hence, the EAC judged that, in the absence of any direct comparator trial data, estimates from separate studies, i.e. effectively indirect comparisons, should be used in order to make best use of the evidence that was available.

There were several challenges and learning points associated with the revised cost model. Long-term data on complications and health states were not available from the literature. In the revised model, all complications were assumed to occur in the short-term, i.e. shortly after the procedure. Complications occurring in the longer term are likely to be rare but will still have cost implications. Decision analytic models were used in the analysis. This was considered appropriate given the questions that were addressed and the data availability, but more sophisticated models (e.g. Markov models, discrete event simulations) may allow for more refined analyses of the cost consequences of the intervention. The EAC relied on deterministic rather than probabilistic sensitivity analyses, again largely as a result of data limitations, to inform parameter distributions. Review of clinical evidence from the manufacturer supplemented by the systematic review carried out by the EAC revealed that data were available for technology subgroups only and were not available for the comparators. Hence, subgroup analysis of the cost model could not be performed. All complications were assumed to occur separately, but this does not exclude the possibility that, in some individuals, multiple complications may occur. Finally, the implications of using multiple stents during procedures were not included in the cost analysis due to the lack of evidence.

6 Conclusion

Medical technology assessment is challenging due to limitations in the quantity and appropriateness of the evidence base available. The EAC, while fully acknowledging these challenges, has shown how all available evidence may be used to inform decision making and allow guidelines for best clinical practice to be established.

Acknowledgments The authors thank Leonardo Koeser, James Shearer, Anita Patel and Professor Paul McCrone from the Centre for the Economics of Mental and Physical Health, Institute of Psychiatry, King's College London, for their advice on economic modelling and for their contribution to the original EAC report for the NICE.

Disclosures King's Technology Evaluation Centre is funded by the NICE to act as an EAC for the Medical Technologies Evaluation Programme. This summary of the Medical Technology Guidance was produced following the publication of the final guidance report. The

summary has been reviewed by the NICE but has not been externally peer reviewed by *Applied Health Economics and Health Policy*. Two of the authors (CL, SK) are NHS employees; the NHS has a financial interest in the guidance issued by the NICE as a result of this work. All authors (except REC) have received grant support from the NICE through King's Technology Evaluation Centre.

Author contributions The clinical effectiveness section of this paper was written by JP and REC. The economic section and other sections were written by MR and TR. MO, YW, EM, CL, SK contributed to the preparation of the manuscript. The guarantors for overall content are CL and SK.

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