1. Title of the project:
Endovascular stents for abdominal aortic aneurysms.

2. Name of TAR team and ‘lead’
CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York.

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3. Plain English Summary
The aorta is a large blood vessel (artery) that carries oxygenated blood from the heart to the rest of the body. Aortic aneurysms occur when the wall of the aorta is weakened by the constant pressure of blood passing through it, leading to the formation of a balloon-like projection. This in turn leads to stretching of the vessel wall and an increase in tension that can result in rupture. Rupture produces massive internal bleeding with an overall mortality rate of approximately 80%. Even if patients undergo emergency surgery, only about half survive.

Most aneurysms are in the lower (abdominal) section of the aorta and are known as abdominal aortic aneurysms (AAAs). Most AAAs do not produce any symptoms and are discovered by chance during clinical examination or by imaging tests (most people with AAAs also have other problems). When AAAs are small, the risk of rupture is low, but over time the size of the aneurysm, and hence the risk of rupture, is likely to increase. The risk of rupture may be as high as 25% per year for aneurysms with a diameter greater than 6 cm.

AAAs can be treated surgically to prevent rupture. The standard method of surgical repair involves making a large cut in the abdomen and replacing the damaged section of the aorta with a prosthetic graft. This procedure, known as ‘open repair’, involves some risk, particularly as patients with AAA are often elderly with heart, kidney or other disease. Some patients with AAAs are not considered fit enough to undergo this type of surgery.

Endovascular aneurysm repair (EVAR) is a less invasive technique that is considered to be less traumatic for the patient and to lead to shorter hospital stays. EVAR involves the use of an endovascular (‘inside blood vessels’) stent-graft. The stent-graft is a tube made of material such as polytetrafluoroethylene supported by a thin metal framework (stent). The stent-graft is inserted through a small incision in the femoral artery in the groin,
carried to the site of the aneurysm using catheters and guidewires and placed in position under X-ray guidance. Once in position, the stent-graft is expanded and attaches to the wall of the aorta. The graft is stronger than the weakened aorta and allows blood to pass through it without creating pressure on the aneurysm.

The purpose of this project is to assess how effective and safe EVAR is and whether it is a cost-effective procedure for the repair of AAAs. A further objective of our review is to try to identify criteria for selecting patients for whom EVAR would be particularly appropriate.

4. Decision problem

- **Objectives**
  The aim of this project is to determine the clinical and cost-effectiveness of endovascular stent-grafts for repair of infrarenal abdominal aortic aneurysms across a range of patient risk levels, including those who are considered suitable for open repair and those who are not.

- **Background**
  Aortic aneurysms develop when weakening of the vessel wall, often due to atherosclerosis, causes it to bulge, forming a balloon-like projection. This in turn leads to further stretching of the vessel wall and an increase in tension. Eventually, the vessel wall may rupture, leading to massive internal bleeding.

Most aneurysms occur in the abdominal section of the aorta. An abdominal aortic aneurysm (AAA) is defined as an enlargement of the aorta to 1.5 times or more its normal diameter or greater than 3 cm. Most AAAs occur in the lower (infra-renal) part of the abdominal aorta.

Symptoms that may occur as an aneurysm enlarges include a pulsating sensation in the abdomen, back pain and abdominal pain, possibly spreading to the back. Symptomatic AAAs require rapid medical attention. Rupture of an AAA is associated with a mortality rate of about 80%; even when patients undergo emergency surgery, only about half survive beyond 30 days. The risk of rupture increases with the size of the aneurysm. For example, in the UK Small Aneurysm Trial and associated monitoring study, the number of ruptures per 100 patient years was 0.3, 1.5 and 6.5 for patients with AAAs of diameter ≤ 3.9 cm, 4.0–4.9 cm and 5.0–5.9 cm, respectively. The rate of rupture may be up to 25% annually for aneurysms with diameters larger than 6 cm, while a number of studies indicate that without surgery the 5-year survival rate for patients with aneurysms larger than 5 cm is about 20%.

The main risk factors for AAAs include age, high blood pressure, male sex, smoking and family history. Because most AAAs are asymptomatic, it is difficult to estimate the prevalence of the condition, but screening studies in the UK have estimated a prevalence of 1.3–12.7% depending on the age group studied and the definition of AAA. AAAs are about 3 times more common in men than in women. The incidence of symptomatic
AAA in men is approximately 25/100,000 at age 50, increasing to 78/100,000 in those older than 70 years. The overall incidence of AAAs has increased in recent years and is likely to increase further in line with the ageing of the general population.

Most AAAs are detected by chance during clinical examination or investigation (for example, ultrasound or X-ray) for other conditions. Ultrasound screening of the population for early detection of AAAs has been extensively evaluated. In the UK the large Multicentre Aneurysm Screening Study RCT found that screening men aged 65–74 reduced the risk of aneurysm-related death by 42% over 4 years. Screening was marginally cost-effective over 4 years and cost-effectiveness was expected to improve substantially over a longer period. National screening programmes are under consideration by the four UK health departments at the time of writing.

AAAs can be treated by surgical repair to prevent rupture. Conventional (‘open’) surgical repair involves making a large incision in the abdomen and inserting a prosthetic graft to replace the damaged section of the aorta. In current UK clinical practice, elective surgery is generally recommended for aneurysms between 5 and 5.5 cm in diameter, as well as for those of diameter > 4.5 cm with an increase in size of > 0.5 cm in the last 6 months. The UKSAT and ADAM trials indicated that there was no mortality advantage of immediate (open) surgical repair over imaging surveillance in patients with aneurysms of less than 5.5 cm diameter. Open repair of AAA carries substantial risk of mortality and morbidity, particularly because many patients with an AAA have significant co-morbidities (e.g. heart or kidney disease) that reduce their fitness for surgery. Approximately 25% of patients with an AAA requiring surgery are considered unfit for open surgery. Patients who are considered unfit for open repair may be offered medical therapy to reduce risk factors, for example smoking cessation and blood pressure reduction.

An alternative to open repair has been developed. Endovascular aneurysm repair (EVAR) is a minimally-invasive technique that involves placing a stent-graft prosthesis at the site of the aneurysm. The stent-graft is inserted through a small incision in the femoral artery in the groin, carried to the site of the aneurysm using catheters and guidewires and placed in position under X-ray guidance. Once in position, the stent-graft is deployed and anchored to the wall of the aorta using a variety of fixing mechanisms. The graft is stronger than the weakened aorta and allows blood to pass through it without creating pressure on the aneurysm. The main types of endovascular stent-grafts are aortic tube grafts (no longer used in the UK), aortic uni-iliac grafts and aortic bi-iliac (bifurcated) grafts, with most procedures in the UK using bi-iliac stents. EVAR is carried out under general, regional or local anaesthesia.

EVAR has been used to treat both patients classified as fit for open repair and those classified as unfit. It is used both as an elective procedure and to treat symptomatic and ruptured aneurysms. Patient suitability for EVAR also depends on the anatomical situation of the aneurysm. This is assessed by diagnostic imaging, usually computed tomography (CT) scanning and occasionally angiography or magnetic resonance imaging (MRI).
Potential advantages of EVAR over open repair include reduced time under general anaesthesia, elimination of the pain and trauma associated with major abdominal surgery, reduced length of stay in the hospital and intensive care unit, and reduced blood loss. Potential disadvantages include the development of endoleaks, which occur when blood continues to flow through the aneurysm because the graft does not seal completely or because of backfilling of the aneurysm from other small vessels arising from the aneurysm wall. Thus, while open repair does not require any special follow-up, patients who have undergone EVAR require regular CT scans to check for the presence of late endoleaks. In addition, if the EVAR procedure is unsuccessful or complications arise during the procedure, conversion to open repair may be necessary in patients initially considered unfit for open surgery.

The objective of this assessment is to determine the clinical and cost-effectiveness of endovascular stent-grafts for repair of infrarenal abdominal aortic aneurysms in patients at varying levels of risk, including those who are appropriate for open repair and those who are not. The assessment will build on the information already available, including recent systematic reviews. There remains uncertainty, however, about longer-term outcomes, about the variables and risk factors that influence the effectiveness and safety of EVAR and whether there are subgroups of patients for whom EVAR is particularly appropriate.

5. Report methods for synthesis of evidence of clinical effectiveness
A systematic review of the evidence for the clinical effectiveness and safety of endovascular stent-grafts for repair of infrarenal abdominal aortic aneurysms will be conducted following the general principles recommended in CRD Report 4. The review will include two assessments: overall efficacy and safety of EVAR and the effects of baseline risks on outcome of EVAR.

• Search strategy
Recent systematic reviews by Drury and colleagues and Lederle and colleagues will be used to identify randomised controlled trials (RCTs) and other clinical studies. Additional searches will be conducted to search for recent RCTs (2005–7), publications relating to the registries named in this protocol and for studies relating to baseline risks. Searches will not be restricted by language or study design. Regular current awareness searches will be carried out during the review. Further details and a draft search strategy can be found in the Appendix.

• Inclusion and exclusion criteria
Two reviewers will independently screen all titles and abstracts. Full paper manuscripts that may be relevant will be obtained where possible and the relevance of each study assessed independently by two reviewers according to the criteria below. Discrepancies will be resolved by discussion, or by referral to a third reviewer when necessary. Studies that do not fulfil all of the criteria will be excluded with documented reasons for their exclusion.
Population
Patients with asymptomatic or symptomatic, ruptured or unruptured infrarenal abdominal aortic aneurysms (AAAs) that are anatomically and clinically suitable for endovascular stent-graft repair (EVAR). The study authors’ definition of aneurysm status and suitability for EVAR will be used. Studies of patients with aneurysms of any size will be included.

Interventions
Elective or emergency EVAR of infrarenal AAAs using uni-iliac or bi-iliac stent grafts. It is recognised that not all devices evaluated in the research literature will have a CE mark and that several devices have undergone a number of changes. It is also recognised that manufacturers’ devices have varying indications for use and contraindications. Hence studies of any EVAR device will be eligible but, where data allow, analysis will focus on devices commonly used in UK practice.

Comparators
For patients for whom conventional open repair is a treatment option according to study authors’ criteria, conventional open repair is the appropriate comparator.

For patients for whom conventional open repair is not a treatment option according to study authors’ criteria, the appropriate comparator is non-surgical treatment for AAA (sometimes referred to as ‘watchful waiting’). Such treatment will vary across studies but will normally represent best medical care and typically include a range of strategies to manage vascular risk factors.

Outcomes
Only studies reporting at least one of the following outcomes will be included:

- 30 day mortality rate
- Aneurysm-related mortality
- All-cause mortality.
- Health-related quality of life.
- Adverse effects and complications. This will include aneurysm-related outcomes such as rupture and events specific to EVAR e.g. frequency of endoleaks and device migration. Major morbidity, for example cardiac events, will also be assessed.
- Re-intervention rates including conversion from EVAR to open procedure and secondary intervention.
**Study designs**

Estimates of the treatment effect and safety outcomes of EVAR will be derived from RCTs and large registries of relevance to UK practice. The registries to be used are RETA and EUROSTAR for EVAR, and the National Vascular Database for open surgery.

In order to identify criteria for selecting patients appropriate for EVAR, studies that have modelled the spectrum of risk will also be included. Risk modelling studies to be included will be specific to AAA, focus on risk of mortality following EVAR and use appropriate statistical modelling techniques (for example, Kaplan–Meier survival analysis, multiple linear or logistic regression or Cox proportional hazards analysis). They will be based on a trial, registry or a series of at least 1000 patients from developed countries of relevance to UK practice.

**Data extraction strategy**

Data relating to both study design and quality will be extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for missing data. For studies with multiple publications those with the greatest number of participants, the longest follow up or the latest publication presenting the largest amount of outcome data will be extracted. Extraction will include data on: study details (e.g. study identifier/EndNote ID, author, year, country, setting, number of participants, and duration of follow up), patient characteristics (e.g. age, gender, causal/risk factors, comorbidities, aneurysm size/anatomy), intervention (type of stent-graft), comparison (details of open repair or medical management), study quality, and reported outcomes relating to efficacy and safety as specified above. Careful note will be made of definitions used by study authors in relation to fitness for surgery and AAA-related mortality.

**Quality assessment strategy**

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of RCTs will be assessed using standard checklists adapted as necessary to incorporate topic-specific quality issues. The quality of audit/registry data will be assessed by adapting a framework developed by the Agency for Healthcare Research and quality (AHRQ).

**Methods of analysis/synthesis**

Data extracted from the studies will be tabulated and discussed in a narrative review. The results of the quality assessment will be tabulated, and where possible, the effect of study quality on effectiveness data and the findings of the review will be discussed. Where appropriate, meta-analysis will be employed to estimate a summary measure of treatment effect on relevant outcomes based on intention to treat analyses. Meta-analysis will be carried out using fixed or random effects models, using appropriate software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the $\chi^2$ test for
homogeneity and the $I^2$ statistic. If the evidence allows, meta-analysis will be carried out on subgroups including types of device and aneurysm neck angulation.

Data from studies of risk models will be explored to establish different categories of patient risk for patients being treated with and without EVAR. Where data allow, the absolute mortality with EVAR according to patient risk will be calculated.


**Identifying and systematically reviewing published cost-effectiveness studies**

The sources detailed in Section 5 will be used to identify studies of the cost-effectiveness of EVAR compared to open surgery and non-surgical therapy. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modeling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond et al. This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Clinical Excellence (NICE). This information will be tabulated and summarised within the text of the report. In particular information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of-life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review. The presence of any data gaps (e.g. resource use data) that may need to be filled during the development of the model will be identified and additional searches may be required.

**Development of a new decision-analytic model**

Subject to the availability of existing models and evidence, a new decision-analytic model will be developed to estimate the cost-effectiveness of EVAR, open surgery and non-surgical treatment. The perspective will be that of the National Health Services and Personal Social Services. Productivity costs, such as time to return to normal activities,
are not included within this perspective but may be included as a secondary analysis. Both cost and QALY will be discounted at 3.5%.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients’ care and subsequent prognosis and the impacts of alternative therapies, in a way which is clinically acceptable.
- To populate this model using the most appropriate data identified systematically from published literature and routine data sources.
- To relate intermediate outcomes to final health outcomes, expressed in terms of quality-adjusted life years (QALYs). This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the mean cost-effectiveness of EVAR compared with standard care, based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- Consistent with available evidence to report cost-effectiveness of alternative treatments for specific sub-groups of patient. This may include cost-effectiveness by patients underlying risk of particular clinical events.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, decision uncertainty. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- To inform future research priorities in the NHS, the model will be used to undertake analyses of the expected value of perfect information. These take the decision uncertainty associated with analysis and quantify the cost of this uncertainty in terms of health gain forgone and resources wasted by making the wrong decision. This cost of uncertainty represents the value of perfect information, and this can be estimated for the model overall and for individual parameters.

The specific details of the data to be used to populate the model will have to await the development of the structure and the systematic searches of the literature. However, we expect to derive estimates of the relative effectiveness of EVAR (compared to open surgery and non-surgical intervention) from available randomised trials. More detailed consideration of patients’ underlying risks of clinical events may use observational evidence relevant to UK clinical practice identified by the review of clinical effectiveness.
Although the estimate of relative treatment effect would be obtained from published randomised trials, and there may be little evidence that this varies according to patient groups, whether a given treatment is cost-effective often depend on absolute as well as relative risks. Observational data may be useful to identify and estimate the baseline risk factors associated with operative mortality following open surgery, in order to identify clinically important patient sub-groups between which the cost effectiveness of EVAR versus open surgery may vary. Furthermore, it may be possible to use long term observational data to predict the incidence of complications and failures of the EVAR device in these patient groups, in order to inform the cost-effectiveness model. It is likely that these analyses would require access to and/or further analysis of the individual participant data from the registries.

7. Handling the company submission(s)
All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 5 December 2007. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in company submissions, provided they comply with NICE’s advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any ‘commercial in confidence’ data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors
Researchers at the Centre for Health Economics (including David Epstein and Mark Sculpher) have undertaken, and published, previous work on the effectiveness and cost-effectiveness of EVAR devices funded by the NHS Health Technology Assessment Programme. Also Mark Sculpher has undertaken consultancy work for Medtronic in clinical areas unrelated to vascular disease or EVAR.

There are no other competing interests.

9. References

Appendix: Literature searching

Current Awareness

Throughout the life of the project a range of current awareness services will be used to ensure that the review team is kept as up to date as possible with recent publications. A number of approaches will be used including:

1. Zetoc and Zetoc Alert service
   These provide access to the British Library’s electronic table of contents of journals and conference proceedings. Using the search term “endovascular” identified a number of journals for which search alerts were generated:
   - European Journal of Vascular and Endovascular Surgery
   - Italian Journal of Vascular and Endovascular Surgery
   - Journal of Endovascular Therapy
   - Perspectives in Vascular Surgery and Endovascular Therapy
   - Vascular and Endovascular Surgery

   An alerting service was also created to notify the team of any conferences where the words EVAR, aneurysms, or endovascular stents appeared in the conference title.

2. ScienceDirect

   A similar alerting service for journal contents pages was created for journals identified by searching for “vascular surgery” within ScienceDirect:
   - Annals of Vascular Surgery
   - The Asia Pacific Journal of Thoracic & Cardiovascular Surgery
   - Cardiovascular Surgery
   - European Journal of Vascular Surgery
   - European Journal of Vascular and Endovascular Surgery
   - Interactive Cardiovascular and Thoracic Surgery
   - The Journal of Thoracic and Cardiovascular Surgery
   - Journal of Vascular Surgery
   - Operative Techniques in Thoracic and Cardiovascular Surgery
   - Seminars in Thoracic and Cardiovascular Surgery
   - Seminars in Vascular Surgery

3. OvidAutoAlerts were created in both the MEDLINE and EMBASE databases to notify the review team of papers with EVAR in title, original title, abstract.
Handsearching

To ensure that all newly published relevant papers not identified by database searches are considered by the review team, handsearching of key journals will also be conducted. The journals will be selected by combining a number of approaches i.e. by using the Journal Citation Reports via ISI Web of Knowledge to check for journals specific to the topic, by checking through the results of the initial searches that were carried out to develop the search strategy in the protocol, and by consulting with the clinical expert on the review.

Sources to be searched
MEDLINE (via OvidWeb) was searched to inform the scope of the TAR and the protocol. For the full review, update searches will be run on MEDLINE and in addition the following databases will be searched:

For RCTs and Systematic Reviews
BIOSIS Previews
Cochrane Central Register of Controlled Trials
CINAHL
EMBASE
MEDLINE
MEDLINE in-process
Science Citation Index (SCI)

For Ongoing Trials
ClinicalTrials.gov
Current Controlled Trials
National Research Register (NRR)

For Economic Evaluations
EconLIT
IDEAS
Office of Health Economics Health Economic Evaluations Database (HEED)
NHS Economic Evaluation Database (NHS EED)

For Guidelines and Systematic Reviews
Clinical Evidence
Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Health Evidence Bulletin Wales
Health Technology Assessment (HTA) database
National Guidelines Clearinghouse
NICE website
NLH Guidelines Finder
SIGN
TRIP+

For Conference Proceedings
ISI Proceedings
Zetoc
The websites of relevant organisations, e.g. ACGBI will also be searched.

Search strategy for EVAR
The following draft strategy was developed for MEDLINE. It will be revised as required on acceptance of the protocol and adapted to run effectively on the other databases listed above. The searches for the information to inform the economic model will be developed in collaboration with the health economists working on the project and will be designed pragmatically to capture relevant information to inform model parameters as necessary.

1. EVAR.ti,ab.
2. endovascular stent$.ti,ab.
3. endovascular repair.ti,ab.
4. endovascular treat$.ti,ab.
5. endovascular surg$.ti,ab.
6. vascular surgical procedures/
7. 1 or 2 or 3 or 4 or 5 or 6
8. AAA.ti,ab.
9. exp Aortic Aneurysm, Abdominal/
10. 8 or 9
11. 7 and 10
12. AAA endograft$.ti,ab.
13. 11 or 12
14. eurostar collaborators.au.
15. eurostar group.au.
16. (EUROSTAR and (stent$ or graft$ or aneurysm)).ti,ab.
17. (DREAM and (stent$ or graft$ or aneurysm)).ti,ab.
18. EUROSTAR registry.ti,ab.
19. Registry of Endovascular Treatment of Aneurysms.ti,ab.
20. RETA.ti,ab.
21. or/14-20
22. 13 or 21
23. limit 22 to yr="2005 - 2007"