Health Technology Assessment Programme

National Institute for Health Research

NETSCC, HTA
29 November 2013

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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Final Protocol

Short Report commissioned by the NIHR HTA Programme

Title of project: The use of fenestrated and branched endovascular grafts (fEVAR & bEVAR) for juxta-renal and thoraco-abdominal aneurysms: a systematic review and cost effectiveness analysis.

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1. Background:

An aneurysm is a localised or diffuse dilatation which is at least 50% greater than the normal size of the aorta.[1] The normal aorta is shaped like a walking cane. Figure 1(a) shows a picture of the normal aorta following a course through the chest (thoracic aorta) and abdomen (abdominal aorta). Abdominal aortic aneurysms (AAA) (Figure 1(c)) account for 75% of all aortic aneurysms and are located, by definition of the abdomen, below the diaphragm[2], most below the renal arteries.[3] Those that do not involve but are close to the origin of a target vessel such as a renal artery (implying juxta-renal) (JRAAA) account for about 16% of AAAs.[4] Thoracic aortic aneurysms (TAAs) (Figure 1(b)) account for the other 25% of aortic aneurysms (AAs). Of these, 15% extend into the abdomen and are therefore referred to as thoraco-abdominal aneurysms (TAAAs).[5]

Figure 1: Aorta and aortic aneurysms[2]

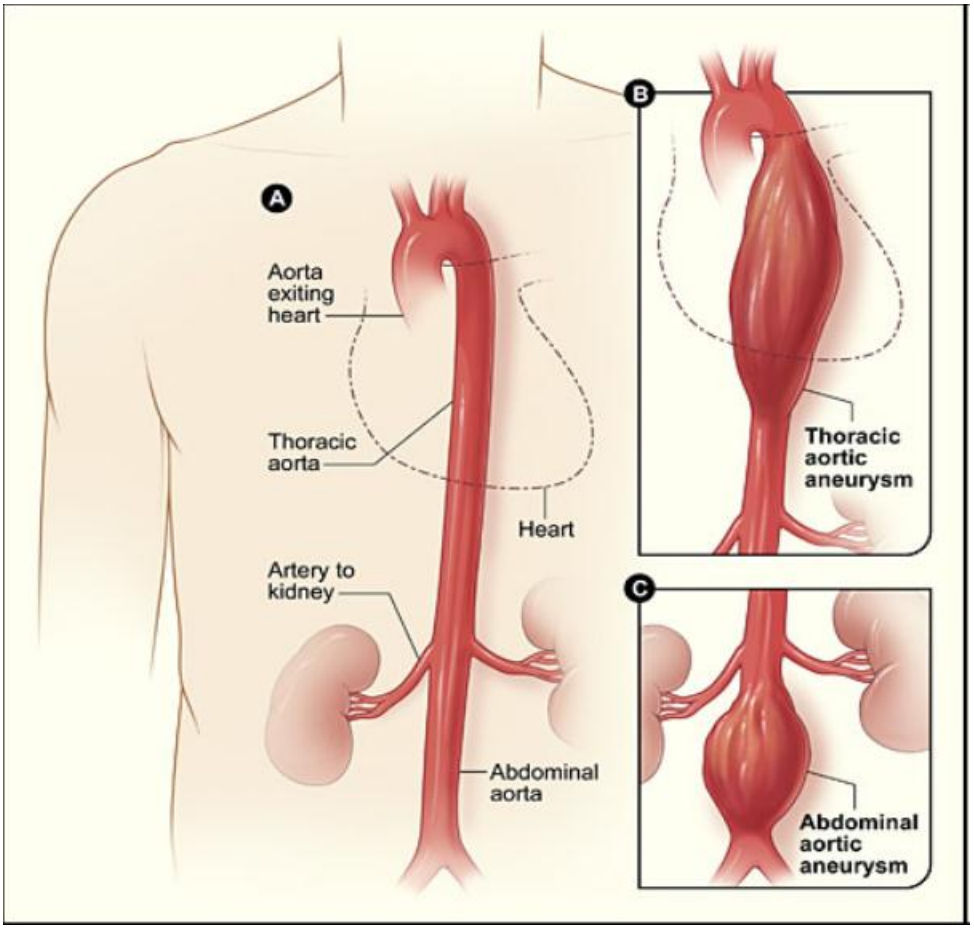
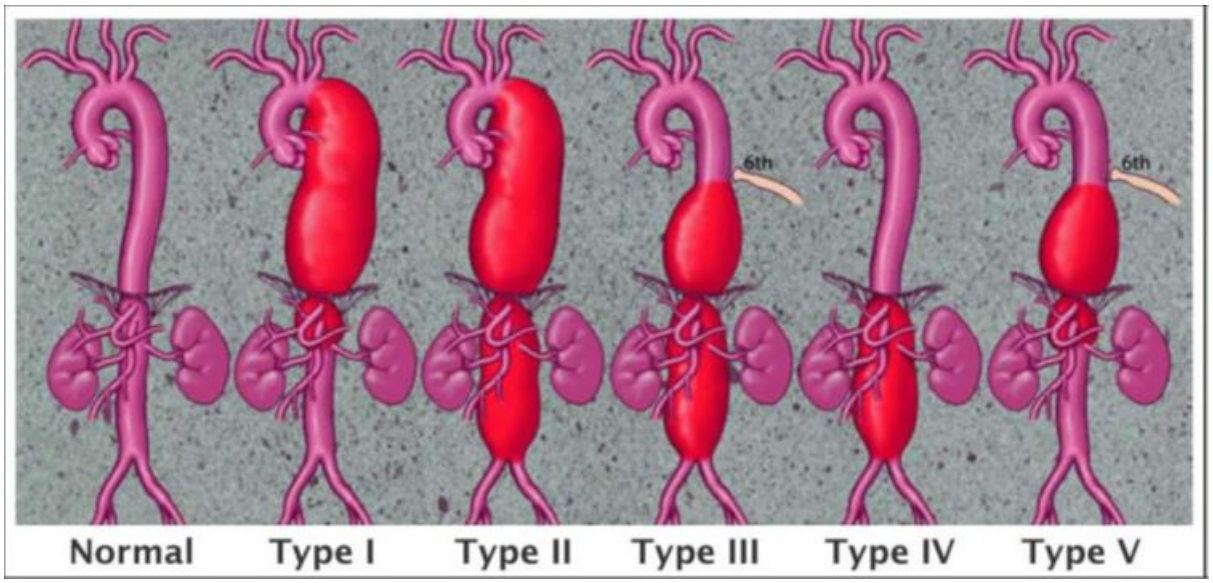


Figure 2: Crawford Classification of Thoraco-Abdominal Aortic Aneurysms [6]



TAAAs are stratified using the Crawford classification system based on their distribution within the aorta (figure 2).[6] The Crawford classification system subdivides TAAAs into:

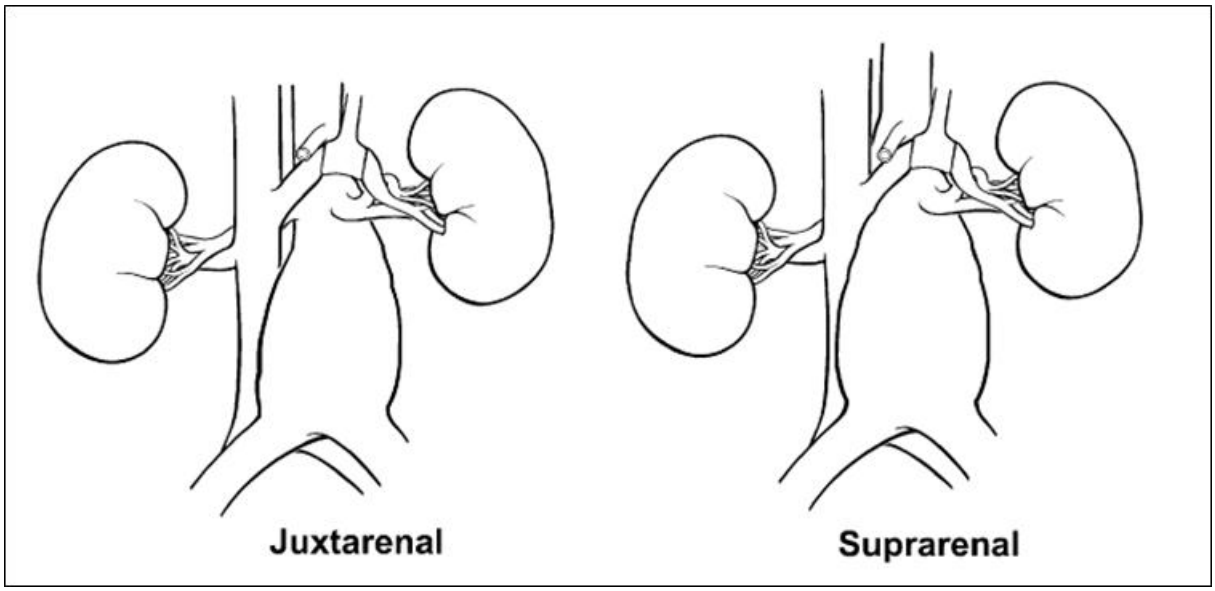
- Type I: Descending thoracic aorta (distal to the left subclavian artery) to the abdominal aorta above the renal arteries
- Type II: Descending thoracic aorta (distal to the left subclavian artery) to the renal arteries and may continue on to the bifurcation
- Type III: Mid to distal descending thoracic aorta and involves most of the abdominal aorta as far as the bifurcation and
- Type IV: This includes the upper abdominal aorta and all or none of the infra renal 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 celiac and superior mesenteric origins but not the renal arteries (modified by Saif's group)[6]

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 AAA in men is approximately 25 per 100,000 patient years at age 50, increasing to 78 per 100,000 in those older than 70 years.[3] For TAAA the incidence estimated varied from under one to about three per 100,000 patient years.[7] In Scotland over seven years (2001 to 2007) 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 (Figure 3).

Table 1: Numbers of TAAA repairs by type conducted in Scotland (2001-2007)

	Type I	Type II	Type III	Type IV	Type V	Supra Renal
Number	7	11	12	38	1	7
Percentage	9%	14%	16%	50%	1%	9%

Figure 3. juxta-renal and suprarenal aortic aneurysms.[8]



In terms of aetiology, the most common cause of aortic aneurysm is weakening of the arterial wall, usually associated with atherosclerosis. Other causes include trauma, vasculitis, cystic medial necrosis, and postsurgical anastomotic disruption.[5] AAAs are about three times more common in men than in women.[3]

AAAs enlarge at varying rates and symptoms 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 six 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 five year survival rate for patients with aneurysms larger than five cm is about 20%. For TAAA, the five year survival without operation has been reported between 7 and 20%.[7] The national screening programme care pathway recommends screening men from age 65 and that those of at least 5.5cm should be referred for consideration for elective surgery.[9]

As well as concomitant medical treatment for any other cardiovascular disease, there are two main methods of repair, open surgical repair (OSR) and endovascular aneurysm repair (EVAR). In the most recent appraisal by NICE in 2009[3], EVAR was recommended as an option for unruptured AAA that was infra-renal 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 open surgery
- 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 TAAA 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]."[7] Also, the Joint Working Group to produce guidance on delivering an Endovascular Aneurysm Repair (EVAR) Service has produced guidance on all aspects of EVAR delivery, which covers both TAAs and AAAs, which is currently available from the MHRA website.[10]

The latest American Heart Association (AHA) 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 pseudo aneurysms…".[11] They do not specifically recommend EVAR for TAAAs except to refer to previous guidance, which includes a recommendation for its use.[12] 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, open repair is recommended. Therefore, there is clearly uncertainty about how to treat TAAAs.

In addition, there is uncertainty about how to treat JRAAAs (Figure 3). 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. 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 ostium. Therefore, it is not possible to conduct a standard EVAR without having a 'window' (fenestra) to the stent-graft fabric, which lies over the target vessel ostium. 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.[13] [14] Known as fenestrated EVAR (fEVAR), this

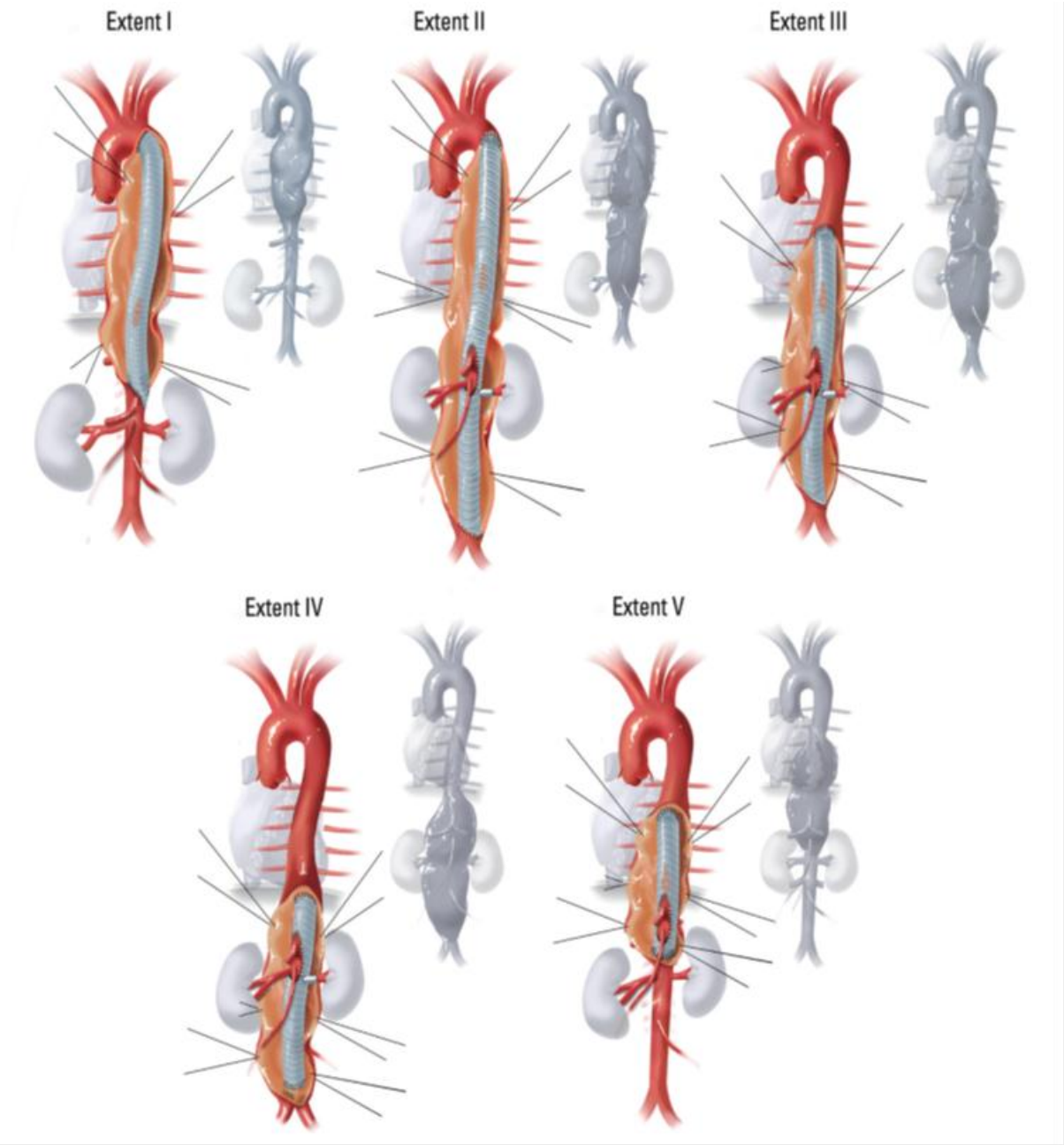
technology is enabling an expansion of the patient population, increasing the number that may be eligible for endovascular repair.[11]

TAAAs 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 ostium of the target vessel (Figure 4). 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 main body of aortic stent graft and target vessels and not to any actual branch from graft itself.[14] Where the aneurysm is suprarenal (Figure 3) 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'.[15] This lack of evidence is compounded by potentially many comparators given variations in the basic procedure.[16]

Commissioners are receiving increasing requests for fEVAR and bEVAR, but it is not clear whether the extra cost of fEVAR or bEVAR compared with the alternative of open repair is justified by advantages for patients.[15] In the absence of recent UK evidence based guidance on JRAAA and TAAAs, evidence synthesis with economic modelling is needed to answer these questions.

Figure 4: Position of the stent graft in relation to the Crawford Classifcation of TAAAs [17]



The purpose of this project is to assess the effectiveness, safety and cost effectiveness of fEVAR and bEVAR by a systematic review and, where possible, synthesis of the evidence and construction of an economic model, which uses this evidence.

2. Intervention:

Fenestrated endovascular aortic repair (fEVAR) and branched endovascular aortic repair (bEVAR) are specially manufactured stent-grafts with openings to allow blood to reach branches of the aorta.

Endovascular repair of abdominal aortic aneurysm (AAA) allows the exclusion of the dilated aneurismal 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 juxta-renal aortic aneurysm (JRAAA) is too short for a standard endovascular repair. Fenestrated endovascular aortic repair (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 ostial diameter of the renal and visceral arteries. There are three varieties fenestration, small, large, and scallop, and their location needs to be customised to fit the anatomy of the patient.[4] 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. In such cases, conversion to open surgery may become the only option as fenestrated endografts are not retrievable.

Branched endovascular aortic repair (bEVAR) provides a solution when the target vessels arise from the aneurysm. 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 is bridged by these branches. Any branches coming off the stent-graft are called cuffs (not branches). Branches in the form of stents between the aortic stent-graft and the target vessels can be 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 one or more fenestrations for some target vessels and one or more side branches for some target vessels. In this case a combination of fEVAR and bEVAR may be required for same aneurysm.[14]

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

3. Population:

The target patient population for fEVAR and bEVAR is those adult patients (≥ 18 years) who are at risk of rupture with juxta-renal AAA or TAAAs (distal to left subcalvian 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 open surgery due to the presence of significant comorbid conditions, and who are unsuitable for treatment with a standard EVAR because of the presence of a short proximal neck at those positions.

The decision to repair AAA using fEVAR and bEVAR requires careful patient selection to identify those patients who will most likely benefit from the repair as the decision depends upon 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 endovascular or open, which depends on the fitness of the patients and also on the success rate of the treating physician's institution.

3) Estimated longevity of the patient if not for the aneurysm.

Sub-groups 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 (since renal artery perfusion not needed).

4. Comparators:

The comparators considered relevant for this assessment are:

1) Open surgical repair (OSR) is the historic treatment method for juxta-renal or thoraco-abdominal aortic aneurysms.
2) No surgery (medical 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 'surgical equivalent' of bEVAR is greater. This is because the higher the aneurysm the higher the aortic clamp must be placed and thus the greater the pressure on the heart and the more extensive the potential ischemia e.g. to viscera and spinal cord. Also, open surgery for TAAA usually requires cardiopulmonary bypass or even circulatory arrest, which increases the risk [17]. Since, no clamping is needed for EVAR; this differential risk does not apply between fEVAR and bEVAR. Hence, any study assessing open surgery performed in a population eligible for fEVAR cannot be compared to on eligible for bEVAR.

In 2008 a study by Greenberg et al. reported that the patients selected to undergo OSR for TAAA are faced with a mortality risk ranging from 3% to 17%, with an incidence of perioperative death at centres with extensive experience <10%.[16] Also, the risk of spinal cord ischemia remains between 4% and 11% and the postoperative renal complications such as worsening of renal function are also considerable ranging between 17% and 25% and up to 15% of patients ultimately might require haemodialysis. [16] Also, cardiopulmonary complications after aortic surgery are common.[16]

5. Current evidence:

A HTA review in 2009 assessed the outcomes of treatment with fEVAR and compared with the outcomes after OSR in patients with JRAAA.[4] This review included five single centre, single arm prospective cohort studies on fEVAR and seven studies on OSR (one prospective and six retrospective). The author's concluded that results up to two years follow up in f-EVAR studies compare favourably with the outcomes in the open surgery studies. fEVAR had lower 30 day mortality than OSR (1.8% versus 3.1%) and a lower late mortality over the period of time that patients were followed (12.8% versus 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 JRAAA[18] and the other in TAAA[19], have attempted to make a comparison between OSR and fEVAR and bEVAR respectively. Bakoyiannis et al found seven case series of endovascular repair 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 a one using a Hybrid approach) and generally found similarity in outcomes with for example 30 day mortality of 7.1% for bEVAR versus 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'.

In JRAAA, Nordon et al also compared 'cohorts' from one set of studies of fEVAR to those from another set of studies of OSR. They did find a higher 30 day mortality with OSR (Relative risk (RR) 1.03, 95% Confidence interval (CI) 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'.

More recently, in 2012 a review by the College voor Zorgverzekeringen in the Netherlands of both fEVAR and bEVAR in the Netherlands 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 prostheses 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.' (translated from the summary).[20]

However, to date, no similar assessment has been carried out for the UK setting. The current assessment will therefore attempt to evaluate the effectiveness, safety and cost-effectiveness of fEVAR or bEVAR) in comparison to conventional treatment for juxta-renal or thoraco-abdominal aortic aneurysms in the UK.

6. Decision problem

6.1 Aims & objectives:

Aim: The aim of this project is 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 effectiveness and safety of fEVAR and bEVAR in comparison to conventional treatment i.e. no surgery or OSR (including any hybrid alternatives) for two populations: juxta-renal and thoraco-abdominal aortic aneurysms

2) To assess, from an NHS perspective, the cost-effectiveness of fEVAR and bEVAR in comparison to conventional treatment i.e. no surgery or open repair or any hybrid alternatives for two populations: juxta-renal and thoraco-abdominal aortic aneurysms.

7. Methods of assessing clinical effectiveness

The systematic review will be conducted using methods as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[21] and the Cochrane Handbook for reviews of intervention studies.[22]

7.1 Inclusion and Exclusion criteria:

Population: Studies including adult patients who are eligible for fEVAR (≥ 18 years) with juxta-renal aneurysms or eligible for bEVAR with thoraco-abdominal aortic aneurysms i.e. with proximity to/involvement of target vessels such that EVAR is unsuitable.

Setting: Secondary care

Intervention: Fenestrated endovascular aortic repair (fEVAR) and branched endovascular aortic repair (bEVAR)

Comparator (clinical effectiveness studies only): Open surgical repair (including Hybrid Repair) or no surgery for patients considered unsuitable for open surgery

Outcomes:

- Probability of technical success (Target Vessel Perfusion)-primary outcome
- Risk of death: all-cause mortality and aneurysm-related mortality
- Durability (risk of relapse)
- Risk of adverse events:
    a. Graft infection
    b. Device migration
    c. Endoleaks (early/late, Type I/Type III)
    d. Target vessel stenosis/occlusion
    e. Aneurysm growth
    f. Structural disintegration
    g. Modular separation
    h. Kinking leading to thrombosis
    i. Stent comes off or breaks
    j. Aortic rupture
    k. Stroke
    l. Paraplegia/spinal cord ischemia

- Re-intervention (any reason, for a stated adverse event)
- Annual radiation dosage

Study Design:

Step 1: Randomised and non-randomised trials where participants are assigned to the intervention group or comparator group, and which report at least one of the listed outcomes.

Step 2: If no controlled trials can be found then studies with a cohort design will be included if they make a comparison with a control group.

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.

The following study/publication types will be excluded:

- Case series/case reports
- Pre-clinical and animal
- Reviews, editorials, and opinion pieces

7.2 Search strategy

Searches will be undertaken in several stages to identify relevant information, such as clinical effectiveness, cost-effectiveness and quality of life. Search strategies will be based on the target conditions, juxta-renal and thoraco-abdominal aneurysms. Searches will not be limited by language or publication status (unpublished or published). Additional supplementary searches for data to populate the economic model will be carried out as necessary.

Rapid appraisal for existing systematic reviews on juxta-renal and thoraco-abdominal aneurysms

In order to identify existing and ongoing systematic reviews, guidelines and guidance on juxta-renal and thoraco-abdominal aneurysms, a rapid appraisal of appropriate sources will be undertaken, in sources such as:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (Wiley)
- Health Technology Assessment Database (HTA) (Wiley)
- NHS Economic Evaluation Database (NHS EED) (Wiley)
- Guidelines International Network (GIN)
  http://www.g-i-n.net/

- National Guideline Clearinghouse (NGCH)
  http://www.guideline.gov/
- NICE Guidance
  http://guidance.nice.org.uk/
- National Institute for Health Research (NIHR HTA)
  http://www.hta.ac.uk/
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet)
  http://www.crd.york.ac.uk/prospero/
- US Food and Drug Administration (FDA)
  http://www.fda.gov/

Clinical effectiveness

Searches will be undertaken to identify any studies investigating treatment of juxta-renal and thoraco-abdominal aneurysms. Full search strategies covering clinical effectiveness are presented in Appendix 1. The following resources will be searched without date limits:

- Medline (OvidSP)
- Medline In-Process & Other Non-Indexed Citations (OvidSP)
- Medline Daily Update (OvidSP)
- Embase (OvidSP)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)

If appropriate, supplementary searches may be undertaken to identify conference abstracts, grey literature, completed and ongoing trials. This will be identified in consultation with clinical experts.

Cost-effectiveness

Resources will be searched to identify cost-effectiveness studies of treatments for juxta-renal and thoraco-abdominal aneurysms. The search strategies will use a cost-effectiveness filter. Full search strategies covering cost-effectiveness are presented in Appendix 1. The following databases will be searched with no date limit:

- Medline (OvidSP)
- Medline In-Process & Other Non-Indexed Citations (OvidSP)
- Medline Daily Update (OvidSP)
- Embase (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (Wiley)
- EconLIT (EBSCO)

Quality of life

Focussed searches will be undertaken if appropriate to identify literature on HRQoL in juxta-renal and thoraco-abdominal aneurysms, which might be used to inform any economic model.

Handling of citations

Identified references will be downloaded into Endnote X6 software for further assessment and handling. Rigorous records are maintained as part of the searching process. Individual records within the Endnote reference libraries are tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enables 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 will be independently peer reviewed by a second Information Specialist, using the CADTH peer review checklist.[23, 24]

7.3 Data extraction strategy

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

Data relating to study details, participants, intervention, comparator and outcome measures will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

7.4 Quality assessment strategy

The methodological quality of included studies will be assessed using standard tools. Where possible, the quality of each individual study will be assessed in order to ensure that the conclusions and findings of this review are based on the best available evidence and that any potential sources of bias in the data are identified. Randomised trials will be assessed using the Cochrane Collaboration 2011 checklist[25] and observational studies (cohort studies) will be assessed using a checklist that is based on that by Downs and Black .[26]

The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

7.5 Methods of analysis/synthesis

A narrative summary of all of the included studies will be presented. This will include a summary of the characteristics (e.g. study aim, study design, population size, geographical location, year, baseline population characteristics, detailed diagnosis (including any relevant vascular anatomy), outcome definition and assessments, study conclusions) and methodological quality of the studies. This will include the identification of any risks which may introduce bias into the data or any factors which may limit the generalisability of the findings. The data will be summarised using text and where relevant, accompanying tables and figures (graphs, bar charts, etc.) will be used. Studies will also be grouped according to the treatment aim (i.e. primary prevention or secondary prevention or both).

Non-controlled trials will not be pooled, but consideration will be given to pooling of 'head-to-head' comparisons of comparator treatments in controlled in line with the Cochrane Handbook.[22] Forest plots of effect sizes will be prepared for each outcome in Cochrane Review Manager Version 5.1 (RevMan 5.1). Dichotomous outcomes (e.g. number of patients experiencing a success) will be reported as relative risks (RRs) with 95% confidence intervals (CIs), continuous outcomes (e.g. quality of life) as mean differences (MDs) with SDs.

Pooled effect sizes (RRs/weighted mean difference (WMD)/HRs) and 95% CIs using random effects (inverse-variance, I-V) methods will only be reported where trials are considered to be clinically and statistically homogeneous.

The judgment of clinical homogeneity will be based on the baseline characteristics of the trial populations, e.g., age, concomitant treatments. Statistical homogeneity will be assessed by means of the I^2 statistic. This describes the percentage of total variation across studies that are due to heterogeneity rather than the play of chance. The value of I^2 lies between 0% and 100%. For the purposes of this review (and as often used), a simplified categorisation of heterogeneity will be used: low (0 to 25%), moderate (26 to 75%), and high (>75%). Studies will only be considered to be sufficiently similar for the purposes of pooling if I^2<75 %.[22]

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this

will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed.

A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

Subgroup analysis

Outcomes will be analysed to look for differences according to:

- 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 (since renal artery perfusion not needed).

8. Methods of assessing cost-effectiveness:

The economic component of the project will consist of two parts. First a review of the economic literature will be performed. Secondly, a de novo cost-effectiveness model may be developed, depending on the evidence available regarding clinical effectiveness.

8.1 Identifying and reviewing published cost-effectiveness studies

The objective of the review of economic evaluations is to summarise methods and findings of existing peer reviewed studies.

Exploration of the literature regarding published economic evaluations will be performed in the databases listed in the systematic review part of this protocol: an example search strategy is included in Appendix 1. The intention of this component of the project is not to perform a systematic review, but to use the studies identified to support the development of an economic model that will aim to answer the research questions of this project. Therefore, the searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses studying not only fEVAR and bEVAR versus open surgical repair or no surgery but also EVAR versus open surgical repair or no surgery. Clinical trials as well as modelling studies and cohort studies will be considered relevant within the frame of our project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance. Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

8.2 Evaluation of costs, quality of life and cost-effectiveness

Depending on the amount of evidence found in the clinical review part of the project, a model will be developed to assess the cost-effectiveness of fEVAR/bEVAR versus the alternatives. The perspective will be that of the NHS and the time horizon used will be chosen such that all relevant costs and effects are taken into account. If possible, the model structure will be defined in such a way that all aspects that are relevant for the comparison of costs and effects of fEVAR/bEVAR versus the alternatives are incorporated, such as success rate of the procedure, length of hospital stay, 30 day mortality, long-term survival, and the rate of complications and adverse events. Besides the costs of the procedures themselves, the follow-up costs will be included. In addition, we will

investigate if it is possible to also include the effects of repeated exposure to radiation due to frequent CT-scans.

It is extremely important to note that final choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts.

Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs[27], Personal Social Services Research Unit (PSSRU)[28], British National Formulary (BNF)[29]), and expert opinion where necessary.

Any assumption used in the models and any parameter value will be based primarily on literature and supplemented by clinical expert opinion as appropriate. Extensive one way sensitivity analyses will be performed, besides a comprehensive probabilistic sensitivity analysis. If assessed, longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects. Decision uncertainty regarding the alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

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Appendix 1: Search strategies

Clinical effectiveness search strategies

Medline (OvidSP):1946-2013/08/wk 4
Searched 6. 9.13

1 aortic aneurysm/ (17821)
2 Aortic aneurysm, abdominal/ (13379)
3 Aortic aneurysm, thoracic/ (8024)
4 or/1-3 (37628)
5 (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal ot thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck$ or shortneck$).ti,ab,ot,hw. (5220)
6 4 and 5 (1041)
7 ((juxta-renal or juxtarenal) adj5 aneur?sm$).ti,ab,ot,hw. (192)
8 ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm$).ti,ab,ot,hw. (1616)
9 ((pararenal or para-renal) adj5 aneur?sm$).ti,ab,ot,hw. (82)
10 ((suprarenal or supra-renal) adj5 aneur?sm$).ti,ab,ot,hw. (224)
11 ((short-neck$ or shortneck$) adj5 aneur?sm$).ti,ab,ot,hw. (15)
12 (visceral aortic segment$ adj5 aneur?sm$).ti,ab,ot,hw. (3)
13 or/7-12 (1994)
14 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1320)
15 aneur?sm$.ti,ab. (81909)
16 14 and 15 (285)
17 6 or 13 or 16 (2452)
18 animals/ not (animals/ and humans/) (3934860)
19 17 not 18 (2317)
20 letter.pt. (798920)
21 editorial.pt. (332272)
22 historical article.pt. (298693)
23 or/20-22 (1415503)
24 19 not 23 (2248)

Medline In-Process (OvidSP): up to 2013/09/05
Medline Daily Update (OvidSP): up to 2013/09/05
Searched 6.9.13

1 aortic aneurysm/ (2)
2 Aortic aneurysm, abdominal/ (10)
3 Aortic aneurysm, thoracic/ (14)
4 or/1-3 (26)
5 (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal ot thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck$ or shortneck$).ti,ab,ot,hw. (418)
6 4 and 5 (0)
7 ((juxta-renal or juxtarenal) adj5 aneur?sm$).ti,ab,ot,hw. (23)
8 ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm$).ti,ab,ot,hw. (85)

9 ((pararenal or para-renal) adj5 aneur?sm$).ti,ab,ot,hw. (6)
10 ((suprarenal or supra-renal) adj5 aneur?sm$).ti,ab,ot,hw. (13)
11 ((short-neck$ or shortneck$) adj5 aneur?sm$).ti,ab,ot,hw. (4)
12 (visceral aortic segment$ adj5 aneur?sm$).ti,ab,ot,hw. (0)
13 or/7-12 (122)
14 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (81)
15 aneur?sm$.ti,ab. (5142)
16 14 and 15 (17)
17 6 or 13 or 16 (123)
18 animals/ not (animals/ and humans/) (1837)
19 17 not 18 (123)
20 letter.pt. (23319)
21 editorial.pt. (14027)
22 historical article.pt. (119)
23 or/20-22 (37454)
24 19 not 23 (123)

Embase (OvidSP): 1974-2013/09/04
Searched 5.9.13

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$).ti,ab,ot,hw. (5)
15 or/1-14 (2643)
16 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1805)
17 aneur?sm$.ti,ab. (107498)
18 16 and 17 (408)
19 15 or 18 (2669)
20 animal/ (1886529)
21 animal experiment/ (1712212)
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. (5802448)
23 or/20-22 (5802448)
24 exp human/ (14928364)
25 human experiment/ (315976)
26 or/24-25 (14929805)

27 23 not (23 and 26) (4626466)
28 19 not 27 (2564)
29 Letter.pt. (839238)
30 Editorial.pt. (446547)
31 Note.pt. (582792)
32 or/29-31 (1868577)
33 28 not 32 (2414)

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to Issue 8:2013
Searched 6.9.13

#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 ot thoracic abdominal or pararenal or para renal or suprarenal or supra renal or short neck* or shortneck*):ti,ab,kw 767
#6 #4 and #5 21
#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 JPAAs 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 56

Cochrane Central Register of Controlled Trials search retrieved 41 records

Cost-effectiveness search strategies

Medline (OvidSP): 1946-2013/08/wk 4
Searched 6. 9.13

1 aortic aneurysm/ (17821)
2 Aortic aneurysm, abdominal/ (13379)
3 Aortic aneurysm, thoracic/ (8024)
4 or/1-3 (37628)
5 (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal ot thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck$ or shortneck$).ti,ab,ot,hw. (5220)
6 4 and 5 (1041)
7 ((juxta-renal or juxtarenal) adj5 aneur?sm$).ti,ab,ot,hw. (192)
8 ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm$).ti,ab,ot,hw. (1616)
9 ((pararenal or para-renal) adj5 aneur?sm$).ti,ab,ot,hw. (82)

10 ((suprarenal or supra-renal) adj5 aneur?sm$).ti,ab,ot,hw. (224)
11 ((short-neck$ or shortneck$) adj5 aneur?sm$).ti,ab,ot,hw. (15)
12 (visceral aortic segment$ adj5 aneur?sm$).ti,ab,ot,hw. (3)
13 or/7-12 (1994)
14 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1320)
15 aneur?sm$.ti,ab. (81909)
16 14 and 15 (285)
17 6 or 13 or 16 (2452)
18 economics/ (27095)
19 exp "costs and cost analysis"/ (181704)
20 economics, dental/ (1866)
21 exp "economics, hospital"/ (19335)
22 economics, medical/ (8563)
23 economics, nursing/ (3879)
24 economics, pharmaceutical/ (2598)
25 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (424009)
26 (expenditure$ not energy).ti,ab. (17433)
27 (value adj1 money).ti,ab. (22)
28 budget$.ti,ab. (17115)
29 or/18-28 (547970)
30 ((energy or oxygen) adj cost).ti,ab. (2678)
31 (metabolic adj cost).ti,ab. (756)
32 ((energy or oxygen) adj expenditure).ti,ab. (16365)
33 or/30-32 (19116)
34 29 not 33 (543741)
35 letter.pt. (798920)
36 editorial.pt. (332272)
37 historical article.pt. (298693)
38 or/35-37 (1415503)
39 34 not 38 (515843)
40 17 and 39 (40)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Medline In-Process (OvidSP): up to 2013/09/05
Medline Daily Update (OvidSP): up to 2013/09/05
Searched 6.9.13

1 aortic aneurysm/ (2)
2 Aortic aneurysm, abdominal/ (10)
3 Aortic aneurysm, thoracic/ (14)
4 or/1-3 (26)
5 (juxta-renal or juxtarenal or thoraco-abdominal or thoracoabdominal ot thoracic abdominal or pararenal or para-renal or suprarenal or supra-renal or short-neck$ or shortneck$).ti,ab,ot,hw. (418)
6 4 and 5 (0)
7 ((juxta-renal or juxtarenal) adj5 aneur?sm$).ti,ab,ot,hw. (23)

8 ((thoraco-abdominal or thoracoabdominal or thoracic abdominal) adj5 aneur?sm$).ti,ab,ot,hw. (85)
9 ((pararenal or para-renal) adj5 aneur?sm$).ti,ab,ot,hw. (6)
10 ((suprarenal or supra-renal) adj5 aneur?sm$).ti,ab,ot,hw. (13)
11 ((short-neck$ or shortneck$) adj5 aneur?sm$).ti,ab,ot,hw. (4)
12 (visceral aortic segment$ adj5 aneur?sm$).ti,ab,ot,hw. (0)
13 or/7-12 (122)
14 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (81)
15 aneur?sm$.ti,ab. (5142)
16 14 and 15 (17)
17 6 or 13 or 16 (123)
18 economics/ (1)
19 exp "costs and cost analysis"/ (124)
20 economics, dental/ (0)
21 exp "economics, hospital"/ (9)
22 economics, medical/ (0)
23 economics, nursing/ (0)
24 economics, pharmaceutical/ (0)
25 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (39233)
26 (expenditure$ not energy).ti,ab. (1147)
27 (value adj1 money).ti,ab. (4)
28 budget$.ti,ab. (1816)
29 or/18-28 (41102)
30 ((energy or oxygen) adj cost).ti,ab. (219)
31 (metabolic adj cost).ti,ab. (68)
32 ((energy or oxygen) adj expenditure).ti,ab. (860)
33 or/30-32 (1111)
34 29 not 33 (40766)
35 letter.pt. (23319)
36 editorial.pt. (14027)
37 historical article.pt. (119)
38 or/35-37 (37454)
39 34 not 38 (40333)
40 17 and 39 (1)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Embase (OvidSP): 1974-2013/09/04
Searched 5.9.13

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$).ti,ab,ot,hw. (5)
15 or/1-14 (2643)
16 (JRAAA or JRAAAs or PAAA or PAAAs or TAAA or TAAAs or JPAA or JPAAs or SRA or SRAs or SRAA or SRAAs).ti,ab. (1805)
17 aneur?sm$.ti,ab. (107498)
18 16 and 17 (408)
19 15 or 18 (2669)
20 health-economics/ (33148)
21 exp economic-evaluation/ (204342)
22 exp health-care-cost/ (195937)
23 exp pharmacoeconomics/ (168735)
24 or/20-23 (468668)
25 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (584167)
26 (expenditure$ not energy).ti,ab. (23143)
27 (value adj2 money).ti,ab. (1300)
28 budget$.ti,ab. (23410)
29 or/25-28 (607767)
30 24 or 29 (878172)
31 letter.pt. (839238)
32 editorial.pt. (446547)
33 note.pt. (582792)
34 or/31-33 (1868577)
35 30 not 34 (792146)
36 (metabolic adj cost).ti,ab. (863)
37 ((energy or oxygen) adj cost).ti,ab. (3141)
38 ((energy or oxygen) adj expenditure).ti,ab. (19784)
39 or/36-38 (22983)
40 35 not 39 (787123)
41 exp animal/ (19258068)
42 exp animal-experiment/ (1715713)
43 nonhuman/ (4123494)
44 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4987559)
45 or/41-44 (20597520)
46 exp human/ (14928364)
47 exp human-experiment/ (315976)
48 46 or 47 (14929805)
49 45 not (45 and 48) (5668684)
50 40 not 49 (728107)
51 19 and 50 (57)

Costs filter:

Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 17.3.11]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

NHS Economic Evaluation Database (NHS EED) (Wiley): up to Issue 3:2013
Searched 6.9.13

#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 ot thoracic abdominal or pararenal or para renal or suprarenal or supra renal or short neck* or shortneck*):ti,ab,kw 767
#6 #4 and #5 21
#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 JPAAs 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 56

NHS Economic Evaluation Database search retrieved 2 records

EconLit (EBSCO): 1886-2013/09/06
Searched 6.9.13

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 JPAAs 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 -	0

			Advanced Search Database - EconLit	
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