National Institute for Health and Care Excellence

Draft for consultation

Abdominal aortic aneurysm: diagnosis and management

Evidence review T: Effectiveness of endovascular aneurysm repair compared with open surgical repair of ruptured abdominal aortic aneurysms

NICE guideline <number>

Evidence reviews

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Draft for Consultation

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Effectiveness of endovascular aneurysm repair compared with open surgical repair of ruptured abdominal aortic aneurysms

Review question

What is the effectiveness of EVAR compared to open repair surgery in repairing ruptured abdominal aortic aneurysms?

Introduction

This review question aims to assess the advantages and disadvantages of emergency endovascular aneurysm repair in comparison with conventional open surgical repair for the treatment of ruptured abdominal aortic aneurysms (AAAs). Furthermore, this question aims to explore the subgroup effects of various patient characteristics, leading to more tailored recommendations.

PICO table

Table 1: Inclusion criteria

Parameter	Inclusion criteria
Population	People undergoing surgery for a ruptured AAA Subgroups: fitness for surgery, age, sex, comorbidities (including cardiovascular disease, renal disease, COPD, obesity), ethnicity
Interventions	Emergency standard (on-IFU) EVAR for infrarenal and juxtarenal AAAs Emergency complex EVAR for infrarenal, juxtarenal and suprarenal AAAs, including: fenestrated EVAR EVAR with chimneys EVAR with snorkels branched grafts 'CHIMPS' (CHIMneys, Periscopes, Snorkels) infrarenal devices used for juxtarenal AAA – that is, off-IFU use of standard devices Open repair Non-surgical management
Comparators	Each other
Outcomes	Mortality/survival Peri- and post-operative complications Successful exclusion of the aneurysm, aneurysm rupture, or further aneurysm growth Need for reintervention 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 recent update of a Cochrane systematic review (Badger et al. 2017) comparing EVAR and open surgical repair of ruptured infrarenal AAAs was identified as a source of randomised controlled trials (RCTs) relevant to this review question. Data were extracted from the systematic review, and individual RCTs within it, to compare the efficacy of emergency EVAR with that of open surgical repair of ruptured infrarenal aneurysms. Since the Cochrane systematic review did not consider complex aneurysm anatomies (such as juxtarenal and suprarenal type IV aneurysms) a supplementary literature search was performed. Non-randomised comparative studies, and prospective cohort studies comparing EVAR and open surgical repair of ruptured complex AAAs were included.

Studies were excluded if they:

- were not in English
- were not full reports of the study (for example, published only as an abstract)
- were not peer-reviewed.

Clinical evidence

Included studies

Standard EVAR

In relation to standard EVAR, searches for the initial 2014 Cochrane review and the 2017 update yielded a total of 365 abstracts. Of these, 21 were identified as being potentially relevant. Following full-text review 4 RCTs (published across 16 publications) were included. An update literature search was performed and provided by Cochrane, in December 2017. The search yielded a total of 296 abstracts. None of which were identified as potentially relevant.

Complex EVAR

Since the Cochrane systematic review did not include complex aneurysms, a supplementary literature search was conducted by NICE in August 2017. The search yielded 2,220 abstracts. Of these, 9 studies were identified as being potentially relevant. Following full-text review none of these studies were included. An update search was conducted by NICE in December 2017. The search yielded 191 abstracts; of which, none of which were considered relevant.

Excluded studies

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

Summary of clinical studies included in the evidence review

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

55 **Table 2: Included studies**

Study	Details
Badger S, Bedenis R, Blair PH et al. (2017) Endovascular treatment for ruptured abdominal aortic aneurysm. Cochrane Database Syst Rev;(5):CD005261. doi: 10.1002/14651858.CD005261.pub4	Study design: systematic review Location: UK Population: patients with ruptured AAA Sample size: 4 RCTs including 868 participants Follow-up: 30 days, 6 months and 1 year Intervention: EVAR using any type of endovascular device Comparators: open surgical repair Outcomes: endoleak; complications and mortality at 30-day, 6-month and 1-year follow-up; quality of life
AJAX trial (results reported in multiple publications)	Study design: multicentre, non-blinded, randomised controlled trial Location: Netherlands Population: patients with ruptured infrarenal AAA Sample size: 116; 85.3% male Follow-up: 6 months Intervention: EVAR Comparators: Open surgical repair Outcomes: All-cause mortality, severe complications, length of hospital and ICU stay, duration of intubation/ventilation and occurrence of endoleaks
ECAR trial (results reported in multiple publications)	Study design: multicentre, non-blinded, randomised controlled trial Location: France Population: patients with ruptured aorto-iliac AAA Sample size: 107; 90.7% male Follow-up: Up to 1 year Intervention: EVAR Comparators: Open surgical repair Outcomes: All-cause mortality, postoperative morbidity (cardiac, pulmonary, digestive, renal, and neurological), length of stay in ICU and complications.
Hinchcliffe 2006 trial (results reported in multiple publications)	Study design: single centre, non-blinded, randomised controlled trial Location: UK Population: patients with ruptured infrarenal AAA Sample size: 32; 75% male Follow-up: 30 days Intervention: EVAR Comparators: Open surgical repair Outcomes: 30-day mortality and complications
IMPROVE trial (results reported in multiple publications)	Study design: multicentre, non-blinded, randomised controlled trial Location: UK and Canada Population: patients with a ruptured AAA or ruptured aorto-iliac aneurysm Sample size: 613; 78.3% male Follow-up: mean of 4.9 years Intervention: EVAR Comparators: Open surgical repair

Study	Details
	Outcomes: All-cause mortality, costs, cost-effectiveness, and the need for re-intervention

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables, highlighting the quality of evidence from the included studies.

Economic evidence

Included studies

A systematic review of economic literature was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AAA (see Appendix B). A total of 5,173 studies was identified. The studies were reviewed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of emergency procedures to repair ruptured AAA. Studies that met the eligibility criteria were assessed using the quality appraisal criteria as outlined in the Guidelines Manual (2014).

Following an initial review of titles and abstracts, the full texts of 46 studies were retrieved for detailed consideration. Following full-text review, 5 of the 46 studies were judged to be potentially applicable cost–utility analyses for emergency AAA repair. Three of the 5 studies were excluded because they were judged to be subject to very serious limitations.

An update search was conducted in December 2017, to identify any relevant cost–utility analyses that had been published during guideline development. This search returned 814 studies. Following review of titles and abstracts, the full texts of 8 studies were retrieved for detailed consideration. Two were determined to be potentially applicable. One of these (Powell et al. 2017) was an analysis of the IMPROVE trial, using more recent data than another IMPROVE analysis that was identified by the original search (Powell et al. 2015). The earlier study was therefore excluded. The other potentially relevant study from the update search was excluded as it had very serious limitations. A total of 2 studies was therefore included as economic evidence for emergency repair of ruptured AAA.

Excluded studies

Studies that were excluded after full-text review, and reasons for exclusion, are provided in Appendix J – Excluded studies.

Summary of studies included in the economic evidence review

Kapma et al. (2014)

Kapma et al. performed a cost–utility analysis alongside the AJAX trial, an RCT comparing EVAR with open surgical repair for the repair of 116 ruptured AAAs conducted in 2 centres in the Netherlands. No extrapolation beyond the 6-month data was conducted. Hospital resource use data collected in AJAX included primary procedure, reintervention and subsequent care resources, costed at 2010 prices. The EQ-5D questionnaire was used to elicit health-related quality of life data, with general population quality of life assumed to prevail prior to aneurysm rupture. Bootstrapping was performed to characterise uncertainty in the estimates of incremental costs and QALYs, generating 25,000 samples.

Base-case results found that EVAR patients typically accrued 0.026 additional QALYs than open surgical repair patients, though, at a 95% confidence level, the data were consistent with no difference. EVAR was €10,189 more expensive than open surgical repair in terms of total costs, mainly due to the primary procedure cost and a higher incidence of subsequent hospital resource use. The ICER for EVAR was €391,885 per QALY gained, with a probability of less than 25% that the true ICER is under €80,000. Results were not sensitive to scenario analyses. The primary limitation of this analysis is its short time horizon. Additionally, the AJAX study is a relatively small trial, with its results based on 57 EVAR patients and 59 open surgical repair patients.

Table 3: Kapma et al. (2014) cost–utility model results

Randomised group	*Total*		*Incremental*		*ICER (€/QALY)*
	Costs (€)	*QALYs*	*Costs (€)*	*QALYs*	
OSR	31,616	0.298			
EVAR	41,350	0.324	10,189	0.026	391,885

Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR: open surgical repair; QALYs, quality-adjusted life years.

Powell et al. (2017)

A within-trial cost–utility analysis was also undertaken for the IMPROVE study (Powell et al., 2017), a pragmatic trial randomising people with suspected ruptured AAAs to either open surgical repair or a strategy in which EVAR was used for anatomically suitable AAAs (and OSR used if EVAR was not possible). This was the only UK economic evaluation identified that was informed by trial-based effectiveness evidence for ruptured AAA repair. Resource-use data included the primary procedure and subsequent use of critical, specialist or routine care, including staff time, costed using standard UK sources (2011–12 prices). The EQ-5D-3L questionnaire was used to elicit quality of life data, with elective repair baseline quality of life assumed to prevail prior to AAA rupture. Bootstrapping was performed to characterise uncertainty in the estimates of incremental costs and QALYs.

Base-case results suggest that participants randomised to the ‘EVAR if possible’ strategy typically accrued 0.166 additional QALYs than open surgical repair at 3 years. The mean total cost of EVAR study subjects was lower than open surgical repair, due to fewer days spent in critical care and a lower incidence of transfer to a different hospital. EVAR was therefore found to dominate open surgical repair, with more than a 90% likelihood of being cost effective if QALYs are valued at £20,000 each. This result was found to be robust to a number of sensitivity analyses around costs and how the trial data were analysed (e.g. unadjusted vs. adjusted for baseline variables, and adjusting for compliance to the randomised intervention). Like the Kapma et al. (2014) analysis, the study is limited by its relatively short time horizon. It is based on 3-year data from the IMPROVE study with no extrapolation, though 6-year Kaplan-Meier plots are presented, depicting a higher mortality rate for trial participants who were randomised to EVAR than those randomised to open surgical repair beyond 3 years.

Table 4: Powell et al. (2017) cost–utility analysis results

Randomised group	Total		Incremental		ICER (£/QALY)	Probability ICER <£20K/QALY
	Costs (£)	QALYs	Costs (£)	QALYs		
EVAR where possible	16,878	1.41				
OSR	19,483	0.97	-2,605	0.166	EVAR dominates	>90%

Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR: open surgical repair; QALYs, quality-adjusted life years.

Economic model

The effectiveness of EVAR compared with open surgical repair for the repair of ruptured AAAs was identified as an area of priority for new economic analysis. New clinical evidence has become available since the existing technology appraisal (TA 167) was published, particularly the IMPROVE trial, in the UK setting, and the European AJAX and ECAR trials. A new economic model was therefore developed to support decision-making in this area.

Methods

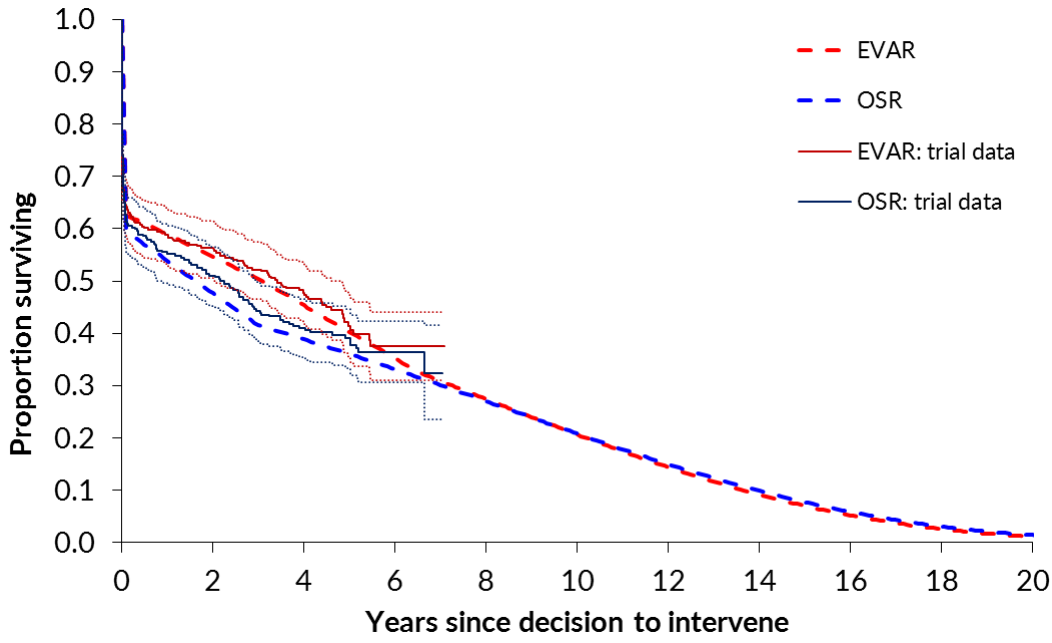
The model took a state-transition structure, from the point at which an individual arrives at hospital with a ruptured AAA. The analysis perspective on costs was those incurred by the NHS and Personal Social Services (PSS), and the perspective on outcomes was the direct health effects for people using AAA services. Two distinct populations were modelled: (1) those for whom open surgical repair is a suitable intervention, comparing EVAR with open surgical repair; and (2) those for whom open surgical repair is not a suitable intervention, because their operative risk is considered to be too high, comparing EVAR with no intervention. The main outcomes were incremental costs and QALYs, and the resulting ICER. The model time horizon was the lifetime of the patient (to a maximum age of 100), from a baseline cohort age of 76 years, composed of 1-month cycles. All outcomes were discounted by 3.5% per year (Developing NICE guidelines 2014).

First, modelled patients were at risk of perioperative (30-day) death, for 1 cycle. In the base-case model, this was informed by the National Vascular Registry (2016) data on open surgical repair for ruptured AAA (40.4%), representing a current snapshot of UK practice outcomes. The relative perioperative mortality rate with EVAR was informed by a Cochrane systematic review of emergency AAA repair trials (odds ratio: 0.88; Sweeting et al. 2017), leading to an estimated perioperative mortality of 37.4%. In the population for whom open surgical repair is an unsuitable intervention, there is no directly relevant randomised comparative data to inform EVAR perioperative mortality. To do so, the 30-day EVAR mortality rates in the EVAR-2 trial (open repair not suitable) and the EVAR-1 trial (open repair suitable) were compared, and the difference between them was used to estimate an 'unfit for OSR' mortality effect. The model applies this effect to the IMPROVE EVAR 30-day mortality rate, thereby estimating a mortality rate associated with emergency EVAR in people for whom OSR is not suitable. For this population, a strategy of 'no intervention' is associated with a 100% mortality rate.

Surviving patients move into the post-perioperative survival phase of the model, capturing their long-term mortality hazard after surviving the AAA repair procedure and full 30-day perioperative period. Long-term survival outcomes were informed by the IMPROVE trial, for which anonymised patient-level survival data were obtained. General population mortality rates were calibrated to post-perioperative mortality, on the OSR arm of IMPROVE, using a piecewise hazard ratio to produce a curve that fits the data accurately. Beyond the 7-year

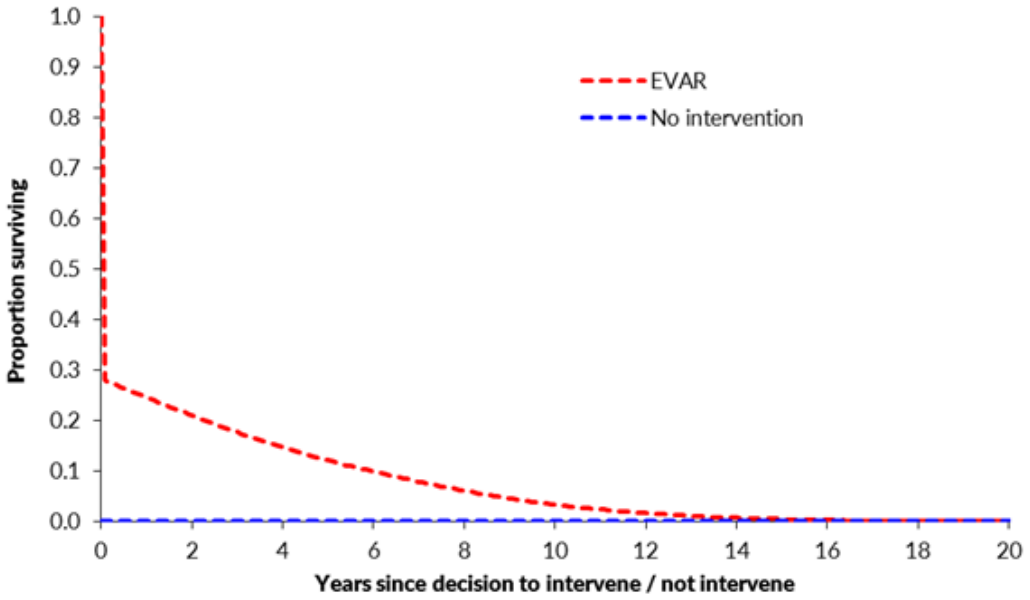
IMPROVE data, projecting the relative effect produces a notable long-term survival benefit from OSR; however, the true difference in long-term survival is not known. In the base case, therefore, at the point at which the IMPROVE follow-up data is exhausted, the hazard ratio between EVAR and OSR is informed by the more-mature post-perioperative data in the elective setting (see Evidence review K). Throughout the model, patients are at risk of complications leading to reintervention, informed by the IMPROVE trial.

In order to explore subgroup effects, the model was configured so that both perioperative and long-term survival estimates could be influenced by effect modifiers; in particular, age, AAA diameter and sex were tested by logistic regression analysis using the IMPROVE data. For perioperative mortality, age was a significant predictor of death. Being female was a significant predictor of death with open surgical repair, while females were less likely than males to experience perioperative death with EVAR. For post-perioperative mortality, multivariable Cox regressions using the IMPROVE dataset found EVAR to be associated with improved survival for up to 3 years, while being female was associated with worse survival beyond 3 years. The effect of age was implicitly captured in this by our use calibrated of general population survival data. Base case overall survival curves are presented in Figure 1 and Figure 2.



Note: The survival profiles used in the model may appear somewhat to underpredict survival in the IMPROVE trial; however this does not occur. The visible differences are explained by the use of UK registry data and multiple RCTs (as meta-analysed in the Cochrane review) to inform perioperative survival, and the calibration of general population survival to the OSR arm of IMPROVE (with different baseline characteristics to the entire IMPROVE cohort). A figure presenting the high accuracy of fit to the data when these intentional deviations are removed is provided in the separate health economics appendix..

Figure 1: Base-case overall survival profile – population for who open surgical repair is an option, versus IMPROVE trial data



Note: There is no randomised comparative evidence for this population against which our base-case survival profiles can be validated. The guideline committee advised that it is reasonable to assume that an untreated rupture will be fatal in 100% of cases.

Figure 2: Base-case overall survival profile – population for whom open surgical repair is not an option, versus EVAR-2 trial data

Complex aneurysms were not simulated for the emergency repair of ruptured AAA (unlike elective, unruptured cases; see Evidence review K). This is because complex grafts, which usually need to be custom-made for the individual, are less likely to be option for emergency AAA repair. Additionally, there is an absence of clinical evidence for emergency repair outcomes in the complex population.

Resource use was obtained from the published IMPROVE data (Powell et al. 2015; Powell et al. 2017), to which up-to-date national unit costs were applied. The cost of an EVAR graft was obtained from NHS Trusts by members of the guideline development committee. No costs were assumed to be incurred by a strategy of 'no intervention'. Quality of life was primarily informed by the published IMPROVE 3-year EQ-5D data, supplemented by decrements for complications identified by informal searches. In the IMPROVE study, the EVAR arm can be interpreted as an 'EVAR if possible' arm; EVAR was used where it was determined to be anatomically suitable (infrarenal) by CT scan, and 40% of participants randomised to it went on to receive open surgical repair instead. Its resource use and quality-of-life data reflect this, as does its survival data, and therefore much of our model. Our analysis should therefore be interpreted as comparing a world that permits emergency EVAR, where anatomically appropriate, with a world in which EVAR is not permitted at all (i.e. 'open surgical repair only' or 'no intervention' only).

Results

In the base-case model, in a cohort for whom open surgical repair is a suitable option, a strategy that uses EVAR where possible was found to have an ICER of £5,699 per QALY gained (Table 5) compared with open surgical repair. Probabilistic sensitivity analysis showed that its ICER was £20,000 per QALY gained or better in 80% of 1,000 model iterations (Figure 3). The only individual parameters that reversed this result were the perioperative mortality odds ratio and post-perioperative mortality hazard ratios; if they were

at the 95% confidence limits that most favoured open surgical repair, unlikely based on the available evidence, then the EVAR strategy would not be cost effective. The ICER in women was £3,465, and in men was £8,611; this difference reflects the significantly higher perioperative mortality rate among women with open surgical repair. In men, the strategy that permits EVAR had an ICER below £20,000 at ages 71 and above (Figure 4). It was cost-effective at all ages (50 to 100) in women, to such an extent that it is cost-effective, on average, in a population that matches the IMPROVE cohort.

In the population for whom open surgical repair is not a suitable option, an EVAR strategy was compared with offering no AAA repair (with a 100% mortality rate). The ICER was found to be £25,514 per QALY gained (Table 6). For this population, the NICE 'end of life criteria' are applicable: life expectancy without intervention is less than 24 months; intervention is expected to produce at least 3 additional months of life; and the expected patient population is small. In probabilistic sensitivity analysis, 23% of iterations had an EVAR ICER below £20,000, while 95% were below £50,000 (Figure 3). The only parameter that caused the ICER to exceed £50,000 per QALY gained was age; namely, in men aged 84 or over, and in women aged 85 or over, due to the high risk of perioperative death and limited long-term survival thereafter (Figure 5).

For detailed results, sensitivity analyses and discussion, including limitations and comparison with published analyses, please see the separate health economics appendix.

Table 5: NICE cost–utility model results, population for whom open surgical repair is an option

Treatment strategy	*Total*		*Incremental*		*ICER (£/QALY)*
	Costs (£)	*QALYs*	*Costs (£)*	*QALYs*	
OSR only	£25,422	2.734			
EVAR where possible	£27,063	3.022	£1,641	0.288	£5,699

Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR: open surgical repair; QALYs, quality-adjusted life years.

Table 6: NICE cost–utility model results, population for whom open surgical repair is not an option

Treatment strategy	*Total*		*Incremental*		*ICER (£/QALY)*
	Costs (£)	*QALYs*	*Costs (£)*	*QALYs*	
No intervention	£0	0			
EVAR where possible	£19,640	0.770	£19,640	0.770	£25,514

Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

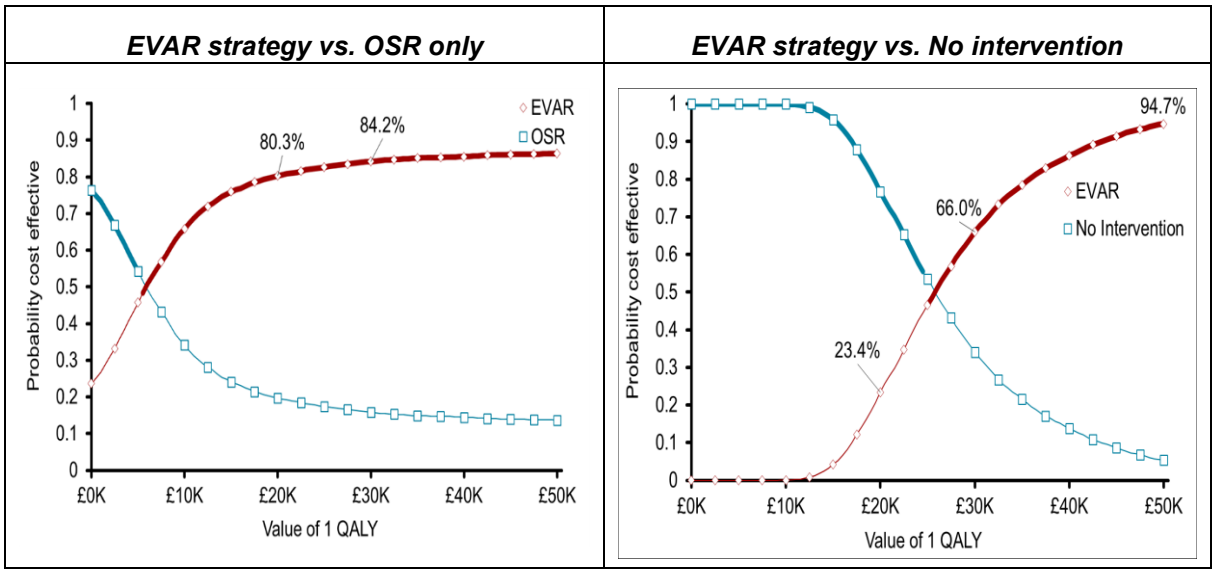
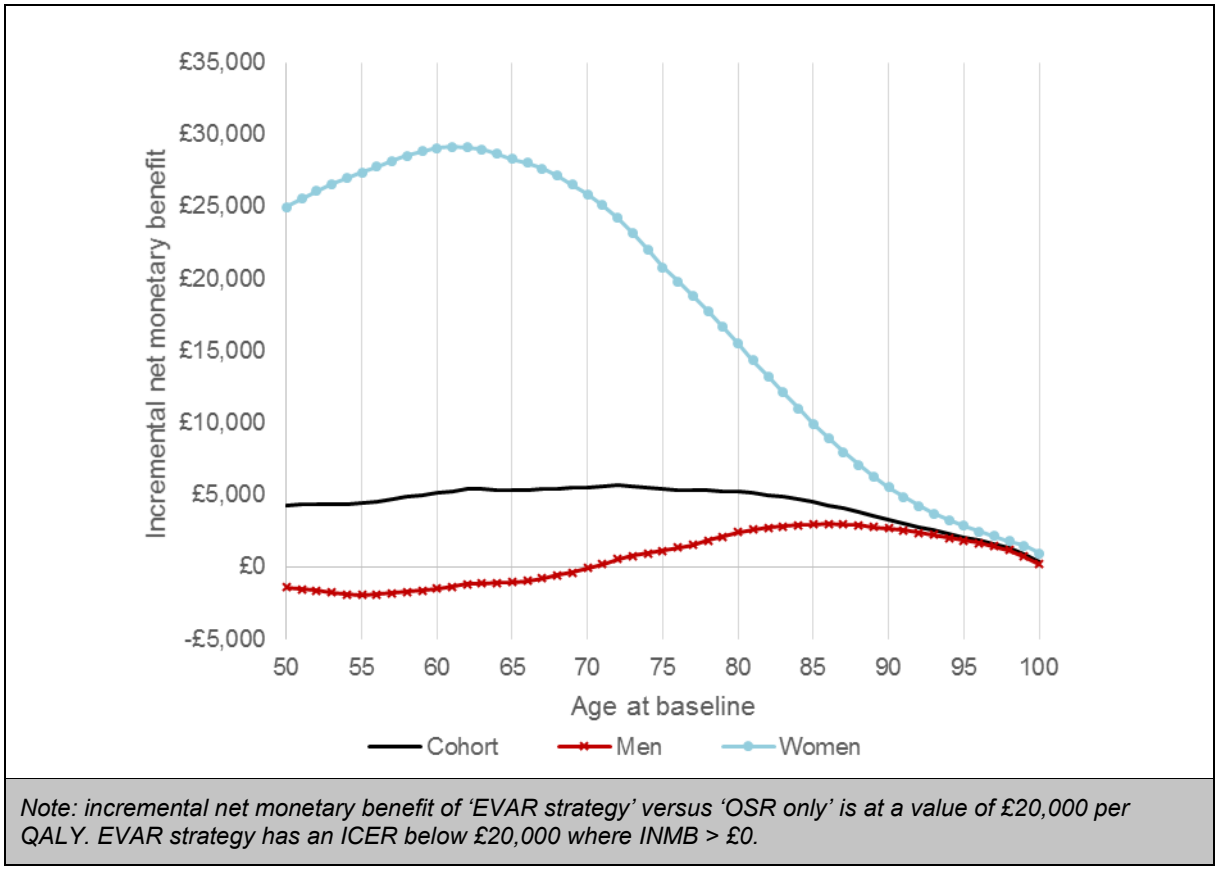
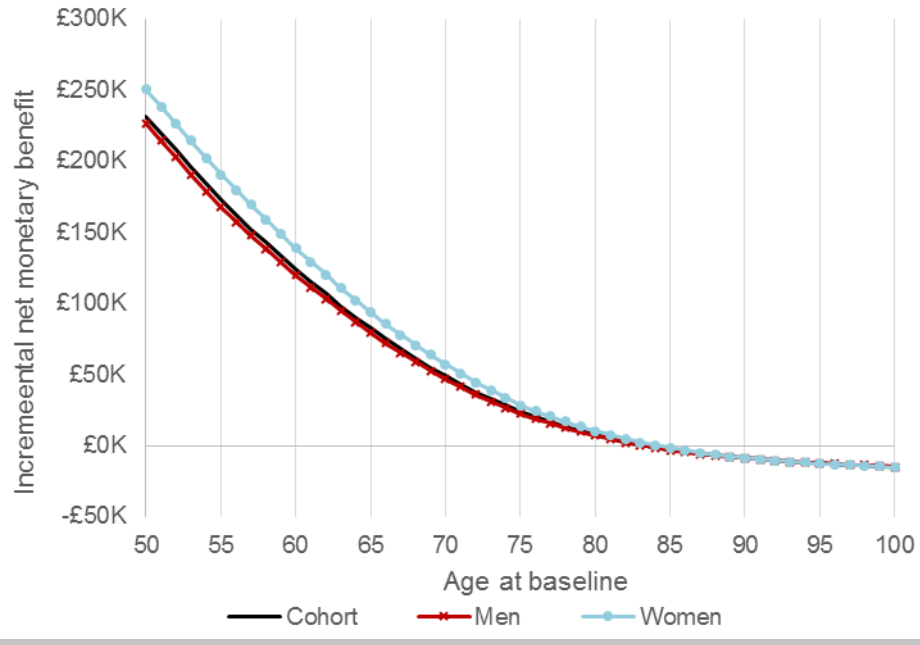


Figure 3: Cost-effectiveness acceptability results from 5,000 probabilistic sensitivity analysis runs



Note: incremental net monetary benefit of 'EVAR strategy' versus 'OSR only' is at a value of £20,000 per QALY. EVAR strategy has an ICER below £20,000 where INMB > £0.

Figure 4: Incremental net monetary benefit of EVAR strategy compared with open surgical repair by cohort sex and baseline age, at £20,000 per QALY



Note: incremental net monetary benefit of 'EVAR strategy' versus 'no intervention' is at a value of £50,000 per QALY. EVAR strategy has an ICER below £50,000 where INMB > £0.

Figure 5: Incremental net monetary benefit of EVAR strategy compared with 'no intervention' in people for whom open surgical repair is not a suitable option, by cohort sex and baseline age, at £50,000 per QALY

Evidence statements

Clinical evidence

Ruptured infrarenal AAA

- All-cause mortality:
  - Perioperative mortality (30-day or in-hospital mortality) cannot be differentiated between emergency EVAR and open repair (moderate-quality evidence from 4 RCTs, including 868 people).
  - All-cause mortality is lower with emergency EVAR than open repair at 3–36 months (moderate-quality evidence from 1 RCT including 613 people).
  - All-cause mortality cannot be differentiated between emergency EVAR and open repair at 0–6 months (low-quality evidence from 1 RCT including 116 people), 0–1 year (moderate-quality evidence from 2 RCTs including 718 people) and a mean follow-up of 0–4.9 years (moderate-quality evidence from 1 RCT including 613 people).
- Moderate-quality evidence from 1 RCT, including 613 people with ruptured AAAs, could not differentiate AAA-related mortality rates between patients treated by emergency EVAR and those treated by open repair at a mean follow-up of 4.9 years.
- Low-quality evidence from 2 RCTs, including up to 223 people with ruptured AAAs, could not differentiate major complication rates between patients treated by emergency EVAR and those treated by open repair at 30-day and 1-year follow-up.
- Low-quality evidence from 2 RCTs, including up to 223 people with ruptured AAAs, reported lower rates of bowel ischaemia in patients treated by emergency EVAR compared to those treated by open repair at 30-day follow-up. Very low- to low-quality

evidence from 4 RCTs, including up to 255 people with ruptured AAAs, could not differentiate rates of myocardial infarction, stroke, renal complications, cardiac complications, respiratory failure, spinal cord ischaemia, and amputation between patients treated by emergency EVAR and those treated by open repair at 30-day follow-up.

- Moderate-quality evidence from 1 RCT, including up to 223 people with ruptured AAAs, reported lower renal complication rates in patients treated by emergency EVAR compared to those treated by open repair at 6-month follow-up. Low-quality evidence from 1 RCT, including to 106 people with ruptured AAAs, could not differentiate rates of stroke, cardiac complications, bowel ischaemia, spinal cord ischaemia, and amputation between patients treated by emergency EVAR and those treated by open repair at 6-month follow-up.
- Low-quality evidence from 3 RCTs, including up to 613 people with ruptured AAAs, could not differentiate reintervention rates between patients treated by emergency EVAR compared with those treated by open repair at 30-day, 6-month and 3-year follow-up.
- High-quality evidence from 1 RCT, including 317 people with ruptured AAAs, reported better quality of life outcomes (measured by EQ-5D scores) in patients treated by emergency EVAR compared with those treated by open repair at 3-month follow-up. Moderate-quality evidence from the same trial could not differentiate EQ-5D scores between groups at 1-year and 3-year follow-up.
- Moderate-quality evidence from 3 RCTs, including up to 255 people with ruptured AAAs, could not differentiate length of stay in intensive care and length of hospital stay between patients treated by emergency EVAR and those treated by open repair.

Ruptured complex AAA

No evidence was identified comparing the efficacy of EVAR with open surgical repair of ruptured complex AAA.

Economic evidence

Published evidence

Ruptured infrarenal AAA

- One directly applicable cost–utility analysis with potentially serious limitations, based on data from the IMPROVE trial, found that a strategy of using EVAR where anatomically appropriate, otherwise open repair, was associated with QALY gains and lower costs compared with using open repair only, over 3 years, with at least a 90% probability of having an ICER of £20,000 per QALY gained or better.
- One partially applicable cost–utility analysis with potentially serious limitations, based on data from the AJAX trial, found that EVAR was associated with an ICER of €391,885 per QALY gained compared with open repair over 6 months.

Ruptured complex AAA

No evidence was identified comparing the efficacy of EVAR with open surgical repair of ruptured complex AAA.

NICE model

- One directly applicable cost–utility analysis with minor limitations found that allowing EVAR where anatomically suitable, otherwise using open repair, was associated with an ICER of £5,699 per QALY gained, compared with using open repair in all cases, in people for whom open repair is a suitable intervention, based on a cohort composed of 78% men with a mean age of 76. The ICER had a 80% probability of being lower than £20,000. This

result was sensitive to sex: in men, EVAR had a net health benefit only at ages 71 and over; in women, EVAR had a net health benefit at all ages from 50 to 100.

- One directly applicable cost–utility analysis with minor limitations found that EVAR was associated with an ICER of £25,514 per QALY gained, compared with no surgical intervention, in people for whom open repair is not a suitable intervention, based on a cohort composed of 78% men with a mean age of 76. The ICER had a 23% probability of being £20,000 or lower, and a 95% probability of being £50,000 or lower. This result was sensitive to age: at ages above 84 in men, and 85 in women, the ICER for EVAR was higher than £50,000 per QALY gained.

Recommendations

T1. Consider endovascular repair (EVAR) or open surgical repair for people with a ruptured infrarenal abdominal aortic aneurysm (AAA). Be aware that:

- EVAR provides more benefit than open surgical repair for most people, especially women and men over the age of 70.
- open surgical repair is likely to provide a better balance of benefits and harms in men under the age of 70.

T2. Consider open surgical repair for people with a ruptured complex AAA.

T3. Do not offer complex EVAR to people with a ruptured AAA if open surgical repair is suitable, except as part of a randomised controlled trial comparing complex EVAR with open surgical repair.

Research recommendation

RR10. What is the effectiveness and cost-effectiveness of complex EVAR versus open surgical repair in people with a ruptured AAA for whom open surgery is a suitable option?

Rationale and impact

Why the committee made the recommendations

The evidence showed that, compared with open surgical repair, a strategy that uses EVAR (where anatomically possible) to repair ruptured infrarenal AAAs provides a reasonable balance of benefits and costs.

As the average cost-effectiveness results for EVAR were favourable, the committee discussed whether they should recommend EVAR whenever it is possible. They decided not to, for 2 reasons.

Firstly, there is uncertainty in the evidence for EVAR. People who had EVAR for a ruptured AAA were followed up for at most 7 years. People who had EVAR for an unruptured AAA were followed up for 15 years, and the committee noted that these data suggested that EVAR may be worse than open surgical repair in the long run (see why the committee made the recommendations on repairing unruptured aneurysms). There are some signs that a similar long-term pattern may develop in trials of ruptured AAA, so it is possible that longer-term data would show EVAR to be worse than open surgical repair for people with ruptured AAA as well.

Secondly, there was evidence that the balance of benefits and costs of EVAR varies between different groups of people with ruptured AAA. In particular, women clearly have better short-term survival after EVAR, whereas the evidence favours open surgical repair for

younger men. Therefore, the committee recommended that either EVAR or open repair can be considered, and provided detail on the groups for which each approach is likely to be best. Complex EVAR is only recommended within the context of an RCT because there is currently no evidence to support it as an option for people with ruptured complex AAA.

Impact of the recommendations on practice

The recommendations will have little impact on current practice, as both standard EVAR and open surgery are currently offered to people with ruptured infrarenal AAA. In relation to complex EVAR, the recommendation not to use it outside of randomised trials will limit the use of a technically complex and expensive procedure in people for whom open surgery is a safe and suitable option.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the outcomes that matter most are long-term survival, as well as a reduction in the need for reintervention. This is because committee members believed that, apart from the fundamental need for any intervention to increase the immediate chances of a person surviving a ruptured AAA, the intervention should also ensure that they live as long as possible and have the best quality of life possible following rupture.

The quality of the evidence

The committee had no serious concerns about the overall quality of the evidence retrieved from literature searches but noted that no long-term data were available. All but 1 trial (ECAR trial) were considered to have a low risk of bias. The committee noted that the ECAR trial may have been prone to selection bias as patients were allocated to groups by week; patients were treated by open repair during the first week and subsequent odd numbered weeks. The committee considered that this study did not sway the results of most meta-analyses because it was allocated a small weighting.

The committee noted that, from a clinician's point of view, the design of the IMPROVE RCT could be considered confusing, as a large proportion of people with suspected ruptured AAA who were randomised to the 'EVAR' arm actually underwent open repair (because their AAA was anatomically unsuitable for standard EVAR). However, it agreed that this design reflected the decision problem at a commissioning level – that is, whether a service should offer emergency EVAR where possible – and, therefore, it would not be appropriate to downgrade the evidence for providing a biased estimate of effect.

Although the review protocol outlined that data from the National Vascular Registry, and testimony from expert witnesses would be considered in this review question, no such evidence was available to inform committee discussions.

Benefits and harms

The committee noted that medium-term follow up data from the IMPROVE trial indicated that EVAR offered a significant survival benefit (lower mortality rates) between 3 months and 3 years after surgery. However, no benefit was observed between EVAR and open surgery at the mean follow-up of 4.9 years. It was also noted that no differences in 3-year reintervention rates or quality of life (measured by EQ-5D scores) were observed between the groups. Upon consideration of these data, the committee concluded that there was substantial

uncertainty about the relative long-term benefits and harms of EVAR and open surgery. When considering short-term outcomes, the committee noted that patients treated by EVAR and open surgery were not significantly different in terms of 30-day mortality, reintervention rates, and all complications apart from renal complications. The committee were surprised by the results of the AJAX trial, which reported that fewer renal complications occurred in patients treated by EVAR than those treated by open repair and agreed that this observation was inconsistent with their own clinical experience. Upon consideration of the clinical evidence, as a whole, the committee agreed that there was insufficient evidence demonstrating that EVAR was superior to open surgery. As a result, the committee drafted a recommendation highlighting that either approach could be considered for people with ruptured infrarenal AAA whose anatomy made EVAR a suitable option for them.

In the absence of evidence relating to complex EVAR for ruptured AAA, the committee discussed the potential for harm if patients who were suitable for open surgical repair were offered complex EVAR instead. Committee members agreed that, compared with infrarenal EVAR, complex EVAR is more technically demanding and less frequently available. However, they were mindful that the potential benefit of EVAR had been shown when limited to infrarenal cases, so it is plausible that an endovascular approach would prove to be reasonable in some complex emergency cases. Therefore, while the committee were clear that it would be inappropriate to recommend the use of complex EVAR as standard practice, it agreed that it would be valuable to explore the benefits, harms and costs of the approach in an RCT. This will ensure that data would be collected to inform future updates of the guideline.

Cost effectiveness and resource use

The committee discussed the published cost-effectiveness evidence for the repair of ruptured infrarenal AAA. It noted that a within-trial UK cost–utility analysis alongside the IMPROVE trial found the pragmatic EVAR strategy to dominate an open surgical repair strategy over a 3-year period, whereas a partially applicable study in the Dutch setting determined that EVAR was not cost-effective over a 6-month period. The committee agreed that the time horizons of both analyses were too short to accurately reflect the cost-effectiveness of EVAR, particularly because 6-year IMPROVE follow-up data have been published showing that the EVAR survival benefit over the first 3 years is eroded thereafter. This trend suggests that the long-term outcomes of EVAR relative to open surgical repair for ruptured AAA may be similar to those observed in elective cases for unruptured AAA. The committee agreed that the published evidence should be supplemented by new modelling, in particular to capture the population for whom open surgical repair is not a suitable intervention, and complex AAA repair, and the longer-term data from the IMPROVE trial. The committee therefore considered evidence from the new economic model developed for this guideline.

The committee were satisfied with the modelling approach of: (1) using the UK National Vascular Registry data to inform baseline perioperative mortality; (2) using a Cochrane meta-analysis of RCTs to inform relative perioperative mortality rates; (3) projecting long-term survival by calibrating general population mortality to IMPROVE survival data, conditional on surviving the intervention, and; (4) applying long-term relative survival estimates based on mature elective repair data, from the point at which the IMPROVE follow-up expires. The committee understood that the economic model evaluating the population for whom open surgical repair is not a suitable option provides weaker evidence, as there is no RCT evidence for emergency repair in this population, and it was therefore supplemented with evidence from the EVAR-2 trial.

The committee discussed the appropriateness of using the IMPROVE trial to inform much of the model; in particular, the fact that it is a pragmatic RCT, in which 40% of participants randomised to the EVAR arm actually received open surgical repair. It agreed that this

approach does not provide a direct comparison of EVAR with open surgical repair in the emergency repair population, but that it does provide a comparison of a strategy that permits EVAR if the AAA is anatomically suitable, and open repair if it is not, with one that uses open surgical repair for all cases.

The committee agreed that the new economic model provides evidence that, on average across a population of people for whom open surgical repair is a suitable option, a strategy that permits EVAR where anatomically suitable – otherwise open surgical repair – is likely to be cost effective compared with using open repair in all cases. The base-case model results suggest that, for the average person, the EVAR strategy produces more QALYs than open surgery, at an additional cost to the NHS and PSS that represents good value for money. The base-case ICER is £5,699 per QALY gained, with an 80% probability of this being less than £20,000. This positive ICER reflects that the EVAR strategy was more costly, per person, than the open surgical repair strategy, whereas the published IMPROVE cost–utility analysis estimated that EVAR was less costly than open repair. The committee understood that this was because the NICE model used publicly available UK cost sources (alongside the published IMPROVE resource data), rather than the unit costs from the IMPROVE trial centres, and captured reintervention costs over a longer period. Results of the NICE model were sensitive to age and sex: the ICER is above £20,000 per QALY gained in men below 71 years old, but in women it remains £20,000 or better at all ages. This is primarily because of worse perioperative survival from open surgical repair in women. The committee agreed to reflect that EVAR may confer greater benefits in women in their recommendations.

The ICER for EVAR compared with 'no intervention', in the population for whom open surgical repair is not a suitable option, was £25,514 per QALY gained. The committee were aware that the 'end of life criteria' may be applicable for this population: life expectancy without intervention for a ruptured AAA is 0 years; EVAR is expected to gain more than 3 months of additional life (0.770 QALYs); and the population affected is likely to be small. The committee therefore considered that the base-case ICER provided acceptable value for money to the NHS and PSS, noting that the ICER had a 95% probability of being less than £50,000 per QALY gained.

These results were sensitive to age, with the EVAR ICER exceeding £50,000 in men aged 84 or over, and women aged 85 or over; however, the committee advised that this represents only a small subgroup of the relevant population. The committee also agreed that if an older person has a ruptured AAA and open surgical repair is not a suitable option, but the person is still deemed to be a candidate for emergency EVAR, then they are likely to be systematically different to the 'average' individual captured by the model. In practice, if emergency AAA repair is being considered then the treating clinician must believe that the person has a reasonable probability of surviving the procedure and life expectancy thereafter. In this way, the committee advised that the model results in this population at older ages are less likely to reflect clinical reality, and that EVAR is more likely to be cost effective at older ages than the model results suggest. The committee also agreed that there may be some costs associated with choosing to provide 'no intervention' for people presenting with ruptured aneurysms – rather than the £0 applied in the model – which would reduce the ICER for EVAR at all ages.

Other factors the committee took into account

While the committee agreed that permitting EVAR for the emergency repair of ruptured infrarenal AAAs is likely to be cost effective, based on the available evidence, it recognised that there may be practical difficulties in implementing such a recommendation alongside the more compelling evidence that EVAR is not cost effective for the elective repair of unruptured AAA. In particular, the committee recognised that it may be difficult to retain EVAR capacity and expertise for use in the relatively small number of infrarenal AAA ruptures seen in

practice, without being able to conduct EVAR relatively frequently in the elective setting. The committee agreed that there is no simple solution to this implementation difficulty and that the current evidence is clear that EVAR should be retained as a cost-effective option for emergency infrarenal AAA repair. However, the committee were clear that maintaining capacity to provide emergency EVAR is, on its own, an insufficient reason to offer elective EVAR, as the QALYs forgone by retaining elective EVAR would outweigh the QALYs saved by having it available in the emergency setting.

The committee discussed the use of complex EVAR in the context of emergency AAA repair, noting that the new economic model had not captured this population, owing to the lack of clinical evidence. Complex EVAR is not typically used in the emergency setting, as shown by the IMPROVE study protocol. To repair a complex AAA, EVAR devices must be custom-designed for the individual and ordered in advance, and this is not possible in the emergency setting. The committee advised that complex emergency EVAR occasionally does happen in practice using physician-modified grafts or advanced adjunct to standard, infrarenal EVAR devices. The committee agreed that such practice is speculative, and saw no evidence to advise on the effectiveness or cost-effectiveness of this approach, compared with open surgical repair. The committee therefore decided to recommend complex emergency EVAR only within the context of an RCT.

Appendices

Appendix A – Review protocol

Review protocol for assessing the effectiveness of endovascular aneurysm repair compared with open surgical repair of ruptured abdominal aortic aneurysms

<table>
<tr><th>Review question 23</th><th>What is the effectiveness of EVAR compared to open repair surgery in repairing ruptured abdominal aortic aneurysms?</th></tr>
<tr><td>Objectives</td><td>To assess the advantages and disadvantages of emergency endovascular aneurysm repair in comparison with conventional open surgical repair for the treatment of ruptured abdominal aortic aneurysms
To explore the subgroup effects of various patient characteristics, leading to more tailored recommendations</td></tr>
<tr><td>Type of review</td><td>Intervention</td></tr>
<tr><td>Language</td><td>English</td></tr>
<tr><td>Study design</td><td>i) Systematic reviews of study designs listed below
Randomised controlled trials
Quasi-randomised controlled trials
Non-randomised controlled trials for comparisons in people eligible for complex EVAR only
Prospective cohort studies for comparisons in people eligible for complex EVAR only
ii) Analysis of UK registry data (National Vascular Registry)
<table>
<tr><td></td><td colspan="3">Interventions</td></tr>
<tr><td></td><td rowspan="2">Standard (on-IFU) EVAR</td><td colspan="2">Complex EVAR</td></tr>
<tr><td>Off-IFU use of standard EVAR</td><td>Other complex EVAR</td></tr>
<tr><td>Infrarenal</td><td>Systematic reviews
RCTs
Quasi-RCTs</td><td>Systematic reviews
RCTs
Quasi-RCTs
Non-randomised controlled trials
Prospective cohort studies
UK registry data (National Vascular Registry)</td><td>Systematic reviews
RCTs
Quasi-RCTs
Non-randomised controlled trials
Prospective cohort studies
UK registry data (National Vascular Registry)</td></tr>
<tr><td>Juxtarenal</td><td>Systematic reviews
RCTs
Quasi-RCTs</td><td>Systematic reviews
RCTs
Quasi-RCTs
Non-randomised controlled trials
Prospective cohort studies
UK registry data (National Vascular Registry)</td><td>Systematic reviews
RCTs
Quasi-RCTs
Non-randomised controlled trials
Prospective cohort studies
UK registry data (National Vascular Registry)</td></tr>
<tr><td>Suprarenal / ‘type IV’</td><td>-</td><td>-</td><td>Systematic reviews
RCTs
Quasi-RCTs
Non-randomised controlled trials
Prospective cohort studies</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Review question 23</td><td>What is the effectiveness of EVAR compared to open repair surgery in repairing ruptured abdominal aortic aneurysms?</td></tr>
<tr><td></td><td><table><tr><td></td><td></td><td></td><td>UK registry data (National Vascular Registry)</td></tr></table></td></tr>
<tr><td>Status</td><td>Published papers only (full text)
No date restrictions</td></tr>
<tr><td>Population</td><td>People undergoing surgery for a ruptured abdominal aortic aneurysm
Subgroups: fitness for surgery, age, sex, comorbidities (including cardiovascular disease, renal disease, COPD, obesity), ethnicity</td></tr>
<tr><td>Intervention</td><td>Emergency standard (on-IFU) EVAR for infrarenal and juxtarenal abdominal aortic aneurysms
Emergency complex EVAR for infrarenal, juxtarenal and suprarenal abdominal aortic aneurysms, including:
fenestrated EVAR
EVAR with chimneys
EVAR with snorkels
branched grafts
‘CHIMPS’ (CHIMneys, Periscopes, Snorkels)
infrarenal devices used for juxtarenal AAA – that is, off-IFU use of standard devices
Open repair
Summary:
<table>
<tr><td></td><td>No surgery</td><td>Open repair</td><td>Standard (on-IFU) EVAR</td><td>Off-IFU use of standard EVAR</td><td>Other complex EVAR</td></tr>
<tr><td>Infrarenal</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>Iliac-branched only</td></tr>
<tr><td>Juxtarenal</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>Suprarenal / ‘type IV’</td><td>✓</td><td>✓</td><td>-</td><td>-</td><td>✓</td></tr>
</table></td></tr>
<tr><td>Comparator</td><td>Each other</td></tr>
<tr><td>Outcomes</td><td>Mortality/survival
Peri- and post-operative complications
Successful exclusion of the aneurysm, aneurysm rupture, or further aneurysm growth
Need for reintervention
Quality of life
Resource use, including length of hospital or intensive care stay, and costs</td></tr>
<tr><td>Other criteria for inclusion / exclusion of studies</td><td>Exclusion:
Non-English language
Abstract/non-published</td></tr>
<tr><td>Baseline characteristics to be extracted in evidence tables</td><td>Age
Sex
Size of aneurysm
Comorbidities</td></tr>
<tr><td>Search strategies</td><td>See Appendix B</td></tr>
<tr><td>Review strategies</td><td>i) Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.
The update of Badger et al’s 2014 Cochrane review (ongoing at the time of protocol development) comparing endovascular and open surgical repair of ruptured AAAs will be used as the RCT evidence base for this review question
Data on all included studies will be extracted into evidence tables.</td></tr>
</table>

Review question 23	What is the effectiveness of EVAR compared to open repair surgery in repairing ruptured abdominal aortic aneurysms?
	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	None identified.

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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 23

Badger S, Bedenis R, Blair PH et al. (2017) Endovascular treatment for ruptured abdominal aortic aneurysm. Cochrane Database Syst Rev;(5):CD005261. doi: 10.1002/14651858.CD005261.pub4

Medline Strategy, searched 22nd June 2016 **Search Strategy:**
#1 MESH DESCRIPTOR Aneurysm, Ruptured EXPLODE ALL TREES
#2 MESH DESCRIPTOR Aneurysm, Dissecting
#3 MESH DESCRIPTOR Aorta EXPLODE ALL TREES WITH QUALIFIERS SU
#4 ((aneurysm* or abdom* or thoracoabdom* or thoraco-abdom* or aort*) near (ruptur* or tear or bleed* or trauma)):TI,AB,KY
#5 RAAA:TI,AB,KY
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MESH DESCRIPTOR Endovascular Procedures EXPLODE ALL TREES
#8 MESH DESCRIPTOR Stents EXPLODE ALL TREES
#9 MESH DESCRIPTOR Vascular Surgical Procedures

Medline Strategy, searched 22nd June 2016 **Search Strategy:**
#10 MESH DESCRIPTOR Blood Vessel Prosthesis EXPLODE ALL TREES #11 MESH DESCRIPTOR Blood Vessel Prosthesis Implantation EXPLODE ALL TREES #12 endovasc*:TI,AB,KY #13 endostent*:TI,AB,KY #14 endoluminal:TI,AB,KY #15 endoprosthe*:TI,AB,KY #16 (graft or endograft*):TI,AB,KY #17 percutaneous*:TI,AB,KY #18 stent*:TI,AB,KY #19 (Palmaz or Zenith or Dynalink or Hemobahn or Luminex* or Memotherm or Wallstent):TI,AB,KY #20 (Viabahn or Nitinol or Intracoil or Tantalum):TI,AB,KY #21 EVAR:TI,AB,KY #22 EVRAR:TI,AB,KY #23 TEVAR:TI,AB,KY #24 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 #25 #6 AND #24 #26 * NOT SR-PVD:CC AND 31/03/2014 TO 31/07/2016:DL #27 #25 AND #26

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/ 8 Budgets/

Medline Strategy

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.
24 quality of well-being.tw.
25 qwb.tw.

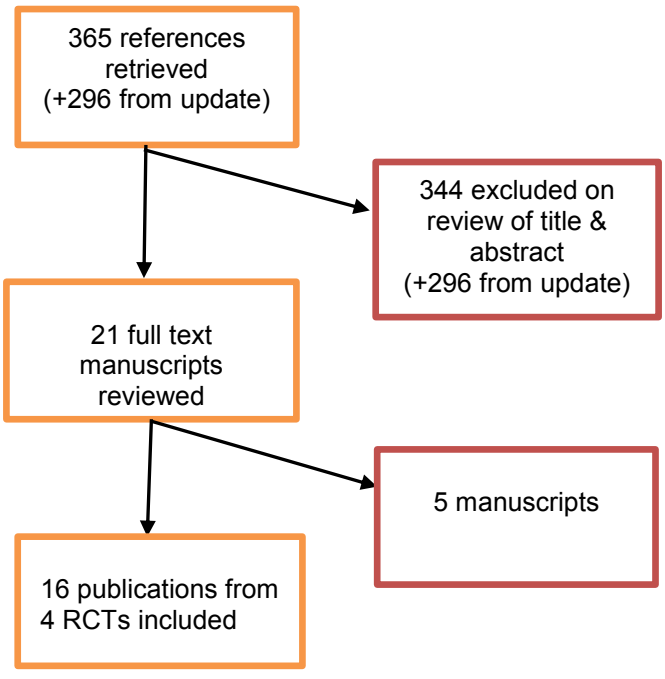
Medline Strategy	
26	willingness to pay.tw.
27	standard gamble*.tw.
28	time trade off.tw.
29	time tradeoff.tw.
30	tto.tw.
31	or/1-30

566

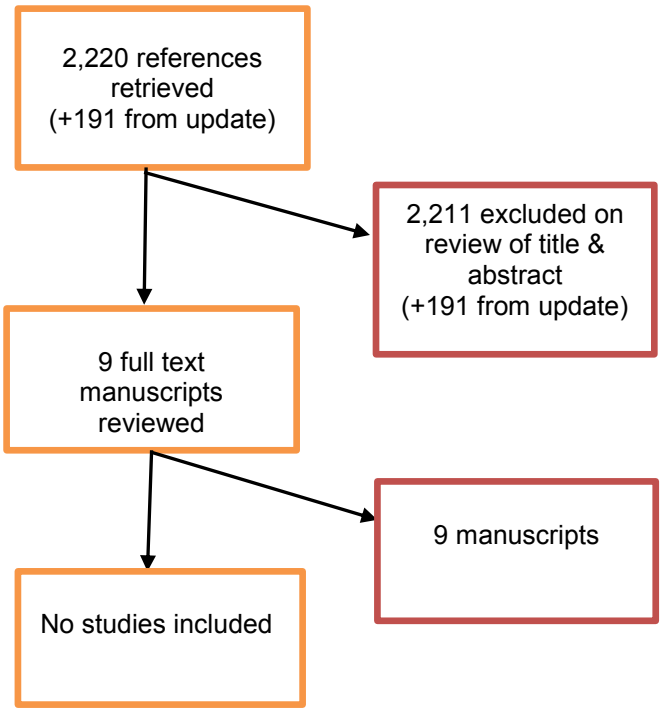
567

Appendix C – Clinical evidence study selection

Cochrane systematic review study selection



Complex EVAR versus open surgery study selection



Appendix D – Clinical evidence tables

Full citation	**Badger S, Bedenis R, Blair PH et al. (2017) Endovascular treatment for ruptured abdominal aortic aneurysm. Cochrane Database Syst Rev;(5):CD005261. doi: 10.1002/14651858.CD005261.pub4**
Study details	Study type: systematic review Location: UK Aim(s): to assess the advantages and disadvantages of emergency endovascular aneurysm repair in comparison with conventional open surgical repair for the treatment of ruptured AAA. Study dates: literature searched for publications up to June 2016 Follow-up: 30 days, 6 months and 1 year Sources of funding: this study was supported by funding from the UK National Institute of Health Research (NIHR)
Participants	Population: patients with ruptured AAA diagnosed by computed tomography, angiography, magnetic resonance angiography, or objective acute symptoms suggestive of rupture of the aneurysm Sample size: 4 RCTs (AJAX, ECAR, IMPROVE, and Hinchliffe 2016 trials) including 868 participants Inclusion criteria: RCTs in which patients with a clinically or radiologically diagnosed ruptured AAA were randomly allocated to emergency EVAR or open surgical repair Exclusion criteria: not reported
Methods	This systematic review is an update of a systematic review published in 2014. 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 World Health Organisation International Clinical Trials Registry, ClinicalTrials.gov website and the ISRCTN register. 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.
Intervention	EVAR using any type of endovascular device
Comparison	Open surgical repair
Outcomes measures	Endoleak; complications and mortality at 30-day, 6-month and 1-year follow-up; quality of life
Study Appraisal using AMSTAR	1. Was an 'a priori' design provided? Yes 2. Was there duplicate study selection and data extraction? Yes

Full citation	**Badger S, Bedenis R, Blair PH et al. (2017) Endovascular treatment for ruptured abdominal aortic aneurysm. Cochrane Database Syst Rev;(5):CD005261. doi: 10.1002/14651858.CD005261.pub4**
(Assessing the Methodological Quality of Systematic Reviews)	3. Was a comprehensive literature search performed? Yes 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? Not explicitly stated; however authors state that conference proceedings and other grey literature sources were searched to identify relevant studies. 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? Yes 11. Was the conflict of interest included? Yes Directness: Directly applicable

Studies included in the systematic review by Badger et al.

Full citation	AJAX trial (results reported in multiple publications)
Study details	Study type: multicentre, non-blinded, randomised controlled trial Location: Netherlands Aim: to compare outcomes of EVAR with those of open repair in patients with a ruptured AAA Study dates: April 2004 to February 2011 Follow-up: 6 months Sources of funding: the study was partially funded by the Dutch Heart foundation
Participants	Population: patients with ruptured infrarenal AAA Sample size: 116; 85.3% male Inclusion criteria: people over 18 years with a clinical diagnosis of ruptured AAA accompanied by acute haemorrhage outside the aortic wall were included. Exclusion criteria: extension of the aneurysm to juxta- or suprarenal aorta, kidney transplant, horseshoe kidney, allergy to intravenous contrast, connective tissue disease, severe haemodynamic instability precluding computed tomography (CT) Baseline characteristics: Mean age: EVAR group, 74.9 years; Open surgery group, 74.5 years Sex: EVAR group, 86% male; Open surgery group, 85% male Mean aneurysm diameter: not reported Diabetes: EVAR group, 4%; Open surgery group, 2% Hypertension: EVAR group, 23%; Open surgery group, 17% Hyperlipidaemia: EVAR group, 23%; Open surgery group, 32% Renal disease: EVAR group, 2%; Open surgery group, 3% Pulmonary disease: EVAR group, 12%; Open surgery group, 5% Cardiac disease: EVAR group, 28%; Open surgery group, 24%
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	All-cause mortality, severe complications, length of hospital and ICU stay, duration of intubation/ventilation and occurrence of endoleaks
Risk of bias assessment (from	1. Random sequence generation (selection bias): Low risk – randomisation was performed generated by and independent clinical research unit that allocated participants to groups on a 1:1 basis using random block sizes of 4 or 6

Full citation	AJAX trial (results reported in multiple publications)
the Cochrane review)	2. Allocation concealment (selection bias): Low risk – Allocations were concealed using sequentially numbered opaque sealed envelopes 3. Blinding of participants and personnel (performance bias): Low risk – it was not possible to blind participants but this was unlikely to bias results as objective outcomes were measured 4. Blinding of outcome assessment (detection bias): Low risk – double database entry was performed; adjudication and safety committees were blinded 5. Incomplete outcome data (attrition bias): Low risk – "All participants were accounted for in a CONSORT diagram; both treatment arms had similar dropout rates and reasons" 6. Selective reporting (reporting bias): Low risk – All pre-specified outcomes were reported 7. Other bias: Low risk – None Overall risk of bias: Low Directness: Directly applicable

Full citation	ECAR trial (results reported in multiple publications)
Study details	Study type: multicentre, non-blinded, randomised controlled trial Location: France Aim: to compare postoperative mortality between open surgical repair and EVAR for aorto-iliac abdominal aortic aneurysms in a homogeneous group of patients Study dates: 2008 to 2013 Follow-up: Up to 1 year Sources of funding: a grant obtained from the French Ministry of Health covered the cost of the study.
Participants	Population: patients with ruptured aorto-iliac AAA Sample size: 107; 90.7% male Inclusion criteria: patients with a CT confirmed ruptured aorto-iliac AAA with bleeding outside the aorto-iliac aneurysm wall were included. All patients had to be haemodynamically stable (systolic blood pressure >80mmHg unassisted by high-dose catacholamines) on arrival. Exclusion criteria: not reported Baseline characteristics: Mean age: EVAR group, 75.0 years; Open surgery group, 73.8 years Sex: EVAR group, 90.0% male; Open surgery group, 91.0% male Mean aneurysm diameter: not reported Comorbidities: not reported
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	All-cause mortality, postoperative morbidity (cardiac, pulmonary, digestive, renal, and neurological), length of stay in ICU and complications.
Risk of bias assessment (from the Cochrane review)	1. Random sequence generation (selection bias): High risk – No randomisation was performed. Patients were allocated to groups by week; patients were treated by open repair during the first week and subsequent odd numbered weeks. 2. Allocation concealment (selection bias): High risk – Treatment assignment was based on weeks of the study. 3. Blinding of participants and personnel (performance bias): Low risk – It was not possible to blind participants but this was unlikely to bias results as objective outcomes were measured 4. Blinding of outcome assessment (detection bias): Low risk – Assessors were not blinded, but this is unlikely to affect outcomes

Full citation	ECAR trial (results reported in multiple publications)
	5. Incomplete outcome data (attrition bias): Low risk – All participants were accounted for; no participants were lost to follow-up 6. Selective reporting (reporting bias): 7. Other bias: All pre-specified outcomes were reported Overall risk of bias: Moderate Directness: Directly applicable

Full citation	Hinchcliffe 2006 trial (results reported in multiple publications)
Study details	Study type: single centre, non-blinded, randomised controlled trial Location: UK Aim: to test the hypothesis that EVAR can reduce the perioperative mortality associated with ruptured AAA compared with open repair Study dates: 1999 to 2004 Follow-up: 30 days Sources of funding: not reported
Participants	Population: patients with ruptured infrarenal AAA Sample size: 32; 75% male Inclusion criteria: patients with clinically and radiologically confirmed ruptured infrarenal AAA were included. Exclusion criteria: age <50 years, unconscious patients, allergy to radiological contrast, severe comorbidity that would preclude intensive care treatment following open repair; previous EVAR, women of childbearing potential not taking contraception and pregnant or lactating women Baseline characteristics: Mean age: EVAR group, 74 years; Open surgery group, 80 years Sex: EVAR group, 84% male; Open surgery group, 86% male Mean aneurysm diameter: not reported Ischaemic heart disease: EVAR group, 20%; Open surgery group, 29%

Full citation	Hinchcliffe 2006 trial (results reported in multiple publications)
	COPD: EVAR group, 0%; Open surgery group, 18% Peripheral vascular disease: EVAR group, 7%; Open surgery group, 12% Renal disease: EVAR group, 7%; Open surgery group, 12% Hypertension: EVAR group, 29%; Open surgery group, 47%
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	30-day mortality and complications
Risk of bias assessment (from the Cochrane review)	1. Random sequence generation (selection bias): Unclear risk – Authors did not explicitly state how randomisation was performed 2. Allocation concealment (selection bias): Low risk – Randomisation was then performed from sealed opaque envelopes kept in the hospitals Accident and Emergency Department 3. Blinding of participants and personnel (performance bias): Low risk – It was not possible to blind participants but this was unlikely to bias results as objective outcomes were measured 4. Blinding of outcome assessment (detection bias): Low risk – Assessors were not blinded, but this is unlikely to affect outcomes 5. Incomplete outcome data (attrition bias): Low risk – All participants were accounted for, with numbers of cross-overs and dropouts reported in detail 6. Selective reporting (reporting bias): Low risk – most of the study protocol was outlined in the manuscript and all relevant outcomes were reported 7. Other bias: Unclear risk – The study was underpowered; 32 of the required 100 participants recruited Overall risk of bias: Low Directness: Directly applicable

Full citation	IMPROVE trial (results reported in multiple publications)
Study details	Study type: multicentre, non-blinded, randomised controlled trial Location: UK and Canada Aim: to assess whether EVAR versus open repair reduces mortality for people with suspected RAAA Study dates: 2002 to 2008 Follow-up: mean of 4.9 years Sources of funding: This project was funded by the UK National Institute for Health Research Health Technology Assessment programme
Participants	Population: patients with a ruptured AAA or ruptured aorto-iliac aneurysm Sample size: 613; 78.3% male Inclusion criteria: people over 50 years with a clinical diagnosis of ruptured AAA or ruptured aorto-iliac aneurysm were included Exclusion criteria: previous aneurysm repair, rupture of an isolated internal iliac aneurysm, aorto-caval or aorto-enteric fistulae, connective tissue disorders, anatomical features precluded EVAR, no absolute requirements will be set for the study, proximal neck morphology with a diameter >32 mm or a length <10 mm, iliac artery diameters <8 mm and >22 mm Baseline characteristics: Mean age: EVAR group, 76.0 years; Open surgery group, 76.2 years Sex: EVAR group, 81% male; Open surgery group, 80% male Mean aneurysm diameter: not reported Comorbidities: not reported
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	All-cause mortality, costs, cost-effectiveness, and the need for re-intervention
Risk of bias assessment (from the Cochrane review)	1. Random sequence generation (selection bias): Low risk – An independent contractor performed telephone randomisation, assigning patients to groups on a 1:1 basis using computer-generated sequences 2. Allocation concealment (selection bias): Low risk – An independent contractor provided telephone randomisation, with computer generated assignation of patients 3. Blinding of participants and personnel (performance bias): Low risk – It was not possible to blind participants but this was unlikely to bias results as objective outcomes were measured

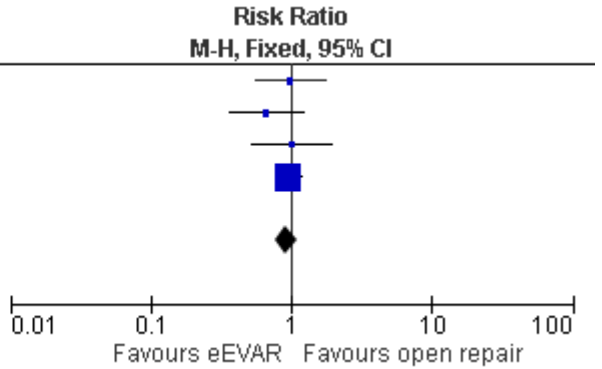
Full citation	IMPROVE trial (results reported in multiple publications)
	4. Blinding of outcome assessment (detection bias): Low risk – Data verification was performed centrally; it was unclear if there was blinding, but this was unlikely to influence outcomes 5. Incomplete outcome data (attrition bias): Low risk – All participants were accounted for, with numbers and reasons for dropouts reported in detail 6. Selective reporting (reporting bias): Low risk – All pre-specified outcomes were accounted for 7. Other bias: Low risk – None Overall risk of bias: Low Directness: Directly applicable

Appendix E – Forest plots

Note: all data reported in GRADE tables relate to ruptured infrarenal AAA. No evidence comparing EVAR with open surgical repair of ruptured complex AAA were identified. Short-term mortality (30-day and in-hospital)

	eEVAR		Open repair			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
AJAX	16	57	17	59	10.5%	0.97 [0.55, 1.74]
ECAR	13	56	18	51	11.9%	0.66 [0.36, 1.20]
Hinchliffe 2006	8	15	9	17	5.3%	1.01 [0.52, 1.93]
IMPROVE	112	316	111	297	72.2%	0.95 [0.77, 1.17]
Total (95% CI)		**444**		**424**	**100.0%**	**0.92 [0.77, 1.10]**
Total events	149		155			

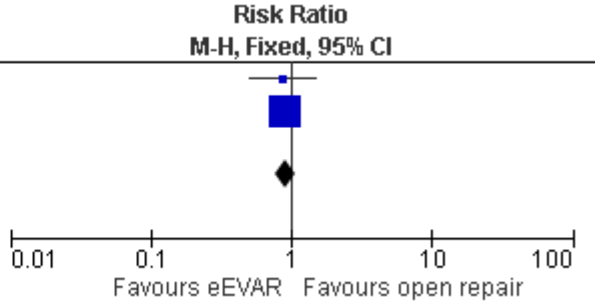
Heterogeneity: Chi² = 1.38, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)



Mortality at 1 year

	eEVAR		Open repair			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
ECAR	17	56	18	51	12.0%	0.86 [0.50, 1.48]
IMPROVE	130	316	133	295	88.0%	0.91 [0.76, 1.10]
Total (95% CI)		**372**		**346**	**100.0%**	**0.91 [0.76, 1.08]**
Total events	147		151			

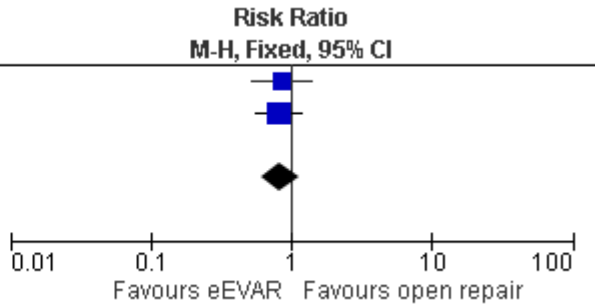
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)



Major complications at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AJAX	18	57	22	59	42.5%	0.85 [0.51, 1.40]
ECAR	25	56	28	51	57.5%	0.81 [0.55, 1.19]
Total (95% CI)		**113**		**110**	**100.0%**	**0.83 [0.61, 1.13]**
Total events	43		50			

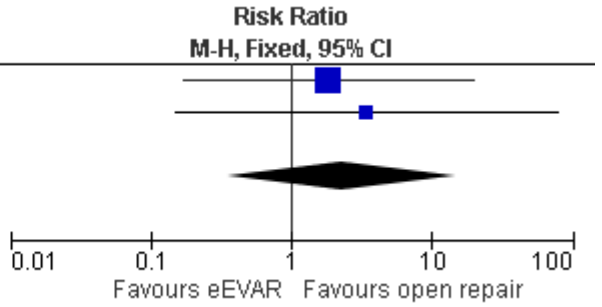
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)



Myocardial infarction at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ECAR	2	56	1	51	69.0%	1.82 [0.17, 19.49]
Hinchliffe 2006	1	15	0	17	31.0%	3.38 [0.15, 77.12]
Total (95% CI)		**71**		**68**	**100.0%**	**2.30 [0.36, 14.93]**
Total events	3		1			

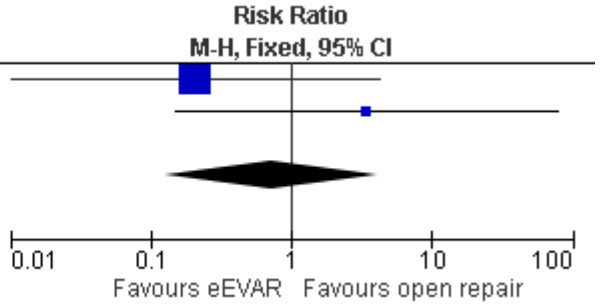
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)



Stroke at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AJAX	0	57	2	59	83.9%	0.21 [0.01, 4.22]
Hinchliffe 2006	1	15	0	17	16.1%	3.38 [0.15, 77.12]
Total (95% CI)		**72**		**76**	**100.0%**	**0.72 [0.13, 4.10]**
Total events	1		2			

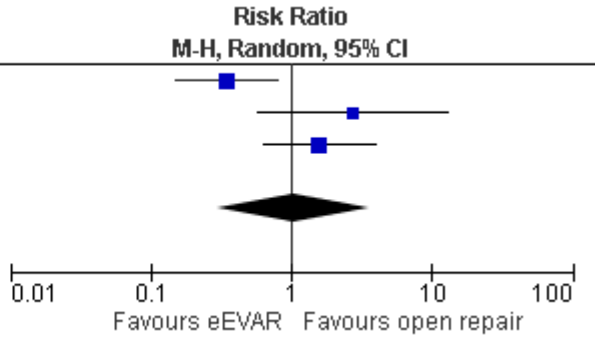
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.38 (P = 0.71)



Renal complications at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Random, 95% CI
AJAX	6	57	18	59	37.2%	0.35 [0.15, 0.81]
ECAR	6	56	2	51	26.5%	2.73 [0.58, 12.93]
Hinchliffe 2006	7	15	5	17	36.2%	1.59 [0.64, 3.96]
Total (95% CI)		**128**		**127**	**100.0%**	**1.04 [0.30, 3.63]**
Total events	19		25			

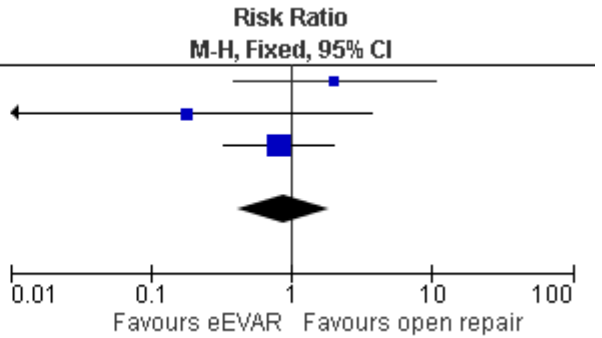
Heterogeneity: Tau² = 0.91; Chi² = 8.35, df = 2 (P = 0.02); I² = 76%
Test for overall effect: Z = 0.06 (P = 0.95)



Cardiac complications at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AJAX	4	57	2	57	17.9%	2.00 [0.38, 10.49]
ECAR	0	56	2	51	23.4%	0.18 [0.01, 3.71]
Hinchliffe 2006	5	15	7	17	58.7%	0.81 [0.32, 2.02]
Total (95% CI)		**128**		**125**	**100.0%**	**0.88 [0.41, 1.86]**
Total events	9		11			

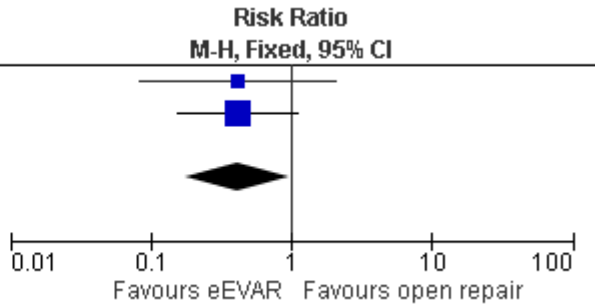
Heterogeneity: Chi² = 2.02, df = 2 (P = 0.36); I² = 1%
Test for overall effect: Z = 0.34 (P = 0.73)



Bowel ischaemia at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AJAX	2	57	5	59	29.9%	0.41 [0.08, 2.05]
ECAR	5	56	11	51	70.1%	0.41 [0.15, 1.11]
Total (95% CI)		**113**		**110**	**100.0%**	**0.41 [0.18, 0.96]**
Total events	7		16			

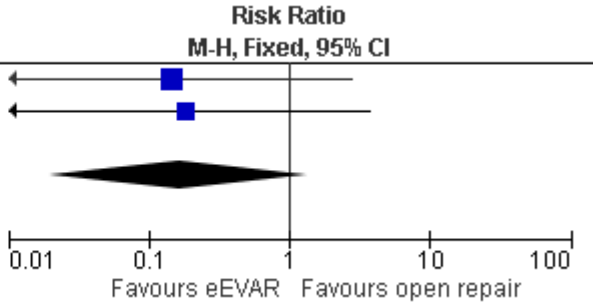
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)



Amputation at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AJAX	0	57	3	59	56.8%	0.15 [0.01, 2.80]
ECAR	0	56	2	51	43.2%	0.18 [0.01, 3.71]
Total (95% CI)		**113**		**110**	**100.0%**	**0.16 [0.02, 1.34]**
Total events	0		5			

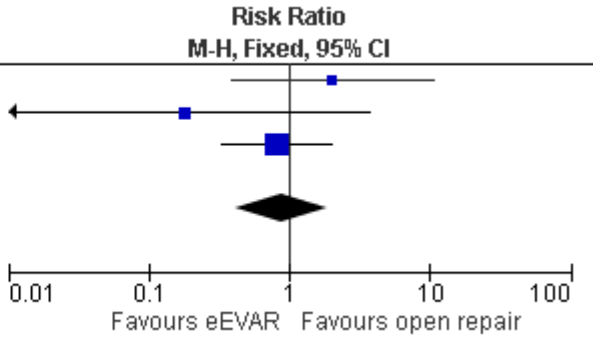
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)



Reoperation at 30 days

Study or Subgroup	eEVAR Events	eEVAR Total	Open repair Events	Open repair Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AJAX	4	57	2	57	17.9%	2.00 [0.38, 10.49]
ECAR	0	56	2	51	23.4%	0.18 [0.01, 3.71]
Hinchliffe 2006	5	15	7	17	58.7%	0.81 [0.32, 2.02]
Total (95% CI)		**128**		**125**	**100.0%**	**0.88 [0.41, 1.86]**
Total events	9		11			

Heterogeneity: Chi² = 2.02, df = 2 (P = 0.36); I² = 1%
Test for overall effect: Z = 0.34 (P = 0.73)



Appendix F – GRADE tables

Note: all data reported in GRADE tables relate to ruptured infrarenal AAA. No evidence comparing EVAR with open surgical repair of ruptured complex AAA were identified.

Mortality

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
All-cause Perioperative mortality (30-day or in-hospital mortality); effect sizes below 1 favour EVAR									
4 (AJAX, ECAR, IMPROVE & Hinchcliffe trials)	RCTs	Not serious	Not serious	Not serious	Serious[1]	444	424	RR 0.92 (0.77, 1.10)	Moderate
All-cause mortality at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[2]	57	59	RR 0.92 (0.52, 1.62)	Low
All-cause mortality at 1 year; effect sizes below 1 favour EVAR									
2 (IMPROVE & ECAR trials)	RCTs	Not serious	Not serious	Not serious	Serious[1]	372	346	RR 0.91 (0.76, 1.08)	Moderate
All-cause mortality between 3 months and 3 years; effect sizes below 1 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Serious[1]	316	297	HR 0.57 (0.36, 0.90)	Moderate
All-cause mortality at mean follow-up of 4.9 years; effect sizes below 1 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Serious[3]	316	297	HR[a] 0.90 (0.73, 1.10)	Moderate
AAA-related mortality at mean follow-up of 4.9 years; effect sizes below 1 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Serious[3]	316	297	HR[a] 0.88 (0.68, 1.15)	Moderate

a. Hazard ratios were reported adjusting for age, sex, Hardman index, and lowest systolic blood pressure.
1. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.
2. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
3. Non-significant result (95% confidence interval crosses the line of no effect), downgrade 1 level.									

Major complications

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Major complications at 30 days; effect sizes below 1 favour EVAR									
2 (AJAX & ECAR trials)	RCT	Serious[1]	Not serious	Not serious	Serious[2]	113	110	RR 0.83 (0.61, 1.13)	Low
Major complications at 1 year; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 0.89 (0.55, 1.47)	Low
1. Method of randomisation was not reported a study (ECAR trial) which had a high weighting (over 33%) in the meta-analysis, downgrade 1 level 2. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), 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.									

Specific complications

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Endoleaks at final follow-up									
3 (AJAX, ECAR & Hinchcliffe trials)	RCTs	Not serious	Not serious	Not serious	Very serious[1]	128	N/A	- 34.4% (44/128) Note: authors stated meta-analysis was not possible as endoleaks are only a result of EVAR.	Low
Myocardial infarction at 30 days; effect sizes below 1 favour EVAR									
2 (ECAR & Hinchcliffe trials)	RCTs	Serious[2]	Not serious	Not serious	Very serious[3]	71	68	RR 2.30 (0.36, 14.93)	Very low
Stroke at 30 days; effect sizes below 1 favour EVAR									
2 (AJAX, & Hinchcliffe trials)	RCTs	Not serious	Not serious	Not serious	Very serious[3]	72	76	RR 0.72 (0.13, 4.10)	Low
Stroke at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCTs	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 0.21 (0.01, 4.22)	Low
Renal complications at 30 days; effect sizes below 1 favour EVAR									
3 (AJAX, ECAR & Hinchcliffe trials)	RCTs	Not serious	Not serious	Very serious[5]	Very serious[3]	128	127	RR 1.04 (0.30, 3.63)	Very low
Renal complications at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Serious[6]	57	59	RR 0.35 (0.15, 0.81)	Moderate
Cardiac complications at 30 days ; effect sizes below 1 favour EVAR									
3 (AJAX, ECAR & Hinchcliffe trials)	RCTs	Not serious	Not serious	Not serious	Very serious[3]	128	125	RR 0.88 (0.41, 1.86)	Low
Cardiac complications at 6 months; effect sizes below 1 favour EVAR									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 1.67 (0.42, 6.65)	Low
Respiratory failure at 30 days; effect sizes below 1 favour EVAR									
1 Hinchliffe (2006)	RCT	Not serious	Not serious	N/A	Very serious[3]	15	17	RR 3.38 (0.15, 77.12)	Low
Bowel ischaemia at 30 days; effect sizes below 1 favour EVAR									
2 (AJAX & ECAR trials)	RCTs	Serious[2]	Not serious	Not serious	Serious[6]	113	110	RR 0.41 (0.18, 0.96)	Low
Bowel ischaemia at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 0.41 (0.08, 2.05)	Low
Spinal cord ischaemia at 30 days; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 3.10 (0.15, 74.64)	Low
Spinal cord ischaemia at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 3.10 (0.15, 74.64)	Low
Amputation at 30 days; effect sizes below 1 favour EVAR									
2 (AJAX & ECAR trials)	RCTs	Serious[2]	Not serious	Not serious	Very serious[3]	113	110	RR 0.16 (0.02, 1.34)	Very low
Amputation at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT in Badger systematic review	Not serious	Not serious	N/A	Very serious[3]	57	59	RR 0.15 (0.01, 2.80)	Low

1. Effect sizes and measures of dispersion were not reported as meta-analysis was not possible, downgrade 2 levels.
2. Method of randomisation was not reported in a study (ECAR trial) which had a high weighting (over 33%) in the meta-analysis, 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.
5. I^2 value >66.7%, downgrade 2 levels.
6. 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 reintervention

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**EVAR**	**Open repair**	**Summary of results**	
Any reintervention at 30 days; effect sizes below 1 favour EVAR									
3 (AJAX, ECAR & Hinchcliffe trials)	RCTs	Not serious	Not serious	Serious[1]	Very serious[2]	128	125	RR 0.88 (0.41, 1.86)	Very low
Any reintervention at 6 months; effect sizes below 1 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Very serious[2]	57	59	RR 1.21 (0.61, 2.38)	Low
Any reintervention at 3 years; effect sizes below 1 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Serious[3]	316	297	HR[a] 1.04 (0.80, 1.35)	Moderate

a. Hazard ratios were reported adjusting for age, sex, Hardman index, and lowest systolic blood pressure.
1. I^2 value > 40%, downgrade 1 level.
2. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.
3. Non-significant result (95% confidence interval crosses the line of no effect), downgrade 1 level.

Quality of life

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**EVAR**	**Open repair**	**Summary of results**	
SF-36 Physical domain at 6 months; effect sizes below 0 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Serious[1]	29	27	MD 3.56 (-2.0, 9.0)	Moderate
SF-36 mental domain at 6 months; effect sizes below 0 favour EVAR									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Serious[1]	29	27	MD -5.25 (-11.0, 0)	Moderate
EQ-5D at 3 months; effect sizes below 0 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Not serious	167	150	MD 0.087 (0.017, 0.158)	High
EQ-5D at 12 months; effect sizes below 0 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Serious[1]	161	140	MD 0.068 (-0.004, 0.140)	Moderate
EQ-5D at 3 years; effect sizes below 0 favour EVAR									
1 IMPROVE trial	RCT	Not serious	Not serious	N/A	Serious[3]	N=262		MD 0.013 (-0.069, 0.096)	Moderate

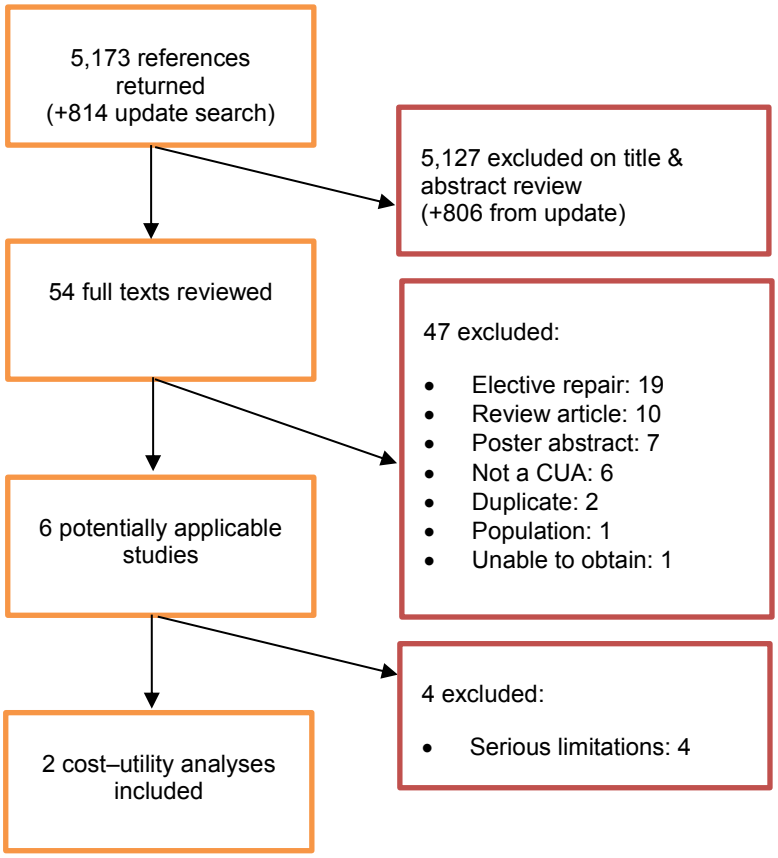
1. Non-significant result (95% confidence interval crosses the line of no effect), downgrade 1 level.

Length of stay

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**EVAR**	**Open repair**	**Summary of results**	
Length of stay in ICU (hours)									
1 AJAX trial	RCT	Not serious	Not serious	N/A	Serious[1]	57	59	AJAX diff in medians: 18 (Non-significant according to the Mann-Whitney test)	Moderate
Length of Hospital stay (days)									
3 (AJAX, ECAR & Hinchcliffe trials)	RCT	Not serious	Not serious	Not serious	Serious[1]	128	127	AJAX diff in medians: 4 ECAR diff in medians: 2.8 (Both non-significant according to the Mann-Whitney or Wilcoxon rank test) Hinchliffe diff in medians: 2 (statistical significance not reported)	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	Results			Conclusions	Uncertainty
			Cost (€)	Effect (QALYs)	ICER (€)		
Kapma et al. (2014) Within-trial cost–utility analysis as part of the AJAX study. Netherlands. **Partially applicable** [a] **Potentially serious limitations** [b,c,d]	Effects: AJAX study (RCT comparing EVAR [n=57] with OSR [n=59] for rAAA). Costs: Hospital perspective. Primary procedure, perioperative and follow-up resource use from AJAX (1 centre). Costs from national sources and hospital records. Utilities: Derived from EQ-5D-3L questionnaire, administered 1, 3 & 12 months after intervention.	6-month time horizon (therefore outcomes not subjected to discounting). Price year 2010 (€). Missing EQ-5D data backwards imputed if possible (else LOCF). Trial data were bootstrapped (n=25,000) to characterise uncertainty in incremental costs and QALYs.	EVAR: 41,350 OSR: 31,616 Increment: **10,189** 95% CI: [-2477, 24,506]	EVAR: 0.324 95% CI: [0.198, 0.445] OSR: 0.298 95% CI: [0.164, 0.433] Increment: **0.026**	€391,885	'Treatment of rAAA using EVAR was not cost-effective compared with [OSR] in this study.'	Conclusions robust to cost scenarios and analysis based on age subgroups. EVAR may be cost-effective if the device cost is 50% lower than the list price. EVAR ICER was €80,000 or less in fewer than 25% of bootstrap iterations.

Key: CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; LOCF, last observation carried forward; OSR, open surgical repair; QALY, quality-adjusted life year; rAAA, ruptured abdominal aortic aneurysm; RCT, randomised controlled trial.

a. EVAR appears to have been conducted only where there was anatomical suitability, which is likely to mean infrarenal aneurysms.
b. Relatively small study sample size (n=116).
c. Short time horizon (6 months).
d. Resource use and cost data only available from 1 of the 2 study hospitals.

Study, Population, Country and Quality	Data Sources	Other Comments	Results			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER		
Powell et al. (2017) Within-trial cost–utility analysis as part of the IMPROVE study: 3-year update. UK. **Directly applicable** **Potentially serious limitations** [a,b]	Effects: IMPROVE study (pragmatic trial comparing EVAR strategy [n=316] with OSR strategy [n=297] for rAAA). Costs: Primary procedure perioperative hospital care and follow-up care resource use from IMPROVE. Costs from standard UK sources (2012). Utilities: Derived from EQ-5D-3L questionnaire, administered in IMPROVE 3, 12 and 36 months after intervention (QALYs estimated by AUC).	3-year time horizon, outcomes discounted by 3.5% annually. Price year appears to be 2011-12, based on source data for unit costs. Primary analysis by randomised group (intention-to-treat). Missing data were imputed from available data from rAAA participants for whom repair was commenced, conditional on other, fully observable variables (e.g. age) Trial data were bootstrapped to characterise uncertainty in the estimated incremental costs and QALYs (number of simulations NR).	EVAR: 16,878 OSR: 19,483 Increment: **-2605** 95% CI: [-5966, 702]	EVAR: 1.14 OSR: 0.97 Increment: **0.166** 95% CI: [0.022, 0.331]	**EVAR dominant**	'This mid-term follow-up provides convincing support for the benefits of an endovascular strategy (EVAR if morphologically feasible) versus open repair to treat patients with ruptured abdominal aortic aneurysm. At three years, the endovascular strategy offers an increase in QALYs, without an excess of reinterventions, and is cost effective.'	Results consistent when analysing only participants with confirmed AAA rupture, in an intention-to-treat analysis and when attempting to adjust for trial crossover (complier average causal effect analysis). EVAR ICER dominant in 88% of simulations, cost-effective in over 90% of bootstrap simulations at all cost per QALY thresholds.

Key: AUC, area under the curve; CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR, open surgical repair; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; rAAA, ruptured abdominal aortic aneurysm.

a. Pragmatic trial (not truly randomised at the point of intervention), though an attempt to adjust for this crossover has been undertaken in sensitivity analysis.

b. Short time horizon (3 years), despite longer-term survival data that indicate an acceleration of EVAR mortality beyond 3 years, almost converging with OSR at year 6. 3-year analysis duration is may censor lasting differences between interventions in readmission and reintervention rates.

Appendix J – Excluded studies

Clinical studies

No.	Study	Reason for exclusion
1	Antoniou G A, Georgiadis G S, Antoniou S A et al. (2013) Endovascular repair for ruptured abdominal aortic aneurysm confers an early survival benefit over open repair. United States: Mosby Inc. (11830 Westline Industrial Drive, St. Louis MO 63146, United States)	Systematic review including studies that employed various study designs. Individual studies were assessed to determine if they met inclusion criteria for this review question.
2	Braithwaite B, Greenhalgh R M, Grieve R, Hassan et al. (2015) Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: One-year outcomes from the IMPROVE randomized trial. European heart journal 36(31), 2061-2069-2069	Study is included in the Cochrane systematic review.
3	Desgranges P, Kobeiter H, Katsahian S, et al (2015) ECAR (Endovasculaire ou Chirurgie dans les Anevrysmes aorto-iliaques Rompus): A French Randomized Controlled Trial of Endovascular Versus Open Surgical Repair of Ruptured Aorto-iliac Aneurysms. :	Study is included in the Cochrane systematic review.
4	Improve trial, and investigators (2014) Observations from the IMPROVE trial concerning the clinical care of patients with ruptured abdominal aortic aneurysm. British journal of surgery 101, 216-224	Study is included in the Cochrane systematic review.
5	Powell J T, Sweeting M J, Thompson M et al. (2014) Endovascular or open repair strategy for ruptured abdominal aortic aneurysm: 30 day outcomes from IMPROVE randomised trial.	A more recent publication of this study was available and is included in the Cochrane systematic review.
6	Qin C, Chen L, and Xiao Y B (2014) Emergent endovascular vs. open surgery repair for ruptured abdominal aortic aneurysms: a meta-analysis.	Systematic review including studies that employed various study designs. Individual studies were assessed to determine if they met inclusion criteria for this review question.
7	Reimerink J J, Hoornweg L L, Vahl A C, et al. (2013) Endovascular repair versus open repair of ruptured abdominal aortic aneurysms: a multicenter randomized controlled trial. Annals of surgery 258(2), 248-256	Study is included in the Cochrane systematic review.
8	Sweeting M J, Balm R, Desgranges P, et al. (2015) Individual-patient meta-analysis of three randomized trials comparing endovascular versus open repair for ruptured abdominal aortic aneurysm.	Individual patient meta-analysis based on data from 3 RCTs. It is unclear whether a systematic approach was used to select and include the 3 studies. These studies have been included, in the Cochrane systematic review.

No.	Study	Reason for exclusion
9	van Beek , S C, Conijn A P, Koelemay M J et al. (2014) Editor's Choice - Endovascular Aneurysm Repair Versus Open Repair for Patients with a Ruptured Abdominal Aortic Aneurysm: a Systematic Review and Meta-analysis of Short-term Survival.	Systematic review including studies that employed various study designs. Individual studies were assessed to determine if they met inclusion criteria for this review question.

Economic studies

Study	*Primary reason for exclusion*
Selectively excluded	
Hayes et al. (2010). Cost-effectiveness analysis of endovascular versus open surgical repair of acute abdominal aortic aneurysms based on worldwide experience. *J Endovasc Ther,* 17: 174-82.	Very serious limitations
Patel et al. (2000). The cost-effectiveness of repairing ruptured abdominal aortic aneurysms. *J Vasc Surg,* 32: 247-57.	Very serious limitations
Powell et al. (2015). Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial. *Eur Heart J,* 35: 2061-9.	Population (emergency repair)
Rollins et al. (2014). Mid-term cost-effectiveness analysis of open and endovascular repair for ruptured abdominal aortic aneurysm. *Br J Surg,* 101: 225-31.	Very serious limitations
Takayama (2017). A Cost-Utility Analysis of Endovascular Aneurysm Repair for Abdominal Aortic Aneurysm. *Ann Vasc Dis*, 10(3): 185-91.	Very serious limitations
Excluded based on study selection criteria	
Armstrong et al. (2014). The use of fenestrated and branched endovascular aneurysm repair for juxtarenal and thoracoabdominal aneurysms: a systematic review and cost-effectiveness analysis. *HTA,* 18(70).	Not a CUA
Badger et al. (2014). Endovascular treatment for ruptured abdominal aortic aneurysm (review). *Cochrane Database of Systematic Reviews,* 7.	Review article, no additional CUAs
Blackhouse et al. (2009). A cost-effectiveness model comparing endovascular repair to open surgical repair of abdominal aortic aneurysm in Canada. *Value in Health,* 12(2): 245-52.	Population (elective repair)
Bosch et al. (2002). Abdominal aortic aneurysms: cost-effectiveness of elective endovascular and open surgical repair. *Radiology,* 225(2): 337-44.	Population (elective repair)
Bowen et al. (2005). Systematic review and cost-effectiveness analysis of elective endovascular repair compared to open surgical repair of abdominal aortic aneurysms. Interim report. Ontario Ministry of Health & Long-term Care.	Population (elective repair)
Brown et al. (2012). The UK endovascular aneurysm repair (EVAR) trials: randomised trials of EVAR versus standard therapy. *HTA,* 16(9).	Population (elective repair)
Burgers et al. (2016). Cost-effectiveness of Elective Endovascular Aneurysm Repair Versus Open Surgical Repair of Abdominal Aortic Aneurysms. *Eur J Vasc Endovasc Surg*, 52: 29-40.	Population (elective repair)
Chambers et al. (2009). Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model. *HTA,* 13(48).	Population (elective repair)
Epstein et al. (2008). Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. *Br J Surg,* 95: 183-90.	Population (elective repair)
Epstein et al. (2014). Long-term cost-effectiveness analysis of endovascular versus open repair for abdominal aortic	Population (elective repair)

aneurysm based on four randomized clinical trials. *Br J Surg,* 101(6): 623-31.	
Forbes et al. (2002). A cost-effectiveness analysis of standard versus endovascular abdominal aortic aneurysm repair. *J Can Chir,* 45(6): 420-4.	Not a CUA
Greenhalgh et al. (2005). Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *The Lancet,* 365(9458): 2179-86.	Not a CUA
Hynes et al. (2007). A prospective clinical, economic, and quality-of-life analysis comparing endovascular aneurysm repair (EVAR), open repair, and best medical treatment in high-risk patients with abdominal aortic aneurysms suitable for EVAR: The Irish patient trial. *J Endocasc Ther,* 14: 763-76.	Population (elective repair)
Jonk et al. (2007). Cost-effectiveness of abdominal aortic aneurysm repair: a systematic review. *Int J Tech Assess Health Care,* 23(2): 205-15.	Review article, no additional CUAs
Kapma et al. (2007). Emergency abdominal aortic aneurysm repair with a preferential endovascular strategy: mortality and cost-effectiveness analysis. *J Endovasc Ther,* 14: 777-84.	Not a CUA
Lederle. (2009). Repair of nonruptured abdominal aortic aneurysm: a systematic review of randomized trials. *Vascular,* 17: S71.	Poster abstract
Lederle et al. (2012). Cost-effectiveness at two years in the VA open versus endovascular repair trial. *Eur J Vasc Endovasc Surg,* 44: 543-8.	Population (elective repair)
Lederle et al. (2016). Long-term cost-effectiveness in the vetereans Affairs Open vs Endovascular Repair Study of aortic abdominal aneurysm: a randomised clinical trial. *JAMA Surg,* 151(12): 1139-1144.	Population (elective repair)
Luebke et al. (2014). Cost-effectiveness of endovascular versus open repair of acute complicated type B aortic dissections. *J Vasc Surg,* 59: 1247-55.	Population (thoracic aortic dissection)
Mandavia et al. (2015). The role of cost-effectiveness for vascular surgery service provision in the United Kingdom. *J Vasc Surg,* 61: 1331-9.	Review article, no additional CUAs
McCarron et al. (2013). The impact of using informative priors in a Bayesian cost-effectiveness analysis: an application of endovascular versus open surgical repair for abdominal aortic aneurysms in high-risk patients. *Med Decis Mak,* 33(3): 437-50.	Population (elective repair)
Medical Advisory Secretariat Ontario (2002). Endovascular repair of abdominal aortic aneurysm: an evidence-based analysis. *Ontario HTA Series,* 2(1).	Review article, no additional CUAs
Michaels et al. (2005). Cost-effectiveness of endovascular abdominal aortic aneurysm repair. *Br J Surg,* 92(8): 960-7.	Population (elective repair)
Michaels et al. (2014). Long-term cost-effectiveness analysis of endovascular versus open repair for abdominal aortic aneurysms based on four randomized clinical trials. *Br J Surg,* 101(6): 632.	Commentary, no additional CUAs
Patel et al. (1999). The cost-effectiveness of endovascular repair versus open surgical repair of abdominal aortic aneurysms: a decision analysis model. *J Vasc Surg,* 29(6): 958-72.	Population (elective repair)
Perras et al. (2009). Elective endovascular abdominal aortic aneurism repair versus open surgery: a review of the clinical and cost-effectiveness.	Review article, no additional CUAs
Prinssen et al. (2007). Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: Results of a randomized trial. *J Vasc Surg,* 46: 883-90.	Population (elective repair)
Sala-Almonicil et al. (2017). Fenestrated and chimney endovascular aneurysm repair versus open surgery for complex abdominal aortic aneurysms. *J Cardiovasc Surg,* 58(6): 801-13.	Not a CUA.

Sousa et al. (2014). Cost-effectiveness of the endovascular repair of abdominal aortic aneurysm in Portugal. *Angiol Cir Vasc,* 10(2): 41-8.	Population (elective repair)
Stroupe et al. (2012). Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm in the OVER trial. *J Vasc Surg,* 56: 901-10.	Duplicate of Lederle et al. (2012)
Silverstein et al. (2005). Abdominal aortic aneurysm (AAA): cost-effectiveness of screening, surveillance of intermediate-sized AAA, and management of symptomatic AAA. *BUMC Proceedings,* 18: 345-67.	Review article, no additional CUAs
Sultan et al. (2009a). A prospective clinical and quality of life analysis of open repair (OR), endovascular repair (EVAR), and best medical treatment in high-risk patients: cost-effectiveness during global recession. *Vascular,* (17): S2.	Poster abstract
Sultan et al. (2009b). Five-year experience with EVAR without fenestration for juxtarenal AAA repair: clinical efficacy, reintervention rates, and cost-effectiveness. *Vascular,* 17: S74.	Not found
Sultan & Hynes (2010a). Five-year experience with pararenal endovascular aortic repair (PEVAR) without fenestration: clinical efficacy, reintervention rates & cost-effectiveness. *J Vasc Surg,* 51(6): S89.	Poster abstract
Sultan & Hynes (2010b). Five-year experience with pararenal endovascular aortic repair (PEVAR) without fenestration: clinical efficacy, reintervention rates & cost-effectiveness. *J Vasc Surg,* 51(4): 1068-9.	Poster abstract
Sultan & Hynes (2010c)	Poster abstract
Sultan & Hynes (2011a). Clinical efficacy and cost per quality-adjusted life years of pararenal endovascular aortic aneurysm repair compared with open surgical repair. *J Endovasc Ther,* 18: 181-96.	Population (elective repair)
Sultan & Hynes (2011b). A mid- to long-term experience of clinical efficacy and cost per quality-adjusted-life years with pararenal endovascular aortic repair (PEVAR) without fenestration for pararenal AAA compared with open surgical repair. *Cardiovasc Interv Radiol,* 3 (332/677).	Poster abstract
Sultan & Hynes (2012). Clinical efficacy and cost per quality-adjusted life years of para-renal endovascular aortic aneurysm repair compared with open surgical repair. *JACC,* 60(17): B38.	Poster abstract
Sweeting et al. (2015). Individual-patient meta-analysis of three randomized trials comparing endovascular versus open repair for ruptured abdominal aortic aneurysm. *Br J Surg,* 102: 1229-39.	Review article, no additional CUAs
Tarride et al. (2008). Cost-effectiveness analysis of elective endovascular repair compared with open surgical repair of abdominal aortic aneurysms for patients at a high surgical risk: A 1-year patient-level analysis conducted in Ontario, Canada. *J Vasc Surg,* 48: 779-87.	Population (elective repair)
Tarride et al. (2011). Should endovascular repair be reimbursed for low risk abdominal aortic aneurysm patients? Evidence from Ontario, Canada. *Int J Vasc Med,* 2011.	Not a CUA
Taylor et al. (2012). EVAR is now cost effective and should replace open surgery for all suitable patients: con. *Cardiovasc Interv Radiol,* 35: S48.	Review article, no additional CUAs
Tremont et al. (2016). Endovascular Repair for Ruptured Abdominal Aortic Aneurysms has Improved Outcomes Compared to Open Surgical Repair. Vasc Endovasc Surg, 50(3) 147-55.	Not a CUA
Van Bochove et al. (2016). Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm. *J Vasc Surg,* 3: 827-38.	Population (elective repair)
Weinkauf et al. (2017). Open versus endovascular aneurysm repair trial review. *Surgery,* 162(5): 974-78.	Population (elective repair)
Wilt et al. (2006). Comparison of endovascular and open surgical repairs for abdominal aortic aneurysm. *Evid Rep Technol Assess,* 144: 1-113.	Review article, no additional CUAs

Key: CUA, cost–utility analysis.

Appendix K – Research recommendation

Research recommendation	What is the effectiveness and cost-effectiveness of complex EVAR versus open surgical repair in people with a ruptured AAA for whom open surgery is a suitable option?
Population	People undergoing surgery for a ruptured abdominal aortic aneurysm Sub-grouped by: age, sex, comorbidities (including cardiovascular disease, renal disease, COPD, obesity) and ethnicity
Intervention(s)	• Emergency complex EVAR for infrarenal, juxtarenal and suprarenal abdominal aortic aneurysms, including: • fenestrated EVAR • EVAR with chimneys • EVAR with snorkels • branched grafts • 'CHIMPS' (CHIMneys, Periscopes, Snorkels) • infrarenal devices used for juxtarenal AAA – that is, off-IFU use of standard devices
Comparator(s)	Open surgical repair
Outcomes	• Mortality/survival • Peri- and post-operative complications • Successful exclusion of the aneurysm, aneurysm rupture, or further aneurysm growth • Need for reintervention • Quality of life • Resource use, including length of hospital or intensive care stay, and costs
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	EVAR is a widely performed non-invasive alternative to open surgical repair. However, it is more expensive and more difficult to perform. Although EVAR has been shown to produce comparable long-term outcomes to open surgical in people with ruptured infrarenal aneurysms, it is less clear whether these benefits are maintained in people with ruptured juxtarenal, suprarenal type IV, and branched infrarenal aneurysms. As a result, research is needed to identify how effective complex EVAR is in these populations.
Relevance to NICE guidance	High priority: it is currently not possible to make specific recommendations related to complex EVAR, other than to state that the procedure should not be performed on aneurysms that could be treated by open surgical repair, unless it is performed within the context of a randomised controlled trial.
Current evidence base	Randomised controlled trials have been performed to assess the efficacy of standard EVAR for unruptured or ruptured AAA, and complex EVAR of unruptured AAA. However, no RCTs have been performed to determine the efficacy of complex EVAR in people with ruptured juxtarenal, suprarenal type IV, and branched infrarenal aneurysms. In the absence of this type of evidence the committee recognised the potential for harm if patients who could receive open surgery were offered complex speculative EVAR for the wrong reasons. As a result, they agreed that complex EVAR should be performed in well-controlled environments, like that of an RCT to ensure that data will be collected to inform future updates of the guideline.
Equality	No specific equality concerns are relevant to this research recommendation.

Potential criterion	Explanation
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

Appendix L – 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.