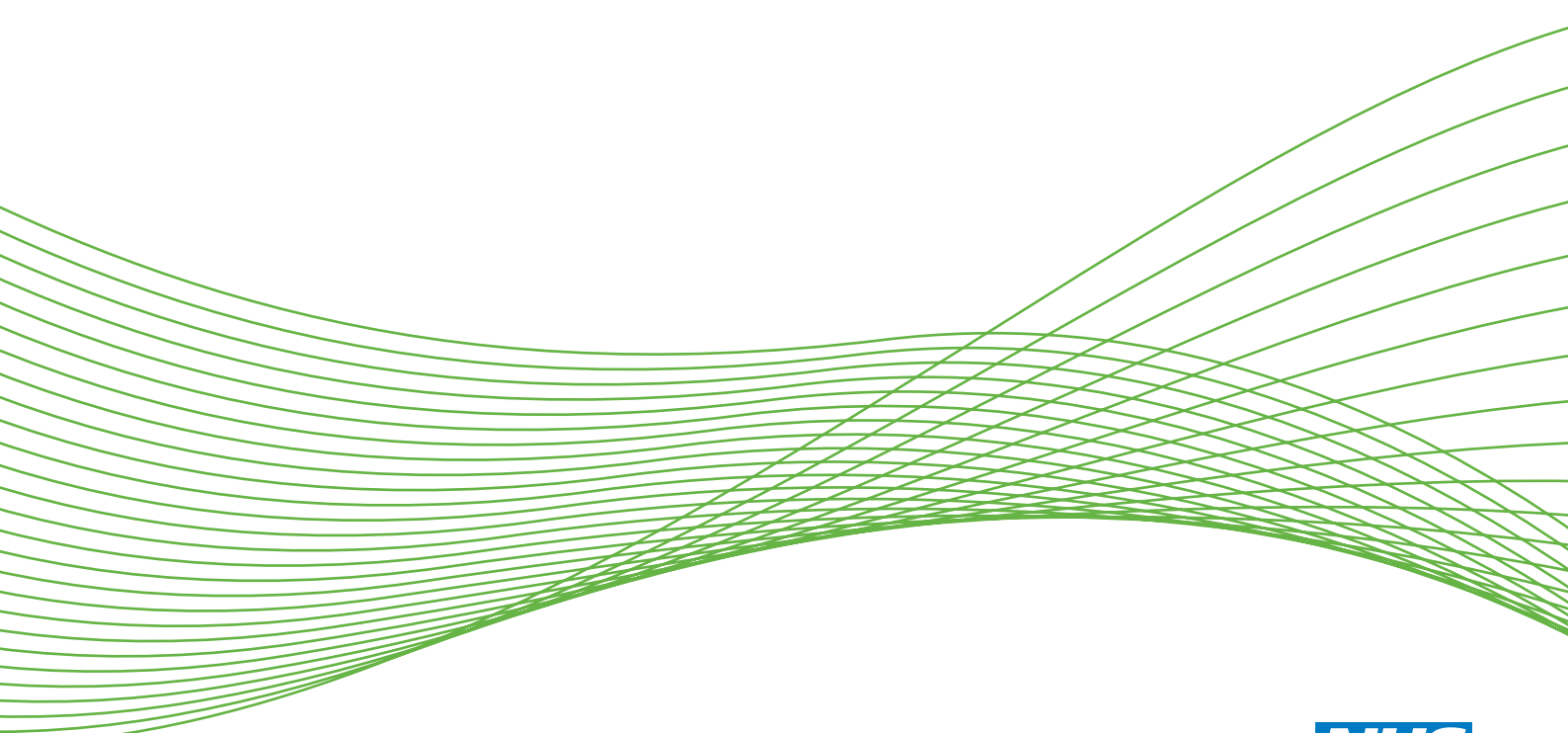


# HEALTH TECHNOLOGY ASSESSMENT

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## The use of fenestrated and branched endovascular aneurysm repair for juxtarenal and thoracoabdominal aneurysms: a systematic review and cost-effectiveness analysis

*Nigel Armstrong, Laura Burgers, Sohan Deshpande, Maiwenn Al, Rob Riemsma, SR Vallabhaneni, Peter Holt, Johan Severens and Jos Kleijnen*



**National Institute for  
Health Research**



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# Abstract

## The use of fenestrated and branched endovascular aneurysm repair for juxtarenal and thoracoabdominal aneurysms: a systematic review and cost-effectiveness analysis

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**Background:** Patients with large abdominal aortic aneurysms (AAAs) are usually offered reparative treatment given the high mortality risk. There is uncertainty about how to treat juxtarenal AAAs (JRAAAs) or thoracoabdominal aortic aneurysms (TAAAs). Endovascular repair of an abdominal aortic aneurysm (EVAR) is often seen as safer and easier than open surgical repair (OSR). However, endovascular treatment of JRAAAs or TAAAs requires specially manufactured stent grafts, with openings to allow blood to reach branches of the aorta. Commissioners are receiving increasing requests for fenestrated EVAR (fEVAR) and branched EVAR (bEVAR), but it is unclear whether or not the extra cost of fEVAR or bEVAR is justified by advantages for patients.

**Objective(s):** To assess the clinical effectiveness, safety and cost-effectiveness of fEVAR and bEVAR in comparison with conventional treatment (i.e. no surgery) or OSR for two populations: JRAAAs and TAAAs.

**Data sources:** Resources were searched from inception to October 2013, including MEDLINE (OvidSP), EMBASE (OvidSP) and the Cochrane Central Register of Controlled Trials (Wiley) and, additionally, for cost-effectiveness, NHS Economic Evaluation Database (NHS EED; Wiley) and EconLit (EBSCOhost). Conference abstracts were also searched.

**Review methods:** Studies were included based on an intervention of either fEVAR or bEVAR and a comparator of either OSR or no surgery. For clinical effectiveness, observational studies were excluded only if they were not comparative, i.e. explicitly selected on the basis of prognosis.

**Results:** For clinical effectiveness, searches retrieved 5253 records before deduplication. Owing to overlap between the databases, 1985 duplicate records were removed. Of the remaining 3268 records, based on titles and abstracts, 3244 records were excluded, leaving 24 publications to be ordered. All 24 studies were excluded as none of them satisfied the inclusion criteria. Sixteen studies were excluded on study design, six on intervention and two on comparator. Five out of 16 studies excluded on study design reported a comparison. However, all of the studies acknowledged that they had groups that were not comparable at baseline given that they had selectively assigned younger, fitter patients to OSR. Therefore,

these studies were considered 'non-comparative'. For cost-effectiveness, searches identified 104 references before deduplication. Owing to overlap between the databases, 34 duplicate records were removed. Of the remaining 70 records, seven were included for the full assessment based on initial screening. After a full-text review, no studies were included. Because of the lack of clinical effectiveness evidence and difficulty in estimating costs given the rapidly changing and variable technology, a cost-effectiveness analysis (CEA) was not performed. Instead a detailed description of modelling methods was provided.

**Conclusions:** Despite a thorough search, no studies could be found that met the inclusion criteria. All studies that compared either fEVAR or bEVAR with either OSR or no surgery explicitly selected patients based on prognosis, i.e. essentially the populations for each comparator were not the same. Despite not being able to conduct a CEA, we have provided detailed methods for the conduct if data becomes available.

**Future work:** We recommend at least one clinical trial to provide an unbiased estimate of effect for fEVAR/bEVAR compared with OSR or no surgery. This trial should also collect data for a CEA.

**Study registration:** This study is registered as PROSPERO CRD42013006051.

**Funding:** The National Institute for Health Research Health Technology Assessment programme.



# Contents

<b>List of tables</b>	<b>ix</b>
<b>List of figures</b>	<b>xi</b>
<b>List of abbreviations</b>	<b>xiii</b>
<b>Plain English summary</b>	<b>xv</b>
<b>Scientific summary</b>	<b>xvii</b>
<b>Chapter 1 Background</b>	<b>1</b>
Current evidence	3
<b>Chapter 2 Aims and objectives</b>	<b>5</b>
Aim	5
Objectives	5
<b>Chapter 3 Decision problem</b>	<b>7</b>
Population	7
Intervention	7
Comparators	8
<b>Chapter 4 Clinical effectiveness review</b>	<b>9</b>
Methods of clinical effectiveness review	9
<i>Inclusion and exclusion criteria</i>	9
<i>Search strategy</i>	10
<i>Screening strategy</i>	11
<i>Methods of analysis/synthesis</i>	11
Results of clinical effectiveness review	11
<i>Summary of inclusion/exclusion</i>	11
<i>Summary of reasons for exclusion</i>	11
<b>Chapter 5 Cost-effectiveness review</b>	<b>15</b>
Methods of cost-effectiveness review	15
<i>Inclusion and exclusion criteria</i>	15
<i>Search strategy</i>	15
<i>Screening strategy</i>	16
<i>Methods of analysis/synthesis</i>	16
Results of cost-effectiveness review	16
<i>Summary of inclusion/exclusion</i>	16

<b>Chapter 6 Cost-effectiveness analysis</b>	<b>19</b>
Design	19
Population	19
Interventions and comparators	20
Model structure	20
<i>Short-term model (fit for open surgical repair)</i>	20
<i>Short-term model (unfit for OSR)</i>	22
<i>Long-term model</i>	22
<i>Assumptions regarding model structure</i>	22
Input parameters	24
<i>Transition probabilities</i>	24
<i>Costs</i>	25
<i>Outcomes</i>	25
Analyses	28
<i>Base case</i>	28
<i>Subgroup analyses</i>	28
<i>Sensitivity analyses</i>	28
<b>Chapter 7 Discussion</b>	<b>29</b>
Clinical effectiveness findings	29
Cost-effectiveness findings	30
Strengths and limitations of the clinical effectiveness review	30
<i>Strengths</i>	30
<i>Limitations</i>	30
Strengths, limitations and uncertainties of the cost-effectiveness analysis	30
Conclusions	30
Suggested research priorities	31
<b>Acknowledgements</b>	<b>33</b>
<b>References</b>	<b>35</b>
<b>Appendix 1 Search strategies</b>	<b>41</b>
<b>Appendix 2 Summary of studies excluded at full paper, clinical effectiveness review</b>	<b>59</b>
<b>Appendix 3 Quality of cost-effectiveness studies of endovascular repair of abdominal aortic aneurysm</b>	<b>61</b>
<b>Appendix 4 Summary of studies for recommended cost-effective analysis</b>	<b>63</b>
<b>Appendix 5 PRISMA checklist</b>	<b>65</b>

# List of tables

<b>TABLE 1</b>	Numbers of TAAA repairs by type conducted in Scotland (2001–7)	<b>1</b>
<b>TABLE 2</b>	Cost data required for the CEA	<b>26</b>
<b>TABLE 3</b>	Estimates of key parameters to estimate the costs of OSR	<b>27</b>
<b>TABLE 4</b>	Estimates of key parameters to estimate the costs of fEVAR/bEVAR	<b>27</b>
<b>TABLE 5</b>	Quality-of-life estimates (EQ-5D) EVAR 1 trial	<b>27</b>
<b>TABLE 6</b>	Quality-of-life estimates (EQ-5D) EVAR 2 trial	<b>28</b>



# List of figures

<b>FIGURE 1</b>	Flow of studies through the screening process: clinical effectiveness review	<b>12</b>
<b>FIGURE 2</b>	Flow of studies through the screening process: cost-effectiveness review	<b>16</b>
<b>FIGURE 3</b>	Short-term decision model: fit for surgery	<b>21</b>
<b>FIGURE 4</b>	Short-term decision model: unfit for surgery	<b>23</b>
<b>FIGURE 5</b>	Long-term Markov model	<b>24</b>



## List of abbreviations

AA	aortic aneurysm	fEVAR	fenestrated endovascular repair of an abdominal aortic aneurysm
AAA	abdominal aortic aneurysm		
ASA	American Society of Anesthesiologists	JRAAA	juxtarenal abdominal aortic aneurysm
bEVAR	branched endovascular repair of abdominal aortic aneurysm	LY	life-year
CDSR	Cochrane Database of Systematic Reviews	MeSH	medical subject heading
CEA	cost-effectiveness analysis	MHRA	Medicines and Healthcare products Regulatory Agency
CENTRAL	Cochrane Central Register of Controlled Trials	MI	myocardial infarction
CRD	Centre for Reviews and Dissemination	NHS EED	National Health Service Economic Evaluation Database
CT	computerised tomography	NICE	National Institute for Health and Care Excellence
CvZ	College voor Zorgverzekeringen	OSR	open surgical repair
DARE	Database of Abstracts of Reviews of Effects	QALY	quality-adjusted life-year
EQ-5D	European Quality of Life-5 Dimensions	RCT	randomised controlled trial
EVAR	endovascular repair of abdominal aortic aneurysm	SMA	superior mesenteric artery
		TAA	thoracic aortic aneurysm
		TAAA	thoracoabdominal aortic aneurysm





## Plain English summary

An aneurysm is a widening of a blood vessel. Of aneurysms involving a major blood vessel called the aorta, 75% are located in the abdomen [abdominal aortic aneurysms (AAAs)], whereas the others are located in the chest. Depending on the age group studied and the definition of AAAs, 1.3–12.7% of the population have an AAA. Patients with an acute AAA need rapid medical attention given the high risk of rupture and the fact that there is an 80% risk of death if repair is not carried out. In open surgical repair (OSR), the abdominal and chest cavities need to be opened to repair the aneurysm, whereas in endovascular repair of abdominal aortic aneurysm (EVAR) a hollow tube (stent graft) is inserted through a blood vessel in the groin. When the aneurysm is close to branches from the aorta (e.g. to the kidneys), 'fenestrated' EVAR (fEVAR) is required, where the stent graft extends over the arteries to the kidneys, but blood flows through windows (fenestrations) to the branches. When the aneurysm includes the branch, the term 'branched' EVAR (bEVAR) is used. This study aimed to assess the medical effects (clinical effectiveness) and the value for money (cost-effectiveness) of fEVAR and bEVAR compared with OSR or no surgery. However, no studies that made this comparison were found. Mainly because of the lack of clinical effectiveness data, the cost-effectiveness could not be estimated. Instead, detailed methods for assessing cost-effectiveness are described.



# Scientific summary

## Background

An aneurysm is dilatation of an artery. Abdominal aortic aneurysms (AAAs) account for 75% of all aortic aneurysms (AAs) and are located, by definition of the abdomen, below the diaphragm, most below the renal arteries. Those aneurysms that do not involve, but are close to the origin of, the renal arteries [juxtarenal AAAs (JRAAs)] account for about 16% of AAAs. Thoracic AAs account for the other 25% of AAs. Of these, 15% extend into the abdomen and are therefore referred to as thoracoabdominal aortic aneurysms (TAAAs).

Because most aneurysms are asymptomatic, it is difficult to estimate their prevalence, but screening studies in the UK have estimated a prevalence of AAAs of 1.3–12.7%, depending on the age group studied and the definition of AAA. The incidence of symptomatic AAAs in men is approximately 25 per 100,000 patient-years at age 50 years, increasing to 78 per 100,000 in those older than 70 years of age. For TAAAs, the incidence estimate varies from under one to about three per 100,000 patient-years.

Patients with symptomatic TAAAs or AAAs need rapid medical attention given that the risk of rupture increases with the size of the aneurysm, and those aneurysms larger than 6 cm in diameter have an annual risk of rupture of 25%. Among patients with a ruptured AAA, the mortality rate is about 80%; even when they undergo emergency surgery, only about half survive beyond 30 days. Several studies indicate that without surgery the 5-year survival rate for patients with aneurysms larger than 5 cm is about 20%. For TAAAs, the 5-year survival without operation has been reported to be between 7% and 20%.

As well as concomitant medical treatment for any other cardiovascular disease, there are two main methods of repair, open surgical repair (OSR) and endovascular repair of an abdominal aortic aneurysm (EVAR). In the most recent appraisal by the National Institute for Health and Care Excellence (NICE), in 2009, EVAR was recommended as an option for an unruptured AAA that was infrarenal, i.e. below the renal arteries. It was recommended that EVAR for ruptured aneurysms be reserved for research only. For TAAAs there is no NICE guidance.

Recent solutions for more complicated aneurysms are 'fenestrated' EVAR (fEVAR) and 'branched' EVAR (bEVAR). fEVAR is where the stent graft fabric extends over the renal arteries, but perfusion to these arteries is preserved via accurately placed windows (fenestrations) within the stent graft fabric. The term 'branched' refers to the need to bridge the gap (created by increased diameter of aorta) between the main body of aortic stent graft and target vessels and not to any actual branch from the graft itself. The fEVAR and bEVAR procedures are more challenging than standard EVAR as graft positioning requires both longitudinal and rotational alignment of the fenestrations with the target vessels. Any misalignment can lead to partial or total covering of the ostia of the target vessel (shuttering), resulting in reduced blood flow or occlusion. Commissioners are receiving increasing requests for fEVAR and bEVAR, but it is not clear if the extra cost of fEVAR or bEVAR compared with the alternative of OSR is justified by advantages for patients. In the absence of recent UK evidence-based guidance on JRAA and TAAAs, evidence synthesis with economic modelling is needed to answer these questions.

The current assessment will therefore attempt to evaluate the clinical effectiveness, safety and cost-effectiveness of fEVAR or bEVAR in comparison with conventional treatment for JRAAs or TAAAs in the UK.

## Methods

A systematic review was conducted using methods as recommended in the Centre for Reviews and Dissemination guidance for undertaking reviews in health care and the Cochrane Handbook for reviews of intervention studies. The target patient population for the review was adult patients who were eligible for fEVAR (age  $\geq 18$  years) with JRAAs or eligible for bEVAR with TAAAs, i.e. with proximity to/involvement of target vessels such that EVAR was unsuitable.

The interventions under consideration were fEVAR and bEVAR, which use specially manufactured stent grafts with openings to allow blood to reach branches of the aorta. The comparators considered relevant for this assessment were OSR, which is the historic treatment method for JRAAs or TAAAs, and no surgery (best medical therapy only).

In the first instance, randomised and non-randomised trials in which participants are assigned to the intervention group or comparator group were included. As no controlled trials were likely to be found, studies with a cohort design were included if they made a comparison with a control group. These studies are referred to as comparative. To qualify as comparative, studies had to demonstrate that there had been some attempt to make the populations receiving each of the treatments comparable and that any evidence of intent to select based on some prognostic factor would imply exclusion. Cost studies and cost-effectiveness analyses (CEAs) were also included.

Seven databases were searched from inception up to October 2013, including MEDLINE, EMBASE, Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED). Two reviewers independently screened titles and abstracts of all reports identified by searches and discrepancies were discussed. Full copies of all studies deemed potentially relevant, after discussion, were obtained and two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus or discussion with a third reviewer. Given that no studies met all of the inclusion criteria, a narrative account of the number of studies screened for inclusion and reasons for excluding studies was given.

## Results

The literature searches for clinical effectiveness studies retrieved 3268 records that were screened at title and abstract stage. Based on titles and abstracts, 24 publications were ordered for full-paper screening. All 24 studies were excluded as none of the studies satisfied the inclusion criteria.

Sixteen studies were excluded on study design, six studies were excluded on intervention and two on comparator (chimney grafts). Among the six studies which were excluded on intervention, three studies were excluded because they compared EVAR with OSR, with no indication of fEVAR or bEVAR being used; one used EVAR with suprarenal fixation; and the other two were excluded because they reported results from surgeon-modified fenestrated–branched stent grafts, which are not considered as appropriate interventions for this evaluation. Five out of 16 studies that were excluded on study design reported a comparison. However, for all of the studies, the authors acknowledged that they had included groups which were not comparable at baseline as they had selectively assigned patients to the groups being compared, i.e. not the same population. Therefore, these studies were considered to be non-comparative studies.

The health economics search identified 70 titles and abstracts. Of these, seven were ordered for the full assessment based on initial screening. After full-text review no studies were included. Six of these seven studies estimated the cost-effectiveness of EVAR compared with OSR for patients with pararenal AAA who were defined as unsuitable for EVAR and, thus, these studies were excluded based on the population. Furthermore, five of them were presented at conferences and these abstracts were not presented in such a way that data could be extracted from them. The other study reported costs of fEVAR, but this was reported without sufficient details.

Our objective was to perform an economic evaluation of fEVAR and bEVAR for patients with JRAAs and TAAAs. However, it was decided that a CEA evaluating fEVAR and bEVAR was not possible, partly because the systematic review assessing the clinical effectiveness showed that no comparative study has been done that could provide clinical effectiveness data. In addition, it was not feasible to obtain valid estimates for the other input parameters. Consequently, we decided to describe how an economic evaluation could be performed if more data were available. This includes those data that ideally would come from a randomised controlled trial (RCT) in each of two populations, i.e. those fit enough and those not fit enough for OSR, which would inform two distinct models.

## Conclusion

The systematic review of clinical effectiveness studies showed that no comparative study has been done that could provide reliable clinical effectiveness data. All studies that compared either fEVAR or bEVAR with either OSR or no surgery explicitly selected patients based on prognosis, i.e. essentially the populations for each comparator were not the same. Therefore, it was decided that a CEA evaluating fEVAR and bEVAR was not possible. Consequently, we decided to describe how an economic evaluation could be performed if more data were available. This includes those data that ideally would come from a RCT in each of two populations, i.e. those fit enough and those not fit enough for OSR, which would inform two distinct models.

We recommend at least one clinical trial to provide an unbiased estimate of effect for fEVAR/bEVAR compared with OSR or no surgery. This trial should also collect data for a CEA.

## Study registration

This study is registered as PROSPERO CRD42013006051.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.



## Chapter 1 Background

An aneurysm is a permanent, localised (i.e. focal) dilatation of an artery having at least a 50% increase in diameter compared with the expected normal diameter of the artery in question.<sup>1</sup> The normal aorta is shaped like a walking cane, following a course through the chest (thoracic aorta) and abdomen (abdominal aorta). Abdominal aortic aneurysms (AAAs) account for 75% of all aortic aneurysms (AAs) and are located, by definition of the abdomen, below the diaphragm,<sup>2</sup> most below the renal arteries.<sup>3</sup> Those that do not involve, but are close to the origin of, the renal arteries [juxtarenal AAAs (JRAAs)] account for about 16% of AAAs.<sup>4</sup> Thoracic aortic aneurysms (TAAs) account for the other 25% of AAs. Of these, 15% extend into the abdomen and are therefore referred to as thoracoabdominal aortic aneurysms (TAAAs).<sup>5</sup>

Thoracoabdominal aortic aneurysms are stratified using the Crawford classification system based on their distribution within the aorta.<sup>6</sup> The Crawford classification system subdivides TAAAs into:

- Type I: descending thoracic aorta (distal to the left subclavian artery) to the abdominal aorta above the renal arteries.
- Type II: descending thoracic aorta (distal to the left subclavian artery) to the renal arteries and may continue on to the bifurcation.
- Type III: mid to distal descending thoracic aorta and involves most of the abdominal aorta as far as the bifurcation.
- Type IV: this includes the upper abdominal aorta and all or none of the infrarenal aorta, thus including the origins of the visceral arteries (renal, superior mesenteric and coeliac).
- Type V: this extends from the distal thoracic aorta including the coeliac and superior mesenteric origins, but not the renal arteries (modified by Safi's group).<sup>6</sup>

Because most aneurysms are asymptomatic it is difficult to estimate their prevalence, but screening studies in the UK have estimated a prevalence of AAAs of 1.3–12.7% depending on the age group studied and the definition of the AAA. The incidence of symptomatic AAAs in men is approximately 25 per 100,000 patient-years at age 50 years, increasing to 78 per 100,000 in those older than 70 years of age.<sup>3</sup> For TAAAs, the incidence estimate varies from under one to about three per 100,000 patient-years.<sup>7</sup> In Scotland, over 7 years (2001–7), the breakdown of TAAAs by type is shown in *Table 1*. Note that suprarenal implies inclusion of at least one renal artery origin, with no extension to the coeliac or superior mesenteric arteries above.

True aneurysm formation is a distinct aetiopathological process, with some similarities to atherosclerosis and an increasingly understood genetic basis. Other causes include trauma, vasculitis, cystic medial necrosis and postsurgical anastomotic disruption.<sup>5</sup> AAAs are about three times more common in men than in women.<sup>3</sup>

**TABLE 1** Numbers of TAAA repairs by type conducted in Scotland (2001–7)

Measure	Type I	Type II	Type III	Type IV	Type V	Suprarenal
Number	7	11	12	38	1	7
Percentage	9	14	16	50	1	9

Abdominal aortic aneurysms enlarge at varying rates and symptoms (although very rare) that can occur as an aneurysm enlarges include a pulsating sensation in the abdomen, back pain and abdominal pain that may spread to the back. Patients with a symptomatic TAAA or AAA need rapid medical attention given that the risk of rupture increases with the size of the aneurysm, and those aneurysms larger than 6 cm in diameter have an annual risk of rupture of 25%. Among patients with a ruptured AAA, the mortality rate is about 80%; even when they undergo emergency surgery, only about half survive beyond 30 days. Several studies indicate that, without surgery, the 5-year survival rate for patients with aneurysms larger than 5 cm is about 20%. For TAAAs, the 5-year survival rate without operation has been reported between 7% and 20%.<sup>7</sup> The national screening programme care pathway recommends screening men from age 65 years and that those aneurysms of at least 5.5 cm should be referred for consideration for elective surgery.<sup>8</sup>

As well as concomitant medical treatment for any other cardiovascular disease, there are two main methods of repair: open surgical repair (OSR) and endovascular repair of an abdominal aortic aneurysm (EVAR). In the most recent appraisal by the National Institute for Health and Care Excellence (NICE), in 2009,<sup>3</sup> EVAR was recommended as an option for an unruptured AAA that was infrarenal, i.e. below the renal arteries, although the decision was recommended to be based on:

- aneurysm size and morphology
- patient age, general life expectancy and fitness for OSR
- the short- and long-term benefits and risks of the procedures including aneurysm-related mortality and operative mortality.

It was recommended that EVAR for ruptured aneurysms be reserved for research only. For TAAAs there is no NICE guidance, although National Services Scotland stated that '... endovascular stent repair is a relatively new procedure, but is becoming accepted practice within vascular medicine for treatment of certain types of aneurysm and is recommended by the National Institute for Health and Clinical Effectiveness [NICE].'<sup>7</sup> Also, the Joint Working Group to produce guidance on delivering an EVAR Service has produced guidance on all aspects of EVAR delivery, which covers both TAAs and AAAs, and is currently available from the Medicines and Healthcare products Regulatory Agency (MHRA) website.<sup>9</sup>

The latest American Heart Association TAA guidelines state that '... endovascular stent grafting should be strongly considered when feasible ... for patients with degenerative or traumatic aneurysms ... exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms ...'.<sup>10</sup> They do not specifically recommend EVAR for TAAAs except to refer to previous guidance, which includes a recommendation for its use.<sup>11</sup> Indeed, for patients with chronic dissection, particularly if associated with a connective tissue disorder, but without significant comorbid disease, and a descending thoracic aortic diameter exceeding 5.5 cm, OSR is recommended. Therefore, there is clearly uncertainty about how to treat TAAAs.

In addition, there is uncertainty about how to treat JRAAAs. This is because the normal EVAR procedure requires that the endograft extends to the healthy parts of the running aorta above and below the aneurysm to attach the stent graft. A JRAAA implies that the aneurysm, although it does not include the origin of the renal artery, is so close to the origin that there is insufficient space to attach the stent graft to the aorta without overlapping the ostia of renal arteries. A solution that has been developed for this situation is fenestrated EVAR (fEVAR), where the stent graft fabric extends over the renal arteries, but perfusion to these arteries is preserved via accurately placed windows (fenestrations) within the stent graft fabric. Aortic branches such as renal arteries that would lose perfusion if not for such fenestrations are called target vessels. Customised fenestrated stent grafts with up to four openings to the target vessels (two renal arteries, superior mesenteric artery and coeliac artery) have thus been developed to allow perfusion of the target vessels.<sup>12,13</sup> fEVAR technology is enabling an expansion of the patient population, increasing the number that may be eligible for EVAR.<sup>10</sup>



Thoracoabdominal aortic aneurysms, by definition, extend through the diaphragm from the thoracic to the abdominal cavity, thus including the origin of at least one of the visceral arteries [from top to bottom, coeliac, superior mesenteric artery (SMA) and renal arteries]. The fact that a target vessel origin is included means that the target vessel arises from the aneurysm, thus implying that a gap must be bridged from any fenestra in the stent graft within the aorta to the ostia of the target vessel. The procedure required in this population is then referred to as branched EVAR (bEVAR). The term branched refers to the need to bridge the gap (created by increased diameter of aorta) between the main body of aortic stent graft and target vessels and not to any actual branch from the graft itself.<sup>13</sup> Where the aneurysm is suprarenal, it involves at least one renal artery and it does not extend high enough to reach the diaphragm, thus falling short of a type IV TAAA. In this case, it is strictly neither a JRAAA nor a TAAA, but given that it requires bEVAR it can be included within the TAAA population.

The implantation of standard EVAR is a relatively simpler procedure, requiring accurate longitudinal placement of the graft. The fEVAR and bEVAR procedures are more challenging, as graft positioning requires both longitudinal and rotational alignment of the fenestrations with the target vessels. Any misalignment can lead to partial or total covering of the ostia of the target vessel (shuttering), resulting in reduced blood flow or occlusion. Furthermore, although Field *et al.* concluded that there was a case for providing a UK service, it should be confined to highly specialised centres and that this was in the context of 'no data published on survival with and without intervention in the UK'.<sup>14</sup> This lack of evidence is compounded by potentially many comparators given variations in the basic procedure.<sup>15</sup>

Commissioners are receiving increasing requests for fEVAR and bEVAR, but it is not clear whether or not the extra cost of fEVAR or bEVAR compared with the alternative of OSR is justified by advantages for patients.<sup>14</sup> In the absence of recent UK evidence-based guidance on JRAAA and TAAAs, evidence synthesis with economic modelling is needed to answer these questions.

## Current evidence

A health technology assessment (HTA) review in 2009 assessed the outcomes of treatment with fEVAR compared with the outcomes after OSR in patients with JRAAAs.<sup>4</sup> This review included five single-centre, single-arm prospective cohort studies on fEVAR and seven studies on OSR (one prospective and six retrospective). The authors concluded that results up to 2 years' follow-up in fEVAR studies compare favourably with the outcomes in the OSR studies. fEVAR had lower 30-day mortality than OSR (1.8% vs. 3.1%) and a lower late mortality over the period of time that patients were followed (12.8% vs. 23.7%). However, there was uncertainty regarding long-term outcomes and all of these observations were based on low-quality evidence.

Two further systematic reviews, one in JRAAAs<sup>16</sup> and the other in TAAAs,<sup>17</sup> have attempted to make a comparison between OSR, and fEVAR and bEVAR, respectively. Bakoyiannis *et al.*<sup>17</sup> found seven case series of EVAR of TAAA in a total of 155 patients. They compared results from these studies with those from a selected set of studies on OSR (including one using a hybrid approach) and generally found similarity in outcomes with, for example, 30-day mortality of 7.1% for bEVAR compared with a range of 5% to 19% for OSR. However, given that no comparative studies were found, their only conclusions were that bEVAR has '... encouraging results for patients considered unfit for conventional open repair'.<sup>17</sup>

In JRAAAs, Nordon *et al.*<sup>16</sup> also compared 'cohorts' from one set of studies of fEVAR with those from another set of studies of OSR. They did find a higher 30-day mortality with OSR (relative risk 1.03, 95% confidence interval 1.01 to 1.04). However, given again a lack of comparative studies, their only conclusions were that '... selectivity within the study groups and lack of a rigorous classification prohibit more robust comparison'.<sup>16</sup>

More recently, in 2012 a review by the College voor Zorgverzekeringen (CvZ) in the Netherlands of both fEVAR and bEVAR also found no comparative studies and, thus, concluded that there was insufficient evidence to recommend either procedure:

*From this review, it appears that there is insufficient evidence of good methodological quality to conclude that the endovascular treatment of aneurysms of the complex aorta can be regarded as effective. The endovascular treatment with fenestrated and/or branched devices does not meet the required level of knowledge and practice and cannot be considered to ensure medical care performance under the Health Insurance and related regulations.*

*De Groot et al.<sup>18</sup> [translated from the summary]*

However, to date, no similar assessment has been carried out for the UK setting. The current assessment will therefore attempt to evaluate the clinical effectiveness, safety and cost-effectiveness of fEVAR or bEVAR in comparison with conventional treatment for JRAAAs or TAAAs in the UK.

## Chapter 2 Aims and objectives

### Aim

The aim of this project was to assess the impact of fEVAR and bEVAR on patient outcomes and NHS resources, to propose possible changes in patient management and make recommendations for further research.

### Objectives

1. To assess the clinical effectiveness and safety of fEVAR and bEVAR in comparison with conventional treatment, i.e. no surgery or OSR (including any hybrid alternatives) for two populations – JRAAA and TAAA.
2. To assess, from a NHS perspective, the cost-effectiveness of fEVAR and bEVAR in comparison with conventional treatment, i.e. no surgery, or OSR or any hybrid alternatives for two populations – JRAAA and TAAA.



## Chapter 3 Decision problem

### Population

The target patient population for fEVAR and bEVAR is those adult patients (aged  $\geq 18$  years) who are at risk of rupture of JRAAs or TAAAs (distal to left subclavian, i.e. excluding aortic arch) which involve, or are close enough to, at least one aortic branch such that a standard EVAR would occlude the branch. This would include patients who are unsuitable for OSR because of the presence of significant comorbid conditions and those who are unsuitable for treatment with a standard EVAR as a result of the presence of a short proximal neck at those positions.

The decision to repair AAAs using fEVAR and bEVAR requires careful patient selection to identify those patients who will most likely benefit from the repair as the decision depends on consideration of three important risk factors such as:

1. estimated risk of aneurysm ruptures if the patient is not treated
2. estimated risk of death due to surgery, either EVAR or OSR, which depends on the fitness of the patient and also on the success rate of the treating physician's institution
3. estimated longevity of the patient if not for the aneurysm.

Subgroups of interest are as follows:

- elective asymptomatic [detected mainly incidentally (majority) or by screening]
- elective symptomatic (uncommon)
- number of target vessels [one, two, three or four (two renal arteries plus SMA and coeliac)]
- patients who are on dialysis (as renal artery perfusion not needed).

### Intervention

Fenestrated EVAR and bEVAR are specially manufactured stent grafts with openings to allow blood to reach branches of the aorta.

Endovascular repair of AAAs allows the exclusion of the dilated aneurysmal segment of the aorta from the systematic circulation. The procedure requires, however, that the endograft extends to the healthy parts of the aorta above and below the aneurysm. However, the neck of a JRAAA is too short for a standard EVAR. fEVAR provides a solution to overcome this problem by enabling the continuation of blood flow to the renal and visceral arteries through holes or fenestrations in the fabric of the stent graft. These fenestrations are designed to match the ostium of the renal and visceral arteries. There are three varieties of fenestration (small, large and scallop) and their location needs to be customised to fit the anatomy of the patient.<sup>4</sup> If the device is not properly designed, if the alignment is inaccurate, or if the catheterisation of the visceral arteries is not possible, the procedure may fail.

Branched EVAR provides a solution when the target vessels arise from a segment of the aneurysmal aorta. A branched stent graft is deployed in a dilated aorta and, therefore, there is a gap created between the target vessels and stent graft, which requires bridging. Any branches coming off the stent graft are called cuffs (not branches). Branches in the form of covered stents between the aortic stent graft and the target vessels are indicated for both fEVAR and bEVAR in order to anchor the stent graft (i.e. to prevent migration), although for bEVAR they have the additional purpose of bridging the gap. Some aneurysms

may require a combination of one or more fenestrations and one or more branches. In this case, a combination of fEVAR and bEVAR may be required.<sup>13</sup>

It is essential to realise that there is a close correspondence between each of the two populations and each of the two interventions. JRAAA implies that the aneurysm is close to, but does not involve, the opening to the branches, which are the renal arteries. Therefore, the term 'branched' is not appropriate and, thus, JRAAA patients are eligible only for fEVAR. A TAAA implies that the aneurysm extends from the abdominal into the thoracic cavity and, thus, given the proximity of the renal branches to the diaphragm, is very likely to involve the branches, therefore implying the term 'branched'. Therefore, TAAA patients are eligible only for bEVAR. Both patients with JRAAs and those with TAAs are also eligible for OSR or no surgery depending on the general fitness of the patient.

Once a graft is placed in a patient, life-long follow-up at regular intervals is necessary to ensure that the graft remains in its intended location, that the components have adequate overlap and the aneurysm remains excluded from systemic blood flow and blood pressure. Should the need arise, routine follow-up allows the performance of timely and appropriate intervention through detection of events that could affect the long-term outcomes.

## Comparators

The comparators considered relevant for this assessment are:

1. OSR is the historic treatment method for JRAAs or TAAs
2. no surgery (best medical therapy only).

No surgery (and thus optimal conservative care) is a valid comparator in those patients considered unfit for OSR. For OSR, it is important to distinguish between the populations for which fEVAR and bEVAR are indicated as the morbidity and mortality of the 'open surgical equivalent' is greater. This is because the higher the aneurysm, the higher the aortic clamp must be placed and, thus, the greater the stress on the heart and the more extensive the potential ischaemia (e.g. to viscera and spinal cord). Also, OSR for a TAAA usually requires left-heart bypass or hypothermic circulatory arrest, which increases the risk.<sup>19</sup> As no aortic clamp is needed for EVAR, this differential risk does not apply between fEVAR and bEVAR. Hence, any study assessing OSR performed in a population eligible for fEVAR cannot be compared with one eligible for bEVAR.

In 2008, Greenberg and Lytle reported that the patients selected to undergo OSR for a TAAA are faced with a mortality risk ranging from 3% to 17%, with an incidence of perioperative death at centres with extensive experience < 10%.<sup>15</sup> Moreover, the risk of spinal cord ischaemia remains between 4% and 11% and the postoperative renal complications, such as worsening of renal function, are also considerable, with an incidence ranging between 17% and 25%; up to 15% of patients ultimately might require haemodialysis.<sup>15</sup> In addition, cardiopulmonary complications after aortic surgery are common.<sup>15</sup>

## Chapter 4 Clinical effectiveness review

The systematic review was conducted using methods as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care<sup>20</sup> and the Cochrane Handbook for reviews of intervention studies.<sup>21</sup>

### Methods of clinical effectiveness review

#### *Inclusion and exclusion criteria*

##### Population

Studies including adult patients who were eligible for fEVAR (aged  $\geq 18$  years) with JRAAs or eligible for bEVAR with TAAAs, i.e. with proximity to, or involvement of, target vessels such that EVAR was unsuitable.

##### Setting

Secondary care.

##### Intervention

Fenestrated EVAR and bEVAR.

##### Comparator (clinical effectiveness studies only)

Open surgical repair (including hybrid repair) or no surgery for patients considered unsuitable for OSR.

##### Outcomes

- Risk of death: all-cause mortality and aneurysm-related mortality – primary outcome.
- Probability of technical success (target vessel perfusion).
- Durability (risk of relapse).
- Risk of adverse events:
  - graft infection
  - device migration
  - endoleaks (early/late, type I/type III)
  - target vessel stenosis/occlusion
  - aneurysm growth
  - structural disintegration
  - modular separation
  - kinking leading to thrombosis
  - stent comes off or breaks
  - aortic rupture
  - stroke
  - paraplegia/spinal cord ischaemia.
- Reintervention (any reason, for a stated adverse event).
- Annual radiation dosage.

##### Study design

###### *Step 1*

Randomised and non-randomised trials in which participants are assigned to the intervention group or comparator group, and which report at least one of the listed outcomes.

**Step 2**

As no controlled trials were likely to be found, studies with a cohort design were included if they make a comparison with a control group. These studies were referred to as comparative.

Step 2 is included given the likely lack of controlled trials and in order to permit the review of evidence that makes a comparison even if the evidence is of low quality, in particular a high risk of selection bias. Note that, to qualify as comparative, studies had to demonstrate that there had been some attempt to make the populations receiving each of the treatments comparable and that any evidence of intent to select based on some prognostic factor would imply exclusion.

The following study/publication types were excluded:

- case series/case reports
- pre-clinical and animal studies
- reviews, editorials and opinion pieces.

**Search strategy**

Search strategies were based on the target conditions, i.e. JRAAs and TAAAs. Searches were not limited by language or publication status (unpublished or published).

**Rapid appraisal for existing systematic reviews on juxtarenal abdominal aortic aneurysms and thoracoabdominal aortic aneurysms**

In order to identify existing and on-going systematic reviews, guidelines and guidance on JRAAs and TAAAs, a rapid appraisal of appropriate sources was undertaken on the following resources:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley). Searched issue 7: 2013.
- Database of Abstracts of Reviews of Effects (DARE) (Wiley). Searched issue 3: 2013.
- HTA Database (Wiley). Searched issue 3: 2013.
- NHS Economic Evaluation Database (NHS EED) (Wiley). Searched issue 3: 2013.
- International Guidelines Network Library (internet). Searched up to 19 August 2013. URL: [www.g-i-n.net/](http://www.g-i-n.net/).
- National Guideline Clearinghouse (internet). Searched up to 19 August 2013. URL: [www.guideline.gov/](http://www.guideline.gov/).
- NICE Guidance (internet). Searched up to 19 August 2013. URL: <http://guidance.nice.org.uk/>.
- National Institute for Health Research (NIHR) HTA (internet). Searched up to 19 August 2013. URL: [www.nets.nihr.ac.uk/programmes/hta](http://www.nets.nihr.ac.uk/programmes/hta).
- International Prospective Register of Systematic Reviews (PROSPERO) (internet). Searched up to 19 August 2013. URL: [www.crd.york.ac.uk/prospéro/](http://www.crd.york.ac.uk/prospéro/).
- US Food and Drug Administration (internet). Searched up to 20 August 2013. URL: [www.fda.gov/](http://www.fda.gov/).
- MHRA (internet). Searched up to 20 August 2013. URL: [www.mhra.gov.uk/](http://www.mhra.gov.uk/).

**Clinical effectiveness**

Searches were undertaken to identify studies investigating treatment of JRAAs and TAAAs. Full strategies for the clinical effectiveness searching are presented in *Appendix 1*. The following resources were searched from inception:

- MEDLINE (OvidSP). Searched 1946 to week 3 September 2013.
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). Searched up to 30 September 2013.
- MEDLINE Daily Update (OvidSP). Searched up to 30 September 2013.
- EMBASE (OvidSP). Searched 1974 to 4 September 2013.
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley). Searched issue 8: 2013.



## Conference searches

The following conference proceedings were searched:

- VEITHsymposium™ (internet): 2011–13.
- Charing Cross Symposium (internet): 2011–13.
- Vascular Annual Meeting (internet): 2011–13.

## Handling of citations

Identified references were downloaded into EndNote (Thomson Reuters, CA, USA) software for further assessment and handling. Rigorous records were maintained as part of the searching process. Individual records within the EndNote reference libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

## Quality assurance within the search process

For all searches undertaken by Kleijnen Systematic Reviews Information Team, the main EMBASE strategy for each set of searches were independently peer reviewed by a second information specialist, using the Canadian Agency for Drugs and Technologies in Health peer-review checklist.<sup>22</sup>

## Screening strategy

Two reviewers independently screened titles and abstracts of all reports identified by searches and discrepancies were discussed. Full copies of all studies deemed potentially relevant, after discussion, were obtained and two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus or discussion with a third reviewer.

## Methods of analysis/synthesis

Given that no studies met all of the inclusion criteria, a narrative account of the number of studies screened for inclusion and reasons for excluding studies was given.

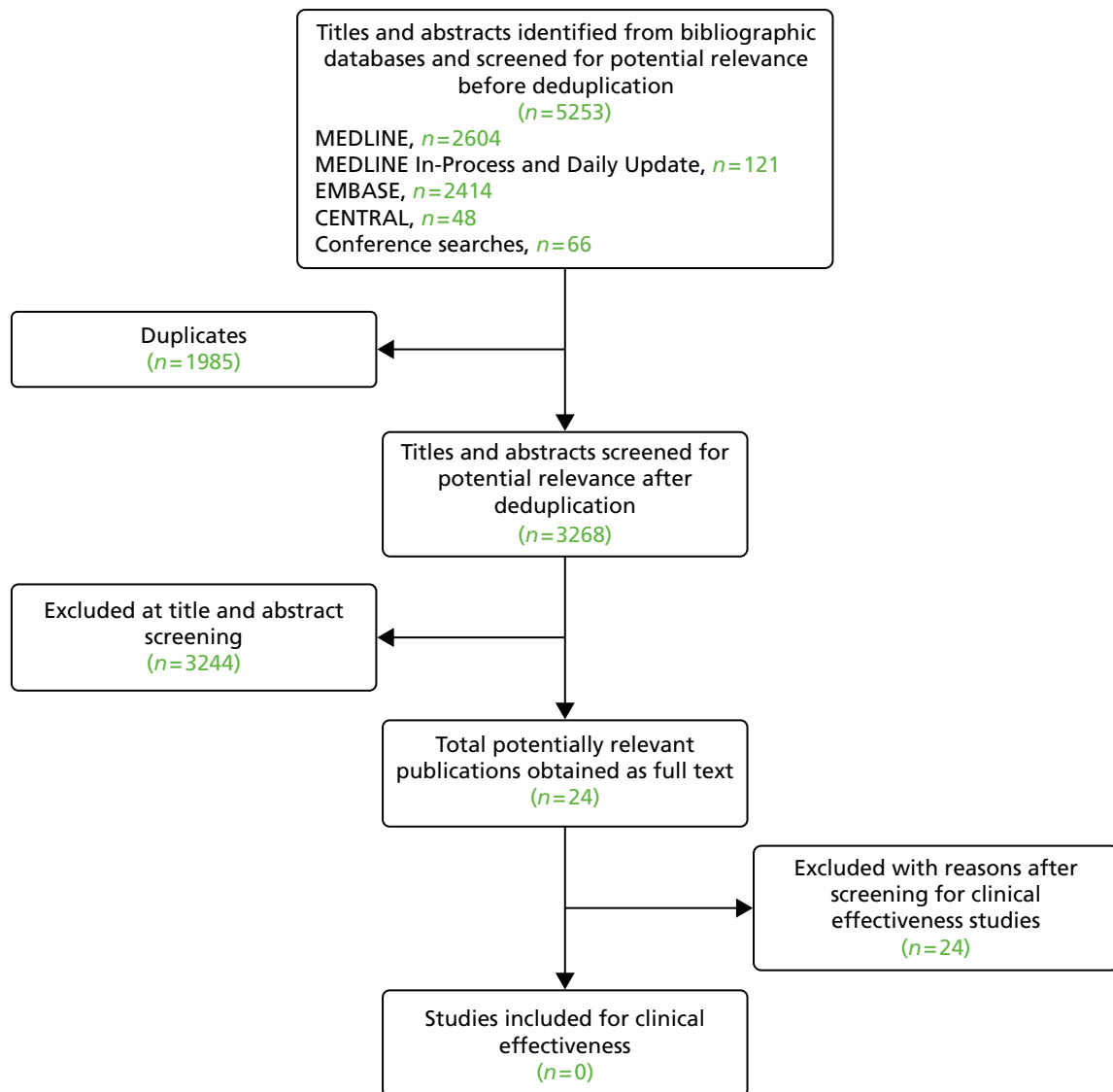
## Results of clinical effectiveness review

### Summary of inclusion/exclusion

The literature searches retrieved 5253 records before deduplication. Owing to overlap between the databases, 1985 duplicate records were removed. The remaining 3268 records were screened at title and abstract stage. Based on titles and abstracts, 3244 records were excluded, leaving 24 publications to be ordered. All 24 studies were excluded as none of the ordered studies satisfied our inclusion criteria. *Figure 1* shows the flow of studies through the review process and *Appendix 2* provides details, with reasons for exclusion, of all publications excluded at the full-paper screening stage.

### Summary of reasons for exclusion

Sixteen studies were excluded on study design, six studies were excluded on intervention and two on comparator (chimney grafts). Among the six studies which were excluded on intervention, three studies were excluded because they compared EVAR with OSR, with no indication of fEVAR or bEVAR being used;<sup>23–25</sup> one used EVAR with suprarenal fixation;<sup>26</sup> and the other two were excluded because they reported results from surgeon-modified fenestrated–branched stent grafts, which are not considered as appropriate interventions for this evaluation.<sup>27,28</sup>



**FIGURE 1** Flow of studies through the screening process: clinical effectiveness review.

Five out of 16 studies that were excluded on study design reported a comparison. However, all of the studies acknowledged that they had groups which were not comparable at baseline given that they had selectively assigned patients to the groups being compared, i.e. not the same population. Therefore, these studies were considered to be 'non-comparative studies'. Below are examples and quotes from the five studies.

In all studies patients were selected by the clinicians based on their characteristics and, generally, patients who were deemed younger and physiologically fitter underwent OSR<sup>29</sup> whereas, in contrast, older and high-risk patients were chosen for EVAR. One study reported that 'All [EVAR] patients were not considered suitable for [OSR].'<sup>30</sup> One study quoted:

*The policy for implanting a fenestrated stent-graft was based on high risk for open surgery (old age, severe comorbidities, previous aortic reconstruction, or need for suprarenal clamping) and whenever the quality of the neck was too poor to provide a seal with a standard stent-graft that would be durable for the expected lifespan of the patient.*

Chisci et al.<sup>31</sup>

One study appeared to be comparative at first instance, because the study explicitly stated that: 'In all patients who underwent OSR, anatomic suitability for fEVAR was assessed through CT [computerised tomography] review.'<sup>32</sup> However, it was excluded because of the following quote:

*When f-EVAR is technically feasible, the physicians usually recommended younger and generally fit patients to have an open repair, as was the case for patients with very large aneurysms. Older patients and those with multiple comorbidities were recommended to have fEVAR. Exceptions occurred due to patient preference and availability of funding. Patients selected by the clinicians based on their characteristics.*

Canavati et al.<sup>32</sup>

According to Greenberg et al.<sup>33</sup>:

*Patients treated with ER [endovascular repair] were on average 8.6 years older ( $71.3 \pm 12$  versus  $62.7 \pm 13$  years,  $p < 0.001$ ) than those treated with an SR [surgical repair], but no gender differences between repair types were found. Our bias has been to treat patients who are younger or have fewer comorbid factors with conventional surgery, a tendency that is readily reflected in the preoperative patient characteristics (Table 3).*

The above quote clearly demonstrates that selecting patients based on their clinical characteristics can cause a significant baseline imbalance between two groups, making them non-comparable. This evidence further supports our decision to exclude studies that were non-comparative.



# Chapter 5 Cost-effectiveness review

## Methods of cost-effectiveness review

The systematic review was conducted using methods in line with those recommended in the CRD guidance for undertaking reviews in health care<sup>20</sup> and the Cochrane Handbook for reviews of intervention studies.<sup>21</sup>

### Inclusion and exclusion criteria

#### Population

Studies including adult patients who were eligible for fEVAR (aged  $\geq 18$  years) with JRAAs or eligible for bEVAR with TAAAs, i.e. with proximity to, or involvement of, target vessels such that EVAR was unsuitable.

#### Setting

Secondary care.

#### Intervention

fEVAR and bEVAR.

#### Comparator (clinical effectiveness studies only)

OSR or no surgery for patients considered unsuitable for OSR.

#### Outcomes

- Cost-effectiveness.
- Health-care cost.
- Social care costs.

#### Study design

- Cost-effectiveness analysis (CEA).
- Cost study.

### Search strategy

Search strategies were based on the target conditions, JRAAs and TAAAs. Searches were not limited by language or publication status (unpublished or published). Resources were searched to identify cost-effectiveness studies of treatments for JRAAs and TAAAs. Where appropriate, strategies incorporated a cost-effectiveness search filter. Full strategies for the cost-effectiveness searching are presented in *Appendix 1*. The following resources were searched from inception:

- MEDLINE (OvidSP). Searched 1946 to week 3 September 2013.
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). Searched up to 1 October 2013.
- MEDLINE Daily Update (OvidSP). Searched up to 1 October 2013.
- EMBASE (OvidSP). Searched 1974 to 27 September 2013.
- NHS EED (Wiley). Searched issue 3: 2013.
- EconLit (EBSCOhost). Searched up to 30 September 2013.

### Screening strategy

Titles and abstracts of all reports identified by the searches were screened by one reviewer and ambiguities were resolved by consulting a second reviewer. Full copies of all studies deemed potentially relevant were obtained and were assessed by one reviewer for inclusion; any ambiguities were resolved by consulting a second reviewer.

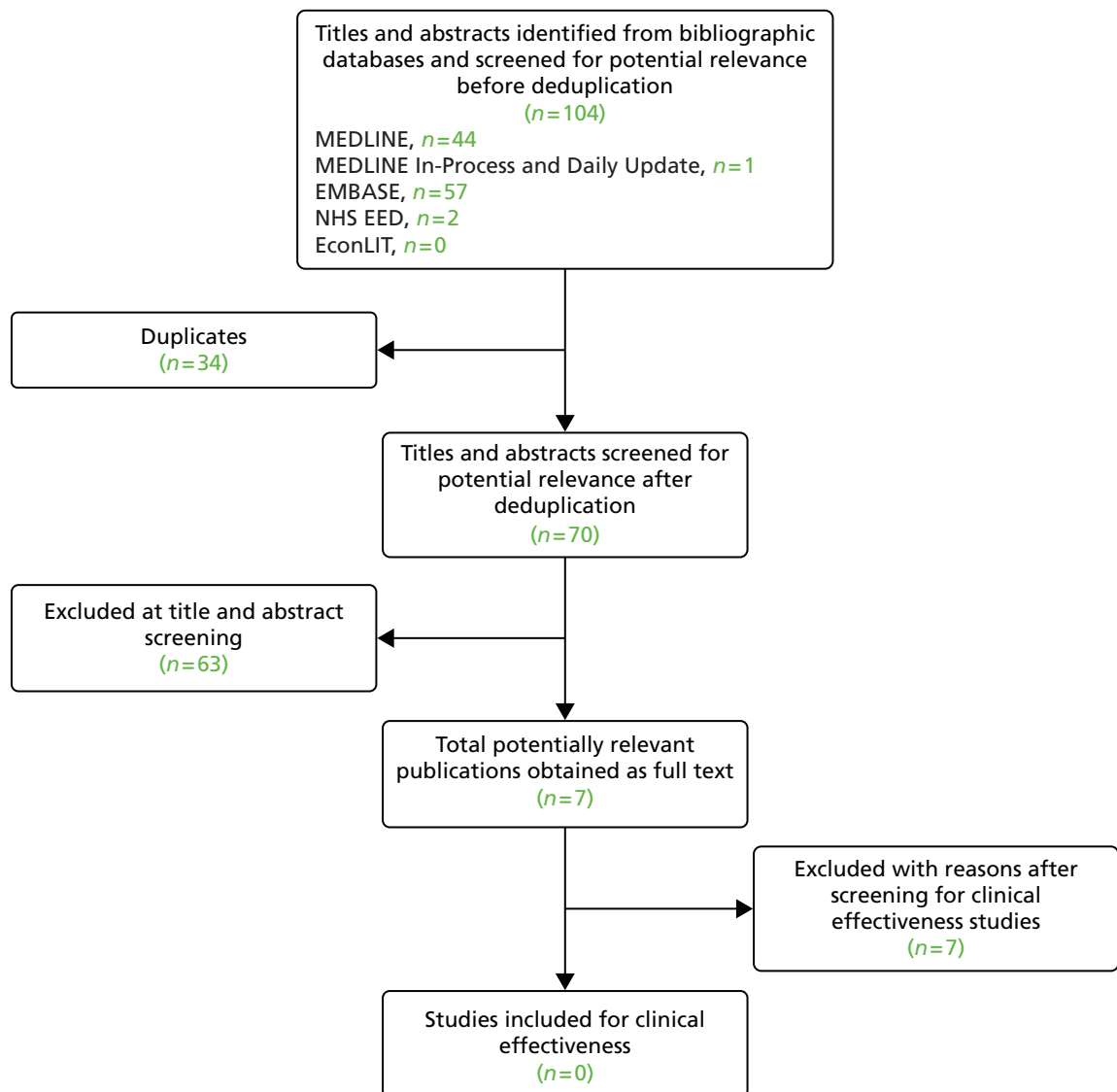
### Methods of analysis/synthesis

Given that no studies met all of the inclusion criteria, a narrative account of the number of studies screened for inclusion and reasons for excluding studies was given.

## Results of cost-effectiveness review

### Summary of inclusion/exclusion

The health economics search identified 104 references before deduplication. Owing to overlap between the databases, 34 duplicate records were removed. The remaining 70 records were screened. Of these, seven were included for the full assessment based on initial screening. After full-text review no studies were included, as presented in *Figure 2*. Six of these seven studies estimated the cost-effectiveness of



**FIGURE 2** Flow of studies through the screening process: cost-effectiveness review.

EVAR compared with OSR for patients with a pararenal AAA who were defined as unsuitable for EVAR<sup>25,34-38</sup> and, thus, these studies were excluded based on the population. Furthermore, five of them,<sup>34-38</sup> were presented at conferences, and these abstracts were not presented in such a way that data could be extracted from it. The other study<sup>39</sup> reported costs of fEVAR, but this was reported without sufficient details and in Canadian dollars.





## Chapter 6 Cost-effectiveness analysis

This chapter will focus on the economic impact of fEVAR and bEVAR. Our objective had been to perform an economic evaluation of these interventions for patients with JRAAs and TAAAs. However, for several reasons it was decided that a CEA evaluating fEVAR and bEVAR was not possible. First, the systematic review assessing the clinical effectiveness (see *Chapter 4*) showed that no comparative study had been done that could provide clinical effectiveness data. Besides the clinical effectiveness, it was also not feasible to obtain valid estimates for the other input parameters. In particular, the stent grafts used vary widely between patients and between centres. The stent grafts used in fEVAR/bEVAR are not a homogeneous product as they are custom made and, therefore, it is difficult to obtain reliable cost estimates for the graft itself. Furthermore, different manufacturers also make these stent grafts and hospitals receive discounts from these manufacturers, leading to even more uncertainty in the costs. The large variation observed also makes it difficult to estimate resource use (besides the stent grafts) based on the opinion of only a few experts. To have any validity, expert opinion should be sought from a large group of experts with fEVAR and bEVAR experience, and this was not feasible within the constraints of this short report. Finally, according to the experts consulted (SV and PH), this intervention is a rapidly changing area and, therefore, an economic evaluation will project the cost-effectiveness of fEVAR and bEVAR only at this moment, and these results will not be valid for the near future. Consequently, this chapter will describe how an economic evaluation could be performed if more data were available. Furthermore, we will provide suggestions for data collection (see *Analyses*).

### Design

An economic evaluation performed for the UK health-care setting usually adopts the NHS perspective, including only direct costs and consequences. Outcomes should be measured in quality-adjusted life-years (QALYs) and life-years (LYs). Costs and outcomes need to be discounted at 3.5% per year<sup>40</sup> and are preferably estimated for a lifetime horizon.

### Population

The population is patients with JRAAs and TAAAs and, thus, are considered unsuitable for EVAR. In fact, there would be two main subgroups: those fit for OSR and those unfit for OSR. Without the existence of the interventions fEVAR or bEVAR, patients would be treated with an OSR if considered to be fit enough. Patients who are not fit for OSR would be treated with no surgery, i.e. medication only. Fitness of patients for an OSR can be determined based on the fitness criteria that were used for the EVAR trials,<sup>41</sup> which evaluated EVAR with either OSR (EVAR 1 trial) or medication (EVAR 2 trial) for the treatment of AAAs depending on the fitness of the patient. Patients were considered unfit for OSR if a patient had (1) an American Society of Anesthesiologists (ASA) grade of IV, (2) cardiac symptoms, (3) renal symptoms or (4) respiratory symptoms. However, it seems that the guidelines for assessing the fitness for OSR are subject to treatment variation. Aneurysm size was also important for determining the fitness of a patient, as patients who were earlier described as 'unfit for open repair' and later developed a larger aneurysm were suddenly deemed 'fit for the procedure'.<sup>42</sup>

## Interventions and comparators

Based on the fitness for OSR, two treatment comparisons for this population should be evaluated: (1) fEVAR/bEVAR compared with OSR and (2) fEVAR/bEVAR compared with no surgery. The surgical procedures are described in *Chapter 3, Intervention* and *Chapter 3, Comparators*. The no-surgery strategy can be defined as optimal conservative care, i.e. patients should receive statins, beta-blockers, antihypertensive agents, antiplatelet drugs, and/or lifestyle advice. Ideally, the cost-effectiveness of fEVAR and bEVAR must be evaluated separately.

## Model structure

To estimate the lifetime cost-effectiveness of fEVAR and bEVAR it is essential that a decision model should be constructed to include all sources of evidence and to extrapolate short-term results. It could be useful to create two separate models, one for short-term outcomes and one for long-term outcomes. The short-term model can be a simple decision tree estimating costs and effects preoperatively (including the effect of waiting time), intraoperatively and postoperatively up to 30 days. A long-term model should be used to estimate the lifetime costs and effects for the individuals who have survived the initial procedure and the 30-day postoperative period. The long-term model structure can be adopted from previously published HTA reports for the evaluation of EVAR by Brown *et al.*<sup>42</sup> and Chambers *et al.*,<sup>43</sup> as it is likely that the treatment and disease pathways of EVAR and fEVAR or bEVAR are comparable, even if the input parameters are not. See *Appendix 3* for the quality of these studies based on the Drummond and Jefferson checklist.<sup>44</sup>

### *Short-term model (fit for open surgical repair)*

It is likely that patients have to wait until the actual surgery can be performed. In particular, patients who will be treated with fEVAR or bEVAR have to wait as a large proportion of the patients will have to wait for custom-made devices while the inventory of off-the-shelf devices is expanding. The inclusion of *waiting time* in the model is deemed to be important as a difference in waiting time could lead to differences in mortality. It might also lead to a reduction in quality of life during this time period, although this might be difficult to measure.

Patients who actually receive fEVAR or bEVAR may be converted to an OSR because of, for example, an endoleak or stent graft migration. It is important that these *conversions* are incorporated into the model. Chambers *et al.*<sup>43</sup> assumed that a conversion takes place during the time span of the short-term model. In their model, conversion from OSR to EVAR was not included as it is unlikely and the EVAR 1 trial showed that none of the OSR patients were converted.<sup>45</sup>

Furthermore, *mortality* (all-cause and aneurysm related) and *complications* during the first 30 days need to be incorporated in the short-term model, if a difference between interventions exists. Complications can be categorised into four types: cardiac complications [e.g. myocardial infarction (MI)], pulmonary complications (e.g. respiratory failure), renal complications (e.g. renal failure) and neurological complications (e.g. stroke). Furthermore, it is important that reinterventions are also incorporated into the model because EVAR is associated with more reinterventions than OSR<sup>46</sup> for standard EVAR and, thus, it is possible that the same may be true for fEVAR/bEVAR. A reintervention for patients who underwent fEVAR or bEVAR could either be an OSR or, again, an endovascular procedure.

*Figure 3* shows a possible structure for a short-term decision model for this comparison. Reinterventions are included as complications.

The disease progression of patients who have survived the initial preoperative and postoperative days can be simulated with the long-term model. Furthermore, for patients who have suffered from complications such as (disabling) stroke it could be useful to use an additional model or disease state to estimate their

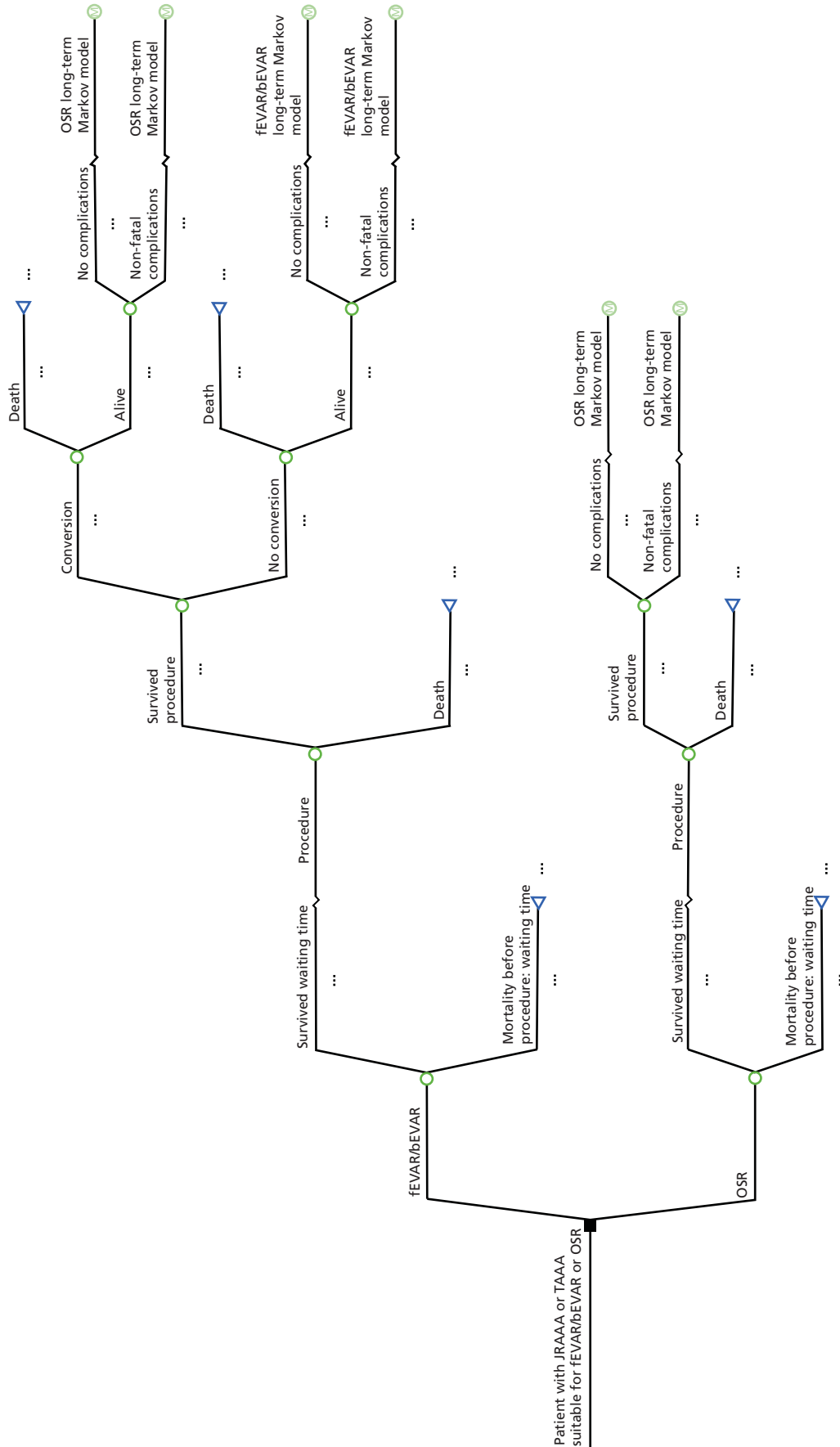


FIGURE 3 Short-term decision model: fit for surgery.

lifetime costs and QALYs as those patients often generate more costs and have a lower quality of life than the rest of the population.

### Short-term model (unfit for OSR)

The same suggestions as described above for those fit for OSR apply for this comparison, although waiting time is not an issue for patients treated with medication only and conversion from fEVAR or bEVAR to OSR might not be possible as patients are considered not fit for OSR. However, conversions to OSR could be possible when serious complications occur during fEVAR/bEVAR or the aneurysm has been ruptured before the planned fEVAR/bEVAR takes place. *Figure 4* shows a possible structure for a short-term decision model for this comparison.

### Long-term model

The long-term model should estimate lifetime costs and effects of patients who have survived the waiting time before the procedure and the 30-day postoperative period. For such a long-term model, a Markov model would be most appropriate. This model could consist of two chronic health states: (1) event-free and (2) (non-)aneurysm-related death and this structure is similar to the economic evaluation of EVAR compared with OSR presented by Chambers *et al.*<sup>43</sup> Patients start out in the event-free state and are exposed to the risk of experiencing a non-fatal event. Patients could be readmitted to the hospital if, for example, a reintervention is required. Note that the readmission state is a temporary health state: after the readmission, patients move back to the event-free state. Eventually, all patients will die from aneurysm-related causes or from non-aneurysm-related causes. *Figure 5* shows this structure. It could be useful to include an additional state if there is a difference in non-fatal complications (e.g. stroke) that have a substantial impact on the quality of life of patients. Furthermore, the impact of radiation of the CT scans used during follow-up and of the fluoroscopy used during the interventions could be incorporated in the model if this is deemed important. However, the mean age of the patients included in the EVAR 1 trial<sup>46</sup> is relatively high ( $74.1 \pm 6.1$  years) and, thus, the impact of radiation on the incremental costs and effects will probably be negligible.

The cycle length needs to be short enough so that an event occurs at most once per cycle.<sup>47</sup> A cycle length of 6 months could be considered as appropriate according to the timing of the events as used by Brown *et al.*<sup>42</sup> A half-cycle correction needs to be incorporated when it is unknown when in the cycle a transition occurs.<sup>47</sup>

### Assumptions regarding model structure

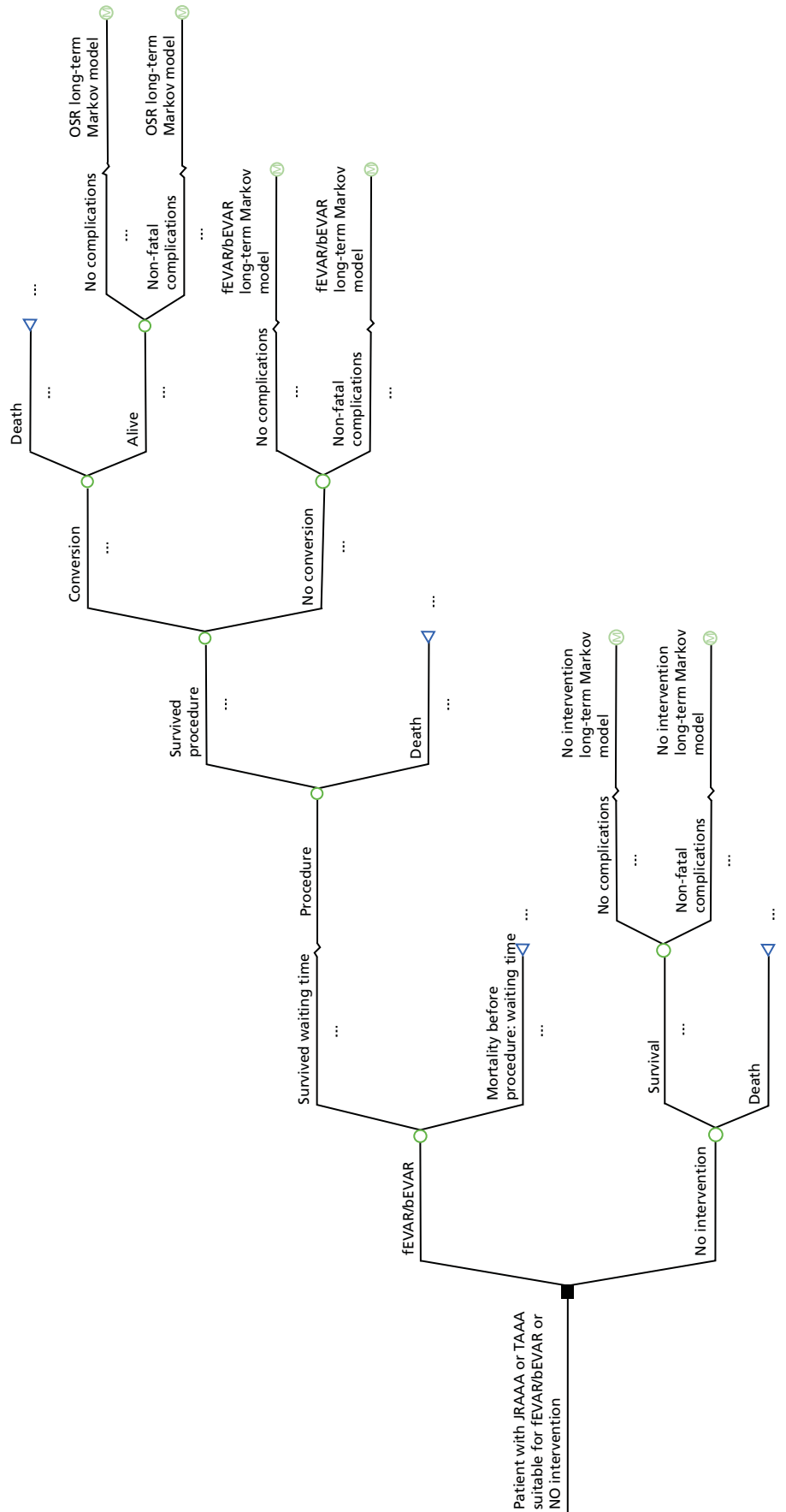
The assumptions detailed below can be made when data are lacking.

#### Conversion

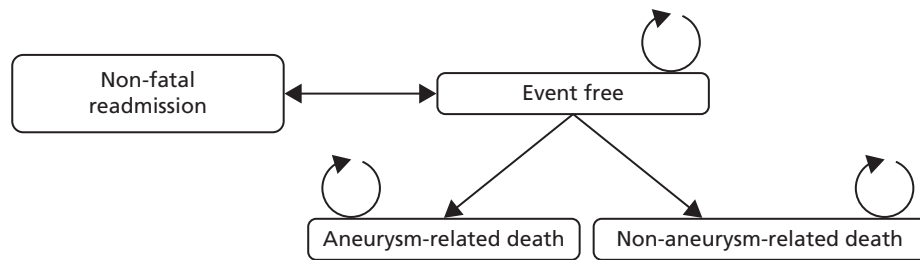
In the economic evaluation by Chambers *et al.*,<sup>43</sup> it was assumed that patients who convert from EVAR to OSR during the primary admission have the same long-term prognosis as patients initially undergoing OSR. We would suggest using the same assumption if follow-up data are not available. Furthermore, they assumed that patients treated initially with EVAR could only convert to OSR before entering the long-term model and, thus, assumed that conversions take place in the first 30 days post procedure. A recent systematic review showed that 1.5% of the patients treated with EVAR will undergo a conversion to OSR in the first 30 days.<sup>48</sup> For late conversion, this is estimated at 2% and, ideally, both late and early conversions are incorporated in the models.

#### Complications

Brown *et al.*<sup>42</sup> did not incorporate clinical events such as MI or stroke in the model as there was no significant difference between the treatment strategies (OSR vs. EVAR) in the randomised controlled trial (RCT). This assumption might be valid for the evaluation of EVAR. However, the results of clinical studies will show if this assumption also holds for an economic evaluation of fEVAR or bEVAR compared with OSR or no surgery. Moreover, a RCT is likely to be underpowered to find significant effects for these events. Generally, when these events are considered clinically relevant, they should be included in the long-term model.



**FIGURE 4** Short-term decision model: unfit for surgery.



**FIGURE 5** Long-term Markov model.

### Extrapolation of treatment clinical effectiveness

Clinical studies showed that EVAR was associated with lower perioperative mortality than OSR, but the risk of late AAA mortality and reinterventions was higher in patients treated with EVAR.<sup>46</sup> However, how the difference in mortality between treatments develops over time is uncertain. Brown *et al.*<sup>42</sup> assumed in the base-case analysis that there is no difference in the rate of AAA deaths between treatments after 8 years, because the risk of AAA death diminishes over time. Chambers *et al.*<sup>43</sup> used a constant hazard ratio (1.072) for non-aneurysm-related death for EVAR compared with OSR until the non-aneurysm-related survival curves converged.

## Input parameters

### Transition probabilities

For the short-term model (see *Figures 3 and 4*) it is important to collect data in the period before the treatment and up to 30 days after the procedure. Data concerning mortality, conversions, reinterventions and complications (cardiac, pulmonary, renal, neurological) are important for this model. The structure of the long-term model (see *Figure 5*) requires three time-dependent transition probabilities: (1) non-aneurysm-related mortality, (2) aneurysm-related mortality and (3) non-fatal readmissions. These transition probabilities need to be based on general population mortality estimates (non-aneurysm-related mortality) and on clinical effectiveness data from comparative studies.

*Chapter 4*, evaluating the clinical effectiveness, showed that there were no comparative studies of fEVAR/bEVAR in either those fit or unfit for OSR. Treatment allocation was often not based on chance and, therefore, patient groups were not comparable (i.e. age and comorbidities).<sup>31</sup> Thus, we have no source of information on the efficacy of fEVAR/bEVAR in preventing mortality and serious complications.

An additional literature search was performed to identify studies that may assist in developing a cost-effectiveness model for fEVAR and bEVAR, i.e. studies that provide information on the many input parameters of a model (see *Appendix 4*).

Ideally, a multicentre RCT of UK patients anatomically unsuitable for EVAR should be conducted to have an unbiased estimate of the clinical effectiveness, while simultaneously providing data on costs and quality of life of those patients treated with fEVAR/bEVAR/OSR or no surgery. Several authors have suggested that a RCT could be necessary to obtain robust estimates for the clinical effectiveness.<sup>32,33,49</sup> However, if a RCT is not possible then a prospective controlled study would be necessary. As in the EVAR trials (EVAR 1 and EVAR 2) it would probably be necessary to conduct two separate trials evaluating two comparisons based on the fitness for OSR: (1) fEVAR or bEVAR compared with OSR and (2) fEVAR or bEVAR compared with no surgery. At least a follow-up of 60 months might be necessary as it seems that the survival of patients treated with EVAR or OSR is comparable after 60 months (see *figure 71* in Chambers *et al.*<sup>43</sup>).

Mortality should also be measured during any waiting time as this could have an impact on the clinical effectiveness of fEVAR and bEVAR. For the model, important *baseline characteristics* of the patients that (at least) should be collected in such a trial are age, sex, aneurysm size, comorbidities, ASA grade, fitness for surgery, smoking status, body mass index, diabetes, systolic blood pressure, diastolic blood pressure, medication history, serum creatinine and serum cholesterol. These baseline characteristics can be used in regression analyses to estimate transition probabilities and long-term costs. As institutional characteristics may be of predictive value as well, these should also be collected.

Extrapolation of the trial results will be necessary because the time horizon of the model will be longer than that of the follow-up of the RCT to capture all differences in costs and effects between treatments. Crucial assumptions concerning survival have to be made when data are lacking. The impact of these assumptions on the cost-effectiveness needs to be explored through sensitivity analyses.

### Costs

When the cost-effectiveness of fEVAR or bEVAR is evaluated for the UK, it is preferred to use the NHS perspective, i.e. direct medical costs. Alongside any prospective controlled study, resource use of patients should be collected. For the short-term model, it is important that valid resource use estimates (e.g. theatre time or blood products) of the procedures are estimated. When a societal perspective is used, it is important that indirect costs (productivity costs, travel costs) are also estimated using diaries.

For unit costs routine, NHS sources (e.g. NHS reference cost, Personal Social Services Research Unit, *British National Formulary*) should be used and this could be supplemented by expert opinion. *Table 2* shows the resource use and unit costs that need to be collected.

*Tables 3* and *4* present estimates of some of the key parameters identified in *Table 2*. This overview is based on the five clinical studies that were identified in the clinical effectiveness review (see *Chapter 4, Summary of reasons for exclusions*) that reported these resource use items. Note that these studies were excluded from the clinical effectiveness review because of selective treatment assignment. Thus, it is crucial to realise that these values should not be used for an economic model without adjustments; instead, they should be seen as indicative for which parameters might differ between treatments.

### Outcomes

The outcomes of interest for the model are LYs and QALYs. LYs are directly estimated in the model using the number of years that patients live after each intervention. Then LYs can be combined with quality-of-life estimates to obtain the number of QALYs for each intervention. It is important to obtain quality-of-life data alongside a prospective controlled study in order to assess differences in QALYs between a minimally invasive procedure (fEVAR/bEVAR) compared with an invasive procedure (OSR) and also to compare fEVAR/bEVAR with no procedure. Quality of life was measured with the European Quality of Life-5 Dimensions (EQ-5D™) alongside the EVAR 1 and 2 trials (*Tables 5* and *6*). These values might also be appropriate for patients with JRAAs or TAAAs as it is likely that these patients have the same quality of life as patients with AAAs. However, ideally quality-of-life measurements should be performed alongside any prospectively controlled study, preferably with the EQ-5D or another instrument that allows valuation of health.<sup>40</sup> Importantly, these patients will receive at least the questionnaire at randomisation (preoperative) and at several time points in the first postoperative year (e.g. 30 days, 6 months, 12 months) depending on the cycle length of the model. Furthermore, it would be useful if the quality of life was also measured after the first postoperative year.

If a societal perspective is adopted it is important to estimate care-related quality of life in informal caregivers based on, for example, the CarerQol questionnaire.<sup>50</sup>

TABLE 2 Cost data required for the CEA

Category	Resource use	Unit costs
<b>Procedure<sup>a</sup></b>		
Preoperative embolisation	–	Per procedure
Cardiopulmonary bypass and reperfusion	–	Per procedure
Theatre time	Minutes	Per minute
Preoperative stay	Days	Per day
ICU stay	Days	Per day
High-dependency unit stay/coronary care unit	Days	Per day
Ward stay	Days	Per day
Red blood cell	Units	Per unit
Platelets	Units	Per unit
Fresh-frozen plasma	Units	Per unit
Fluoroscopic time	Minutes	Per minute
Contrast	ml	Per ml
Device and consumables	–	Actual and list prices
<b>Medication use</b>		
Statins	mg	Per mg
Antiplatelet	mg	Per mg
Anticoagulant	mg	Per mg
Beta-blocker	mg	Per mg
Antihypertensive	mg	Per mg
<b>Follow-up<sup>b</sup></b>		
Outpatient visits	Number of visits	Per visit
CT scan	Number of scans	Per scan
<b>Indirect costs<sup>c</sup></b>		
Productivity costs	–	–
Travel costs	–	–
<b>Complications<sup>d</sup></b>		
ICU stay	Days	Per day
High-dependency unit stay	Days	Per day
Ward stay	Days	Per day
Outpatient visit	Visits	Per visit
Emergency room visit	Visits	Per visit
Procedures <sup>e</sup>	–	Per procedure

ICU, intensive care unit.

a Primary intervention, conversions to OSR and reinterventions. Including complications during primary admission.

b One year and subsequent years.

c Societal perspective.

d Cardiovascular complications, renal complications, pulmonary complications and neurological complications. The resource use should be measured of each complication separately.

e This will depend on the complication.



**TABLE 3** Estimates of key parameters to estimate the costs of OSR

Parameter	Min.	Max.	Mean	Source
Mean theatre time (minutes)	89	150	120	Donas <i>et al.</i> , <sup>29</sup> Chisci <i>et al.</i> <sup>31</sup>
Median theatre time (minutes)	–	–	235	Canavati <i>et al.</i> <sup>32</sup>
Mean blood loss (ml)	–	–	3436	Vallabhaneni <i>et al.</i> <sup>30</sup>
Median blood loss (ml)	1550	2000	1775	Chisci <i>et al.</i> , <sup>31</sup> Canavati <i>et al.</i> <sup>32</sup>
Mean stay (days)	7.2	21.7	14.0	Donas <i>et al.</i> , <sup>29</sup> Vallabhaneni <i>et al.</i> , <sup>30</sup> Chisci, <i>et al.</i> <sup>31</sup>
Median stay (days)	–	–	12	Canavati <i>et al.</i> <sup>32</sup>
Mean ICU stay (days)	7.4	29.3	18.3	Vallabhaneni <i>et al.</i> , <sup>30</sup> Canavati <i>et al.</i> <sup>32</sup>
Median ICU stay (days)	–	–	28	Canavati <i>et al.</i> <sup>32</sup>

ICU, intensive care unit; max., maximum; min., minimum.

**TABLE 4** Estimates of key parameters to estimate the costs of fEVAR/bEVAR

Parameter	Min.	Max.	Mean	Source
Mean theatre time (minutes)	266	290	278	Donas <i>et al.</i> , <sup>29</sup> Chisci <i>et al.</i> <sup>31</sup>
Median theatre time (minutes)	–	–	300	Canavati <i>et al.</i> <sup>32</sup>
Mean blood loss (ml)	–	–	370	Vallabhaneni <i>et al.</i> <sup>30</sup>
Median blood loss (ml)	500	1250	875	Chisci <i>et al.</i> , <sup>31</sup> Canavati, <i>et al.</i> <sup>32</sup>
Mean fluoroscopy time (minutes)	54	88	71	Donas <i>et al.</i> , <sup>29</sup> Chisci <i>et al.</i> <sup>31</sup>
Mean contrast (ml)	156	288	222	Donas <i>et al.</i> , <sup>29</sup> Chisci <i>et al.</i> <sup>31</sup>
Mean stay (days)	3.5	10.5	7.2	Donas <i>et al.</i> , <sup>29</sup> Vallabhaneni <i>et al.</i> , <sup>30</sup> Chisci <i>et al.</i> <sup>31</sup>
Median stay (days)	–	–	7	Canavati <i>et al.</i> <sup>32</sup>
Mean ICU stay (days)	0.9	6.2	3.6	Vallabhaneni <i>et al.</i> , <sup>30</sup> Canavati <i>et al.</i> <sup>32</sup>
Median ICU stay (days)	–	–	4	Canavati <i>et al.</i> <sup>32</sup>

ICU, intensive care unit; max., maximum; min., minimum.

**TABLE 5** Quality-of-life estimates (EQ-5D) EVAR 1 trial

Time point	EVAR (N = 543)			OSR (N = 539)		
	Mean	SD	n	Mean	SD	n
Baseline	0.75	0.22	541	0.74	0.23	531
0–3 months <sup>a</sup>	0.73	0.21	238	0.67	0.25	245
3–12 months <sup>a</sup>	0.71	0.25	476	0.73	0.23	414
12–24 months <sup>a</sup>	0.74	0.24	398	0.75	0.25	371

SD, standard deviation.  
a Post operation.

**TABLE 6** Quality-of-life estimates (EQ-5D) EVAR 2 trial

Time point	EVAR (N = 166)			No surgery (N = 172)		
	Mean	SD	n	Mean	SD	n
Baseline	0.58	0.31	164	0.63	0.28	171
0–3 months <sup>a</sup>	0.57	0.28	48	0.56	0.29	92
3–12 months <sup>a</sup>	0.64	0.28	122	0.60	0.26	120
12–24 months <sup>a</sup>	0.65	0.24	88	0.60	0.30	68

SD, standard deviation.  
a Post operation.

## Analyses

### Base case

The base-case analysis should report the (incremental) cost-effectiveness of fEVAR/bEVAR compared with OSR and fEVAR/bEVAR compared with no surgery in both disaggregated and aggregated forms.

### Subgroup analyses

Important subgroups can be determined by age, sex, whether or not dialysis dependent, aneurysm size, fitness, number of target vessels, whether elective or emergency and symptomatic compared with non-symptomatic as these characteristics may have a substantial impact on the cost-effectiveness. Furthermore, the type of OSR could also be used to determine subgroups as these differ in perioperative mortality.<sup>32</sup>

### Sensitivity analyses

The impact of parameters such as the costs of the endovascular procedures and 30-day mortality on the cost-effectiveness of fEVAR or bEVAR should be evaluated in a univariate sensitivity analysis. Scenario analyses estimating the influence of late non-aneurysm mortality estimates and late aneurysm mortality on the cost-effectiveness should be performed. Furthermore, it could be useful to conduct best- and worse-case scenario analyses and to produce tornado diagrams. Probabilistic sensitivity analysis should be performed to estimate parameter uncertainty and cost-effectiveness acceptability curves could be very informative. Lastly, structural uncertainty should be addressed by varying structural assumptions (e.g. disease progression of patients who are converted from fEVAR/bEVAR to OSR).

## Chapter 7 Discussion

### Clinical effectiveness findings

The question regarding the clinical effectiveness and safety of fEVAR and bEVAR in comparison with conventional treatment was the primary aim of this project and, given that no studies met all of the inclusion criteria, it still remains unanswered. In the past, other systematic reviews have compared the clinical effectiveness and safety of fEVAR technology with OSR. However, none of them found any RCTs or any comparative studies to answer this question. A systematic review by Nordon *et al.*<sup>51</sup> reported that non-RCTs were identified and they included eight cohort studies reporting 368 fEVAR cases and 12 cohort studies reporting 1164 OSRs of JRAAs. One systematic review by Cross *et al.*<sup>52</sup> identified 11 fEVAR studies describing 660 procedures with no comparison. However, this study also acknowledged in its conclusions that 'there are currently no controlled trials comparing fEVAR with OSR, and current evidence is weak with many unanswered questions'.<sup>52</sup>

Another systematic review included five single-arm studies on fEVAR and seven studies on OSR (one prospective and six retrospective).<sup>4</sup> They also identified and included a study in the form of an abstract that compared the results of fEVAR with those of OSR. However, this study was not included in our systematic review because it was clear that the study was non-comparative. First, the groups were not comparable at baseline in that patients in the fEVAR group were older than patients in the OSR group (mean age  $77.6 \pm 6.0$  years vs.  $69.6 \pm 8.0$  years) and had a significantly greater incidence of severe cardiac and pulmonary comorbidities and diabetes.<sup>4</sup> Second, all of the other studies that we screened at full paper stage that were described as comparative turned out to be non-comparative in that they selected based on prognostic characteristics, i.e. they assigned younger, fitter patients to OSR and older, high-risk patients to fEVAR. This was also supported by the baseline characteristics in those excluded studies (see *Chapter 6, Design*). This was not evident from the title and abstract and could be ascertained only by going through the full article in detail.

A Dutch CvZ report, published in 2012, described a systematic review on the endovascular treatment of complex aneurysms of the aorta.<sup>18</sup> The CvZ report concluded that evidence in the form of comparative research, not necessarily randomised, is feasible and required to make a judgement about the clinical effectiveness and safety of interventions such as fEVAR and bEVAR. This was in line with our understanding of the topic that at least a well-conducted comparative study wherein participants are not assigned to a certain intervention by clinicians based on prognostic characteristics (age, fitness and comorbidities) is essential to answer this question. Neither this systematic review nor the CvZ review identified any relevant comparative studies.

Interestingly, all of the apparent comparative studies used the same method of selection, i.e. to allocate those patients with the poorest prognosis to fEVAR or bEVAR. This is unsurprising as publications to date largely reflect the introduction and early evolution of the techniques, which are applicable only to a relatively small proportion of all aneurysm patients and in a much smaller number of centres than OSR is available. It would have been negligent in the early days of fEVAR and bEVAR to offer the then new and unproven technique to patients for whom a proven technique, viz. OSR, is an option with acceptable operative risk. Given that these patients are probably not suitable for OSR, OSR is not the correct comparator, i.e. no surgery would be appropriate. Of course, it might be considered unethical to allocate such people to no surgery and, therefore, the most useful comparison would be between fEVAR or bEVAR and OSR, but in the younger fitter population.

## Cost-effectiveness findings

The systematic review of cost-effectiveness found no economic studies of fEVAR or bEVAR. In addition, because of the lack of clinical effectiveness data and the difficulty in obtaining reliable cost data given huge variation in the nature of procedures between centres and the likely rapid change in technology, it was decided not to perform a CEA. Instead, the methods for performing the analysis as well as the data that would be required have been described. This includes those data that ideally would come from a RCT in each of two populations (those fit enough and those not fit enough for OSR) that would inform two distinct models.

## Strengths and limitations of the clinical effectiveness review

### Strengths

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying studies in this topic no study design search filters were used and search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened. Despite this, none of them met the inclusion criteria of the review.

Clear inclusion criteria were specified in the protocol for this review. Eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for excluding any of the studies considered potentially relevant at initial citation screening. The review process followed recommended methods to minimise the potential for error and/or bias; two reviewers independently screened studies for inclusion and any disagreements were resolved by consensus. Moreover, no previous reviews identified any relevant studies either.

### Limitations

Despite efforts to include evidence, it should be noted that no RCTs were identified and the studies reporting comparative data did not have comparative groups at baseline because all of them selectively assigned patients to the intervention and comparator groups.

## Strengths, limitations and uncertainties of the cost-effectiveness analysis

As for the review of clinical effectiveness, extensive searches were undertaken. Given that no de novo CEA could be conducted, whether fEVAR or bEVAR are cost-effective remains uncertain. However, the current report gives a clear model structure that can be used to inform decisions about which data should be collected, and can be a first step in the development of a final model once data collection has taken place.

## Conclusions

The systematic review of clinical effectiveness studies showed that no comparative study has been done that could provide reliable clinical effectiveness data. All studies that compared either fEVAR or bEVAR with either OSR or no surgery explicitly selected patients based on prognosis, i.e. essentially the populations for each comparator were not the same. Therefore, it was decided that a CEA evaluating fEVAR and bEVAR was not possible. Consequently, we decided to describe how an economic evaluation could be performed if more data were available. This includes those data that ideally would come from a RCT in each of two populations, those fit enough and those not fit enough for OSR, which would inform two distinct models.

## Suggested research priorities

Given that no studies met the inclusion criteria, there is clearly much uncertainty in all outcomes, including probability of technical success (target vessel perfusion), risk of death, durability (risk of relapse), risk of adverse events and quality of life. Therefore, there is clearly a need for a RCT, or at least a well-conducted prospective cohort study with proper comparability at baseline and statistical techniques to adjust for potential confounding. Also, we recommend that this should be at least in the population of younger, fitter patients, i.e. those for whom OSR is suitable, in order answer the question whether fEVAR or bEVAR is clinically effective or cost-effective in comparison with OSR. Ideally, there should also be one RCT for each of fEVAR and bEVAR and consideration should also be given for separate trials in the non-OSR eligible population. Ideally such a trial will be long enough to identify any patients who develop longer-term problems such as renal failure.

When considering a RCT evaluating fEVAR/bEVAR, Canavati *et al.*<sup>32</sup> has identified that it can be a challenge to include a sufficient number of patients so that subgroup analyses with enough statistical power can be performed. Subgroup analyses are important as there will be a large variation in both procedures but especially in open procedures for this indication leading to variation in operative risk. Greenberg *et al.*<sup>33</sup> has also raised the challenge of including sufficient patients. We therefore recommend a multicentre study. However, Greenberg *et al.*<sup>33</sup> also recognised the challenge of disseminating endovascular skills and the rapid technology improvements that occur for branched devices. It is important to keep in mind that a learning effect can exist and this can negatively influence the perioperative mortality of these procedures. Verhoeven *et al.*<sup>49</sup> have recognised this problem and suggested that a learning curve has to be taken into account because half of the occlusions in non-stented fenestrations or scallops occurred in fEVAR interventions that were performed in the early stage. Second, therefore, we recommend strict criteria in terms of surgeon experience, centre experience (e.g. 50 fEVAR and/or 25 bEVAR procedures in the last 3 years), type of stent graft and OSR technique. Also, a 'tracker trial', i.e. one where the intervention is allowed to change with improvements in technology, might be considered.<sup>53</sup> Ideally, subgroup analysis could also be undertaken to investigate the effect of risks such as aneurysm size and presence of comorbidities.

In addition, given the inability to conduct a CEA, due largely to the lack of clinical effectiveness data, we recommend that one be conducted alongside any RCT or other prospective cohort study. Ideally, in order to take into account both the short- and long-term economic consequences, this ought to be constructed as a model as described in *Chapter 6*. Furthermore, in designing the prospective study, there is the opportunity to collect primary data to inform such a model, such as resource use and utilities, as specified in detail in *Chapter 6*.



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**D**iana Hilmer devised and performed the literature searches and provided information support to the project.

## Contributions of authors

**Nigel Armstrong** and **Sohan Deshpande** planned and performed the systematic review and the interpretation of evidence.

**Laura Burgers** and **Maiwenn Al** planned and performed the cost-effectiveness review, and researched and reported the CEA methods.

**Rob Riemsma**, **Johan Severens** and **Jos Kleijnen** provided senior advice and support to the systematic review and CEA sections, respectively.

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# Appendix 1 Search strategies

## Rapid appraisal

### *Cochrane Database of Systematic Reviews (CDSR; Wiley)*

Searched up to issue 7: 2013.

### *Database of Abstracts of Reviews of Effects (DARE; Wiley)*

Searched up to issue 3: 2013.

### *Health Technology Assessment (HTA) Database (Wiley)*

Searched up to issue 3: 2013.

Searched 19 August 2013.

#1 ((juxta-renal or juxtarenal or pararenal or para-renal or thoraco-abdominal or thoracoabdominal or thoracic abdominal) near/5 aneurysm\*):ti,ab,kw (42)

#2 Medical subject heading (MeSH) descriptor: [Aortic Aneurysm, Thoracic] this term only (76)

#3 MeSH descriptor: [Aortic Aneurysm, Abdominal] this term only (554)

#4 (JRA or JRAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs):ti,ab (47)

**#5 #1 or #2 or #3 or #4 (671)**

CDSR search retrieved nine records.

Cochrane DARE search retrieved 80 records.

HTA Database search retrieved 50 records.

### *International Guidelines Network Library*

URL: [www.g-i-n.net](http://www.g-i-n.net)

Searched up to 18 August 2013.

Searched 19 August 2013.

Terms searched	Hits
Free text: juxtarenal AND aneurysm	0
Free text: juxta-renal AND aneurysm	0
Free text: pararenal AND aneurysm	0
Free text: para-renal AND aneurysm	0
Free text: thoraco-abdominal AND aneurysm	0
Free text: thoracoabdominal AND aneurysm	0
Free text: thoracic AND abdominal AND aneurysm	0
Free text: JRA	0
Free text: PAAA	0
Free text: TAAA	0
Free text: JPAA	0
Total (prior to deduplication)	0
Total (after to deduplication)	0

### ***National Guidelines Clearinghouse (internet)***

URL: [www.guideline.gov/](http://www.guideline.gov/)

Searched up to 18 August 2013.

Searched 19 August 2013.

#### **Advanced search**

Terms searched	Hits
((juxta-renal or juxtarenal or pararenal or para-renal or thoraco-abdominal or thoracoabdominal or thoracic abdominal) and aneurysm*)	17
Total	17

### ***National Institute for Health Research Health Technology Assessment (internet)***

URL: [www.hta.ac.uk](http://www.hta.ac.uk)

Searched 19 August 2013.

Browsed by relevant terms found three references.



**International Prospective Register of Systematic Reviews (PROSPERO)**URL: [www.crd.york.ac.uk/prospero/](http://www.crd.york.ac.uk/prospero/)

Searched up to 19 August 2013.

Searched 19 August 2013.

Terms searched	Hits
Free text: juxta-renal	0
Free text: juxtarenal	0
Free text: aneurysm	9
Total	9

**Food and Drug Administration**URL: [www.fda.gov/](http://www.fda.gov/)

Searched up to 20 August 2013.

Searched 20 August 2013.

Medical devices tab.

Terms searched	Hits
Endovascular aneurysm	36
Total	36

**Medicines and Healthcare products Regulatory Agency**URL: [www.mhra.gov.uk/](http://www.mhra.gov.uk/)

Searched up to 20 August 2013.

Searched 20 August 2013.

Full-text search: with all these words.

Terms searched	Hits
Juxta-renal	0
Juxtarenal	0
Endovascular aneurysm	9
Total	9

## Clinical effectiveness

### *MEDLINE (OvidSP): 1946 to week 3 September 2013*

Searched 1 October 2013.

1. aortic aneurysm/ (17,850)
2. Aortic aneurysm, abdominal/ (13,424)
3. Aortic aneurysm, thoracic/ (8062)
4. or/1-3 (37,735)
5. (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal or thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck\$ or shortneck\$).ti,ab,ot,hw. (9228)
6. 4 and 5 (2621)
7. ((juxta-renal or juxtarenal) adj5 aneur?sm\$).ti,ab,ot,hw. (194)
8. ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm\$).ti,ab,ot,hw. (1620)
9. ((pararenal or para-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (83)
10. ((suprarenal or supra-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (227)
11. ((short-neck\$ or shortneck\$) adj5 aneur?sm\$).ti,ab,ot,hw. (15)
12. (visceral aortic segment\$ adj5 aneur?sm\$).ti,ab,ot,hw. (3)
13. or/7-12 (2001)
14. (JRAAA or JRAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1327)
15. aneur?sm\$.ti,ab. (82,158)
16. 14 and 15 (285)
17. 6 or 13 or 16 (2829)
18. animals/ not (animals/ and humans/) (3,941,632)
19. 17 not 18 (2684)
20. letter.pt. (800,927)
21. editorial.pt. (333,488)
22. historical article.pt. (299,119)
23. or/20-22 (1,419,104)
24. **19 not 23 (2604)**

### *MEDLINE In-Process & Other Non-indexed Citations (OvidSP) and MEDLINE Daily Update (OvidSP): up to 30 September 2013*

Searched 1 October 2013.

1. aortic aneurysm/ (17)
2. Aortic aneurysm, abdominal/ (16)
3. Aortic aneurysm, thoracic/ (11)
4. or/1-3 (43)
5. (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal or thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck\$ or shortneck\$).ti,ab,ot,hw. (622)
6. 4 and 5 (2)
7. ((juxta-renal or juxtarenal) adj5 aneur?sm\$).ti,ab,ot,hw. (23)
8. ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm\$).ti,ab,ot,hw. (84)
9. ((pararenal or para-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (5)
10. ((suprarenal or supra-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (10)
11. ((short-neck\$ or shortneck\$) adj5 aneur?sm\$).ti,ab,ot,hw. (4)
12. (visceral aortic segment\$ adj5 aneur?sm\$).ti,ab,ot,hw. (0)
13. or/7-12 (120)

14. (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (77)
15. aneur?sm\$.ti,ab. (5216)
16. 14 and 15 (17)
17. 6 or 13 or 16 (122)
18. animals/ not (animals/ and humans/) (2696)
19. 17 not 18 (122)
20. letter.pt. (24,401)
21. editorial.pt. (14,519)
22. historical article.pt. (132)
23. or/20-22 (39,033)
24. **19 not 23 (121)**

### EMBASE (OvidSP): 1974 to 4 September 2013

Searched 5 September 2013.

1. Juxtarenal aneurysm/ (14)
2. Juxtarenal aortic aneurysm/ (20)
3. Juxtarenal abdominal aortic aneurysm/ (8)
4. ((juxta-renal or juxtarenal) adj5 aneur?sm\$).ti,ab,ot,hw. (281)
5. thoracoabdominal aneurysm/ (55)
6. Thoracoabdominal aortic aneurysm/ (9)
7. Thoracoabdominal aorta aneurysm/ (254)
8. ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm\$).ti,ab,ot,hw. (2127)
9. Pararenal aortic aneurysm/ (11)
10. ((pararenal or para-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (120)
11. Suprarenal aortic aneurysm/ (2)
12. ((suprarenal or supra-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (284)
13. ((short-neck\$ or shortneck\$) adj5 aneur?sm\$).ti,ab,ot,hw. (36)
14. (visceral aortic segment\$ adj5 aneur?sm\$).ti,ab,ot,hw. (5)
15. or/1-14 (2643)
16. (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1805)
17. aneur?sm\$.ti,ab. (107,498)
18. 16 and 17 (408)
19. 15 or 18 (2669)
20. animal/ (1,886,529)
21. animal experiment/ (1,712,212)
22. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5,802,448)
23. or/20-22 (5,802,448)
24. exp human/ (14,928,364)
25. human experiment/ (315,976)
26. or/24-25 (14,929,805)
27. 23 not (23 and 26) (4,626,466)
28. 19 not 27 (2564)
29. Letter.pt. (839,238)
30. Editorial.pt. (446,547)
31. Note.pt. (582,792)
32. or/29-31 (1,868,577)
33. **28 not 32 (2414)**

*Cochrane Central Register of Controlled Trials (Wiley): up to Issue 8: 2013*

Searched 1 October 2013.

1. MeSH descriptor: [Aortic Aneurysm] this term only (118)
2. MeSH descriptor: [Aortic Aneurysm, Abdominal] this term only (556)
3. MeSH descriptor: [Aortic Aneurysm, Thoracic] this term only (77)
4. #1 or #2 or #3 (736)
5. (juxta renal or juxtarenal or thoraco abdominal or thoracoabdominal or thoracic abdominal or pararenal or para renal or suprarenal or supra renal or short neck\* or shortneck\*):ti,ab,kw (1231)
6. #4 and #5 (52)
7. ((juxta renal or juxtarenal) near/5 aneur?sm\*):ti,ab,kw (5)
8. ((thoraco abdominal or thoracoabdominal or thoracic abdominal) near/5 aneur?sm\*):ti,ab,kw (36)
9. ((pararenal or para renal) near/5 aneur?sm\*):ti,ab,kw (2)
10. ((suprarenal or supra renal) near/5 aneur?sm\*):ti,ab,kw (2)
11. ((short neck\* or shortneck\*) near/5 aneur?sm\*):ti,ab,kw (0)
12. (visceral aortic segment\* near/5 aneur?sm\*):ti,ab,kw (0)
13. #7 or #8 or #9 or #10 or #11 or #12 (44)
14. (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs):ti,ab (45)
15. aneur?sm\*:ti,ab (1851)
16. #14 and #15 (6)
17. **#6 or #13 or #16 (63)**

CENTRAL search retrieved 48 records.

*Conference searches***VEITHsymposium: Annual Symposium on Vascular and Endovascular Issues: 2011–13**

URL: [www.veithsymposium.org/index.php?pg=home](http://www.veithsymposium.org/index.php?pg=home)

Searched 9 October 2013.

No free search interface for abstracts existing. Search of programme only free available option.

***39th Veith Symposium, New York, NY, USA, 2012***

URL: [www.veithsymposium.org/index.php?pg=program-2012](http://www.veithsymposium.org/index.php?pg=program-2012)

***38th Veith Symposium, New York, NY, USA, 2011***

URL: [www.veithsymposium.org/index.php?pg=program-2011](http://www.veithsymposium.org/index.php?pg=program-2011)

**Charing Cross International Symposium: 2011–13**

URL: [www.cxvascular.com/cxsymposium](http://www.cxvascular.com/cxsymposium)

Searched 9 October 2013.

No search interface existing, no abstracts findable on webpage.

35th Charing Cross International Symposium, London 6–9 April, 2013.

34th Charing Cross International Symposium, London 14–17 April, 2012.

33th Charing Cross International Symposium, London 9–12 April, 2011.

**Vascular Annual Meeting: 2011–13**

URL: [www.vascularweb.org/educationandmeetings/Pages/default.aspx](http://www.vascularweb.org/educationandmeetings/Pages/default.aspx)

Searched 9 October 2013.

Searches for abstracts only possible per day on the website, no search interface for any of the years.

***Vascular Annual Meeting, San Francisco, CA, USA, 2013***

Searched in *J Vasc Surg* 2013,**57**(Suppl. 5).

***Vascular Annual Meeting, National Harbor, MD, USA, 2012***

Searched in *J Vasc Surg* 2012,**55**(Suppl. 6).

***Vascular Annual Meeting, Chicago, IL, USA 2011***

Searched in *J Vasc Surg* 2011,**53**(Suppl. 6).

Condition	2013	2012	2011	Total
Juxta-renal	0	0	0	0
Juxtarenal	2	1	3	6
thoraco-abdominal	2	1	0	3
Thoracoabdominal	9	7	7	16
Thoracic abdominal	0	0	0	0
Pararenal	1	1	2	4
Para-renal	0	0	0	0
Suprarenal	5	4	6	15
Supra-renal	1	0	1	2
Short-neck	1	1	0	2
Shortneck	0	0	0	0
Short-necks	0	0	0	0
Shortnecks	0	0	0	0
JRAAA	0	0	0	0
JRAAAs	0	0	0	0
PAAA	0	1	0	1
PAAAs	0	0	0	0
TAAA	2	5	4	11
TAAAs	1	4	0	5
JPAA	0	0	0	0
JPAAs	0	0	0	0
SRA	0	0	1	1
SRAs	0	0	0	0
SRAA	0	0	0	0
SRAAs	0	0	0	0
Total (before deduplication)	24	25	15	66
Total (after deduplication)	16	13	13	42

## Cost-effectiveness

### MEDLINE (OvidSP): 1946 to week 3 September 2013

Searched 2 October 2013.

1. aortic aneurysm/ (17,850)
2. Aortic aneurysm, abdominal/ (13,424)
3. Aortic aneurysm, thoracic/ (8062)
4. or/1-3 (37,735)
5. (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal or thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck\$ or shortneck\$).ti,ab,ot,hw. (9228)
6. 4 and 5 (2621)
7. ((juxta-renal or juxtarenal) adj5 aneur?sm\$).ti,ab,ot,hw. (194)
8. ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm\$).ti,ab,ot,hw. (1620)
9. ((pararenal or para-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (83)
10. ((suprarenal or supra-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (227)
11. ((short-neck\$ or shortneck\$) adj5 aneur?sm\$).ti,ab,ot,hw. (15)
12. (visceral aortic segment\$ adj5 aneur?sm\$).ti,ab,ot,hw. (3)
13. or/7-12 (2001)
14. (JRAAA or JRAAA or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1327)
15. aneur?sm\$.ti,ab. (82,158)
16. 14 and 15 (285)
17. 6 or 13 or 16 (2829)
18. economics/ (27101)
19. exp "costs and cost analysis"/ (182,173)
20. economics, dental/ (1866)
21. exp "economics, hospital"/ (19,372)
22. economics, medical/ (8566)
23. economics, nursing/ (3879)
24. economics, pharmaceutical/ (2599)
25. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (425,785)
26. (expenditure\$ not energy).ti,ab. (17,493)
27. (value adj1 money).ti,ab. (22)
28. budget\$.ti,ab. (17,166)
29. or/18-28 (549,953)
30. ((energy or oxygen) adj cost).ti,ab. (2684)
31. (metabolic adj cost).ti,ab. (761)
32. ((energy or oxygen) adj expenditure).ti,ab. (16,404)
33. or/30-32 (19,165)
34. 29 not 33 (545,711)
35. animals/ not (animals/ and humans/) (3,941,632)
36. 34 not 35 (512,158)
37. letter.pt. (800,927)
38. editorial.pt. (333,488)
39. historical article.pt. (299,119)
40. or/37-39 (1,419,104)
41. 36 not 40 (484,528)
42. **17 and 41 (44)**

**Costs filter**

Centre for Reviews and Dissemination. *NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]*. York: CRD; 2010.

URL: [www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) (accessed 28 September 2010).

**MEDLINE In-Process & Other Non-indexed Citations (OvidSP) and MEDLINE Daily Update (OvidSP): up to 1 October 2013**

Searched 2 October 2013.

1. aortic aneurysm/ (22)
2. Aortic aneurysm, abdominal/ (24)
3. Aortic aneurysm, thoracic/ (12)
4. or/1-3 (57)
5. (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal or thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck\$ or shortneck\$).ti,ab,ot,hw. (628)
6. 4 and 5 (2)
7. ((juxta-renal or juxtarenal) adj5 aneur?sm\$).ti,ab,ot,hw. (23)
8. ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm\$).ti,ab,ot,hw. (86)
9. ((pararenal or para-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (5)
10. ((suprarenal or supra-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (10)
11. ((short-neck\$ or shortneck\$) adj5 aneur?sm\$).ti,ab,ot,hw. (4)
12. (visceral aortic segment\$ adj5 aneur?sm\$).ti,ab,ot,hw. (0)
13. or/7-12 (122)
14. (JRAAA or JRAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (78)
15. aneur?sm\$.ti,ab. (5279)
16. 14 and 15 (18)
17. 6 or 13 or 16 (124)
18. economics/ (4)
19. exp "costs and cost analysis"/ (227)
20. economics, dental/ (0)
21. exp "economics, hospital"/ (16)
22. economics, medical/ (5)
23. economics, nursing/ (0)
24. economics, pharmaceutical/ (2)
25. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (40,406)
26. (expenditure\$ not energy).ti,ab. (1194)
27. (value adj1 money).ti,ab. (4)
28. budget\$.ti,ab. (1841)
29. or/18-28 (42,342)
30. ((energy or oxygen) adj cost).ti,ab. (220)
31. (metabolic adj cost).ti,ab. (68)
32. ((energy or oxygen) adj expenditure).ti,ab. (934)
33. or/30-32 (1184)
34. 29 not 33 (42,005)
35. animals/ not (animals/ and humans/) (3777)
36. 34 not 35 (41,892)



37. letter.pt. (25,037)
38. editorial.pt. (14,927)
39. historical article.pt. (187)
40. or/37-39 (40,128)
41. 36 not 40 (41,418)
42. **17 and 41 (1)**

### Costs filter

Centre for Reviews and Dissemination. *NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]*. York: CRD; 2010.

URL: [www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) (accessed 28 September 2010).

### EMBASE (OvidSP): 1974 to 27 September 2013

Searched 30 September 2013.

1. Juxtarenal aneurysm/ (14)
2. Juxtarenal aortic aneurysm/ (20)
3. Juxtarenal abdominal aortic aneurysm/ (8)
4. ((juxta-renal or juxtarenal) adj5 aneur?sm\$).ti,ab,ot,hw. (282)
5. thoracoabdominal aneurysm/ (55)
6. Thoracoabdominal aortic aneurysm/ (10)
7. Thoracoabdominal aorta aneurysm/ (259)
8. ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm\$).ti,ab,ot,hw. (2135)
9. Pararenal aortic aneurysm/ (11)
10. ((pararenal or para-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (121)
11. Suprarenal aortic aneurysm/ (2)
12. ((suprarenal or supra-renal) adj5 aneur?sm\$).ti,ab,ot,hw. (284)
13. ((short-neck\$ or shortneck\$) adj5 aneur?sm\$).ti,ab,ot,hw. (36)
14. (visceral aortic segment\$ adj5 aneur?sm\$).ti,ab,ot,hw. (5)
15. or/1-14 (2653)
16. (JRAAA or JRAAA or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1817)
17. aneur?sm\$.ti,ab. (107,843)
18. 16 and 17 (409)
19. 15 or 18 (2679)
20. health-economics/ (33,215)
21. exp economic-evaluation/ (205,196)
22. exp health-care-cost/ (196,808)
23. exp pharmacoconomics/ (169,268)
24. or/20-23 (470,443)
25. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoconomic\$).ti,ab. (587,202)
26. (expenditure\$ not energy).ti,ab. (23,264)
27. (value adj2 money).ti,ab. (1312)
28. budget\$.ti,ab. (23,482)
29. or/25-28 (610,890)
30. 24 or 29 (882,214)
31. letter.pt. (842,045)
32. editorial.pt. (448,232)
33. note.pt. (585,743)
34. or/31-33 (1,876,020)

35. 30 not 34 (795,803)
36. (metabolic adj cost).ti,ab. (871)
37. ((energy or oxygen) adj cost).ti,ab. (3154)
38. ((energy or oxygen) adj expenditure).ti,ab. (19,870)
39. or/36-38 (23,086)
40. 35 not 39 (790,755)
41. animal/ (1,889,845)
42. animal-experiment/ (1,717,671)
43. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5,818,911)
44. or/41-43 (5,818,911)
45. exp human/ (14,981,558)
46. human-experiment/ (316,795)
47. 45 or 46 (14,982,999)
48. 44 not (44 and 47) (4,638,017)
49. 40 not 48 (753,935)
50. **19 and 49 (57)**

### Costs filter

Centre for Reviews and Dissemination. *NHS EED Economics Filter: EMBASE (Ovid) weekly search [Internet]*. York: CRD; 2010.

URL: [www.york.ac.uk/inst/crd/intertasc/nhs\\_eed\\_strategies.html](http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html) (accessed 17 March 2011).

### *NHS Economic Evaluation Database (Wiley): up to Issue 3 July 2013*

Searched 2 October 2013.

- #1 MeSH descriptor: [Aortic Aneurysm] this term only (118)
- #2 MeSH descriptor: [Aortic Aneurysm, Abdominal] this term only (556)
- #3 MeSH descriptor: [Aortic Aneurysm, Thoracic] this term only (77)
- #4 #1 or #2 or #3 (736)
- #5 (juxta renal or juxtarenal or thoraco abdominal or thoracoabdominal or thoracic abdominal or pararenal or para renal or suprarenal or supra renal or short neck\* or shortneck\*):ti,ab,kw (1231)
- #6 #4 and #5 (52)
- #7 ((juxta renal or juxtarenal) near/5 aneur?sm\*):ti,ab,kw (5)
- #8 ((thoraco abdominal or thoracoabdominal or thoracic abdominal) near/5 aneur?sm\*):ti,ab,kw (36)
- #9 ((pararenal or para renal) near/5 aneur?sm\*):ti,ab,kw (2)
- #10 ((suprarenal or supra renal) near/5 aneur?sm\*):ti,ab,kw (2)
- #11 ((short neck\* or shortneck\*) near/5 aneur?sm\*):ti,ab,kw (0)
- #12 (visceral aortic segment\* near/5 aneur?sm\*):ti,ab,kw (0)
- #13 #7 or #8 or #9 or #10 or #11 or #12 (44)
- #14 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs):ti,ab (45)
- #15 aneur?sm\*:ti,ab (1851)
- #16 #14 and #15 (6)
- #17 **#6 or #13 or #16 (63)**

The NHS EED search retrieved two records.

**EconLit (EBSCOhost): up to 30 September 2013**

Searched 30 September 2013.

S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S7	TX ( ((JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs)) ) AND TX aneur?sm*	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S6	TX (visceral aortic segment* N5 aneur?sm*)	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S5	TX ((short-neck* or shortneck*) N5 aneur?sm*)	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S4	TX ((suprarenal or supra-renal) N5 aneur?sm*)	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S3	TX ((pararenal or para-renal) N5 aneur?sm*)	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S2	TX ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) N5 aneur?sm*)	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0
S1	TX ((juxta-renal or juxtarenal) N5 aneur?sm*)	Search modes – Boolean/phrase	Interface – EBSCOhost Research databases Search screen – advanced search Database – EconLit	0

## Health-related quality of life

**MEDLINE (OvidSP): 1946 to week 3 September 2013**

Searched 2 October 2013.

1. exp aortic aneurysm/ (40,779)
2. (aort\$ adj5 aneur?sm\$).ti,ab,ot,hw. (43,045)
3. 1 or 2 (45,370)
4. (AAA or AAAs or JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (10,194)
5. aneur?sm\$.ti,ab. (82,158)
6. 4 and 5 (5172)
7. 3 or 6 (45,377)
8. (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (15,461)
9. (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (1)
10. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (992)
11. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (3713)
12. (hql or hrql or hqol or hrqol or qol).ti,ab. (26,395)
13. (hye or hyes).ti,ab. (53)
14. health\$ year\$ equivalent\$.ti,ab. (37)
15. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (872)
16. (quality of well being or quality of wellbeing or qwb).ti,ab. (381)
17. (Disability adjusted life year\$ or Disability-adjusted life year\$ or health adjusted life year\$ or health-adjusted life year\$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year\$).ti,ab. (7342)
18. (QALY\$ or HRQOL or HRQL or DALY\$ or HALY\$ or YHL or YPLL or YHLL).ti,ab. (15,631)
19. (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (406)
20. (timetradeoff or Time tradeoff or time trade off or tto).ti,ab. (1124)
21. (standard gamble or vas or visual analog\$).ti,ab. (41,997)
22. (health state\$ utilit\$ or HSUV\$ or health state\$ value\$ or health state\$ preference\$ or HSPV\$).ti,ab. (476)
23. Disutilit\$.ti,ab. (208)
24. Utilit\$.ti,ab. (113,005)
25. life quality.ti,ab. (3335)
26. or/8-25 (199,191)
27. 7 and 26 (382)
28. Animals/ not (animals/ and humans/) (3,941,632)
29. 27 not 28 (373)
30. letter.pt. (800,927)
31. editorial.pt. (333,488)
32. historical article.pt. (299,119)
33. or/30-32 (1,419,104)
34. **29 not 33 (371)**

**MEDLINE In-Process & Other Non-indexed Citations (OvidSP) and MEDLINE Daily Update (OvidSP): up to 1 October 2013**

Searched 2 October 2013.

1. exp aortic aneurysm/ (62)
2. (aort\$ adj5 aneur?sm\$).ti,ab,ot,hw. (1479)
3. 1 or 2 (1483)
4. (AAA or AAAs or JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1153)
5. aneur?sm\$.ti,ab. (5279)
6. 4 and 5 (314)
7. 3 or 6 (1484)
8. (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (1116)
9. (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (0)
10. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (356)
11. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (427)
12. (hql or hrql or hqol or hrqol or qol).ti,ab. (2421)
13. (hye or hyes).ti,ab. (2)
14. health\$ year\$ equivalent\$.ti,ab. (1)
15. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (76)
16. (quality of well being or quality of wellbeing or qwb).ti,ab. (13)
17. (Disability adjusted life year\$ or Disability-adjusted life year\$ or health adjusted life year\$ or health-adjusted life year\$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year\$).ti,ab. (680)
18. (QALY\$ or HRQOL or HRQL or DALY\$ or HALY\$ or YHL or YPLL or YHLL).ti,ab. (1392)
19. (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (32)
20. (timetradeoff or Time tradeoff or time trade off or tto).ti,ab. (87)
21. (standard gamble or vas or visual analog\$).ti,ab. (3338)
22. (health state\$ utilit\$ or HSUV\$ or health state\$ value\$ or health state\$ preference\$ or HSPV\$).ti,ab. (54)
23. Disutilit\$.ti,ab. (23)
24. Utilit\$.ti,ab. (10,198)
25. life quality.ti,ab. (299)
26. or/8-25 (17,678)
27. 7 and 26 (13)
28. Animals/ not (animals/ and humans/) (3777)
29. 27 not 28 (13)
30. letter.pt. (25,037)
31. editorial.pt. (14,927)
32. historical article.pt. (187)
33. or/30-32 (40,128)
34. **29 not 33 (13)**

**EMBASE (OvidSP): 1974 to 27 September 2013**

Searched 30 September 2013.

1. exp aorta aneurysm/ (43,171)
2. (aort\$ adj5 aneur?sm\$).ti,ab,ot,hw. (50,328)
3. 1 or 2 (50,328)
4. (AAA or AAAs or JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (12,813)
5. aneur?sm\$.ti,ab. (107,843)
6. 4 and 5 (6783)
7. 3 or 6 (50,423)
8. (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (21,583)
9. (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (3)
10. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (1508)
11. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (6003)
12. (hql or hrql or hqol or hrqol or qol).ti,ab. (41,749)
13. (hye or hyes).ti,ab. (83)
14. health\$ year\$ equivalent\$.ti,ab. (42)
15. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (1164)
16. (quality of well being or quality of wellbeing or qwb).ti,ab. (415)
17. (Disability adjusted life year\$ or Disability-adjusted life year\$ or health adjusted life year\$ or health-adjusted life year\$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year\$).ti,ab. (9621)
18. (QALY\$ or HRQOL or HRQL or DALY\$ or HALY\$ or YHL or YPLL or YHLL).ti,ab. (22,640)
19. (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab. (611)
20. (timetradeoff or Time tradeoff or time trade off or tto).ti,ab. (1482)
21. (standard gamble or vas or visual analog\$).ti,ab. (60,179)
22. (health state\$ utilit\$ or HSUV\$ or health state\$ value\$ or health state\$ preference\$ or HSPV\$).ti,ab. (692)
23. Disutilit\$.ti,ab. (329)
24. Utilit\$.ti,ab. (147,574)
25. life quality.ti,ab. (5991)
26. or/8-25 (273,757)
27. 7 and 26 (467)
28. animal/ (1,889,845)
29. animal-experiment/ (1,717,671)
30. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5,818,911)
31. or/28-30 (5,818,911)
32. exp human/ (14,981,558)
33. human-experiment/ (316,795)
34. 32 or 33 (14,982,999)
35. 31 not (31 and 34) (4,638,017)
36. 27 not 35 (458)
37. letter.pt. (842,045)
38. editorial.pt. (448,232)
39. note.pt. (585,743)
40. or/37-39 (1,876,020)
41. **36 not 40 (454)**

**Cost-effectiveness Analysis Registry (internet): 1990 to 9 October 2013**URL: <https://research.tufts-nemc.org/cear4/>

Searched 9 October 2013.

Terms searched	Articles	Ratios	Utility weights	Complete
Aorta aneurysm	0	0	0	0
Aorta aneurysms	0	0	0	0
Aortic aneurysm	34	61	93	188
Aortic aneurysms	18	25	58	101
Aorta aneurism	0	0	0	0
Aorta aneurisms	0	0	0	0
Aortic aneurism	0	1	0	1
Aortic aneurisms	0	0	0	0
AAA	27	36	88	151
AAAs	12	18	42	72
Total	91	141	281	513





## Appendix 2 Summary of studies excluded at full-paper, clinical effectiveness review

Study	Final reason for exclusion	Comments
Fillinger, 2012 <sup>54</sup>	Comparator	Chimney
Thompson, 2010 <sup>55</sup>	Study design	Non-comparative
Nordon <i>et al.</i> , 2009 <sup>56</sup>	Study design	Abstract of systematic review
Soltesz and Greenberg, 2010 <sup>57</sup>	Study design	Non-comparative study
Greenberg <i>et al.</i> , 2010 <sup>58</sup>	Study design	Erratum
Salata <i>et al.</i> , 2012 <sup>23</sup>	Intervention	EVAR
Bhamidipati <i>et al.</i> , 2011 <sup>24</sup>	Intervention	EVAR
Sultan and Hynes, 2011 <sup>25</sup>	Intervention	EVAR
Greenberg <i>et al.</i> , 2010 <sup>59</sup>	Study design	Non-comparative study
Greenberg <i>et al.</i> , 2004 <sup>26</sup>	Intervention	EVAR with suprarenal fixation
Vallabhaneni <i>et al.</i> , 2011 <sup>30</sup>	Study design	Non-comparative
Canavati <i>et al.</i> , 2013 <sup>32</sup>	Study design	Non-comparative
Donas <i>et al.</i> , 2012 <sup>29</sup>	Study design	Non-comparative
Chisci <i>et al.</i> , 2009 <sup>31</sup>	Study design	Non-comparative
Tsilimparis <i>et al.</i> , 2013 <sup>27</sup>	Intervention	Surgeon-modified fenestrated–branched stent grafts
Tsilimparis <i>et al.</i> , 2011 <sup>28</sup>	Intervention	Surgeon-modified fenestrated–branched stent grafts
Panuccio <i>et al.</i> , 2011 <sup>60</sup>	Study design	Health economics
Donas <i>et al.</i> , 2012 <sup>61</sup>	Study design	Systematic review
Cross <i>et al.</i> , 2012 <sup>52</sup>	Study design	Systematic review
Siegenthaler and Beyersdorf, 2009 <sup>62</sup>	Study design	Case series
Nordon <i>et al.</i> , 2009 <sup>51</sup>	Study design	Systematic review
Greenberg <i>et al.</i> , 2008 <sup>33</sup>	Study design	Non-comparative
Eide <i>et al.</i> , 2005 <sup>63</sup>	Study design	Health economics
Suominen <i>et al.</i> , 2013 <sup>64</sup>	Study design	Comparator chimney



## Appendix 3 Quality of cost-effectiveness studies of endovascular repair of abdominal aortic aneurysm

Item	Checklist item (Drummond <i>et al.</i> <sup>44</sup> )	Brown <i>et al.</i> <sup>42</sup>	Chambers <i>et al.</i> <sup>43</sup>
1	The research question is stated	✓	✓
2	The economic importance of the research question is stated	x	x
3	The viewpoint of the analysis is clearly stated and justified	✓	✓
4	The rationale for choosing the alternative programmes or interventions compared is stated	✓	✓
5	The alternatives being compared are clearly described	✓	✓
6	The form of economic evaluation used is stated	✓	✓
7	The choice of form of economic evaluation is justified in relation to the question addressed	✓	✓
8	The source of effectiveness estimates used are stated	✓	✓
9	Details of the design and results of effectiveness study are given	✓	✓
10	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	✓
11	The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓
12	Methods to value health states and other benefits are stated	✓	✓
13	Details of the subjects from whom valuations are obtained are given	✓	x
14	Productivity changes are reported separately	NA	NA
15	The relevance of productivity changes to the study question is discussed if included	NA	NA
16	Quantities of resources are reported separately from their unit costs	✓	✓/x <sup>a</sup>
17	Methods for the estimation of quantities and unit costs are described	✓	✓
18	Currency and price data are recorded	✓	✓
19	Details of currency of price adjustments for inflation or currency conversion are given	✓	x
20	Details of any model are given	✓	✓
21	The choice of the model used and the key parameters on which it is based are justified	✓	x
22	Time horizon of costs and benefits is stated	✓	✓
23	The discount rate is stated	✓	✓
24	The choice of rate is justified	x	✓
25	An explanation is given if costs or benefits are not discounted	NA	NA
26	Details of statistical tests and confidence intervals are given for stochastic data	✓	✓
27	The approach to sensitivity analysis is given	✓	✓
28	The choice of variables for sensitivity analysis is justified	✓	✓
29	The ranges over which the variables are varied are stated	✓	✓
30	Relevant alternatives are compared	✓	✓
31	Incremental analysis is reported	✓	✓

Item	Checklist item (Drummond <i>et al.</i> <sup>44</sup> )	Brown <i>et al.</i> <sup>42</sup>	Chambers <i>et al.</i> <sup>43</sup>
32	Major outcomes are presented in both disaggregated and aggregated forms	✓	✓
33	The answer to the study question is given	✓	✓
34	Conclusions follow from the data reported	✓	✓
35	Conclusions are accompanied by the appropriate caveats	✓	✓

✓, fulfilled; ✗, not fulfilled; NA, not applicable.  
a Quantities and resources only separated for primary admission.

## Appendix 4 Summary of studies for recommended cost-effective analysis

Author	Year	Cost-effectiveness	Health-care cost	Social care cost	Disease-specific outcomes	Generic utility	Incidence prevalence	Mortality	Model probability	Year of data	Setting	Time horizon	n
Brown <i>et al.</i> <sup>42</sup>	2012	-	✓	-	-	-	-	-	✓	1999–2009	UK	25 years	NA
Sultan and Hynes <sup>36</sup>	2012	-	-	-	✓	-	-	✓	-	2002–9	NS	3 years	118
Sultan and Hynes <sup>35</sup>	2011	-	-	-	✓	-	-	✓	-	2002–9	NS	3 years	118
Sultan and Hynes <sup>25</sup>	2011	-	-	-	✓	-	-	✓	-	2001–9	USA	3 years	118
Tambyraja <i>et al.</i> <sup>65</sup>	2011	-	-	-	✓	-	-	✓	-	2005–10	UK	> 6 months	29
Bruen <i>et al.</i> <sup>66</sup>	2011	-	-	-	✓	-	-	✓	-	2008–9	USA	30 days	21
Hayes <i>et al.</i> <sup>67</sup>	2010	-	✓	-	-	-	-	-	-	NA	UK	Lifetime	NA
Sultan <sup>34</sup>	2010	-	-	-	✓	-	-	✓	-	2002–9	NS	3 years	118
Sultan and Hynes <sup>37</sup>	2010	-	-	-	✓	-	-	✓	-	2002–9	NS	5 years	92
Sultan and Hynes <sup>68</sup>	2010	-	-	-	✓	-	-	✓	-	2002–9	NS	5 years	118
Chambers <i>et al.</i> <sup>43</sup>	2009	-	✓	-	-	-	-	-	✓	NA	UK	Lifetime	NA
Hynes and Sultan <sup>38</sup>	2009	-	-	-	✓	-	-	✓	-	2002–9	NS	5 years	92
Sultan and Hynes <sup>69</sup>	2009	-	-	-	✓	-	-	-	-	2002–9	NS	5 years	92
Health Quality Ontario <sup>39</sup>	2009	-	✓	-	-	-	✓	-	-	NA	Canada	NA	NA
Epstein <i>et al.</i> <sup>45</sup>	2008	-	✓	-	-	-	-	-	-	NA	UK	Lifetime	NA
Michaels <i>et al.</i> <sup>70</sup>	2005	-	✓	-	-	-	-	-	-	NA	UK	5–15 years	NA
EVAR trial participants (EVAR 2) <sup>71</sup>	2005	-	-	-	-	✓	-	-	-	1999–2003	UK	24 months	338
EVAR trial participants (EVAR 1) <sup>72</sup>	2005	-	-	-	-	✓	-	-	-	1999–2003	UK	24 months	1082
Cambria <i>et al.</i> <sup>73</sup>	2002	-	-	-	✓	-	-	-	-	1987–2001	USA	24 months	333

NA, not applicable; NS, not stated.

## Appendix 5 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
<b>Title</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both	i
<b>Abstract</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	xvii–xix
<b>Introduction</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known	1–4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5
<b>Methods</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number	xix
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	9–10
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	10–11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	<i>Appendix 1</i>
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	11
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	NA
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	NA
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. $I^2$ ) for each meta-analysis	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	NA
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	NA

Section/topic	#	Checklist item	Reported on page #
<b>Results</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	NA
Additional analysis	23	Give results of additional analyses, if done [e.g. sensitivity or subgroup analyses, meta-regression (see item 16)]	NA
<b>Discussion</b>			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health-care providers, users, and policy makers)	46
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review level (e.g. incomplete retrieval of identified research, reporting bias)	47
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	48
<b>Funding</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	2
NA, not applicable.			





A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME  
HS&DR  
HTA  
PGfAR  
PHR**

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