National Institute for Health and Care Excellence

Final

Abdominal aortic aneurysm: diagnosis and management

Evidence review F: Thresholds for abdominal aortic aneurysm repair

NICE guideline NG156

Methods, evidence and recommendations

March 2020

Final

This evidence review was developed by the NICE Guideline Updates Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-3452-2

Contents

Thresholds for abdominal aortic aneurysm repair 6
Review question 6
Introduction 6
PICO table 6
Methods and process 6
Clinical evidence 7
Summary of clinical studies included in the evidence review 7
Quality assessment of clinical studies included in the evidence review 8
Economic evidence 8
Summary of studies included in the economic evidence review 9
Evidence statements 10
The committee's discussion of the evidence 11
Appendices 14
Appendix A – Review protocol 14
Review protocol for review question 7: Thresholds for abdominal aortic aneurysms repair 14
Appendix B – Literature search strategies 16
Clinical search literature search strategy 16
Health Economics literature search strategy 18
Appendix C – Clinical evidence study selection 21
Appendix D – Clinical evidence tables 22
Systematic review 22
Additional evidence from randomised controlled trials 26
Appendix E – Forest plots 30
Mortality at 1 year 30
Mortality at up to 6 years 30
Aneurysm rupture at 1 year 31
Need for reintervention at 1 year 31
Appendix F – GRADE tables 32
Mortality 32
Aneurysm rupture 32
Aneurysm growth 33
Adverse events 33
Need for additional intervention 33
Quality of life 34
Appendix G – Economic evidence study selection 35
Appendix H – Economic evidence tables 36
Appendix I – Health economic evidence profiles 41

Appendix J – Excluded studies 43
Clinical studies 43
Economic studies 47
Appendix K – Glossary 49

Thresholds for abdominal aortic aneurysm repair

Review question

What is the effectiveness of early surgery compared with a continued surveillance approach in reducing morbidity and mortality in people with an unruptured abdominal aortic aneurysm?

Introduction

The aim of this review question was to determine the threshold of asymptomatic abdominal aortic aneurysm (AAA) size at which the benefits of undergoing surgery outweigh the harms, and to explore the clinical and cost effectiveness of 'early' referral and surgery (referral at <5.5 cm) when compared with routine ultrasound surveillance (referral at 5.5 cm) in people with asymptomatic AAAs.

PICO table

Table 1: Inclusion criteria

Parameter	Inclusion criteria
Population	People with an asymptomatic confirmed unruptured AAA
Interventions	Early referral and surgery (before an aneurysm diameter of 5.5cm)
Comparators	Continued surveillance, with referral and surgery at an aneurysm diameter of 5.5cm
Outcomes	Mortality/survival (AAA-related; all-cause) Loss of EVAR-suitability Peri- and post-operative complications Need for reintervention Successful exclusion of the aneurysm, aneurysm rupture, or further aneurysm growth Quality of life Resource use, including length of hospital or intensive care stay, and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

A broad search was used to identify all studies that examine the diagnosis, surveillance or monitoring of AAAs. This was a 'bulk' search that covered multiple review questions. The reviewer sifted the database to identify all studies that met the criteria detailed in Table 1. The relevant review protocol can be found in Appendix A.

Studies were included if they assessed the effectiveness of early surgical intervention for people with asymptomatic AAAs. Randomised and quasi-randomised controlled trials were considered for inclusion. If insufficient studies were identified prospective cohort studies with

a sample size of larger than 500 people and a follow-up of at least 12 months across multiple centres were considered for inclusion. Studies were excluded if they:

- were not in English
- were not full reports of the study (for example, published only as an abstract)
- considered the management of symptomatic or ruptured AAAs
- were not peer-reviewed.

Clinical evidence

Included studies

From a database of 12,786 abstracts, 83 were identified as being potentially relevant. Following full-text review of these articles, 1 systematic review of 4 randomised controlled trials (reported across 13 publications) was identified as meeting the criteria for inclusion. An additional 2 publications relating to 2 of the RCTs that were included in the systematic review were identified and included.

An update search was conducted in December 2017, to identify any relevant studies published during guideline development. The search found 2,598 abstracts; all of which were not considered relevant to this review question. As a result no additional studies were included.

Excluded studies

The list of papers excluded at full-text review, with reasons, is given in Appendix J.

Summary of clinical studies included in the evidence review

A summary of the included studies is provided in the below table.

Table 2: Summary of included studies

Study	Details
Filardo, Powell, Martinez, Ballard (2015) Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. Feb;4:CD001835	Study design: systematic review Location: UK Population: people of any age with an asymptomatic AAA ≥4 cm and <5.5 in diameter. The aneurysm was restricted to the abdominal aorta distal to the renal arteries, was non-tender on examination and the patient should have been considered fit for surgery. Sample size: 4 RCTs including 5,900 participants. 3314 participants fulfilled the inclusion criteria and were randomised. Follow-up: up to 6 years Intervention: Surgical repair of the aneurysm consisting of insertion of a prosthetic inlay graft either by open surgery (abdominal or retroperitoneal route) (2 RCTs) or by endovascular repair imposing anatomical restrictions (2 RCTs). Comparators: Surveillance of the maximum antero-posterior diameter performed regularly, with a maximum interval of six months (4 RCTs). Two RCTs conducted

Study	Details
	routine ultrasound or computed tomography surveillance every 3 months if diameter was 5.0 cm to 5.5 cm. Surgical repair was then performed when the maximum antero-posterior diameter reached 5.5 cm, rapidly increased in size or became asymptomatic. Outcomes: mortality
Cao P, De Rango P, Verzini F, et al. (2011) Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): results from a randomised trial. Eur J Vasc Endovasc Surg.; 41(1):13-25	Study design: non-blinded, randomised controlled trial Location: Italy Population: people between 50 and 70 years with confirmed AAA between 4.0 and 5.0 cm in diameter Sample size: 360 Follow-up: median of 32.4 months Intervention: immediate EVAR Comparator: ultrasound performed every 6 months with repair allowed if the aneurysm grew to 5.5 cm diameter in size, rapidly increased in diameter (> 1 cm/year), or became symptomatic Outcomes: Aneurysm rupture, aneurysm growth, need for reintervention, adverse events & conversion to open repair
Ouriel K, Clair DG, Kent KC, et al (2010). Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) Investigators. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. J Vasc Surg.;51(5):1081-7	Study design: non-blinded, randomised controlled trial Location: USA Population: people between 40 and 90 years with confirmed AAA between 4.0 and 5.0 cm in diameter Sample size: 728 participants Follow-up: mean of 20 months Intervention: immediate EVAR Comparators: scans performed at 1 month, 6 months, and every 6 months. Participants were offered aneurysm became symptomatic reached a diameter 5.5 cm, or when the aneurysm enlarged ≥ 0.5 cm between any 2 6-month assessments Outcomes: Aneurysm rupture, need for reintervention, conversion to open repair

See Appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See Appendix F for full GRADE tables.

Economic evidence

Included studies

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AAA. This search returned a total of 5,173 citations. Following review of all titles and abstracts, the full texts of 19 studies were retrieved for detailed consideration for early surgery compared with continued surveillance. Following this review, 5 studies were included as economic evidence.

An update search was conducted in December 2017, to identify any relevant cost–utility analyses that had been published during guideline development. This search return 814 studies. Following review of titles and abstracts, the full text of 1 study was retrieved for detailed consideration for early intervention. Following this review, the study was excluded.

Excluded studies

The list of papers excluded at full-text review, with reasons, is given in Appendix J.

Summary of studies included in the economic evidence review

An economic evidence profile (summary) is provided in Appendix I. Full evidence tables are provided in Appendix H. A brief description of each study is provided here.

Grant et al. (2015) developed a UK patient-level simulation tool to predict the AAA diameter at which repair should occur in order to maximise the expected QALYs for a given patient. Some QALY-maximising thresholds were found to be smaller than 5.5 cm. For a set of example patients, the authors compared the cost-utility outcomes of repair at the QALY-maximising diameter with repair at 5.5 cm if male or 5.0 cm if female. Results suggest that early intervention may be cost-effective in some circumstances, particularly in younger patients. However, results were highly uncertain, with repair at the QALY-maximising threshold never more than 51% likely to have an ICER of £20,000 or better, compared with current practice.

Young et al. (2010) compared the cost effectiveness of providing EVAR to treat AAAs of 4.0-5.5 cm in diameter with surveillance until 5.5 cm followed by EVAR or OSR. The authors developed a lifetime Markov model of a 68-year old patient cohort, from the US health care provider perspective. It suggested that early EVAR is both more costly and less effective, in terms of total QALYs, than continued surveillance.

Chambers et al. (2009) conducted an exploratory analysis comparing EVAR, open surgical repair (OSR), continued surveillance, and discharge without repair, using a UK model. They used dynamic programming techniques to optimise each treatment decision at 6-monthly scans, based on the expected net benefits of future decisions, assuming that surveillance would never be continued for aneurysms ≥8 cm in diameter. For 4.5 to 5.0 cm AAAs, the optimal strategy was generally immediate EVAR in people with very poor operative fitness, and immediate OSR in people with better operative fitness, particularly in younger patients (up to 71.5 and 75 years old, respectively). The cost-effectiveness of immediate repair increased with aneurysm size and decreased with patient age.

Schermerhorn et al. (2000) compared OSR at different AAA diameter thresholds with continued surveillance until 5.5 cm, at different patient ages, using a US Markov model. This analysis determined that OSR before 5.5 cm may be cost-effective in younger patients (<72 years) and those with larger AAAs (≥4.5 cm).

Katz & Cronenwett (1994) also developed a Markov model, from the US hospital perspective, with a 60-year old male cohort. Comparing OSR for 4.0 cm AAAs with 6-monthly surveillance until 5.0 cm, the study reported that the cost-effectiveness of early OSR is comparable with accepted preventative interventions.

Evidence statements

Clinical evidence

- Very low-quality evidence from 2 RCTs, including 831 people with asymptomatic AAAs 4.0 cm in diameter or larger, could not differentiate 1-year mortality rates between patients who received immediate EVAR and those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate (>0.7 cm in 6 months or >1 cm in 1 year). High-quality evidence from 2 RCTs, including 2,226 people with asymptomatic AAAs 4.0 cm in diameter or larger, found no meaningful difference between 6-year mortality rates of patients who received immediate EVAR and those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate (>0.7 cm in 6 months or >1 cm in 1 year).
- Very low-quality evidence from 2 RCTs, including 1,088 people with asymptomatic AAAs 4.0 cm in diameter or larger, could not differentiate aneurysm rupture rates or the need for additional intervention between patients who received immediate EVAR and those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate at (>0.7 cm in 6 months or >1 cm in 1 year).
- Low-quality evidence from 1 RCT, including 246 people with asymptomatic AAAs 4.0 cm in diameter or larger, could not differentiate conversion to open surgery rates between patients who received immediate EVAR and those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate (>0.7 cm in 6 months or >1 cm in 1 year).
- High-quality evidence from 1 RCTs, including 360 people with asymptomatic AAAs 4.0 cm in diameter or larger, reported higher rates of any type of adverse event in patients who received immediate EVAR compared with those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate at (>0.7 cm in 6 months or >1 cm in 1 year).
- Low-quality evidence from 1 RCTs, including 360 people with asymptomatic AAAs 4.0 cm in diameter or larger, could not differentiate 30-day endoleak rates between patients who received immediate EVAR and those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate at (>0.7 cm in 6 months or >1 cm in 1 year). Moderate-quality evidence from the same trial, reported higher endoleak rates at 1-year follow-up in patients who received immediate EVAR compared with those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate at (>0.7 cm in 6 months or >1 cm in 1 year)
- Moderate-quality evidence from 1 RCT, including 339 people with asymptomatic AAAs 4.0 cm in diameter or larger, could not differentiate long-term quality of life (measured by SF-36 scores) between patients who received immediate EVAR and those who underwent ultrasound surveillance until the aneurysm diameter reached 5.5 cm or it began to expand at an increased rate (>0.7 cm in 6 months or >1 cm in 1 year).

Health economic evidence

- One directly applicable cost–utility analysis with potentially serious limitations compared elective repair at the QALY-maximising AAA diameter with current practice repair thresholds. It found that early repair provided additional QALYs and, in some cases, cost savings, however results were highly uncertain. One partially applicable cost–utility analysis with minor limitations compared using EVAR to treat AAAs of 4.0–5.5 cm in diameter with surveillance until 5.5 cm followed by EVAR or OSR. It suggests that early EVAR is associated with additional total costs and 0.05 fewer QALYs per patient. Three

partially applicable cost–utility analyses with very serious limitations compared elective repair of small AAAs with strategies of continued surveillance and/or no treatment. Their results suggest that early repair may be cost-effective in younger patients (<72 years). This was found to be more likely with increasing AAA size (2 studies) and patient fitness (1 study).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The guideline committee discussed the relative importance of a variety of relevant outcomes, including mortality, aneurysm rupture, aneurysm growth, the need for additional intervention, conversion to open surgery and quality of life. The committee agreed that the most important outcome was mortality.

The quality of the evidence

The committee noted that the quality of evidence ranged from very-low to high. It was considered that the low event rates and small sample sizes may have contributed towards the lack of observed differences. The risk of allocation bias was deemed to be very low: methods of randomisation of the included studies ensured a good balance across study groups. The committee considered that that there was an unclear risk of bias, for example differences between study groups or in the way they were treated because the nature of the interventions did not permit blinding of participants or observers. Low loss to follow-up rates meant that the risk of attrition bias was very low across identified studies. The risk of selective reporting bias was moderate: results of the 4 RCTs were reported across multiple publications, yet data for all of the outcomes of interest were not identified in all of the studies.

The committee were not adequately convinced by the use of 5.0 cm or 5.5 cm thresholds as baselines for comparisons with early intervention. They considered that the evidence was not strong enough to make "offer" recommendations and agreed that they would need stronger evidence to drive any change in current practice. The committee discussed how, in practice, the decision whether to operate is not solely based on aneurysm size or symptoms, and factors such as age and comorbid conditions are taken into consideration. As a result, the committee were mindful of the potential for putting patients in whom surgery is inappropriate at risk if a recommendation to offer (as opposed to consider) surgery when aneurysms reach 5.5cm was made. The committee further agreed that there was insufficient evidence to recommend that clinicians should not offer surgery unless aneurysms reached 5.5 cm in diameter.

The committee discussed whether a strong 'do not consider surgery' recommendation should be made for aneurysms less than 4.0 cm in diameter, despite the absence of any evidence. They agreed that any such recommendation could potentially be misinterpreted in that it could be seen to imply that surgery should be considered for aneurysms greater than 4.0 cm in diameter. The committee were keen to avoid any misinterpretation. As a result, no such recommendation was made.

The committee discussed whether additional research would be helpful, and agreed that uncertainties could be usefully explored in a simulation study – i.e. evidence synthesis and economic modelling. They agreed that this should be combined with the work on surveillance intervals they had recommended in Evidence review D, because there are clear

interdependencies between the questions of how people's AAAs are monitored and when they are considered suitable for intervention. Therefore the research recommendation that appears in that Evidence review was modified to specify that both questions should be considered together.

Benefits and harms

The potential risks associated with surgery mean that the trade-off between benefits and harms can be challenging. Currently, the evidence does not suggest an overall advantage, in relation to mortality, of immediately repairing AAAs with a diameter of 4.0 cm to 5.4 cm compared with ultrasound surveillance. The committee noted that the evidence on clinical effectiveness did not explore whether aneurysm diameter thresholds higher than 5.5 cm were effective at reducing mortality when compared with ultrasound surveillance.

The committee also considered it appropriate to specify that "aneurysm tenderness" and "growth of more than 1cm in 1 year" were suitable criteria for considering surgical repair. They also agreed that it is important to recommend that symptomatic aneurysms should be considered for surgical repair. This is in line with criteria used in the ADAM, CAESAR and UKSAT trials. Using their clinical experience, the committee noted that recommending the aforementioned criteria would not affect clinical practice, but instead would formalise what clinicians should look out for.

Cost effectiveness and resource use

The committee discussed the economic evidence presented and agreed that it was limited in quality and had limited applicability to a UK context. It was noted that all of the studies were performed using a US payer perspective and discount rates were not in line with the 3.5% outlined in NICE's guideline manual. Additionally, only 1 of the identified studies (Young et al., 2010) used a Markov model that adequately considered different health states which could arise in people with AAAs, such as major cardiovascular complications. In the other studies, such complications were not explicitly modelled. Finally, the committee were aware that 2 of the 3 studies (Katz & Cronenwett, 1994 and Schermerhorn et al., 2000) had serious limitations because they did not perform any probabilistic analyses, and agreed that this limited their confidence in the cost–utility results further.

The committee noted that the economic evidence suggests conclusions about the cost effectiveness of early repair may differ by baseline AAA diameter and the person's age at presentation. However, the committee felt that these results did not provide sufficient evidence on which to form different recommendations based on presenting aneurysm size or age, due to poor quality and limited applicability of the underlying models.

The committee discussed the assumption underpinning all of the cost–utility analyses presented: that there is a baseline, current practice threshold for performing surgery that is itself a suitable baseline for cost-effectiveness comparisons. The committee were not adequately convinced by the use of 5.0 cm or 5.5 cm thresholds as baselines for comparisons with early intervention. They noted that the Young et al. (2010) study reported that surgery at 5.0 cm was dominated by surgery when aneurysms reached 5.5 cm; however, investigators did not explore whether higher thresholds (such as 6.0 cm) could be used. It was suggested that the evidence highlighted diameters at which surgical intervention should not occur, rather than when surgical intervention should occur.

The committee noted that the identified studies did not consider the repair of complex AAA, which is more expensive than open surgery and standard EVAR. Based on their clinical experience, they agreed that long-term clinical outcomes in people who survive the repair

procedure for a complex AAA are likely to be no different to people with an infrarenal AAA. However, the short-term outcomes of repairing complex AAA are likely to be worse than infrarenal AAA, and so the balance of benefits and harms of early intervention may be different for this population. The committee noted that there is no evidence regarding early intervention in people with complex AAA, concluding that it was not possible to make a separate recommendation for complex AAA.

The committee considered that the recommendations would not impact on resource use as they reflect current good practice.

Other factors the committee took into account

The committee discussed whether it was necessary to specify what imaging technique should be used to measure aneurysm diameters. They noted that the majority of identified studies used ultrasound; however they agreed that they had not seen enough evidence to be explicit about the imaging technique. The committee however noted that it was important to specify the antero-posterior view (as opposed to lateral) for measuring aneurysm diameter. This was in accordance with techniques used the UKSAT trial.

The committee considered whether specific recommendations should be made for women. It was noted that women were underrepresented in the included studies and no evidence of differences between genders were explored. Since there was no robust evidence to confirm that 5.5 cm was the optimum threshold for considering surgery in men, the committee were reluctant to recommend a different unproven threshold for women. However, they agreed to emphasise in the research recommendation they made in Evidence review D, combining follow-up strategy and threshold for intervention, that research should be stratified according to sex (among other characteristics), in order to tease out any different balance of benefits and harms between men and women.

The committee also discussed whether the size threshold may vary according to age but acknowledged that there was no available evidence indicating that the size and resultant risk of rupture was dependent on age.

As the location of the aneurysm (for example, supra- or infra-renal) may influence which surgical approach is used, the committee considered whether the recommendations should be specific about the type of AAAs. The committee noted that that all the evidence presented was on infra-renal aneurysms; however they were not aware of any further evidence to suggest differential risks of rupture in different types of aneurysms. It was therefore agreed that the same recommendations should be applied to complex aneurysms. The committee noted that it is important that clinicians balance the risks of morbidity from complex surgery with the risks of aneurysm rupture.

Appendices

Appendix A – Review protocol

Review protocol for review question 7: Thresholds for abdominal aortic aneurysms repair

Review question 7	What is the effectiveness of early surgery compared with a continued surveillance approach in reducing morbidity and mortality in people with unruptured abdominal aortic aneurysms?
Objectives	To identify the threshold of asymptomatic AAA size at which the benefits of undergoing surgery outweigh the harms To determine the effectiveness of 'early' referral and surgery (referral at <5.5 cm) when compared with routine ultrasound surveillance (referral at 5.5 cm) in people with asymptomatic AAAs
Type of review	Intervention
Language	English only
Study design	i) Systematic reviews of study designs listed below Randomised controlled trials Quasi-randomised controlled trials ii) Analysis of UK registry data (National Abdominal Aortic Aneurysm Screening Programme)
Status	Published papers only (full text) No date restrictions
Population	People with an asymptomatic confirmed unruptured abdominal aortic aneurysm
Intervention	Early referral and surgery Based on aneurysm diameter; measurement approach to be taken into account
Comparator	'Watchful waiting'/ continued surveillance Referral and surgery at 5.5 cm (large AAA)
Outcomes	i) Mortality/survival (AAA-related; all-cause) Loss of EVAR-suitability Peri- and post-operative complications Need for reintervention Successful exclusion of the aneurysm, aneurysm rupture, or further aneurysm growth Quality of life Resource use, including length of hospital or intensive care stay, and costs ii) Proportion of people who experience rupture between referral for surgery and intervention, by diameter of AAA and age at time of referral
Other criteria for inclusion / exclusion of studies	Exclusion: Symptomatic or ruptured aneurysms Non-English language Abstract/non-published (i only)
Baseline characteristics to be extracted in evidence tables	Age Sex Comorbidities Ethnicity
Search strategies	See Appendix B

Review question 7	What is the effectiveness of early surgery compared with a continued surveillance approach in reducing morbidity and mortality in people with unruptured abdominal aortic aneurysms?
Review strategies	i) Double-sifting of randomly selected 20%. Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. 20% will be appraised by a second reviewer. Available Cochrane review (Filardo, 2015) will be used as a 'seed review'; studies published since 2014 and studies with outcomes of interest not reported in the Cochrane review will be added Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect. All key findings from evidence will be presented in GRADE profiles. ii) Expert witnesses will attend a committee meeting to answer questions from members of the committee. They will be invited to present their evidence at a committee meeting in the form of expert testimony based on a written paper. The Developer will write up the expert testimony and agree this with the witness after the meeting. i and ii) All key findings will be summarised in evidence statements.
Key papers	Filardo G, Powell JT, Martinez MA, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. 2015 Feb;4:CD001835 – SYSTEMATIC REVIEW; included papers: UKSAT ADAM CAESAR PIVOTAL

Appendix B – Literature search strategies

Clinical search literature search strategy

Main searches

Bibliographic databases searched for the guideline

- Cumulative Index to Nursing and Allied Health Literature - CINAHL (EBSCO)
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence for review questions

The searches were conducted between November 2015 and October 2017 for 31 review questions (RQ). In collaboration with Cochrane, the evidence for several review questions was identified by an update of an existing Cochrane review. Review questions in this category are indicated below. Where review questions had a broader scope, supplement searches were undertaken by NICE.

Searches were re-run in December 2017.

Where appropriate, study design filters (either designed in-house or by McMaster) were used to limit the retrieval to, for example, randomised controlled trials. Details of the study design filters used can be found in section 4.

Search strategy review question 7

Medline Strategy, searched 13th April 2016 **Database: Ovid MEDLINE(R) 1946 to March Week 5 2016** **Search Strategy:**
1 Aortic Aneurysm, Abdominal/
2 (aneurysm* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort* or spontan* or juxtarenal* or juxta-renal* or juxta renal* or paraerenal* or para-renal* or para renal* or suprarenal* or supra renal* or supra-renal* or short neck* or short-neck* or shortneck* or visceral aortic segment*)).tw.
3 Aortic Rupture/
4 (AAA or RAAA).tw.
5 (endovascular* adj4 aneurysm* adj4 repair*).tw.
6 (endovascular* adj4 aort* adj4 repair*).tw.
7 (EVAR or EVRAR or FEVAR or F-EAVAR or BEVAR or B-EVAR).tw.
8 (Anaconda or Zenith Dynalink or Hemobahn or Luminex* or Memoth-erm or Wallstent).tw.
9 (Viabahn or Nitinol or Hemobahn or Intracoil or Tantalum).tw.

Medline Strategy, searched 13th April 2016
Database: Ovid MEDLINE(R) 1946 to March Week 5 2016
Search Strategy:

10 or/1-9
11 X-Rays/
12 (x-ray* or x ray* or xray* or x-radiation* or x radiation* or roentgen ray* or grenz ray* or radiograph*).tw.
13 Aortography/
14 aortograph*.tw.
15 Tomography, X-Ray Computed/ (
16 (cat scan* or ct scan* or cine ct or cine-ct or tomodensitomet*).tw.
17 ((computed or computer assisted or computeriz* or computeris* or electron beam* or axial*) adj4 tomograph*).tw.
18 Four-Dimensional Computed Tomography/
19 (4d ct or 4dct or 4-dimensional CT or four dimensional CT).tw.
20 exp Tomography, Spiral Computed/
21 ((helical or spiral) adj4 ct*).tw.
22 exp Magnetic Resonance Imaging/
23 (nmr tomograph* or mr tomograph* or nmr imag* or mri scan* or functional mri* or fmri* or zeugmatograph* or cine-mri* or cinemri*).tw.
24 (proton spin adj4 tomograph*).tw.
25 ((chemical shift or magnetic resonance or magneti* transfer) adj4 imag*).tw.
26 exp Angiography/
27 (angiograph* or arteriograph*).tw.
28 exp Ultrasonography/
29 (ultrasound* or ultrason* or sonograph* or echograph* or echotomograph*).tw.
30 exp Echocardiography/
31 echocardiograph*.tw.
32 Finite element analysis/
33 (finite adj4 element* adj4 analys*).tw.
34 (finite adj4 element* adj4 comput*).tw.
35 FEA.tw.
36 ((wall adj4 stress adj4 analys*) or (wall adj4 stress adj4 comput*)).tw.
37 exp Computer simulation/
38 Software/
39 Image interpretation, computer-assisted/ or Radiographic image interpretation, computer-assisted/
40 Imaging Three-Dimensional/
41 exp Image enhancement/
42 Stress, mechanical/
43 (stress* adj4 mechanical*).tw.
44 (scan* or imag*).tw.
45 Watchful waiting/
46 (watchful adj4 waiting*).tw.
47 Mass screening/
48 screen*.tw.
49 Population surveillance/
50 surveillan*.tw.

Medline Strategy, searched 13th April 2016 **Database: Ovid MEDLINE(R) 1946 to March Week 5 2016** **Search Strategy:**
51 ((period* or test* or frequen* or regular* or routine* or rate or optimal* or optimis* or optimiz* or repeat* or interval*) adj4 (test* or monitor* or observ* or measur* or assess* or screen* or re-screen* or rescreen* or exam* or evaluat*)).tw.
52 ((aneursym* or sign* or diameter or risk*) adj4 (grow* or siz* or measur* or expan* or ruptur* or tear* or progress* or enlarg* or dilat* or bulg* or evaluat*)).tw.
53 Patient Selection/
54 ((patient or subject or criteria or treatment*) adj4 select*).tw.
55 ((follow-up or follow up) adj4 (visit* or repeat* or monitor* or assess* or care*)).tw.
56 Aftercare/
57 (aftercare or after-care).tw.
58 Disease progression/
59 ((disease or illness or condition) adj4 (progress* or worsen* or exacerbat* or deterior* or course or duration or trajector* or improv* or recur* or relaps* or remission)).tw.
60 or/11-59
61 10 and 60
62 animals/ not humans/
63 61 not 62
64 limit 63 to english language
Note: RCT, Systematic Review and Observational study filters appended to strategy.

Health Economics literature search strategy

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley) last updated Dec 2014
- Health Technology Assessment Database – HTA (Wiley) last updated Oct 2016
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to the population and intervention terms to identify relevant evidence. Searches were not undertaken for qualitative RQs. For social care topic questions additional terms were added. Searches were re-run in September 2017 where the filters were added to the population terms.

Health economics search strategy

Medline Strategy
Economic evaluations
1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/

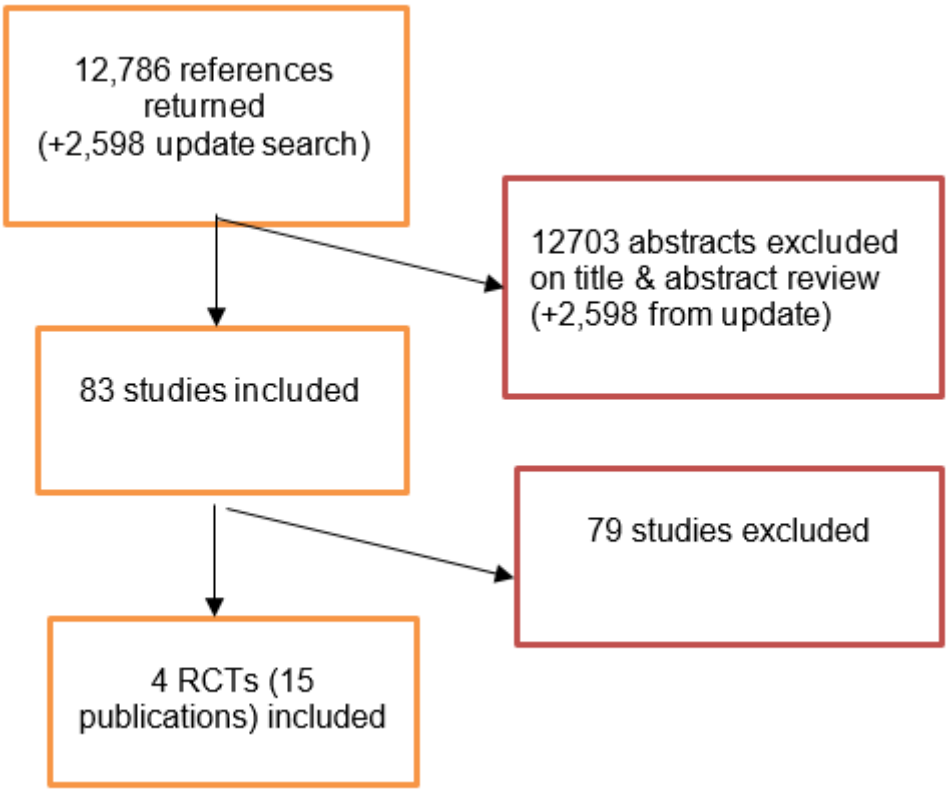
Medline Strategy

8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom*.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov*.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree* or analys*)).tw.
20 (cost or costs or costing* or costly or costed).tw.
21 (price* or pricing*).tw.
22 budget*.tw.
23 expenditure*.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic* or (pharmaco adj economic*)).tw.
26 or/1-25

Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly* or qald* or qale* or qtime*).tw.
7 disability adjusted life.tw.
8 daly*.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health* year* equivalent*.tw.
19 utilit*.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili*.tw.
22 rosser.tw.
23 quality of wellbeing.tw.

Medline Strategy
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble*.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence tables

Systematic review

<table>
<tr><th>Full citation</th><td colspan="2">Filardo G, Powell JT, Martinez MA, Ballard DJ (2015). Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. Feb;4:CD001835</td></tr>
<tr><td>Study details</td><td colspan="2">Study type: systematic review
Location: UK
Aim: To compare mortality, quality of life, and cost effectiveness of immediate surgical repair versus routine ultrasound surveillance in people with asymptomatic AAAs between 4.0 cm and 5.5 cm in diameter
Study dates: literature searched for publications up to February 2014
Follow-up: up to 6 years
Sources of funding (review-level): this study was supported by funding from the UK National Institute of Health Research (NIHR)
Sources of funding (study-level): The CAESAR trial was originally funded by Cook Medical. In December 2006, during the enrolment phase of the trial, Cook Medical withdrew sponsorship, and the trial continued as full spontaneous research. According to the CAESAR study team, the design, data collection, data analysis, data interpretation, and writing of reports regarding the trial were at all times conducted independently from the sponsor. However, we could not exclude a possible conflict of interest in the CAESAR trial given that the sponsor of the study, Cook Medical, withdrew. The PIVOTAL trial was sponsored by Medtronic Vascular, who hold the PIVOTAL trial study database. Two members of the PIVOTAL research team who received funding from and were consultants for Medtronic declared conflicts of interest; a third member of the PIVOTAL research team had previously been a consultant for Medtronic. The Vascular Surgery Academic Co-ordinating Center of the Cleveland Clinic was independently responsible for the conduct of the study and its analysis.</td></tr>
<tr><td>Participants (review level)</td><td colspan="2">Population: people of any age with an asymptomatic AAA ≥4 cm and <5.5 in the maximum external antero-posterior diameter measured by ultrasound or computed tomography. The aneurysm was restricted to the abdominal aorta distal to the renal arteries, was non-tender on examination and the patient should have been considered fit for surgery.
Sample size: 4 RCTs including 5,900 participants. 3314 participants fulfilled the inclusion criteria and were randomised.
Inclusion criteria: RCTs in which patients were randomly allocated to immediate surgery or ultrasound surveillance were included
Exclusion criteria: not reported</td></tr>
<tr><td>Participants (study-level)</td><td colspan="2"><table><tr><td>Study</td><td>Inclusion</td><td>Exclusion</td></tr><tr><td>ADAM</td><td>People with small (4.0 cm to 5.5 cm) non-</td><td>People who were considered unfit for surgery
People who had symptoms associated with the aneurysm</td></tr></table></td></tr>
</table>

Full citation	Filardo G, Powell JT, Martinez MA, Ballard DJ (2015). Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. Feb;4:CD001835		
		tender, asymptomatic AAAs People who were considered fit for surgery People aged 50 to 79 years	People who were unable to attend the follow-up visit People who were unable to give informed consent People who had received a revascularization procedure within three months of enrolment People who had a myocardial infarction within six months of enrolment People who were expected to survive less than five years because of invasive cancer or another life-threatening disease
	CAESAR	People with small (4.0 cm to 5.5 cm) non-tender, asymptomatic AAAs People who were considered fit for surgery People aged 50 to 79 years	People who were considered unfit for surgery People who had symptoms associated with the aneurysm People who were unable to attend the follow-up visit People who were unable to give informed consent People not anatomically suitable for endovascular repair People who had severe co-morbidities or a suprarenal or thoracic aorta equal to or greater than 4.0 cm in diameter People that needed urgent repair
	PIVOTAL	People with small (4.0 cm to 5.5 cm) non-tender, asymptomatic AAAs People who were considered fit for surgery People aged 40 to 90 years	People who were considered unfit for surgery People who had symptoms associated with the aneurysm People who were unable to attend the follow-up visit People who were unable to give informed consent People who had had an abdominal or thoracic repair, an aneurysm originating equal to or less than 1.0 cm from the most distal main renal artery Life expectancy of less than 3 years Society for Vascular Surgery score greater than 2 with the exception of age and controlled hypertension Baseline serum creatinine level greater than 2.5 mg/dL, People who did not meet the indications for use of the endograft device

<table>
<tr><td>Full citation</td><td colspan="2">Filardo G, Powell JT, Martinez MA, Ballard DJ (2015). Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. Feb;4:CD001835</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><td>UKSAT</td><td>People with small (4.0 cm to 5.5 cm) non-tender, asymptomatic AAAs
People who were considered fit for surgery
People aged 60 to 76 years</td><td>People who were considered unfit for surgery
People who had symptoms associated with the aneurysm
People who were unable to attend the follow-up visit
People who were unable to give informed consent</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td colspan="2">Literature searches were performed on the Cochrane Central Register of Controlled trials and the Cochrane Vascular Specialised Register (constructed from weekly electronic searches of MEDLINE, Embase, CINAHL, and AMED databases. Additional searches were also performed on the following conference proceedings: the International Society for Vascular Surgery Congress, the Society for Vascular Surgery Annual Meeting, the Society for Clinical Vascular Surgery Annual Symposium, the European Society for Vascular Surgery Annual Meeting. Bibliographies of included studies were reviewed to identify any additional studies that were relevant to the review question. Two independent reviewers were involved in study selection, data extraction, and risk of bias assessments. Any disagreements were resolved through discussion.</td></tr>
<tr><td>Interventions</td><td colspan="2">Review-level:

Surgical repair of the aneurysm consisting of insertion of a prosthetic inlay graft either by open surgery (abdominal or retroperitoneal route) (2 RCTs) or by endovascular repair imposing anatomical restrictions (2 RCTs).

Study-level:
<table>
<tr><td>Study</td><td>Intervention</td></tr>
<tr><td>ADAM</td><td>Standard open repair within 6 weeks after randomisation</td></tr>
<tr><td>CAESAR</td><td>EVAR a median of 22 days after randomisation</td></tr>
<tr><td>PIVOTAL</td><td>EVAR ≤ 30 days of randomisation</td></tr>
<tr><td>UKSAT</td><td>Standard open repair within 6 weeks after randomisation</td></tr>
</table>
</td></tr>
<tr><td>Comparison</td><td colspan="2">Review-level:

Surveillance of the maximum antero-posterior diameter performed regularly, with a maximum interval of six months. Surgical repair was then performed when the maximum antero-posterior diameter reached 5.5 cm, rapidly increased in size or became</td></tr>
</table>

<table>
<tr><td>Full citation</td><td>Filardo G, Powell JT, Martinez MA, Ballard DJ (2015). Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. Feb;4:CD001835</td></tr>
<tr><td></td><td>asymptomatic (4 RCTs). Two RCTs conducted routine ultrasound or computed tomography surveillance every 3 months if diameter was 5.0 cm to 5.5 cm.

Study-level:
<table>
<tr><td>Study</td><td>Intervention</td></tr>
<tr><td>ADAM</td><td>Followed without repair at similar regular intervals (at minimum once every 6 months), and surgery was performed within 6 weeks if: a) the aneurysm reached 5.5 cm; or b) the aneurysm enlarged by a minimum of 0.7 cm in 6 months or 1.0 cm in 1 year; or c) the aneurysm became symptomatic.</td></tr>
<tr><td>CAESAR</td><td>Seen every 6 months and repair allowed if the aneurysm grew to 5.5 cm diameter in size, rapidly increased in diameter (> 1 cm/year), or became symptomatic</td></tr>
<tr><td>PIVOTAL</td><td>Seen at 1 month, 6 months, and every 6 months thereafter for a minimum of 36 months and a maximum of 60 months after operation; participants were offered aneurysm repair when symptoms thought referable to the aneurysm developed, when the diameter of the aneurysm reached 5.5 cm, or when the aneurysm enlarged ≥ 0.5 cm between any 2 6-month assessments</td></tr>
<tr><td>UKSAT</td><td>Followed without repair at similar regular intervals (at minimum once every 6 months), and surgery was performed within 6 weeks if: a) the aneurysm reached 5.5 cm; or b) the aneurysm enlarged by a minimum 1.0 cm in 1 year; or c) the aneurysm became tender or symptomatic</td></tr>
</table></td></tr>
<tr><td>Outcomes measures</td><td>Mortality</td></tr>
<tr><td>Study Appraisal using AMSTAR (Assessing the Methodological Quality of Systematic Reviews)</td><td>1. Was an 'a priori' design provided? Yes
2. Was there duplicate study selection and data extraction? Yes
3. Was a comprehensive literature search performed? Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? Yes
5. Was a list of studies (included and excluded) provided? Yes
6. Were the characteristics of the included studies provided? Yes
7. Was the scientific quality of the included studies assessed and documented? Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? Yes
9. Were the methods used to combine the findings of studies appropriate? Yes
10. Was the likelihood of publication bias assessed? No, though less than 10 studies (this was not explicitly given as a reason)
11. Was the conflict of interest included? Yes
Overall risk of bias: Low</td></tr>
</table>

Full citation	**Filardo G, Powell JT, Martinez MA, Ballard DJ (2015). Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. Feb;4:CD001835**
	Directness: directly applicable

Additional evidence from randomised controlled trials

Full citation	**Cao P, De Rango P, Verzini F et al. (2011) Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): results from a randomised trial. Eur J Vasc Endovasc Surg. 2011; 41(1):13-25**
Study details	Study type: Randomised controlled trial Location: Italy Aim: to compare results after endovascular aortic aneurysm repair (EVAR) or surveillance in AAA <5.5 cm Study dates: 2004 to 2008 Follow-up: median of 32.4 months Sources of funding: originally funded by Cook Medical. In December 2006, during the enrolment phase of the trial, Cook Medical withdrew sponsorship, and the trial continued as full spontaneous research
Participants	Population: people with confirmed AAA between 4.0 and 5.0 cm in diameter Sample size: 360 participants Inclusion criteria: people aged 50 to 79 years with small (4.0 cm to 5.5 cm) non-tender, asymptomatic AAAs were included. All participants were considered fit for surgery Exclusion criteria: people who were considered unfit for surgery, had symptoms associated with the aneurysm, were unable to attend the follow-up visit, were unable to give informed consent, had aneurysms that were not anatomically suitable for endovascular repair, had severe co-morbidities or a suprarenal or thoracic aorta equal to or greater than 4.0 cm in diameter, or who needed urgent repair were excluded Baseline characteristics: • Men 95.8% male • Mean age: 68.9 years • Smoking: 55.3% • Hypertension: 75.3% • Cardiac disease: 39.2% • Cerebrovascular disease: 15% • Peripheral artery disease: 12.8% • COPD: 28.3%

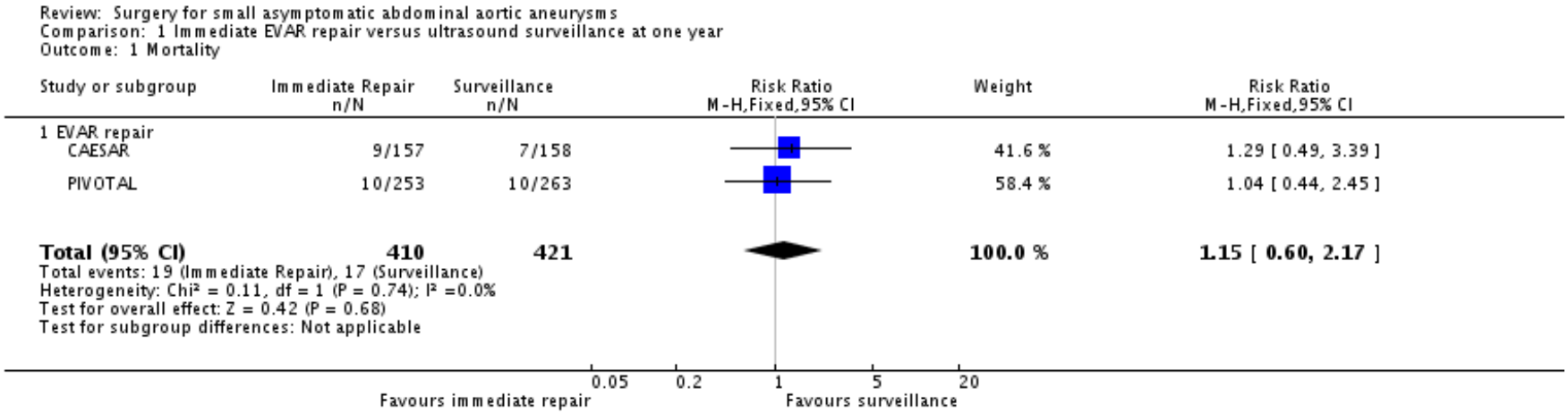
Full citation	Cao P, De Rango P, Verzini F et al. (2011) Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): results from a randomised trial. Eur J Vasc Endovasc Surg. 2011; 41(1):13-25
	• Diabetes: 13.6% • Renal disease: 8.1% • BMI >31 kg/m2: 18.9%
Intervention	Immediate repair: EVAR performed at a median of 22 days after randomisation
Comparison	US surveillance: scans performed every 6 months and repair allowed if the aneurysm grew to 5.5 cm diameter in size, rapidly increased in diameter (> 1 cm/year), or became symptomatic
Outcomes measures	Aneurysm rupture, aneurysm growth, need for reintervention, conversion to open repair
Risk of bias assessment (using Cochrane risk of bias assessment tool)	1. Random sequence generation (selection bias): Low risk – Randomisation was designed with equal probability (1:1 ratio) of assignment to either immediate endovascular repair or surveillance by means of a computed-generated random number list, stratified by centre using a permuted block design and carried out online through the Internet. 2. Allocation concealment (selection bias): Unclear risk – unblended study 3. Blinding of participants and personnel (performance bias): Unclear risk – The nature of the intervention meant it was not possible to blind participants 4. Blinding of outcome assessment (detection bias): Low-risk – Assessors were not blinded; however, this is unlikely to have introduced bias as objective outcomes were assessed 5. Incomplete outcome data (attrition bias): Low risk – There were similarly low losses to follow-up rates between each study arm 6. Selective reporting (reporting bias): Low risk – Authors published findings on the main study outcomes of this review 7. Other bias: Low risk – None identified Overall risk of bias: Low Directness: directly applicable

Full citation	**Ouriel K, Clair DG, Kent KC et al. (2010); Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) Investigators. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. J Vasc Surg; 51(5):1081-7**
Study details	Study type: Randomised controlled trial Location: USA Aim: to compare early endovascular repair and surveillance in patients with small aneurysms Study dates: not specified Follow-up: mean of 20 months Sources of funding: the study was funded by Medtronic Vascular, which now holds the trial database, and the funding source was not specified in the report of trial results, but was specified in the 2009 paper describing the rationale and protocol for the study (PIVOTAL)
Participants	Population: people with confirmed AAA between 4.0 and 5.0 cm in diameter Sample size: 728 participants Inclusion criteria: people aged 40 to 90 years with small (4.0 cm to 5.5 cm) non-tender, asymptomatic AAAs were included. All participants were considered fit for surgery Exclusion criteria: people who were considered unfit for surgery, had symptoms associated with the aneurysm, were unable to attend the follow-up visit, were unable to give informed consent, had an abdominal or thoracic repair, had an aneurysm originating equal to or less than 1.0 cm from the most distal main renal artery, a life expectancy of less than 3 years were excluded Baseline characteristics: • Mean age: 68.9 years • Sex: 86.7% male • Current tobacco use: surveillance 29.0%, immediate EVAR 27.7% • History of family aneurysmal disease: surveillance 23.3%, immediate EVAR 17.5% • History of coronary artery disease: surveillance 56.3%, immediate EVAR 51.0% • History of peripheral vascular disease: surveillance 26.3%, immediate EVAR 17.5% • History of hypertension: surveillance 74.0%, immediate EVAR 79.9% • History of abdominal surgery surveillance 38.7%, immediate EVAR 38.2% • History of gastrointestinal disease: surveillance 36.7%, immediate EVAR 37.9% • White race: surveillance 94.3%, immediate EVAR 92.0% • BMI >31 kg/m2: 18.9%

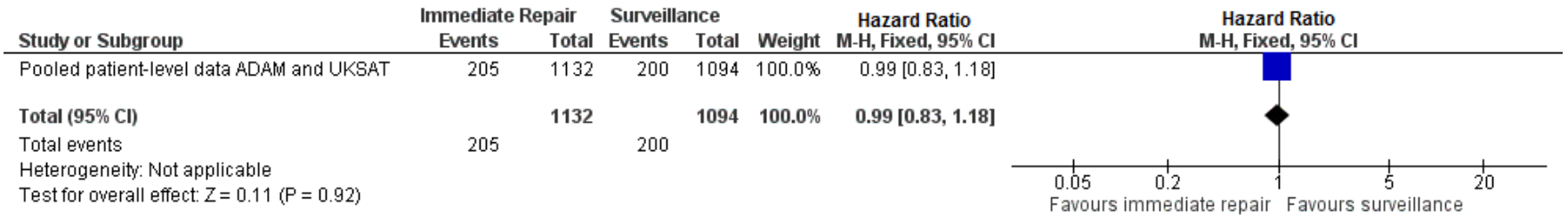
Full citation	**Ouriel K, Clair DG, Kent KC et al. (2010); Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) Investigators. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. J Vasc Surg; 51(5):1081-7**
Intervention	Immediate repair: EVAR ≤ 30 days of randomisation
Comparison	US surveillance: scans performed at 1 month, 6 months, and every 6 months thereafter for a minimum of 36 months and a maximum of 60 months after operation. Participants were offered aneurysm became symptomatic reached a diameter 5.5 cm, or when the aneurysm enlarged ≥ 0.5 cm between any 2 6-month assessments.
Outcomes measures	Aneurysm rupture, need for reintervention, conversion to open repair
Risk of bias assessment (using Cochrane risk of bias assessment tool)	1. Random sequence generation (selection bias): Low risk – The randomisation procedure was designed to provide equal probability of assignment to each of the treatment groups by means of a computer-generated random-number code. 2. Allocation concealment (selection bias): Unclear risk – unblinded study 3. Blinding of participants and personnel (performance bias): Unclear risk – The nature of the intervention meant it was not possible to blind participants. 4. Blinding of outcome assessment (detection bias): Low-risk – Assessors were not blinded; however, this is unlikely to have introduced bias as objective outcomes were assessed. 5. Incomplete outcome data (attrition bias): Low risk – There were similarly low losses to follow-up rates between each study arm 6. Selective reporting (reporting bias): High risk – Authors did not publish findings on all of the main study outcomes of this review 7. Other bias: High risk – The study was funded by the manufacturer who owned and managed the trial database Overall risk of bias: Moderate Directness: directly applicable

Appendix E – Forest plots

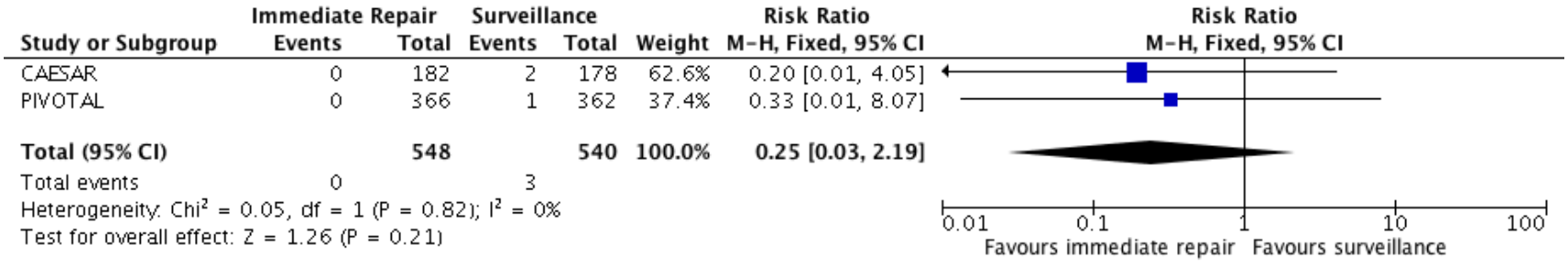
Mortality at 1 year



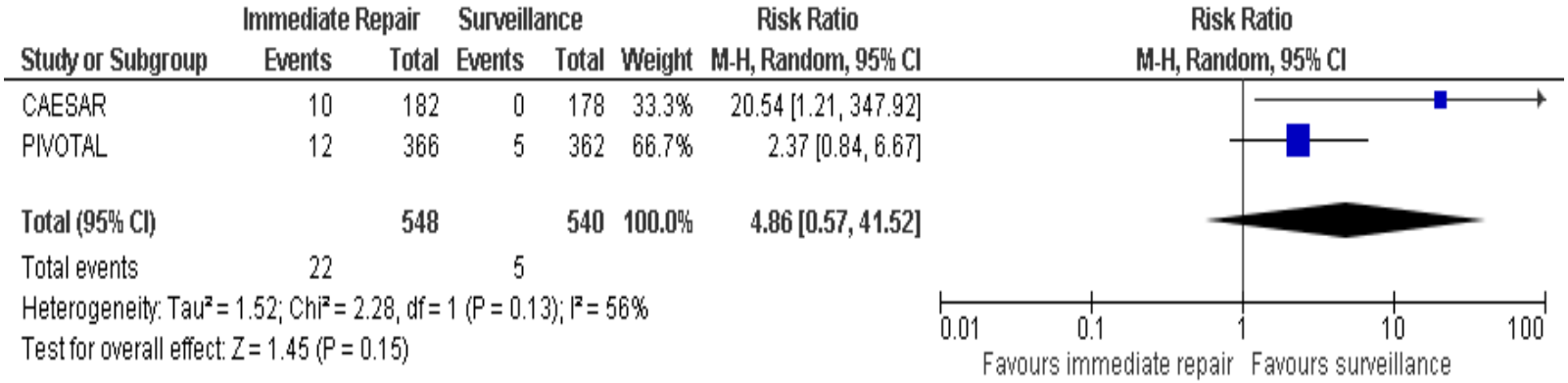
Mortality at up to 6 years



Aneurysm rupture at 1 year



Need for reintervention at 1 year



Appendix F – GRADE tables

Mortality

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Immediate surgery**	**Surveillance**	**Summary of results**	
Immediate EVAR vs surveillance; mortality at 1 year follow-up; effect sizes below 1 favour immediate repair									
2 (CEASAR & PIVOTAL trials)	RCTs	Very serious[1,2]	Not serious	Not serious	Very serious[3]	410	421	RR 1.15 (0.60, 2.17)	Very low
Immediate open repair vs surveillance; mortality at up to 6 years; effect sizes below 1 favour immediate repair									
2 (ADAM & UKSAT trials)	RCTs	Not serious	Not serious	Not serious	Not serious	1132	1194	RR 0.99 (0.93, 1.18)	High

1. Variation in the timing of intervention across studies, downgrade 1 level.
2. A study contributing over 33.3% of the weighting in the meta-analysis was funded by the manufacturer who owned and managed the trial database, downgrade 1 level.
3. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.

Aneurysm rupture

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Immediate surgery**	**Surveillance**	**Summary of results**	
Immediate EVAR vs surveillance; aneurysm rupture at 1 year follow-up; effect sizes below 1 favour immediate repair									
2 (CEASAR & PIVOTAL trials)	RCTs	Very serious[1,2]	Not serious	Not serious	Very serious[3]	548	540	RR 0.25 (0.03, 2.19)	Very low
Referral to AAA surgery; effects below 1 favour antibiotic									

1. Variation in the timing of intervention across studies, downgrade 1 level.
2. A study contributing over 33.3% of the weighting in the meta-analysis was funded by the manufacturer who owned and managed the trial database, downgrade 1 level.
3. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.

Aneurysm growth

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Immediate surgery	Surveillance	Summary of results	
Immediate EVAR vs surveillance; aneurysm growth at 1 year follow-up; effect sizes below 1 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Serious[1]	182	178	HR 10.49 (6.88, 15.98)	Moderate

1. Wide confidence intervals, downgrade 1 level.

Adverse events

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Immediate surgery	Surveillance	Summary of results	
Immediate EVAR repair vs surveillance; any adverse event at 1 year follow-up; effect sizes below 1 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Not serious	182	178	RR 3.42 (1.75, 6.70)	High
Immediate EVAR vs surveillance; major adverse events at 1 year follow-up; effect sizes below 1 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Very serious[1]	182	178	RR 1.17 (0.36, 3.78)	Low
Immediate EVAR vs surveillance; any type of endoleak at 30 days; effect sizes below 1 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Very serious[1]	182	178	RR 1.62 (0.74, 3.54)	Low
Immediate EVAR vs surveillance; any type of endoleak at 1 year follow-up; effect sizes below 1 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Serious[2]	175	71	RR 4.26 (1.03, 17.6)	Moderate

1. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.
2. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.

Need for additional intervention

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Immediate surgery	Surveillance	Summary of results	
Immediate EVAR repair vs surveillance; conversion to open surgery; effect sizes below 1 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Very serious[3]	175	71	RR 3.68 (0.20, 67.5)	Low
Immediate EVAR vs surveillance; need for additional intervention at 1 year follow-up; effect sizes below 1 favour immediate repair									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Immediate surgery**	**Surveillance**	**Summary of results**	
2 (CEASAR & PIVOTAL trials)	RCTs	Very serious[1,2]	Not serious	Serious[4]	Very serious[3]	548	540	RR 4.86 (0.57, 41.52)	Very low
Referral to AAA surgery; effects below 1 favour antibiotic									

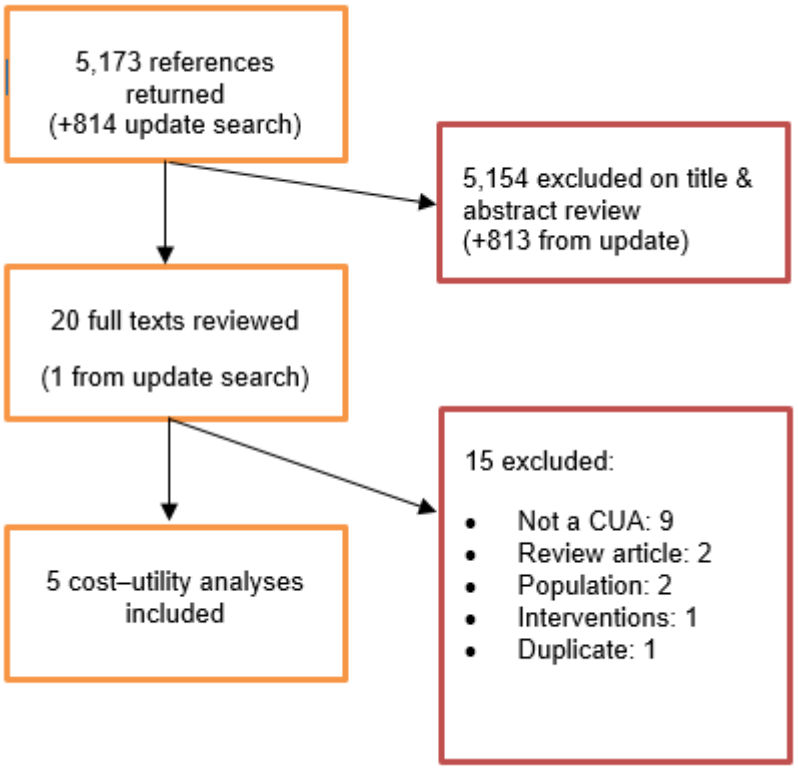
1. Variation in the timing of intervention across studies, downgrade 1 level.
2. A study contributing over 33.3% of the weighting in the meta-analysis was funded by the manufacturer who owned and managed the trial database, downgrade 1 level.
3. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.
4. I^2 value between 33.3% and 66.7%, downgrade 1 level.

Quality of life

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Immediate surgery**	**Surveillance**	**Summary of results**	
Immediate EVAR vs surveillance; quality of life at 1 year follow-up; effect sizes below 0 favour immediate repair									
1 CEASAR trial	RCT	Not serious	Not serious	Not serious	Serious[1]	173	166	RR 2.4 (-1.7, 6.6)	Moderate

1. Non-significant result, downgrade 1 level.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (QALY-maximising repair threshold vs. current practice)			Conclusions	Uncertainty
			Cost (95% CI)	Effect (95% CI)	ICER		
Grant et al. (2015) Economic model comparing QALY-maximising repair strategies with current practice diameter thresholds. UK. **Directly applicable** **Potentially serious limitations** [a,b,c]	Effects: IPD from the Vascular Governance North West database and National Vascular Database for repair outcomes. RESCAN data for AAA growth and rupture rates (n=15,475). EVAR and OSR outcomes assumed to be equivalent after 2 years. Costs: VGNW data and NHS reference costs. Utilities: UK population norms (Kind et al. 1999), surgery-related decrements (systematic review).	Microsimulation model based on risk models to predict peri- and post-operative outcomes. 100,000 runs. Repair by EVAR or OSR. Long-term complications (e.g. MI, stroke) not modelled. Scan every 12 months until 4.5cm, then every 3 months. Repair at 5.5cm in men, 5.0cm in women. Lifetime horizon, 3.5% discount rate applied to all outcomes.	**4.0cm AAA** *Max QALY:* -£172 (-11,646, 18,275)	**Male 65yo** *4.0cm repair* 0.047 (-8.962, 9.055)	**OSR** Early repair dominates	‘The economic model indicates no clear difference in the mean expected costs or QALYs between the [QALY-maximising thresholds], which formally combines aneurysm size and other factors, and the current thresholds for surgery based on the size of the aneurysm alone.’	All QALY-maximising intervention thresholds had a 49% to 51% probability of having an ICER under £20,000 per QALY. The confidence intervals around incremental costs and QALYs are very wide, crossing zero. Cost–utility results are therefore highly uncertain.
			6.8cm AAA *Max QALY:* £162 (-13,823, 13,793)	**Male 65yo** *6.9cm repair* 0.025 (-9.121, 9.073)	**OSR** £6,583		
			4.0cm AAA *Max QALY:* -£405 (-17,655, 13,576)	**Male 86yo** *6.0cm repair* 0.017 (-4.940, 4.926)	**EVAR** Early repair dominates		
			3.8cm AAA *Max QALY:* £2,716 (-13,650, 22,552)	**Female 65yo** *4.0cm repair* 0.044 (-7.901, 7.825)	**OSR** £63,361		
			4.8cm AAA *Max QALY:* £218 (-29,623, 39,303)	**Male 80yo** *4.9cm repair* 0.033 (-7.478, 7.504)	**EVAR** £5,799		
			6.5cm AAA *Max QALY:* £143 (-32,385, 39,933)	**Male 80yo** *6.6cm repair* 0.006 (-7.516, 7.510)	**EVAR** £23,155		

Key: CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR, open surgical repair QALY, quality-adjusted life year; VGNW, Vascular Governance North West; yo, years old.

a. Impact of long-term complications, such as cardiovascular events, not explicitly modelled.

b. EVAR and OSR considered equivalent, and having identical outcomes after 2 years.

c. Cost–utility results presented for specific vignettes. ICERs are not generalisable to people with other characteristics.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Young et al. (2010) Economic model comparing EVAR for AAA 4.0-5.5cm with surveillance until 5.5cm then EVAR or surgical repair. US. **Partially applicable** [a,b] **Minor limitations** [c]	Effects: Various published sources. Costs: Various published sources and Medicare charges (adjusted for mark-up). Utilities: Utility scores sourced from various published sources, including the EVAR-1 trial.	Markov model (observational management, 2x post-repair, stroke, dialysis, amputation, 5x transient complications, dead) with a lifetime horizon. 3% discount rate applied to all outcomes. 68-year old cohort.	*Repair at 5.0cm vs. 5.5cm* $3,000 (2007$)	-0.05 QALYs	Dominated	'This cost-effectiveness analysis supports the current practice of observational management for AAAs <5.5cm in diameter.'	In PSA, observational management until a 5.5cm AAA diameter had an ICER of less than $50,000 per QALY vs. in 79% of iterations compared with early intervention. EVAR for AAAs ≥4.9cm would be cost-effective if post-EVAR mortality was ≤1.91% per year, and for AAAs ≥5.2cm if 5-6cm AAAs had an annual rupture rate of 13.4%. Two-way sensitivity analysis found open surgical repair to be more cost-effective than EVAR.

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; PSA, probabilistic sensitivity analysis.

a. US setting.
b. Discount rates of 3%.
c. Methods of identifying and synthesising baseline outcomes and effects are not clear.

Study, Population, Country and Quality	Data Sources	Other Comments	Net benefit maximising strategy at £20,000 per 1 QALY (incremental costs and QALYs NR)	Conclusions	Uncertainty
Chambers et al. (2009) Modelling analysis comparing immediate EVAR, immediate OSR,	Effects: Baseline risk equations estimated using IPD from the EUROSTAR study. Relative effects from EVAR-1 and DREAM	Lifetime horizon, 3.5% discount rates, Markov model. Risk equations constructed to predict operative mortality,	Very poor fitness (patient suitable for EVAR-2) *4.0 cm AAA:* • Patients up to age 68.5: continue surveillance. • Patient aged 69 or older: discharge (no repair). *4.5 cm AAA:* • Patients up to age 68: immediate OSR.	'For patients … with very poor operative fitness … EVAR might be cost-effective at … £20,000 per QALY up to 71.5 years in patients	The optimal strategy results were relatively robust to a scenario that

Study, Population, Country and Quality	Data Sources	Other Comments	Net benefit maximising strategy at £20,000 per 1 QALY (incremental costs and QALYs NR)	Conclusions	Uncertainty
6-monthly surveillance, and discharge without intervention. UK. **Partially applicable** [a] **Very serious limitations** [b,c,d,e]	RCTs. Untreated cohort modelled based on a historic meta-analysis (Michaels, 1992). Costs: Intervention, monitoring and readmission. Resource use from EVAR-1. Costs from EVAR-1 and UK sources. Utilities: UK population norms (Kind et al. 1999), surgery-related decrements for 6 months (EVAR-1).	post-operative mortality, and readmission. Readmissions are AAA-related only. No long-term CV events. Non-AAA mortality converges after ~3 years. AAA-related mortality benefit of EVAR maintained. Rupture fatality rate assumed 100%. Net benefit of surveillance strategy estimated by backwards optimisation from 'last' decision point, when AAA reaches 8.0cm (assumed that surveillance is no longer an option).	• Patients aged 68.5 to 70.5: immediate EVAR. • Patients aged 71: continued surveillance. • Patients aged 71.5 or older: discharge (no repair). *5.0 cm AAA:* • Patients up to age 71.5: immediate EVAR. • Patients aged 72 to 72.5: continued surveillance. • Patient aged 73 or older: discharge (no repair). Poor fitness (borderline EVAR-1 / EVAR-2) *4.0 cm AAA:* • Patients up to age 73: continue surveillance. • Patient aged 73.5 or older: discharge (no repair). *4.5 cm AAA:* • Patients up to age 75.5: immediate OSR. • Patients aged 76 or older: discharge (no repair). *5.0 cm AAA:* • Patients up to age 76: immediate OSR. • Patients aged 76.5 to 77: continued surveillance. • Patient aged 77.5 or older: discharge (no repair).	with a 5-cm aneurysm. Watchful waiting would be cost-effective for patients with a [4 cm] aneurysm up to age 68.5 years.' For patients with a small aneurysm at the upper margin of fitness for OSR …watchful waiting is cost-effective with an aneurysm of 4 cm up to 75.5 years. For … an aneurysm of 5 cm … EVAR is cost-effective at a threshold of £30,000 per QALY up to about 78 years.'	strongly favours EVAR (cost equal to OSR; reduced readmission rate; 50% lower unit cost of follow-up). No probabilistic analysis was undertaken.

Key: CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; NR, not reported; OSR, open surgical repair QALY, quality-adjusted life year; RCT, randomised controlled trial.

a. Infrarenal aneurysms only, in patients with poor or very poor operative fitness.
b. Impact of rupture (assumed 100% fatal) and long-term non-aneurysm complications not fully captured by model.
c. Assumption of maintained AAA-related mortality difference not supported by 15-year EVAR-1 study data.
d. Untreated cohort modelled using historic data from a 1992 meta-analysis, may not reflect current outcomes of untreated cases.
e. No fully incremental outcomes reported, only optimal strategies, and limited analysis of uncertainty (no probabilistic analysis).

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Schermerhorn et al. (2000) Economic model comparing early open	Effects: Small Aneurysm Trial data.	Markov model (alive pre-surgery, alive post-surgery, dead),	**By horizon:** Lifetime	Lifetime	Lifetime	'Early surgery may be cost-effective … particularly	Scenario analysis: Operative mortality must be less than 3% for early surgery to be considered

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
surgical repair at different AAA diameters versus surveillance. US. **Partially applicable** [a,b] **Very serious limitations** [c,d,e,f]	Costs: Small Aneurysm Trial data. Utilities: Assumption of equivalent quality of life in both surveillance and surgery arms (0.86 from a chronic disease study).	with a lifetime horizon and 6-month cycles. 3% discount rate applied to all outcomes.	$1,510 (96/97$) 6 years $1,510 **By diameter:** *4.0-4.4cm* $1,350 *4.5-4.8cm* $1,410 *4.9-5.5cm* $1,820 **By age:** *60-66* $1,230 *67-71* $1,770 *72-76* $1,550	0.14 QALYs 6 years -0.04 *4.0-4.4cm* -0.27 *4.5-4.8cm* 0.18 *4.9-5.5cm* 0.54 *60-66* 0.20 *67-71* 0.63 *72-76* -0.43	$10,800 $/QALY 6 years Dominated *4.0-4.4cm* Dominated *4.5-4.8cm* $7,800 *4.9-5.5cm* $3,400 *60-66* $6,100 *67-71* $2,800 *72-76* Dominated	younger patients (<72 years of age) with larger AAAs (≥4.5 cm).'	cost-effective over the 6 year time horizon. Even with 0% of operative mortality risk, patients with AAA diameters <4.5cm and/or aged 72 or older did not benefit from early intervention. Sensitivity analysis of the cost of surgery suggested that the ICER remains below $50,000 per QALY at all costs up to $14,000 (i.e. 175% of the actual cost).

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

a. US setting.
b. Discount rates of 3%.
c. No probabilistic sensitivity analysis presented.
d. Limited evidence to inform quality of life estimates other than that of a chronic disease study, applied to all patients.
e. Input data largely obtained from a single study.
f. Potentially important features missing from model structure (complications, AAA growth).

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Katz & Cronenwett (1994) Economic model comparing open surgical repair at 4.0cm AAA diameter with 6-monthly surveillance until 5.0cm. US. **Partially applicable** [a,b] **Very serious limitations** [c,d,e]	Effects: Various published sources. Costs: Physician and hospital charges (adjusted for mark-up). Utilities: Utility scores obtained from literature for chronic renal failure only; otherwise from author assumptions (well=1, stroke=0.5).	Markov model (observational management, elective and emergency repair, post-repair, complications, dead). Time horizon not reported. Observational management was by 6-monthly ultrasound with 100% compliance. 5% discount rate applied to all outcomes. 60-year old male cohort.	*Early surgery vs. wait* ***Aged 60*** $5,858 (1992$) ***Aged 70*** $NR ***Aged 80*** $NR	0.34 QALYs NR NR	$17,404 (£18,829*) $36,589 (£39,584*) $140,972 (£152,513*)	'Our current results indicate that the cost-effectiveness of early surgery for 4cm diameter AAAs in properly selected patients is comparable to that of other commonly accepted preventive interventions.'	Two-way sensitivity analysis found early surgery to be more cost-effective with decreasing operative mortality and with decreasing compliance with ultrasound surveillance. Early surgery was less cost-effective with increasing age at presentation and decreasing AAA rupture rates.

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; PSA, probabilistic sensitivity analysis.
** Estimated ICER conversion: £1=$1.765442 (1992 average, fxtop.com); PSSRU inflation indices (1993/94 to 2015/16): 297.0/155.5; £18,829 per QALY gained.*

a. US setting.
b. Outcomes discounted at 5% per year. Likely to affect long-term results (Katz et al. 1992. JAMA; 268 (19): 2678-86).
c. No probabilistic sensitivity analysis presented
d. A number of utility values are informed by researcher assumptions (Katz et al. 1992. JAMA; 268 (19): 2678-86).
e. Analysis time horizon not reported.

Appendix I – Health economic evidence profiles

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness	
Grant 2015 QALY-maximising repair vs. current practice	Potentially serious limitations [1,2,3]	Directly applicable	Patient simulation model with a lifetime horizon	-£405 to £2,716	0.017 to 0.047	Early repair dominant to £63,361 per QALY gained	Wide confidence intervals around incremental outcomes, ~50% probability of ICER under £20,000.
Young 2010 Early EVAR vs. surveillance until 5.5 cm	Minor limitations [4]	Partially applicable [a,b]	US Markov model with a lifetime horizon	$3,000	-0.05	Early EVAR dominated	EVAR at 4.9 cm cost-effective if post-EVAR mortality was ≤1.91% per year, and at 5.2 cm if 5-6 cm rupture rate was 13.4% per year.
Chambers 2009 Immediate repair vs. surveillance vs. discharge	Very serious limitations [1,5,6,7,8]	Partially applicable [c,d]	Markov model with a lifetime horizon	NR	NR	Early repair may be cost-effective if younger, fitter and/or larger aneurysm	Robust to a scenario that strongly favours EVAR.
Schermerhorn 2000 Early OSR vs. surveillance	Very serious limitations [8,9,10]	Partially applicable [a,b]	US Markov model with a lifetime horizon	$1,350 to $1,820	-0.43 to 0.63	Early OSR dominated to $10,800 per QALY gained	Even with 0% operative mortality, early OSR not beneficial at <4.5cm and/or ages 72 or older.
Katz 1994 Early OSR vs. surveillance until 5 cm	Very serious limitations [8,10,11]	Partially applicable [a,e]	US Markov model, time horizon not reported	$5,858	0.34	$17,404 per QALY gained	Early surgery more cost-effective with decreasing operative mortality and compliance with surveillance. Less cost-effective with increasing age.

1. Long-term complications (e.g. cardiovascular events) not modelled.
2. EVAR assumed equivalent to OSR.
3. Cost-utility results presented for individual patients, may not be generalisable to others.
4. Evidence synthesis methods not reported.
5. Ruptures assumed to be fatal in 100% of cases Rupture repair and post-rupture survival not captured.
6. Untreated cohort informed by historic non-randomised data (1992).
7. Incremental and total cost and QALY results not reported.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	QALYs	Cost effectiveness	
8. No probabilistic sensitivity analysis conducted. 9. Informed by a single clinical study. 10. Limited evidence and/or author assumptions used to inform quality of life inputs. 11. Time horizon not reported.							
a. US setting. b. 3% discount rates. c. Infrarenal aneurysms only. d. Patients with poor or very poor operative fitness only. e. 5% discount rates.							
Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; NR, not reported; OSR, open surgical repair; QALY, quality-adjusted life year.							

Appendix J – Excluded studies

Clinical studies

Short Title	Title	Reason for exclusion
Anonymous (1998)	Health service costs and quality of life for early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. UK Small Aneurysm Trial Participants	Secondary publication of included study
Avgerinos (2010)	Should the size threshold for elective abdominal aortic aneurysm repair be lowered in the endovascular era? No	Not a relevant study design
Ballard (2000)	Surgery for small asymptomatic abdominal aortic aneurysms	Duplicate and/or already included within an included systematic review
Ballard (2008)	Surgery for small asymptomatic abdominal aortic aneurysms	Duplicate and/or already included within an included systematic review
Ballotta (1999)	Elective surgery for small abdominal aortic aneurysms	Not a relevant study design
Baxter (2008)	Medical management of small abdominal aortic aneurysms	Not a relevant study design
Bengtsson (1993)	Expansion pattern and risk of rupture of abdominal aortic aneurysms that were not operated on	Not a relevant study design
Bernstein (1984)	Abdominal aortic aneurysm in high-risk patients. Outcome of selective management based on size and expansion rate	Not a relevant study design
Bjorck (2014)	Commentary on 'a decision aid regarding treatment options for patients with an asymptomatic abdominal aortic aneurysm: A randomised clinical trial'	Not a relevant intervention and/or comparator
Brown (1992)	The selective management of small abdominal aortic aneurysms: the Kingston study	Not a relevant study design
Brown (1996)	Selective management of abdominal aortic aneurysms in a prospective measurement program	Not a relevant study design
Brown (2003)	Selective management of abdominal aortic aneurysms smaller than 5.0 cm in a prospective sizing program with gender-specific analysis	Not a relevant study design
Buckenham (2007)	Abdominal aortic aneurysm surveillance: application of the UK Small Aneurysm Trial to a New Zealand tertiary hospital	Not a relevant study design
Cao (2005)	Comparison of surveillance vs Aortic Endografting for Small Aneurysm Repair (CAESAR) trial: study design and progress	Duplicate and/or already included within an included systematic review

Short Title	Title	Reason for exclusion
Cao (2005)	Comparison of surveillance vs aortic endografting for small aneurysm repair (CAESAR) trial: Study design and progress	Study protocol
Cao (2007)	Regarding "Surveillance of small aortic aneurysms does not alter anatomic suitability for endovascular repair"	Not a peer-reviewed publication
Cappeller (1997)	Possible objectification of a critical maximum diameter for elective surgery in abdominal aortic aneurysms based on one- and three-dimensional ratios	Not a relevant study design
Chun (2016)	Surveillance outcomes of small abdominal aortic aneurysms identified from a large screening program	Not a relevant study design
De Rango (2012)	Effects of diabetes on small aortic aneurysms under surveillance according to a subgroup analysis from a randomized trial	Not a relevant intervention and/or comparator
Dryjski (1994)	The small abdominal aortic aneurysm: the eternal dilemma	Not a relevant study design
Eisenstein (2013)	Economic analysis of endovascular repair versus surveillance for patients with small abdominal aortic aneurysms	Not a relevant study design
Filardo (2012)	Surgery for small asymptomatic abdominal aortic aneurysms	Duplicate and/or already included within an included systematic review
Galland (1998)	The fate of patients undergoing surveillance of small abdominal aortic aneurysms	Not a relevant study design
Galyfos (2015)	Small Abdominal Aortic Aneurysms: Should We Wait?	Not a relevant study design
Georgakarakos (2012)	Technical advances with newer aortic endografts provide additional support to withhold the early endovascular repair of small abdominal aortic aneurysms until it is really needed	Not a relevant study design
Giannoglou (2006)	Predicting the risk of rupture of abdominal aortic aneurysms by utilizing various geometrical parameters: revisiting the diameter criterion	Not a relevant intervention and/or comparator
Gloviczki (2013)	Abdominal aortic aneurysm size: The effect of treatment vs observation on outcome	Not a relevant study design
Golledge (2007)	The outcome of endovascular repair of small abdominal aortic aneurysms	Not a relevant study design
Greenhalgh (1995)	The U.K. small aneurysm trial: Design, methods and progress	Duplicate and/or already included within an included systematic review
Hallett (1993)	Early and late outcome of surgical repair for small abdominal aortic aneurysms: a population-based analysis	Not a relevant study design

Short Title	Title	Reason for exclusion
Hinterseher (2013)	Long-term quality of life of abdominal aortic aneurysm patients under surveillance or after operative treatment	Not a relevant intervention and/or comparator
Johansson (1990)	Survival in patients with abdominal aortic aneurysms. Comparison between operative and nonoperative management	Not a relevant study design
Katz (1992)	Management of small abdominal aortic aneurysms. Early surgery vs watchful waiting	Not a relevant study design
Katz (1994)	The cost-effectiveness of early surgery versus watchful waiting in the management of small abdominal aortic aneurysms	Not a relevant study design
Kontopodis (2014)	Value of volume measurements in evaluating abdominal aortic aneurysms growth rate and need for surgical treatment	Not a relevant study design
Kontopodis (2016)	The - Not So - Solid 5.5cm Threshold for Abdominal Aortic Aneurysm Repair: Facts, Misinterpretations, and Future Directions	Not a relevant study design
Lalka (2005)	Endovascular vs open AAA repair: does size matter?	Not a relevant study design
LeCroy (2008)	Should endovascular repair be used for small abdominal aortic aneurysms?	Not a relevant study design
Lederle (1990)	Management of small abdominal aortic aneurysms	Not a relevant study design
Lederle (1994)	Design of the abdominal aortic Aneurysm Detection and Management Study. ADAM VA Cooperative Study Group	Duplicate and/or already included within an included systematic review
Lederle (1994)	Design of the abdominal aortic aneurysm detection and management study	Study protocol
Lederle (2006)	A summary of the contributions of the VA cooperative studies on abdominal aortic aneurysms	Not a peer-reviewed publication
Lederle (2008)	Comment on "Screening for abdominal aortic aneurysm reduces overall mortality in men"	Not a relevant study design
Lindholt (2000)	Psychological consequences of screening for abdominal aorticaneurysm and conservative treatment of small abdominal aortic aneurysms	Not a relevant study design
May (1997)	Concurrent comparison of endoluminal repair vs. no treatment for small abdominal aortic aneurysms	Not a relevant study design
Myers (2002)	Early surgery or surveillance for small abdominal aortic aneurysms? [letter; comment]	Not a peer-reviewed publication
Ouriel (2003)	Disparate outcome after endovascular treatment of small versus large abdominal aortic aneurysm	Not a relevant study design

Short Title	Title	Reason for exclusion
Ouriel (2009)	Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms	Duplicate and/or already included within an included systematic review
Ouriel (2009)	Randomized clinical trials of endovascular repair versus surveillance for treatment of small abdominal aortic aneurysms	Not a relevant study design
Ouriel (2009)	The PIVOTAL study: a randomized comparison of endovascular repair versus surveillance in patients with smaller abdominal aortic aneurysms	Not a relevant study design
Palamara (2005)	Regarding: "The study of endovascular repair of small (<5.5-cm) aneurysms"	Not a relevant study design
Paraskevas (2011)	The rationale for lowering the size threshold in elective endovascular repair of abdominal aortic aneurysm	Not a relevant study design
Paraskevas (2011)	In some patients with small abdominal aortic aneurysms, an attitude of "watchful waiting" may result in loss of suitability for endovascular repair	Not a relevant study design
Peppelenbosch (2004)	Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR	Not a relevant study design
Powell (1996)	The UK Small Aneurysm Trial	Study protocol
Powell (2003)	Small abdominal aortic aneurysms	Not a relevant study design
Ramo (1995)	Can we achieve better results by operating on smaller abdominal aortic aneurysms?	Not a relevant study design
Roddy (2013)	Comparison of outcomes following endovascular repair of abdominal aortic aneurysms based on size threshold	Not a relevant study design
Schermerhorn (2000)	Cost-effectiveness of surgery for small abdominal aortic aneurysms on the basis of data from the United Kingdom small aneurysm trial	Not a relevant study design
Tsilimparis (2012)	Effect of preoperative aneurysm diameter on long-term survival after endovascular aortic aneurysm repair	Not a relevant study design
Vavra (2014)	Part one: For the motion. evidence supports reducing the threshold diameter to 5 cm for elective interventions in women with abdominal aortic aneurysms	Not a relevant study design
Vavra (2014)	Debate: Whether evidence supports reducing the threshold diameter to 5 cm for elective interventions in women with abdominal aortic aneurysms	Not a relevant study design
Wang (2009)	EVAR in small versus large aneurysms: does size influence outcome?	Not a relevant study design
Welborn (2005)	Endovascular repair of small abdominal aortic aneurysms: a paradigm shift?	Not a relevant study design

Short Title	Title	Reason for exclusion
Young (2010)	Cost-effectiveness of abdominal aortic aneurysm repair based on aneurysm size	Not a relevant study design
Zarins (2005)	Endovascular repair or surveillance of patients with small AAA	Not a relevant study design
Zarins (2006)	Endovascular aneurysm repair at 5 years: Does aneurysm diameter predict outcome?	Not a relevant study design

Economic studies

Short title	Title	Primary reason for exclusion
Filardo (2015)	Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database of Systematic Reviews 2015, Issue 2.	Review article, no CUAs.
Eisenstein (2013)	Economic analysis of endovascular repair versus surveillance for patients with small abdominal aortic aneurysms. J Vasc Surg; 58(2):302-10.	Not a CUA.
Thompson (2013)	Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. Health Technol Assess; 17(41).	Comparisons (monitoring intervals).
Andermann (2012)	Screening for abdominal aortic aneurysm: should we lower the intervention cut-off point? BMJ; 344:e3111.	Not a CUA.
Forbes (2008)	Health service costs and quality of life for early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The Lancet; 352(9141):1656-60.	Not a CUA.
Powell (2007)	Final 12-year follow-up of Surgery versus Surveillance in the UK Small Aneurysm Trial. Br J Surg; 94:702-8.	Not a CUA.
Michaels (2005)	Cost-effectiveness of endovascular abdominal aortic aneurysm repair. Br J Surg; 92:960-7	Population (>5.5 cm AAAs).
Silverstein (2005)	Abdominal aortic aneurysm (AAA): cost-effectiveness of screening, surveillance of intermediate-sized AAA, and management of symptomatic AAA. Proceedings (Baylor University Medical Center); 18(4):345-67.	Review article, no CUAs.
Tomee (2017)	The consequences of real life practice of early abdominal aortic aneurysm repair: a cost-benefit analysis. Eur J Vasc Endovasc Surg; 54: 28-33	Not a CUA.

Connelly (2002)	The detection and management of abdominal aortic aneurysm: a cost-effectiveness analysis. Clin Invest Med; 25(4):127-33.	Outcomes (no relevant cost–utility outcomes).
Katz (2000)	Early Surgery versus Conservative Management of Dissecting Aneurysms of the Descending Thoracic Aorta. Med Decis Making; 20(4):377-93.	Not a CUA.
Finlayson (1999)	Should endovascular surgery lower the threshold for repair of abdominal aortic aneurysms? J Vasc Surg; 29:973-85.	Not a CUA.
Cronenwett & Katz (1995)	Cost-effectiveness of operating on small abdominal aortic aneurysms. Seminars in Vascular Surgery.	Duplicate of Katz & Cronenwett (1994).
King (1995)	Elective surgery for asymptomatic, unruptured, intracranial aneurysms: a cost-effectiveness analysis. Journal of Neurosurgery; 83: 403-12.	Population (intracranial aneurysm).
Katz (1992)	The cost-effectiveness of early surgery versus watchful waiting in the management of small abdominal aortic aneurysms. JAMA; 268(19):2678-86. The cost-effectiveness of early surgery versus watchful waiting in the management of small abdominal aortic aneurysms. JAMA; 268(19):2678-86.	Not a CUA.

Key: CUA, cost–utility analysis.

Appendix K – Glossary

Abdominal Aortic Aneurysm (AAA)

A localised bulge in the abdominal aorta (the major blood vessel that supplies blood to the lower half of the body including the abdomen, pelvis and lower limbs) caused by weakening of the aortic wall. It is defined as an aortic diameter greater than 3 cm or a diameter more than 50% larger than the normal width of a healthy aorta. The clinical relevance of AAA is that the condition may lead to a life threatening rupture of the affected artery. Abdominal aortic aneurysms are generally characterised by their shape, size and cause:

- Infrarenal AAA: an aneurysm located in the lower segment of the abdominal aorta below the kidneys.
- Juxtarenal AAA: a type of infrarenal aneurysm that extends to, and sometimes, includes the lower margin of renal artery origins.
- Suprarenal AAA: an aneurysm involving the aorta below the diaphragm and above the renal arteries involving some or all of the visceral aortic segment and hence the origins of the renal, superior mesenteric, and celiac arteries, it may extend down to the aortic bifurcation.

Abdominal compartment syndrome

Abdominal compartment syndrome occurs when the pressure within the abdominal cavity increases above 20 mm Hg (intra-abdominal hypertension). In the context of a ruptured AAA this is due to the mass effect of a volume of blood within or behind the abdominal cavity. The increased abdominal pressure reduces blood flow to abdominal organs and impairs pulmonary, cardiovascular, renal, and gastro-intestinal function. This can cause multiple organ dysfunction and eventually lead to death.

Cardiopulmonary exercise testing

Cardiopulmonary Exercise Testing (CPET, sometimes also called CPX testing) is a non-invasive approach used to assess how the body performs before and during exercise. During CPET, the patient performs exercise on a stationary bicycle while breathing through a mouthpiece. Each breath is measured to assess the performance of the lungs and cardiovascular system. A heart tracing device (Electrocardiogram) will also record the hearts electrical activity before, during and after exercise.

Device migration

Migration can occur after device implantation when there is any movement or displacement of a stent-graft from its original position relative to the aorta or renal arteries. The risk of migration increases with time and can result in the loss of device fixation. Device migration may not need further treatment but should be monitored as it can lead to complications such as aneurysm rupture or endoleak.

Endoleak

An endoleak is the persistence of blood flow outside an endovascular stent - graft but within the aneurysm sac in which the graft is placed.

- Type I – Perigraft (at the proximal or distal seal zones): This form of endoleak is caused by blood flowing into the aneurysm because of an incomplete or ineffective seal at either end of an endograft. The blood flow creates pressure within the sac and significantly increases the risk of sac enlargement and rupture. As a result, Type I endoleaks typically require urgent attention.

- Type II – Retrograde or collateral (mesenteric, lumbar, renal accessory): These endoleaks are the most common type of endoleak. They occur when blood bleeds into the sac from small side branches of the aorta. They are generally considered benign because they are usually at low pressure and tend to resolve spontaneously over time without any need for intervention. Treatment of the endoleak is indicated if the aneurysm sac continues to expand.

- Type III – Midgraft (fabric tear, graft dislocation, graft disintegration): These endoleaks occur when blood flows into the aneurysm sac through defects in the endograft (such as graft fractures, misaligned graft joints and holes in the graft fabric). Similarly to Type I endoleak, a Type III endoleak results in systemic blood pressure within the aneurysm sac that increases the risk of rupture. Therefore, Type III endoleaks typically require urgent attention.

- Type IV– Graft porosity: These endoleaks often occur soon after AAA repair and are associated with the porosity of certain graft materials. They are caused by blood flowing through the graft fabric into the aneurysm sac. They do not usually require treatment and tend to resolve within a few days of graft placement.

- Type V – Endotension: A Type V endoleak is a phenomenon in which there is continued sac expansion without radiographic evidence of a leak site. It is a poorly understood abnormality. One theory that it is caused by pulsation of the graft wall, with transmission of the pulse wave through the aneurysm sac to the native aneurysm wall. Alternatively it may be due to intermittent leaks which are not apparent at imaging. It can be difficult to identify and treat any cause.

Endovascular aneurysm repair

Endovascular aneurysm repair (EVAR) is a technique that involves placing a stent –graft prosthesis within an aneurysm. The stent-graft is inserted through a small incision in the femoral artery in the groin, then delivered to the site of the aneurysm using catheters and guidewires and placed in position under X-ray guidance.

- Conventional EVAR refers to placement of an endovascular stent graft in an AAA where the anatomy of the aneurysm is such that the ‘instructions for use’ of that particular device are adhered to. Instructions for use define tolerances for AAA anatomy that the device manufacturer considers appropriate for that device. Common limitations on AAA anatomy are infrarenal neck length (usually >10mm), diameter (usually ≤30mm) and neck angle relative to the main body of the AAA

- Complex EVAR refers to a number of endovascular strategies that have been developed to address the challenges of aortic proximal neck fixation associated with complicated aneurysm anatomies like those seen in juxtarenal and suprarenal AAAs. These strategies include using conventional infrarenal aortic stent grafts outside their ‘instructions for use’, using physician-modified endografts, utilisation of customised fenestrated endografts, and employing snorkel or chimney approaches with parallel covered stents.

Goal directed therapy

Goal directed therapy refers to a method of fluid administration that relies on minimally invasive cardiac output monitoring to tailor fluid administration to a maximal cardiac output or other reliable markers of cardiac function such as stroke volume variation or pulse pressure variation.

Post processing technique

For the purpose of this review, a post-processing technique refers to a software package that is used to augment imaging obtained from CT scans, (which are conventionally presented as axial images), to provide additional 2- or 3-dimensional imaging and data relating to an aneurysm's, size, position and anatomy.

Permissive hypotension

Permissive hypotension (also known as hypotensive resuscitation and restrictive volume resuscitation) is a method of fluid administration commonly used in people with haemorrhage after trauma. The basic principle of the technique is to maintain haemostasis (the stopping of blood flow) by keeping a person's blood pressure within a lower than normal range. In theory, a lower blood pressure means that blood loss will be slower, and more easily controlled by the pressure of internal self-tamponade and clot formation.

Remote ischemic preconditioning

Remote ischemic preconditioning is a procedure that aims to reduce damage (ischaemic injury) that may occur from a restriction in the blood supply to tissues during surgery. The technique aims to trigger the body's natural protective functions. It is sometimes performed before surgery and involves repeated, temporary cessation of blood flow to a limb to create ischemia (lack of oxygen and glucose) in the tissue. In theory, this "conditioning" activates physiological pathways that render the heart muscle resistant to subsequent prolonged periods of ischaemia.

Tranexamic acid

Tranexamic acid is an antifibrinolytic agent (medication that promotes blood clotting) that can be used to prevent, stop or reduce unwanted bleeding. It is often used to reduce the need for blood transfusion in adults having surgery, in trauma and in massive obstetric haemorrhage.