

Abdominal aortic aneurysm: diagnosis and management

Evidence review K: Effectiveness of endovascular aneurysm repair, open surgical repair and non-surgical management of unruptured abdominal aortic aneurysms

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Evidence reviews

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1 Effectiveness of endovascular aneurysm 2 repair, open surgical repair and non- 3 surgical management of unruptured 4 abdominal aortic aneurysms

5 Review question

6 What are the relative benefits and harms of EVAR, open surgical repair and non-surgical
7 management in people with unruptured abdominal aortic aneurysms?

8 Introduction

9 This review question aims to assess the advantages and disadvantages of elective
10 endovascular aneurysm repair (EVAR) in comparison with conventional open surgical repair
11 for the treatment of unruptured abdominal aortic aneurysms (AAAs). Furthermore, this
12 question aims to explore advantages and disadvantages of elective EVAR in comparison
13 with non-surgical management when open surgical repair is not possible.

14 PICO table

15 **Table 1: Inclusion criteria**

Parameter	Inclusion criteria
Population	People undergoing surgery for a confirmed unruptured AAA Subgroups: fitness for surgery, age, sex, comorbidities (including cardiovascular disease, renal disease, COPD, obesity), ethnicity
Interventions	Elective standard (on-instructions for use [IFU]) EVAR for infrarenal and juxtarenal AAA Elective complex EVAR for infrarenal, juxtarenal and suprarenal AAA, 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

16 **Methods and process**

17 This evidence review was developed using the methods and process described in
18 [Developing NICE guidelines: the manual \(2014\)](#). Methods specific to this review question are
19 described in the review protocol in Appendix A.

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

21 A Cochrane systematic review (Paravastu et al. 2014) comparing EVAR and open surgical
22 repair of unruptured AAAs was identified as a reliable source of randomised controlled trials
23 (RCTs) relevant to this review question. Since the systematic review was published in 2014,
24 the Cochrane Vascular Group worked in collaboration with the NICE Guideline Updates
25 Team and performed update literature searches to facilitate identification of any RCTs
26 published after publication of the systematic review by Paravastu et al. (2014). Data were
27 extracted from the systematic review, individual RCTs within it, and RCTs identified from
28 update literature searches to compare the efficacy of elective EVAR with that of open
29 surgical repair of 'simple' unruptured infrarenal aneurysms. Since the Cochrane systematic
30 review did not explicitly consider complex aneurysm anatomies (such as juxtarenal and
31 suprarenal type IV aneurysms) a supplementary literature search was performed by NICE.
32 Although RCTs were judged to be the optimal study design for this question, non-randomised
33 comparative studies, and prospective cohort studies comparing EVAR and open surgical
34 repair of unruptured complex AAAs were also included because the committee expected
35 fewer RCTs evaluating complex EVAR to be published since it makes up a small subset of
36 elective EVAR procedures.

37 Studies were excluded if they:

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

41 **Clinical evidence**

42 **Included studies**

43 ***Standard EVAR***

44 The 2014 Cochrane systematic review (Paravastu et al, 2014) included 4 RCTs (reported
45 across multiple publications) comparing EVAR with open surgical repair of infrarenal AAA.
46 The update literature search performed by Cochrane Vascular Group yielded 354 abstracts,
47 of which 4 full manuscripts were ordered. Of the 4 articles reviewed, an additional publication
48 reporting an RCT (EVAR-1 trial) that was already included in the Cochrane review was
49 identified. Thus, a total of 4 RCTs, published across multiple publications, was considered
50 relevant for comparisons between standard EVAR and open surgical repair of unruptured
51 AAAs. The 2014 Cochrane systematic review included 1 RCT (EVAR-2 trial) comparing
52 EVAR with non-surgical management, in patients for whom open surgical repair was
53 considered unsuitable. The update literature search performed by Cochrane Vascular Group
54 yielded 1 publication reporting long-term follow-up of the EVAR-2 trial.

55 In December 2017, Cochrane performed another literature search to identify studies which
56 were published during guideline development. The search yielded a total of 296 abstracts; of
57 which, 4 full manuscripts were ordered. Upon review of these 4 articles, a publication of
58 another RCT (DREAM trial) already included in the Cochrane review was identified.

59 **Complex EVAR**

60 With regard to complex aneurysm anatomies, searches conducted by NICE yielded 2,220
 61 abstracts. Of these, 16 studies were identified as being potentially relevant. Following full-text
 62 review, 1 study was included. An update search was conducted by NICE in December 2017.
 63 The search yielded 191 abstracts; of which, 7 full manuscripts were ordered. Following full-
 64 text review, no new studies were identified.

65 **Excluded studies**

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

67 **Summary of clinical studies included in the evidence review**

68 A summary of the included studies is provided in the tables below.

69 **Standard EVAR compared with open surgical repair of unruptured infrarenal AAA**

Study	Details
Paravastu SC, Jayarajasingam R, Cottam R et al. (2014) Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev;(1): CD004178. doi: 10.1002/14651858.CD004178.pub2.	Study design: systematic review Location: UK Population: patients with unruptured AAA Sample size: 4 RCTs including 2,745 participants Follow-up: 30 days, up to 4 years, up to 8 years Intervention: standard EVAR using any type of endovascular device Comparators: open surgical repair Outcomes: All-cause mortality, aneurysm-related mortality, endograft-related complications, major complications, minor complications, and quality of life. Assessed at the following time points: 30 days, up to 4 years up to 8 years. Note: details about included studies can be found in Appendix D
ACE trial (results reported in multiple publications outlined in the Cochrane systematic review)	Study design: multicentre, non-blinded, randomised controlled trial Location: France Population: patients with asymptomatic unruptured abdominal aortic or aorto-iliac aneurysm Sample size: 299; 99% male Follow-up: up to 4 years Intervention: standard EVAR Comparators: Open surgical repair Outcomes: All-cause mortality, major adverse events (myocardial infarction, permanent stroke, permanent haemodialysis, major amputation, paraplegia and bowel infarction), vascular reinterventions and minor complications
DREAM trial (results reported in multiple publications outlined in the Cochrane systematic review)	Study design: multicentre, non-blinded, randomised controlled trial Location: Netherlands Population: patients with unruptured AAA

Study	Details
NB: a new publication was identified from update searches van Schaik T G, Yeung KK, Verhagen HJ et al. (2017) Long-term survival and secondary procedures after open or endovascular repair of abdominal aortic aneurysms. <i>European Journal of Vascular and Endovascular Surgery</i> 54 (5), 671	Sample size: 351; 91% male Follow-up: up to 15 years 3 Intervention: standard EVAR Comparators: Open surgical repair Outcomes: All-cause mortality, aneurysm-related mortality, complications and reintervention rates
EVAR1 trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches Patel R, Sweeting MJ, Powell JT et al. (2016) Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. <i>Lancet</i> . 388(10058):2366-2374.	Study design: multicentre, non-blinded, randomised controlled trial Location: UK Population: patients with unruptured AAA Sample size: 1,252; 91% male Follow-up: up to 15 years Intervention: standard EVAR Comparators: Open surgical repair Outcomes: All-cause mortality, aneurysm-related mortality, complications and reintervention rates
OVER trial (results reported in multiple publications outlined in the Cochrane systematic review)	Study design: multicentre, non-blinded, randomised controlled trial Location: USA Population: patients with unruptured AAA Sample size: 881; 99% male Follow-up: 8 years Intervention: standard EVAR Comparators: Open surgical repair Outcomes: All-cause mortality, aneurysm-related mortality, complications and reintervention rates

70 Complex EVAR compared with open surgical repair of juxtarenal (complex) aneurysms

Study	Details
Donas Konstantinos P, Eisenack Markus, Panuccio Giuseppe, Austermann Martin, Osada Nani, and Torsello Giovanni (2012) The role of open and endovascular treatment with fenestrated and chimney endografts for patients with juxtarenal aortic aneurysms. <i>Journal of vascular surgery</i> 56, 285-90	Study design: non-randomised comparative study Location: Germany Population: patients with primary degenerative juxtarenal AAAs Sample size: 90; 92% (83/90) male Follow-up: 30-days Intervention: complex EVAR (chimney-EVAR or fenestrated-EVAR) Comparators: open surgical repair Outcomes: 30-day mortality, the need for re-intervention and length of stay,

71 **EVAR vs no intervention for patients in whom open surgery is not considered**
 72 **appropriate**

Study	Details
Sweeting M J, Patel R, Powell J T, and Greenhalgh R M (2017) Endovascular Repair of Abdominal Aortic Aneurysm in Patients Physically Ineligible for Open Repair: Very Long-term Follow-up in the EVAR-2 Randomized Controlled Trial. <i>Annals of Surgery</i> . 24 Note: Other publications relating to this trial that reported data at different follow-up periods were considered	Study design: multicentre, non-blinded, randomised controlled trial Location: UK Population: patients with large aneurysms in whom open surgical repair was considered inappropriate Sample size: 404; sex-specific proportions were not reported Follow-up: 12 years Intervention: EVAR Comparators: open surgical repair Outcomes: All-cause mortality, aneurysm-related mortality, graft-related complications and graft-related re-interventions.

73 See Appendix D for full evidence tables.

74 **Quality assessment of clinical studies included in the evidence review**

75 See Appendix F for full GRADE tables.

76 **Economic evidence**

77 **Included studies**

78 A systematic review of economic literature was conducted jointly for all review questions in
 79 this guideline by applying standard health economic filters to a clinical search for AAA (see
 80 Appendix B). A total of 5,173 studies was identified. The studies were reviewed to identify
 81 cost–utility analyses exploring the costs and effects of elective surgical procedures to repair
 82 unruptured AAAs. Studies that met the eligibility criteria were assessed using the quality
 83 appraisal criteria as outlined in the Developing NICE guidelines: the manual (2014).

84 Following an initial review of titles and abstracts, the full texts of 46 studies were retrieved for
 85 detailed consideration. Following full-text review, 15 of the 46 studies were judged to be
 86 potentially applicable cost–utility analyses for elective repair. Of these, 5 were UK studies. It
 87 was decided to exclude the non-UK studies because of their lower applicability to UK
 88 practice.

89 An update search was conducted in December 2017, to identify any relevant cost–utility
 90 analyses that had been published during guideline development. This search returned 814
 91 studies. Following review of titles and abstracts, the full texts of 8 studies were retrieved for
 92 detailed consideration. Three were determined to be potentially applicable for elective repair;
 93 however they were non-UK studies, and were selectively excluded. A total of 5 studies was
 94 therefore included as economic evidence for the elective repair of unruptured AAA.

95 **Excluded studies**

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

98 Summary of studies included in the economic evidence review**99 Michaels et al. (2005)**

100 Michaels et al. (2005) published the first UK cost–utility analysis comparing EVAR with open
101 surgical repair for the elective repair of infrarenal AAA, based on early (perioperative; 30-day)
102 results of the EVAR-1 and DREAM trials. The analysis modelled a cohort of 70-year old men
103 with an initial AAA diameter of 5.5cm. A decision tree was developed to model the surgical
104 procedure followed by general population survival for 10 years. Other inputs, such as EVAR
105 complications, were derived from a 2005 NICE review of non-RCT data. Costs and QALYs
106 were both discounted by 3.5% per year. Model results (Table 3) suggest that EVAR is
107 associated with a high ICER of over £100,000/QALY compared with open surgical repair,
108 with a near 0% likelihood of the ICER falling under £20,000 per QALY gained.

109 A secondary analysis was also reported comparing EVAR with providing no intervention;
110 however it was based on non-randomised evidence only, therefore these results have been
111 excluded due to possessing very serious limitations.

112 Epstein et al. (2008)

113 Epstein et al. (2008) developed a lifetime Markov model comparing EVAR with open surgical
114 repair in the UK, based on 4-year data from the EVAR-1 randomised study. Perioperative
115 outcomes included mortality and conversion from EVAR to open surgical repair, followed by
116 symptom-free survival subject to risks of major cardiovascular events, AAA-related
117 readmission and death. All-cause mortality rates were assumed to converge after 2 years.
118 Health-related quality of life effects (EQ-5D), resource use and costs were informed by data
119 collected during EVAR-1. All outcomes were discounted by 3.5% per year.

120 The model found EVAR to incur higher total costs and accrue fewer QALYs per patient than
121 open surgical repair (Table 3), and the difference in costs was statistically significant. EVAR
122 had a 1% probability of having an ICER of £20,000 or less per QALY gained, which remained
123 less than 10% in all but extreme scenario analyses.

124 Chambers et al. (2009)

125 Chambers et al. (2009) developed an NIHR-funded cost–utility model as part of their EVAR
126 health technology assessment to support NICE Technology Appraisal 167. It evaluated
127 EVAR in 2 populations: people who are fit enough to undergo open surgical repair and
128 people who are not. For the primary analysis comparing EVAR with open surgical repair, a
129 Markov model was developed using patient-level data from the EUROSTAR registry dataset,
130 with a similar structure to the Epstein et al. (2008) model. The EUROSTAR data informed
131 multivariable models predicting baseline risks of perioperative mortality, postoperative AAA-
132 related mortality and other cause mortality, with relative risks informed by the DREAM and
133 EVAR-1 studies or expert advice. The aneurysm-related mortality benefit associated with
134 EVAR was assumed to persist for the lifetime horizon. Quality of life (EQ-5D) and resource
135 use inputs were informed by the EVAR-1 trial. Outcomes were discounted by 3.5% per year.

136 EVAR was found to be associated with a QALY gain, and to incur a higher cost per patient,
137 compared with open surgical repair, resulting in an ICER was £48,990 per QALY gained
138 (Table 3). The probability of EVAR possessing an ICER below £20,000 was 26%.

139 The secondary analysis evaluated EVAR compared with continued monitoring or discharge
140 without intervention. This analysis included the option of repairing AAA at diameters below

141 5.5 cm, such that the study is relevant to the question of early intervention for this guideline.
142 Its methods and details are described fully in Evidence review F. Briefly, the authors
143 concluded that EVAR may have an ICER below £20,000 compared with providing no
144 intervention in somebody with a 5.5 cm aneurysm aged 73 or younger. In people with larger
145 aneurysms, EVAR became increasingly cost effective, compared with no intervention (e.g. it
146 was cost effective in people aged up to 79 years old if the AAA is 8.0 cm).

147 **Brown et al. (2012)**

148 Brown et al. (2012) conducted an economic evaluation with a Markov model broadly similar
149 to the Epstein et al. (2008) and Chambers et al. (2009) models, with the inclusion of a waiting
150 period via an 'intention to treat' analysis, with outcomes divided into more granular time
151 periods: randomisation to 6 months, 6 months for 4 years, 4–8 years, and after 8 years. Data
152 up to 8 years were informed by mid-term outcomes of EVAR-1. Quality of life (EQ-5D) and
153 resource use inputs were obtained from the EVAR-1 data. Outcomes were discounted by
154 3.5% per year. Results (Table 3) suggest that EVAR is dominated by open surgical repair,
155 with higher overall costs and fewer total QALYs per patient, with the EVAR ICER being
156 £20,000 per QALY gained or better in 1% of model runs.

157 The authors also conducted a within-trial economic analysis based on the EVAR-2 trial,
158 comparing EVAR with 'no intervention' for infrarenal AAA in people deemed unfit for open
159 surgical repair. Quality of life (EQ-5D) and resource use were from the trial, captured in the
160 same manner as the EVAR-1 study. The within-trial intention-to-treat analysis (8-year
161 duration) found EVAR to have a mean ICER of £264,900 per QALY gained over 'no
162 intervention', with 0% probability of the ICER being under £20,000. Results of a lifetime
163 analysis, with survival extrapolated using parametric survival curves fitted to the EVAR-2
164 data, reduced the EVAR ICER to £30,274 per QALY gained. However, costs were not
165 extrapolated beyond the trial.

166 **Epstein et al. (2014)**

167 Epstein et al. (2014) presented a further iteration of the Epstein et al. (2008) model, using
168 outcomes data from the ACE, DREAM, EVAR-1 (8-year data) and OVER studies. Clinical
169 and resource use inputs were obtained from each trial. The trial data were not synthesised.
170 Instead, 4 sets of results were presented. The reintervention rate following open surgical
171 repair was estimated using EVAR-1 trial data, with relative effects from each study used to
172 estimate EVAR reintervention rates. Quality of life was informed by the EVAR-1 EQ-5D data.
173 To normalise country-specific follow-up protocols, the authors applied a single postoperative
174 outpatient CT scan for open surgical repair patients and continued annual monitoring
175 following EVAR. Outcomes were discounted by 3.5% per year.

176 EVAR was dominated by open surgical repair in the EVAR-1 and ACE analyses, with an
177 ICER of almost £3,000,000 per QALY gained in the DREAM analysis (Table 3). Each
178 analysis predicted a 0% probability of EVAR having an ICER below £20,000 per QALY
179 gained compared with open surgical repair. Conversely, the OVER analysis found a cost
180 saving and QALY gain per patient for EVAR, with a 91% probability that its ICER is under
181 £20,000. The authors attribute this to higher hospital costs in the US setting of the OVER
182 trial, and the fact that the OVER trial predicts more favourable long-term survival for EVAR
183 compared with the other trials.

184 **Table 2: Cost–utility results of included economic studies – all infrarenal AAA repair**

Study & comparison	Incremental (EVAR)		ICER	Probability ICER of £20k or better
	Costs (£)	QALYs		
Michaels et al. (2005)				
EVAR vs. OSR	11,449	0.10	£110,000	~0%
Epstein et al. (2008)				
EVAR vs. OSR	3,758	-0.02	Dominated	1.2%
Chambers et al. (2009)				
EVAR vs. OSR	2,002	0.041	£48,990	26.1%
Brown et al. (2012)				
EVAR vs. OSR	3,521	-0.042	Dominated	1%
EVAR vs. no intervention ^a				
Trial analysis	10,214	0.037	£264,900	0%
Lifetime analysis	10,214	0.350	£30,274	23%
Epstein et al. (2014)				
EVAR vs. OSR				
ACE	2,086	-0.01	Dominated	0%
DREAM	3,181	0.00	£2,845,315	0%
EVAR-1	4,014	-0.02	Dominated	0%
OVER	-1,852	0.05	Dominant	91%
Note: (a) The population in this analysis was not considered to be anaesthetically fit to undergo OSR (the EVAR-2 study population).				
Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR, open surgical repair; QALYs, quality-adjusted life years.				

185 Further details of the included economic studies are available in Appendix H – Economic
186 evidence tables and the separate economic analysis appendix.

187 Economic model

188 The effectiveness of EVAR compared with open surgical repair for the repair of unruptured
189 AAAs was identified as a priority for new economic analysis. Clinical evidence has become
190 available since the existing technology appraisal (TA 167) was published, including the ACE
191 and OVER trials, as has longer-term data from the DREAM and EVAR trials. Furthermore,
192 the TA guidance is focused on infrarenal AAA, whereas the scope of this guideline has a
193 wider population containing other types of AAA. A new economic model was therefore
194 developed to support decision-making in this area.

195 Methods

196 The model began at the point when the decision is made to conduct, or not to conduct, the
197 elective repair of an AAA. Two distinct populations were modelled: (1) those for whom open
198 surgical repair is a suitable intervention, comparing EVAR with open surgical repair; and (2)
199 those for whom open surgical repair is not a suitable intervention, because of raised
200 intraoperative risk, comparing EVAR with no intervention. Much of the input data for these 2
201 models was informed by anonymised patient-level survival data from the EVAR-1 and EVAR-
202 2 trials, respectively, which the EVAR trial investigators provided to NICE. Within each

203 population, the model also evaluated infrarenal AAAs and complex AAAs as separate
204 groups. The perspective on costs was those incurred by the NHS and Personal Social
205 Services (PSS), and the perspective on outcomes was the direct health effects for people
206 using AAA services. The main outcomes were incremental costs and QALYs, and the
207 resulting ICER. The model time horizon was the lifetime of the patient (to a maximum age of
208 100), composed of 1-month cycles, with all outcomes discounted by 3.5% per year
209 (Developing NICE guidelines, 2014).

210 In the population for whom open surgical repair is a suitable intervention, modelled patients
211 were first at risk of death while waiting for their elective intervention: 2 months for infrarenal
212 EVAR and any open surgical repair; 4 months for complex EVAR. The extended waiting time
213 for complex EVAR is due to the need for those EVAR devices to be custom-made to suit the
214 patient's aortic anatomy, whereas standard EVAR devices suitable for infrarenal AAAs are
215 readily available. This was followed by 1 perioperative cycle, in which the intervention occurs,
216 with a risk of perioperative mortality. In the base-case model, this was informed by the UK
217 National Vascular Registry (2016) data on EVAR (0.4%), representing a current snapshot of
218 UK practice outcomes. To estimate the OSR perioperative mortality rate relative to EVAR,
219 the model used the results of a Cochrane systematic review of elective AAA repair trials
220 (odds ratio for EVAR versus open surgical repair: 0.33; Paravastu et al., 2014). This
221 approach combined using an estimate of current UK practice outcomes (the registry) for
222 baseline data and the best available randomised evidence for the relative effectiveness
223 between EVAR and OSR from (the Cochrane review).

224 Surviving patients move into the post-perioperative survival (long-term) phase of the model,
225 informed by general population mortality rates, calibrated to post-perioperative survival data
226 from the EVAR-1 open surgical repair arm (though the EVAR arm would have been equally
227 appropriate for this). The long-term relative effectiveness of EVAR was informed by hazard
228 ratio from a meta-analysis of long-term elective repair data (EVAR-1, DREAM and OVER).
229 Throughout the model, patients are at risk of complications requiring reintervention, informed
230 by the EVAR-1 trial. Laparotomy-related reinterventions, such as bowel resection, were also
231 captured based on US Medicare data.

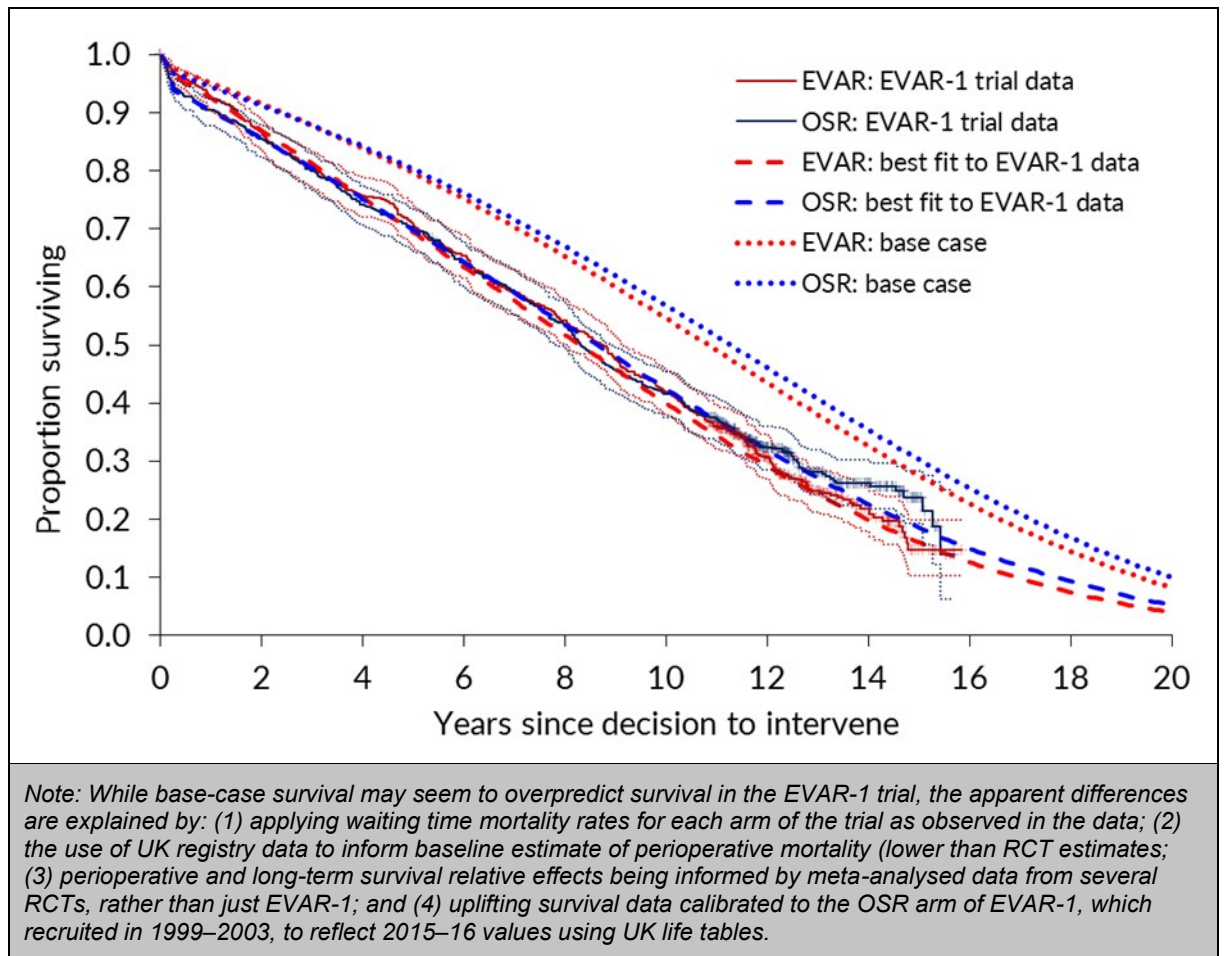
232 In the population for whom open surgical repair is not a suitable intervention, EVAR waiting
233 time, perioperative and long-term mortality data were informed by the only relevant RCT: the
234 EVAR-2 trial. For this population, survival on the comparator strategy of 'no intervention' was
235 modelled from the point of randomisation, with no waiting time or perioperative periods. The
236 'no intervention' survival data were adjusted for the effect of crossover, using the rank
237 preserving structure failure-time (RPSFT) technique, as one-third of participants randomised
238 to this arm instead received EVAR. The RPSFT method is a well established method for
239 accounting for trial crossover, estimating what the survival of trial participants who switched
240 arm would have looked like had they not switched (the counterfactual), and adjusting the
241 observed treatment effect accordingly. The same technique to calibrate general population
242 survival data as described above was then used. Postoperative EVAR complications were
243 included using event rates reported in the EVAR-2 study. On the 'no intervention' arm, the
244 model includes the complication of the unrepaired AAA rupturing. In the EVAR-2 trial, the
245 rate of rupture was reported to be 12.4% per year. This rate is used to determine the
246 proportion of patients in each cycle who require emergency repair (though 89% of EVAR-2
247 ruptures were fatal before emergency intervention could be commenced).

248 In order to explore subgroups effects, the model for both populations was configured so that
249 perioperative and long-term survival estimates could be influenced by effect modifiers. For
250 perioperative mortality, the effects of age, AAA diameter and sex were captured based on
251 data from the European 'Vascunet' registry (Mani et al., 2015). AAA diameter was a

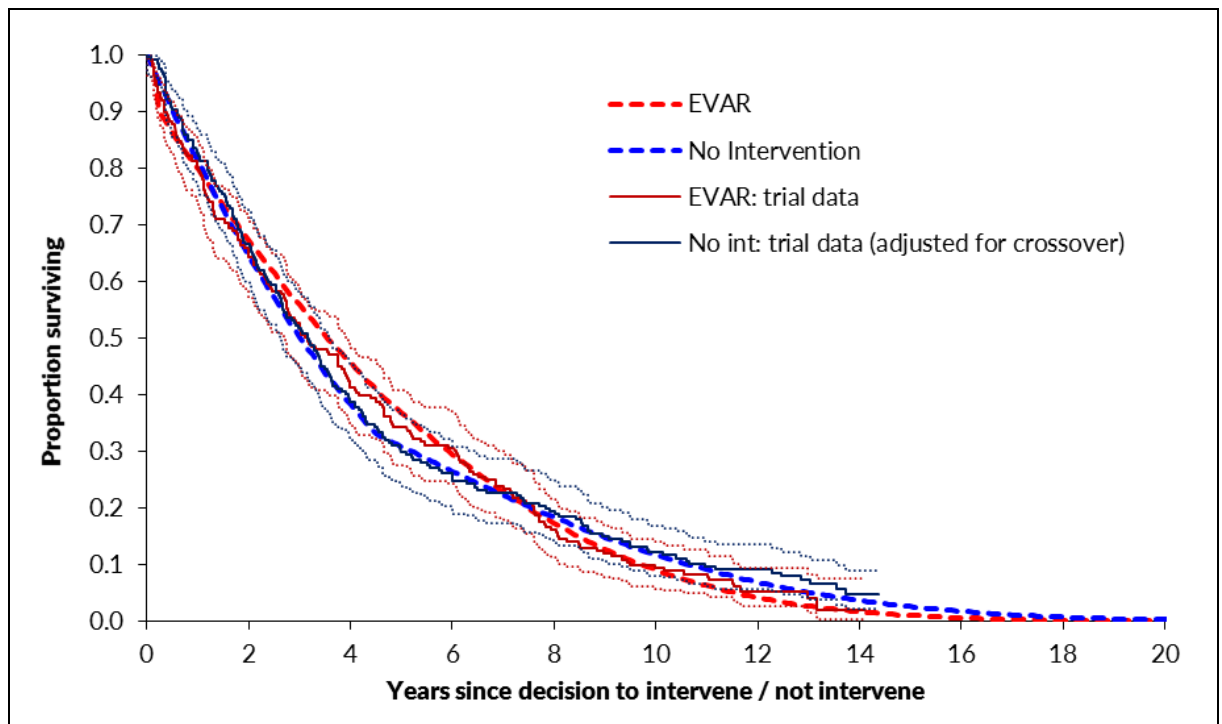
252 significant predictor of death, more prominently for EVAR, and age was a predictor of
 253 perioperative death for open surgical repair. For post-perioperative mortality, multivariable
 254 Cox regressions using the EVAR-1 data found AAA size to be a significant determinant of
 255 long-term survival. Using the EVAR-2 data, being treated with EVAR was associated with
 256 improved survival for up to 4.5 years. The effect of age was implicitly captured in this by our
 257 use of calibrated general population survival data. Effect modifiers were used in specific
 258 subgroup analyses and in probabilistic sensitivity analysis, to fully explore the effect of
 259 uncertain patient characteristics on outcomes. Our base-case deterministic results are
 260 evaluated for the trial mean cohorts.

261 Base case overall survival curves are presented in Figure 1 and Figure 2.

262



263 **Figure 1: Base case (and true fit) overall survival profiles – infrarenal AAAs –**
 264 **population for whom open surgical repair is an option, compared with EVAR-**
 265 **1 trial data**



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

268 People with more complex aneurysms – that is, cases in which a standard EVAR graft
 269 cannot be used within the terms of its instructions for use – were also simulated in the model,
 270 as a separate subpopulation. There are no long-term, randomised data comparing EVAR
 271 and open surgical repair for the repair of complex AAAs. The model therefore used the UK
 272 National Vascular Registry (2016), which reports perioperative mortality rates in UK practice
 273 for complex repair. Taking the registry’s EVAR mortality rate (3.6%) as the starting point, the
 274 model applies the relative effect from the Cochrane meta-analysis of elective infrarenal AAA
 275 repairs to this value to obtain an estimated complex repair perioperative mortality rate for
 276 open surgical repair (10.1%). The relevant effect modifiers may then be applied to the
 277 resulting baseline estimates. In the population for whom open surgical repair is not a suitable
 278 option, the Registry data were used to estimate a ‘relative effect of complexity’ on
 279 perioperative mortality following EVAR, relative to infrarenal EVAR (odds ratio = 8.8). This
 280 relative effect is used to increase the perioperative mortality rate from the EVAR-2 trial, to
 281 estimate the equivalent EVAR perioperative mortality rate in people with complex
 282 aneurysms. Owing to the absence of long-term evidence, post-perioperative survival and
 283 reintervention rates for people with repaired complex aneurysms were assumed to be equal
 284 to those for people with repaired infrarenal aneurysms; the guideline committee advised that
 285 this is a plausible assumption. The overall survival of people on the ‘no intervention’ strategy,
 286 based on EVAR-2 trial data, was assumed to be independent of aneurysm complexity, due to
 287 the absence of long-term survival data in people with untreated complex AAA. Again, the
 288 guideline committee advised that this was a reasonable approach to take.

289 Resource use was obtained from the detailed published EVAR-1 data (Brown et al. 2012), to
 290 which up-to-date national unit costs were applied. The cost of standard and complex EVAR
 291 devices were obtained from NHS Trusts by members of the guideline development
 292 committee. Following advice from the committee, a strategy of ‘no intervention’ is assumed to
 293 incur non-zero costs, associated with a further outpatient attendance and CT scan. Quality of

294 life was primarily informed by the published 1-year EVAR-1 EQ-5D data, supplemented by
295 decrements for complications identified by informal searches.

296 For complete details of model methods and parameters, please see the separate economic
297 analysis appendix.

298 Results

299 In the base-case model, in a cohort for whom open surgical repair is a suitable option,
300 elective EVAR was found to be dominated by open surgical repair, producing fewer QALYs
301 at a higher total NHS and personal social service (PSS) cost (Table 3). Probabilistic
302 sensitivity analysis showed that its ICER had <1% likelihood of being £20,000 per QALY
303 gained or better, and no individual parameter reversed this result when varied between its
304 upper and lower bounds. For the repair of complex AAAs in this population, the base-case
305 ICER was £95,815 per QALY gained. Here, EVAR was associated with a QALY gain of
306 0.166 per patient, due to the wider gap between EVAR and open surgical repair in estimated
307 perioperative mortality – that is, fewer individuals are predicted to survive open surgical
308 repair to experience any improved long-term survival prospects. However, this benefit is
309 offset by the substantially higher device cost associated with complex EVAR, such that it
310 remains highly unlikely (1%) to have an ICER of £20,000 per QALY gained or better. This
311 finding is not sensitive to variation in any individual parameter. No subgroup could be
312 identified in which EVAR represented an effective use of NHS resources, when compared
313 with open surgical repair.

314 In the population for whom open surgical repair is not a suitable option, an EVAR strategy
315 was compared with offering no AAA repair. On the comparator arm, the individual does not
316 undergo any surgical procedure, and therefore faces no waiting time or perioperative
317 mortality risk. However, they continue living with an unrepaired AAA that is at risk of
318 rupturing. The ICER for EVAR compared with this strategy was found to be £460,863 per
319 QALY gained (Table 4), with a modest gain in QALYs (0.033) coming at a high additional
320 cost (£15,438) per patient. No parameter had the capacity to change the conclusion about
321 this ICER in one-way sensitivity analysis, and probabilistic sensitivity analysis showed a 0%
322 probability that the ICER is £20,000/QALY or better. For the repair of complex AAAs in this
323 population, the base-case cost–utility results showed that EVAR was clearly dominated by
324 the ‘no intervention’ strategy. The relatively high perioperative mortality rate associated with
325 complex EVAR, which is never offset by differences in long-term survival, causes a net loss
326 of QALYs, while the high cost of the custom-built device leads to a high incremental cost.
327 Here, too, EVAR has a 0% probability of having an ICER of £20,000 per QALY gained or
328 better. No subgroup could be identified in which standard or complex EVAR represented an
329 effective use of NHS resources, when compared with no intervention in people for whom
330 open surgical repair is not a suitable option.

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

333 **Table 3: NICE cost–utility model results, population for whom open surgical repair is**
 334 **an option**

Treatment strategy	Total		Incremental		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	
Infrarenal AAA repair					
OSR	£13,438	6.640			
EVAR	£19,770	6.480	£6,331	-0.160	EVAR dominated
Complex AAA repair					
OSR	£13,206	6.033			
EVAR	£29,139	6.199	£15,933	0.166	£95,815

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

335 **Table 4: NICE cost–utility model results, population for whom open surgical repair is**
 336 **not an option**

Treatment strategy	Total		Incremental		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	
Infrarenal AAA repair					
No intervention	£909	2.313			
EVAR	£16,363	2.347	£15,438	0.033	£460,863
Complex AAA repair					
No intervention	£942	2.324			
EVAR	£24,556	1.565	£23,632	-0.759	EVAR dominated

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

337 Evidence statements

338 EVAR compared with open repair for patients in whom surgery is considered appropriate

339 Clinical evidence

- 340 • Four RCTs provided moderate to high-quality evidence on all-cause mortality in people
 341 with unruptured AAAs in whom surgery was considered appropriate. The studies reported
 342 that:
- 343 ○ Perioperative mortality (30-day or in-hospital) was lower with EVAR than with open
 344 surgical repair (high-quality evidence; from 4 RCTs, including 2,783 people).
 - 345 ○ 0–4-year mortality could not be differentiated between EVAR and open surgical repair
 346 (moderate-quality evidence from 4 RCTs, including 2,783 people).
 - 347 ○ There was no difference in 0–8-year mortality between EVAR and open surgical repair
 348 (high-quality evidence from 3 RCTs, including 2,484 people).
 - 349 ○ There was no difference in 0–15-year mortality between EVAR and open surgical
 350 repair (high-quality evidence from 2 RCTs, including 1,603 people).
 - 351 ○ 8–15-year mortality was higher with EVAR than with open surgical repair (high-quality
 352 evidence from 1 RCT, including 1,252 people).

- 353 • Four RCTs provided very low- to high-quality evidence on AAA-specific mortality in people
 354 with unruptured AAAs in whom surgery was considered appropriate. The studies reported
 355 that:
- 356 ○ 0–4-year AAA-specific mortality could not be differentiated between EVAR and open
 357 surgical repair (very low-quality evidence from 4 RCTs, including 2,783 people).
 - 358 ○ 0–8- year AAA-specific mortality could not be differentiated between EVAR and open
 359 surgical repair (moderate-quality evidence from 3 RCTs, including 2,484 people).
 - 360 ○ 0–15-year AAA-specific mortality could not be differentiated between EVAR and open
 361 surgical repair (very low-quality evidence from 2 RCTs, including 1,603 people).
 - 362 ○ 8–15-year AAA-specific mortality was higher with EVAR than with open surgical repair
 363 (high-quality evidence from 1 RCT including 1,252 people).
- 364 • Low- to moderate-quality evidence from 4 RCTs, including 2,783 people with unruptured
 365 AAAs, could not differentiate cardiac-, and stroke-related mortality rates between patients
 366 treated by EVAR and those treated by open repair (follow-up not reported). Moderate-
 367 quality evidence from 4 RCTs, including 2,783 people, reported lower rates of pulmonary-
 368 related mortality in patients treated by EVAR than those treated by open surgery.
 - 369 • High-quality evidence from 2 RCTs, including 2,432 people with unruptured AAAs,
 370 reported lower pulmonary complication rates in patients treated by EVAR compared with
 371 those treated by open repair (follow-up not reported). Low-quality evidence from 3 RCTs,
 372 including up to 2,432 people with unruptured AAAs, could not differentiate non-fatal
 373 stroke, sexual dysfunction and renal complication rates between patients treated by EVAR
 374 and those treated by open repair (follow-up not reported).
 - 375 • Very low-quality evidence from 3 RCTs, including 2,484 people with unruptured AAAs,
 376 reported higher rates of any type of reintervention in patients treated by EVAR compared
 377 with those treated by open repair at 4-year and 8-year follow-up. Moderate-quality
 378 evidence from 1 RCT, including 546 people with unruptured AAA, could not differentiate
 379 rates of any type of reintervention between patients treated by EVAR and those treated by
 380 open repair between 8- and 15-year follow-up. When considering total follow-up periods,
 381 high-quality evidence from 2 RCTs including 1,603 people reported higher rates of any
 382 type of reintervention in patients treated by EVAR than those treated by open repair at
 383 follow-up of up to 15 years.
 - 384 • High-quality evidence from 1 RCT, including 351 people with unruptured AAA reported
 385 higher rates of AAA-related reintervention in patients treated by EVAR compared with
 386 those treated by open repair at follow-up of up to 15 years. High-quality evidence from
 387 another RCT including up to 1,252 people with unruptured AAAs, reported higher rates of
 388 life-threatening reintervention in patients treated by EVAR compared with those treated by
 389 open repair at follow-up of up to 15 years.
 - 390 • Moderate-quality evidence from 1 RCT, including 1,341 people with unruptured AAAs,
 391 could not differentiate quality of life measures (SF-36, and EQ-5D scores) between
 392 patients treated by EVAR and those treated by open repair at 2-year follow-up.
 - 393 • High-quality evidence from 4 RCTs, including 2,747 people with unruptured AAAs,
 394 reported shorter length of hospital stay in patients treated by EVAR compared with those
 395 treated by open repair.

396 **Economic evidence**

397 *Published evidence*

- 398 • Five partially applicable cost–utility analyses with potentially serious limitations, based on
 399 data from the ACE, DREAM and EVAR-1 trials, found that EVAR was either dominated by

400 open surgical repair, or associated with an ICER of £48,990 to £2.8 million per QALY
 401 gained. The EVAR ICER was associated with a 0% to 26% probability of being £20,000
 402 per QALY gained or better. One of these studies, when using data from the OVER trial,
 403 found EVAR to have higher incremental QALYs and lower incremental costs than open
 404 surgical repair, with a 91% probability of its ICER being £20,000 per QALY gained or
 405 better.

406 *NICE model*

407 • One directly applicable cost–utility analysis with minor limitations found EVAR to produce
 408 fewer QALYs per patient at a higher cost per patient than open repair, for the elective
 409 repair of infrarenal AAAs in people for whom open repair may be an appropriate
 410 intervention. This result was robust to one-way sensitivity analyses. The ICER had <1%
 411 probability of being £20,000 or better.

412 **Complex EVAR compared with open repair for patients with juxtarenal aneurysms**

413 *Clinical evidence*

- 414 • Very-low quality evidence from 1 non-randomised controlled trial, including 90 people with
 415 unruptured juxtarenal aneurysms, could not differentiate 30-day mortality between
 416 patients treated by EVAR and those treated by open repair.
- 417 • Very-low quality evidence from 1 non-randomised controlled trial, including 90 people with
 418 unruptured juxtarenal aneurysms, could not differentiate haemodialysis, pneumonia,
 419 stroke and reintervention rates between patients treated by EVAR and those treated by
 420 open repair at mean follow-up of 15.2 months.
- 421 • Low-quality evidence 1 non-randomised controlled trial, including 90 people with
 422 unruptured juxtarenal aneurysms, reported shorter length of hospital stay in patients
 423 treated by EVAR compared with those treated by open repair.

424 *Economic evidence*

425 *Published evidence*

- 426 • No cost–utility analyses were identified in this population.

427 *NICE model*

- 428 • One directly applicable cost–utility analysis with potentially serious limitations found EVAR
 429 to have an ICER of £95,815 per QALY gained compared with open repair, for the elective
 430 repair of complex AAAs in people for whom open repair may be an appropriate
 431 intervention. The finding that EVAR is unlikely to be associated with an ICER of £20,000
 432 per QALY or better was robust to one-way sensitivity analyses. The ICER had a 1%
 433 probability of being £20,000 or better.

434 **EVAR vs no intervention for patients in whom open surgery is not considered appropriate**

436 *Clinical evidence*

- 437 • Low- to moderate quality evidence from 1 RCT, including 404 people with unruptured
 438 AAAs that were considered unsuitable for open repair, could not differentiate all-cause
 439 mortality rates between patients treated by EVAR and those who received no intervention
 440 at 6-month, 4-year, 8-year and 12-year follow-up.

- 441 • Low-quality evidence from 1 RCT, including 404 people with unruptured AAAs that were
442 considered unsuitable for open repair, could not differentiate AAA-related mortality rates
443 between patients treated by EVAR and those who received no intervention at 6-month
444 follow-up. Conversely, moderate-quality evidence from the same study reported lower
445 AAA-related mortality rates in patients treated by EVAR compared with those who
446 received no intervention at 4- and 8-year follow-up.
- 447 • Very low-quality evidence from 1 RCT, including 404 people with unruptured AAAs that
448 were considered unsuitable for open repair, could not differentiate rates of fatal
449 myocardial infarction and stroke-related mortality between patients treated by EVAR and
450 those who received no intervention at 4-year follow-up.
- 451 • Low-quality evidence from 1 RCT, including 404 people with unruptured AAAs that were
452 considered unsuitable for open repair, reported higher rates of non-fatal myocardial
453 infarction in patients treated by EVAR than those who received no intervention at 4-year
454 follow-up. Low-quality-evidence from the same trial could not differentiate rates of non-
455 fatal stroke in patients treated by EVAR compared with those who received no
456 intervention at 4-year follow-up.
- 457 • Very low-quality evidence from 1 RCT, including 404 people with unruptured AAAs that
458 were considered unsuitable for open repair, could not differentiate quality of life measures
459 (SF-36, and EQ-5D scores) between patients treated by EVAR and those who received
460 no intervention at 2-year follow-up.

461 **Economic evidence**

462 *Published evidence*

- 463 • One partially applicable cost–utility analysis with potentially serious limitations, based on
464 the EVAR-2 trial, found that EVAR had an ICER of £264,900 per QALY compared with no
465 treatment over 8 years, with 0% probability of this being less than £20,000. A lifetime
466 analysis with very serious limitations had an equivalent ICER of £30,274 and probability of
467 23%.

468 *NICE model*

- 469 • One directly applicable cost–utility analysis with minor limitations found EVAR to be
470 associated with an ICER of £460,863 compared with no intervention, for the elective
471 repair of infrarenal AAAs in people for whom open repair is not considered to be a suitable
472 intervention. This result was robust to one-way sensitivity analyses. The ICER had 0%
473 probability of being £20,000 or better.
- 474 • The equivalent result for the repair of complex AAAs, in an analysis with minor limitations,
475 showed EVAR to be dominated by no intervention, with a 0% probability of its ICER being
476 £20,000 or better.

477 **Recommendations**

- 478 K1. For people with unruptured AAAs meeting criteria in 1.5.1, offer open surgical repair
479 unless there are anaesthetic or medical contraindications.
- 480 K2. Do not offer EVAR to people with an unruptured infrarenal AAA if open surgical repair is
481 suitable.
- 482 K3. Do not offer EVAR to people with an unruptured infrarenal AAA if open surgical repair is
483 unsuitable because of their anaesthetic and medical condition

484 K4. Do not offer complex EVAR to people with an unruptured AAA if open surgical repair is a
485 suitable option, except as part of a randomised controlled trial comparing complex EVAR
486 with open surgical repair.

487 K5. Do not offer complex EVAR to people with an unruptured AAA if open surgical repair is
488 not a suitable option because of their anaesthetic and medical condition.

489 **Research recommendations**

490 RR6. What is the effectiveness and cost-effectiveness of complex EVAR versus open
491 surgical repair in people with an unruptured AAA for whom open surgical repair is a suitable
492 option?

493 **Rationale and impact**

494 **Why the committee made the recommendations**

495 There is no evidence that elective EVAR for people with an unruptured infrarenal AAA
496 provides long-term benefit compared with open surgical repair. While EVAR is associated
497 with fewer perioperative deaths, it has more long-term complications, and these
498 complications mean that people will need further procedures. There is some evidence that
499 EVAR is associated with worse long-term survival than open surgical repair. EVAR also has
500 higher net costs than open surgical repair. The evidence shows that, even if long-term
501 benefits were achievable, they could not plausibly be sufficient to outweigh these costs.

502 Open surgical repair is unsuitable for some people with an unruptured AAA because of their
503 anaesthetic risk and/or medical co-morbidity. For these people, the risks of their AAA
504 rupturing, if no repair is attempted, have to be balanced against the perioperative risks and
505 long-term complications associated with EVAR. The evidence shows that the average person
506 receiving EVAR has an uncertain chance of a small net benefit, compared with the large and
507 certain increase in costs. Therefore, the committee agreed that EVAR for unruptured AAA
508 (elective repair) cannot be considered an effective use of NHS resources in this population.

509 The evidence for complex EVAR was limited in quantity and quality. However, complex
510 EVAR grafts are much more expensive than standard devices, so the difference in cost
511 between EVAR and open surgical repair is even greater than in infrarenal AAAs. The
512 committee also noted that the instructions for use of the grafts that are currently available do
513 not cover complex AAAs. Although there is currently no evidence that complex EVAR has
514 better outcomes than open surgical repair, people with complex AAAs have higher
515 perioperative mortality rates. Because of this, a perioperative survival benefit equivalent to
516 that seen with EVAR for infrarenal AAAs could potentially be more influential in complex
517 AAAs. Therefore, the committee agreed that more information would be helpful, so it
518 recommended that the use of complex EVAR should be restricted to randomised trials.

519 The committee also discussed complex EVAR for people for whom open surgical repair is
520 not a suitable option because of their anaesthetic risk and/or medical comorbidities. They
521 agreed that, in this population, people who need complex EVAR could not plausibly have
522 better outcomes than those who need standard infrarenal EVAR. As they had not
523 recommended standard EVAR in this population, the committee agreed that they could not
524 recommend complex EVAR either. The committee did not recommend using complex EVAR
525 in randomised trials in these circumstances, because it would be unethical to randomise
526 people to a treatment with a high risk of perioperative death when there is no prospect of
527 long-term benefits at reasonable cost.

528 For each of these recommendations, the committee considered whether there were any
529 specific groups that would benefit from standard or complex EVAR for unruptured AAAs.
530 They explored groups defined by age, sex, AAA diameter and life expectancy, but there were
531 no groups in which the benefits would outweigh the harm and costs.

532 **Impact of the recommendations on practice**

533 The recommendations on EVAR will have a large impact on practice, as EVAR is a widely
534 performed procedure. EVAR is currently used more frequently than open surgical repair in
535 some areas, so a diverse group of people both within and outside the national screening
536 programme will need to update their knowledge. The recommendations will also affect the
537 timing and type of information about treatment options given to patients who are diagnosed
538 with small-to-medium AAAs and are being monitored for signs of growth. The
539 recommendations will minimise harm by reducing long-term mortality and the need for
540 reintervention as a result of problems with EVAR. Reductions in EVAR use and subsequent
541 EVAR-related reinterventions will lead to cost savings within the NHS.

542 **The committee's discussion of the evidence**

543 **Interpreting the evidence**

544 ***The outcomes that matter most***

545 The committee agreed that the outcomes that matter most are long-term survival, as well as
546 a reduction in the need for reintervention. This is because committee members believed that,
547 apart from the fundamental need to prevent aneurysm rupture, AAA repair should also
548 ensure that people live as long as possible and have the best quality of life possible following
549 intervention.

550 ***The quality of the evidence***

551 The committee agreed that, in cases of infrarenal AAA, the evidence relating to all-cause
552 mortality and AAA-related mortality was of sufficient quality to conclude that EVAR was
553 superior to open surgery during the first 30 days after repair. However, the evidence that this
554 benefit is not maintained in the long term is also of high quality. Furthermore, in the RCT that
555 was the largest, the most directly applicable and had the longest follow-up (EVAR-1), EVAR
556 was associated with worse all-cause mortality once follow-up extended beyond 8 years.
557 Across all the RCTs, there was also high-quality evidence that EVAR is associated with
558 approximately double the rate of reintervention seen after open surgical repair. The
559 committee noted that large, observational data sources outside the UK (the Swedish
560 vascular registry and the American Medicare registry) mirrored evidence from RCTs included
561 in the review.

562 The committee considered that the single RCT (EVAR-2 trial) comparing EVAR with no
563 intervention highlighted no differences in most outcome measures between groups; however,
564 the study had some limitations. The committee noted that a considerable proportion (34%) of
565 the no intervention group ultimately received EVAR; this was not taken into account by
566 investigators in earlier publications of this study. However, the most recent publication
567 (Sweeting et al., 2017) presented an analysis using an established statistical technique
568 (rank-preserving structural failure time; RPSFT) to correct for any bias introduced in this way,
569 and the committee were also aware that the original modelling undertaken for this guideline
570 had used the same technique. Nevertheless, the committee recognised that, while plausible,
571 the assumptions underpinning the RPSFT cannot be empirically validated.

572 The committee noted that the evidence comparing complex EVAR with open surgical repair
573 was extremely limited in quantity and quality. No RCTs were identified and the single non-
574 randomised comparative study that met this review's inclusion criteria was small in size and
575 only assessed mortality rates at 30-day follow-up. The results of the study, coupled with
576 results from a new health economic model developed for this population (discussed below),
577 led the committee to conclude that there was no evidence that complex EVAR yields a net
578 advantage over open surgery. However, the committee were mindful that longer-term
579 evidence from large RCTs could clarify the clinical utility of complex EVAR, and inform future
580 health economic modelling. Thus, they recommended that the procedure should not be
581 performed outside the confines of an RCT.

582 The committee noted that the evidence on which they based their decision making was from
583 patients randomised between 1999 and 2004 and that there have been several iterations of
584 design amendments to EVAR devices since this time. However, the committee found no
585 evidence that newer devices perform better than their earlier counterparts and did not
586 consider this to be a reason to reject the evidence reviewed

587 **Benefits and harms**

588 The committee agreed that the clinical evidence demonstrated an advantage of EVAR over
589 open surgery in the short-term (30-day and in-hospital mortality). Once people survived the
590 perioperative period, there was no difference in survival between the treatments until 8-years
591 post-surgery. After this point, open surgery yielded better survival than EVAR. The
592 committee also noted clear evidence that reintervention rates are higher – approximately
593 double – with EVAR than with open repair.

594 The committee noted that some clinicians and patients may prefer EVAR, because of the
595 additional risk associated with open surgical repair in the perioperative period. However, they
596 agreed that it would be to the benefit of the average candidate for elective AAA repair if the
597 vascular community shifted its focus to intermediate- to long-term outcomes. The committee
598 recognised that the recommendations represent a substantial change to practice and some
599 resistance to change may be encountered.

600 As the committee were unconvinced by the data relating to complex EVAR, they discussed
601 the potential for harm if patients who could receive open repair are offered complex EVAR.
602 Committee members agreed that, in the absence of evidence of benefit, it would be
603 inappropriate to recommend the use of complex EVAR as standard practice. However, the
604 committee noted that the data relating to open surgical repair for complex AAA are also
605 uncertain, and so the balance of benefits, harms and costs in this population is also
606 uncertain. To reduce this uncertainty, the committee agreed that complex EVAR should only
607 be performed in the well-controlled environment of an RCT. As a result, a research
608 recommendation was made to ensure that data would be collected to inform future updates
609 of the guideline.

610 In the absence of evidence relating to complex EVAR in patients with medical or anaesthetic
611 contraindications to open surgical repair, the committee considered evidence from other AAA
612 patient populations (alongside original health economic modelling; see below). Having seen
613 convincing evidence that, when compared with no intervention, standard EVAR does not
614 represent a reasonable balance of benefits, harms and costs for people with infrarenal AAA,
615 the committee agreed that the most optimistic expectation possible is that EVAR outcomes
616 would be no worse in people with complex AAAs. The more likely outcome is that they will be
617 substantially worse, owing to higher perioperative mortality. Moreover, while it is
618 inconceivable that there would be additional benefits for this population, compared with the

619 infrarenal group, it is certain that complex EVAR grafts cost more than standard EVAR grafts
620 (see below). Therefore, while the committee discussed whether research was warranted in
621 this area, they decided that it would be unethical to randomise people to an expensive
622 intervention that is known to have a high risk of perioperative mortality, when there is no
623 realistic prospect of long-term benefits that would justify the costs.

624 **Cost effectiveness and resource use**

625 ***Unruptured infrarenal AAA***

626 The committee discussed the cost-effectiveness evidence for the repair of unruptured
627 infrarenal AAA. The committee were aware that this population, in people for whom open
628 surgical repair is a suitable option, comprised the majority of both clinical and published
629 economic evidence for this review question. The committee agreed that the published UK
630 economic evidence could only reasonably be interpreted as evidence that EVAR was not
631 likely to be an effective use of NHS resources, though it was noted that none of the studies
632 included the longest-term follow-up that is currently available, namely 15 years of data from
633 the EVAR-1 trial. The committee therefore considered evidence from the new economic
634 model developed for this guideline.

635 The committee were satisfied with the modelling approach of: (1) using National Vascular
636 Registry data to inform baseline perioperative mortality, and the results of a Cochrane meta-
637 analysis to inform relative effects; (2) estimating long-term survival by calibrating general
638 population mortality to the EVAR-1 open surgical repair data conditional on surviving for 30
639 days after the intervention, and; (3) estimating relative long-term survival using a hazard ratio
640 from a meta-analysis of long-term data from 3 RCTs (DREAM, EVAR-1 and OVER). The
641 committee agreed that the new economic model provided compelling evidence that EVAR is
642 not a cost-effective option for infrarenal AAA compared with open surgical repair. The base-
643 case model results indicate that EVAR produces fewer QALYs than open surgery at a higher
644 total cost to the NHS and PSS, and this is reflected in the probabilistic results, with a low
645 probability of its ICER being £20,000 per QALY gained or better. Results were also robust to
646 scenario and one-way sensitivity analyses, including using only EVAR-1 study data.

647 The committee discussed the cost results from the new model, and agreed that the high
648 acquisition cost of EVAR was likely to be the key cost difference between EVAR and open
649 surgery in practice. It advised that the modelled cost of complications following EVAR
650 appeared low compared with clinical experience. However, it was agreed that any increase in
651 EVAR complication costs would strengthen the cost-effectiveness results in favour of open
652 surgical repair, and would therefore not affect interpretation of the evidence. The committee
653 also discussed the cost of routine monitoring following EVAR and advised that, in practice,
654 adherence to scheduled monitoring following EVAR is less than 100%. The committee
655 discussed the implications of this on the cost-effectiveness evidence. It agreed that, although
656 the expected cost of ongoing monitoring per patient may be lower than the model predicts,
657 this would be counteracted to some degree because people who fail to attend scheduled
658 scans may be more likely to experience complications that require reintervention. The
659 committee also saw that the model conclusion did not change when assumptions were
660 applied that were favourable to EVAR, but highly implausible, such as assuming monitoring
661 appointments following EVAR incur no cost, or that no post-EVAR complications occur. It
662 was therefore agreed that, while the effect of non-adherence to follow-up appointments on
663 EVAR cost-effectiveness results is unclear, it cannot plausibly be sufficient to change
664 conclusions drawn from the new economic model.

665 The committee discussed the use of the EVAR-1 trial to inform much of the new model,
666 noting that a potential criticism of the model is its use of the relatively old evidence. The
667 committee were not aware of any evidence to suggest that newer EVAR devices are superior
668 to the generation of devices used in the EVAR-1 trial, in terms of perioperative mortality,
669 long-term mortality, complication rates and secondary interventions (Hammond et al., 2016).
670 The committee highlighted that more recent patient registries, such as the Medicare and
671 SwedVasc databases, include data on patients who received newer-generation EVAR
672 devices, and that the mortality and complications rates used in the new model are consistent
673 with these data sources. The committee therefore agreed that, on balance, the value of the
674 long-term data provided by the EVAR-1 trial offsets the relatively long time since trial
675 recruitment, and more recent registry data serve to validate the model. The committee were
676 aware that the National Vascular Registry data was preferred to inform some baseline model
677 inputs as it is a UK registry, and that randomised trials were preferred to provide estimates of
678 relative effectiveness as they would be subject to less bias than equivalent data from
679 registries.

680 The committee discussed the QALY outcomes of the model, recognising that incremental
681 QALYs were small in absolute terms, and the point estimate was more uncertain than for
682 incremental costs. However, the unequivocal high incremental cost associated with EVAR
683 led the committee to agree that the 'true' QALY gain for EVAR would need to be implausibly
684 high for EVAR to be cost effective compared with open surgery (via, for example, superior
685 long-term survival in EVAR patients, counter to the available long-term evidence). To achieve
686 an ICER of £20,000 per QALY gained, EVAR would need to generate 0.317 QALYs more
687 than open surgery per patient, compared with a base-case estimate of 0.160 QALYs less
688 than open surgery. The committee were aware that modelled and empirical survival curves
689 crossed over, with a longer-term survival benefit associated with open surgical repair
690 offsetting its worse perioperative outcomes. The committee saw that the model suggests
691 open surgical repair is increasingly cost-effective in younger patients, and agreed that this
692 was consistent with its expectations, as younger people will typically be more likely to survive
693 the open surgery procedure and experience the long-term survival benefit.

694 The committee discussed whether the cost-effectiveness results for EVAR might be
695 influenced by a person's underlying life expectancy. In particular, if it were possible to identify
696 individuals who were less likely to live to experience the long-term survival benefit associated
697 with open surgical repair, might EVAR be a cost-effective intervention for those people. A
698 threshold analysis was conducted in which the hazard ratio used to calibrate general
699 population survival to 'match' the EVAR-1 population was varied between 1 and 15. These
700 values indicated a relatively healthy population with a mortality hazard equal to the general
701 population of the same age, and a relatively unhealthy population with mortality hazard of 15-
702 times the general population, respectively. Across this range of underlying life expectancies,
703 EVAR remained dominated by open surgical repair.

704 The committee advised that patients often express a preference for EVAR compared with
705 open surgical repair, typically due to the increased short-term risks associated with open
706 surgery. However, the committee were not aware of any evidence formally eliciting patient
707 preference over EVAR and open surgery. The committee heard that this preference was
708 implicitly captured in the model to some extent by applying a larger quality of life decrement
709 following open surgery, compared with EVAR, and by discounting health outcomes over
710 time. The committee noted that, while individual choice is important in all care provided by
711 the NHS, this did not compel them to recommend care that is not cost effective, as per
712 Principle 5 of NICE's Social Value Judgements. Given this, and based on its assessment of
713 the evidence from the new economic model (and other published economic evaluations), the
714 committee made strong recommendations that people with an unruptured infrarenal AAA for

715 whom open surgical repair is a suitable option should be offered open surgical repair, and
716 that EVAR should not be offered in such cases

717 The committee then considered the cost-effectiveness evidence for infrarenal AAA repair in
718 people for whom open surgical repair is not a suitable option due anaesthetic risk and/or
719 medical comorbidity. This evidence comprised 1 published, UK cost–utility analysis, and
720 modelling conducted for this guideline. The committee were aware of the extensive trial
721 crossover that occurred in EVAR-2, from the ‘no intervention’ control arm to EVAR, and that
722 its per-protocol analysis breaks trial randomisation in a way that is likely to bias in favour of
723 EVAR (as it can be expected that participants who ‘crossed over’ to receive EVAR were the
724 fittest members of the cohort, with the longest life expectancy). The committee therefore
725 placed greater emphasis on the economic model, which adjusted for crossover using a well-
726 established statistical method (RPSFT). These data did not show any long-term survival
727 benefit for EVAR compared with no intervention. The committee explained that many people
728 with AAAs die with – rather than from – their aneurysms, and this would be particularly true in
729 a population which is defined by the presence of comorbidities that are invariably life-limiting.

730 The committee advised that, since the population for which open surgical repair is unsuitable
731 is defined by substantial anaesthetic risk and/or medical comorbidity, the most appropriate
732 analysis uses calibrated general population life tables at 1999–2001 levels; not inflating the
733 analysis to 2015–16 lifetables, which would reflect a general increase in the health of the UK
734 population. The committee then discussed its preferred base-case ICER for EVAR, which
735 exceeded £460,000 per QALY gained compared with ‘no intervention’, and agreed that this
736 indicates EVAR for this population is not an effective use of NHS resources. The committee
737 also understood that variation of parameters to extreme values – for example, assuming no
738 survival differences beyond 5 years, and assuming there are no EVAR graft complications at
739 any time – do not cause the ICER to fall to a level that would be considered to represent
740 good value for money. To achieve an ICER of £20,000 per QALY gained in this population,
741 compared with providing no intervention, EVAR would need to generate 0.772 incremental
742 QALYs per patient, compared with a base case estimate of 0.033 QALYs.

743 The committee discussed whether the cost-effectiveness evidence suggested that there may
744 be differences in the balance of benefits and harms between men and women, both when
745 open surgical repair is a suitable option and when it is not, for the elective repair of
746 unruptured infrarenal AAA. None of the preferred ICERs were sensitive to the sex of the
747 cohort; nor were they sensitive to differences in age or AAA size. The committee therefore
748 determined that there was no identifiable subgroup for whom EVAR represents a reasonable
749 use of NHS resources, so its recommendations were appropriate to the relevant population
750 as a whole.

751 ***Unruptured complex AAA***

752 The committee discussed the cost-effectiveness evidence for the repair of unruptured
753 complex AAA. The committee agreed that here the term ‘complex’ has a broad meaning,
754 generally referring to non-standard AAA repairs. Typically, a complex AAA is one for which a
755 standard EVAR device cannot be used within the terms of its instructions for use (IFU), and a
756 complex device is one that is custom made, requiring bespoke adaptations, such as
757 fenestrations and branches. As no published economic evidence was identified for this
758 population, the committee considered only the new economic model.

759 The committee were aware that there is no randomised comparative evidence evaluating
760 complex AAA repair, and consequently the economic model relies on a degree of
761 assumption, particularly regarding the transferability of data on infrarenal AAA. The

762 committee advised that once a person has survived to 30 days after their intervention,
763 survival thereafter is expected to be relatively similar to people with repaired infrarenal AAA.
764 On this basis, the use of data for infrarenal AAA to model long-term survival was agreed to
765 be a reasonable approach. The committee were also aware that the bespoke nature of
766 complex EVAR devices had implications for obtaining reliable unit costs. However, they were
767 satisfied that an average cost obtained from 3 NHS Trusts was likely to adequately reflect a
768 typical UK cost, significantly in excess of the cost of a standard EVAR device.

769 The committee reviewed the ICERs predicted by the new economic model for the repair of
770 unruptured, complex AAA. The committee noted that EVAR was associated with more net
771 QALYs than open surgery in this population, as it is predicted to have a larger perioperative
772 survival benefit than in the infrarenal population, which means fewer patients are expected to
773 survive to experience any long-term survival benefits of open surgery. The committee agreed
774 that these results were plausible, though less certain than in the unruptured infrarenal
775 population, because of the lack of directly applicable clinical evidence. However, they agreed
776 that the magnitude of these uncertain benefits were unlikely to be sufficient to outweigh the
777 unambiguous additional costs associated with complex EVAR compared with open surgical
778 repair, as reflected in a base-case ICER of over £95,000 per QALY gained and a very small
779 probability of the true figure being £20,000 or better. To achieve an ICER of £20,000 per
780 QALY gained, complex EVAR would need to generate 0.797 QALYs more than open surgery
781 per patient, compared with a base case estimate of 0.166 QALYs.

782 The committee discussed other assumptions applied in the model, such as the complication
783 rates used. They agreed that complex AAA repairs are likely to be more susceptible to
784 subsequent complications and reintervention than infrarenal aneurysm repairs. The
785 committee noted that a scenario analysis had been included in the model that applied a
786 complication rate double that of infrarenal repair, and that this has no material impact on
787 cost-effectiveness results.

788 The committee advised that the 30-day mortality rate reported in the National Vascular
789 Registry for open repair in this population (19.6%) is high compared with clinical experience,
790 and that the estimate for EVAR (3.6%) is more representative of current practice. They
791 agreed that anatomical complexity is less problematic for open repair, during which a
792 surgeon can tailor the graft to suit the anatomy during the procedure, and that this is not
793 typically possible with EVAR, for which custom devices are built in advance of the procedure.
794 As such, the difference between the Registry's infrarenal and complex open surgical repair
795 mortality rates (3.0% and 19.6%) was agreed to be too large. The committee advised that the
796 Registry data, particularly for complex AAA repairs, are likely to be subject to substantial
797 selection and reporting biases, with EVAR repairs reported to the Registry as complex cases
798 likely to be inherently less complex than open repairs reported as complex. For example,
799 AAAs with a short infrarenal 'neck' would be considered routine if addressed with open
800 surgery, whereas the same anatomy would render a case 'complex' for EVAR, as it would be
801 outside the terms of the devices' IFUs. In this way, the committee concluded that the model
802 may be biased in favour of EVAR by using the Registry to source its baseline perioperative
803 mortality data for complex AAA. The committee agreed that, due to the likely selection and
804 reporting biases underlying the Registry data, a cost-effectiveness analysis using the
805 reported complex repair perioperative mortality rates directly would not provide a meaningful
806 comparison of EVAR and open surgical repair. Rather, the preferred approach was to take
807 the EVAR Registry data as the baseline mortality rate – as it more closely reflects clinical
808 experience than the open surgical repair value – and then apply a measure of relative effect
809 to this, derived from RCT evidence, to estimate the mortality rate for open surgical repair.

810 The committee also considered the transferability of resource-use data for infrarenal AAA
811 repair to complex cases. Based on clinical experience, they advised that a longer hospital
812 stay is typically observed for all complex AAA patients compared with infrarenal AAA
813 patients, but proportionally more so in complex EVAR patients. The committee agreed that
814 reflecting this in the new model would reduce the incremental cost of hospital resources for
815 open repair compared with EVAR, thereby increasing the ICER associated with EVAR
816 beyond the base-case value of £95,815.

817 The committee was satisfied that the new model provides a reasonable prediction of the
818 likely cost-effectiveness of EVAR in people with a complex unruptured AAA for whom
819 surgical repair is a suitable option. However, they were cautious about the lack of directly
820 applicable, randomised comparative evidence underlying the model, as this increased
821 uncertainty regarding the true ICER for EVAR in this population, and the committee were
822 also mindful that the model had plausibly demonstrated that the benefits of complex EVAR
823 may outweigh its harms, albeit at a cost that was very unlikely to be justified by any gains.
824 The committee therefore made a recommendation that the use of EVAR in this population
825 should be limited to the context of an RCT (that should include resource-use in its data
826 collection), to ensure that any use of EVAR in this population provides direct, comparative
827 clinical effectiveness and cost-effectiveness evidence.

828 The committee then discussed complex AAA repair in people for whom open surgical repair
829 is not a suitable option, due to concerns regarding anaesthetic risk and/or medical
830 comorbidity. The committee agreed that outcomes associated with complex EVAR would
831 certainly be no better than infrarenal EVAR, and would probably be worse, whereas
832 outcomes in complex AAA patients who receive no intervention are not likely to be different
833 to infrarenal AAA patients who receive no intervention. The committee were also aware that
834 bespoke EVAR devices for complex repair are more expensive than standard EVAR devices
835 for infrarenal repair, and that the ICER for infrarenal AAA repair in this population was
836 £460,000 per QALY gained. The committee therefore agreed that complex EVAR will be
837 more expensive than standard EVAR and will provide health outcomes that are at best
838 equivalent and at worst substantially less favourable, meaning there is no possibility that
839 EVAR could be cost effective in this population compared with a strategy of 'no intervention'.
840 This result is clearer than in people with complex AAA for whom open surgery is a suitable
841 option, where the base-case ICER for EVAR compared with open surgery was £95,000
842 (described above). In this population, it is feasible that EVAR may be more likely to be cost-
843 effective than in infrarenal cases, because AAA complexity also worsens the expected
844 outcomes from open surgery.

845 The committee were aware that there is no published cost-effectiveness evidence in this
846 population, and so the only evidence was from the economic model developed by NICE. The
847 base-case model found EVAR to be dominated by a strategy of 'no intervention', though the
848 committee recognised that the analysis had necessarily been informed by some
849 assumptions, such as generalising long-term survival data from the EVAR-2 population, and
850 low-quality data, namely estimating a 'complexity effect' from the National Vascular Registry.
851 The estimated EVAR perioperative mortality rate of 41% was felt to be higher than observed
852 in clinical practice; therefore this analysis was deemed to be more speculative than the
853 infrarenal AAA repair analyses conducted for this guideline. However, the unequivocal result
854 of EVAR being dominated was seen to be supportive of the committee's view that complex
855 EVAR cannot be cost effective in this population. The committee therefore made a strong
856 recommendation against the use of EVAR in people with a complex unruptured AAA for
857 whom surgical repair is not a suitable option.

858 The committee considered whether the cost-effectiveness evidence suggests there may be
859 differences in the balance of benefits and harms between men and women, for the elective
860 repair of unruptured complex AAA. None of the preferred ICERs from the modelling were
861 sensitive to the sex of the cohort; nor were they sensitive to differences in age or AAA size.
862 The committee therefore determined that there was no identifiable subgroup for whom
863 complex EVAR represents a reasonable use of NHS resources, so its recommendations
864 were appropriate to the relevant population as a whole.

865 **Other factors the committee took into account**

866 The committee noted that complex EVAR is a procedure-related term which encompasses a
867 variety of different AAA anatomies, stent designs and surgical difficulties which have been
868 grouped together.

869 The committee agreed it was not necessary to specify AAA symptomatology in the
870 recommendations because it was considered that the evidence relating to asymptomatic
871 aneurysms was transferrable to symptomatic aneurysm.

872 The committee discussed any potential differences between postoperative outcomes of
873 EVAR between men and women. They agreed that, although the majority of the evidence
874 presented was in men, there was no reason to believe that outcomes would differ in women.
875 Therefore no recommendations were made specific to women.
876

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for assessing the effectiveness of endovascular aneurysm 4 repair compared with open surgical repair of unruptured abdominal 5 aortic aneurysms

Review question 12	<p>The original question was: What is the effectiveness of EVAR compared to open repair surgery in reducing morbidity and mortality in people with unruptured abdominal aortic aneurysms?</p> <p>The committee agreed to retrospectively change the question to: What are the relative benefits and harms of EVAR, open surgical repair and non-surgical management in people with unruptured abdominal aortic aneurysms?</p>		
Objectives	<p>To assess the advantages and disadvantages of elective endovascular aneurysm repair in comparison with conventional open surgical repair for the treatment of unruptured abdominal aortic aneurysms</p> <p>To explore the subgroup effects of various patient characteristics, leading to more tailored recommendations</p>		
Type of review	Intervention		
Language	English only		
Study design	<p>i) Systematic reviews of study designs listed below</p> <p>Randomised controlled trials</p> <p>Quasi-randomised controlled trials</p> <p>Non-randomised controlled trials for comparisons in people eligible for complex EVAR only</p> <p>Prospective cohort studies for comparisons in people eligible for complex EVAR only</p> <p>ii) Analysis of UK registry data (National Vascular Registry)</p>		
		Interventions	
		Standard (on-IFU) EVAR	Complex EVAR
			Off-IFU use of standard EVAR
			Other complex EVAR
	Infrarenal	Systematic reviews RCTs Quasi-RCTs	Systematic reviews RCTs Quasi-RCTs Non-randomised controlled trials Prospective cohort studies UK registry data (National Vascular Registry)
	Juxtarenal	Systematic reviews RCTs Quasi-RCTs	Systematic reviews RCTs Quasi-RCTs Non-randomised controlled trials

Review question 12	<p>The original question was: What is the effectiveness of EVAR compared to open repair surgery in reducing morbidity and mortality in people with unruptured abdominal aortic aneurysms?</p> <p>The committee agreed to retrospectively change the question to: What are the relative benefits and harms of EVAR, open surgical repair and non-surgical management in people with unruptured abdominal aortic aneurysms?</p>																													
			Prospective cohort studies UK registry data (National Vascular Registry)	Prospective cohort studies UK registry data (National Vascular Registry)																										
	Suprarenal / 'type IV'	-	-		Systematic reviews RCTs Quasi-RCTs Non-randomised controlled trials Prospective cohort studies UK registry data (National Vascular Registry)																									
Status	Published papers only (full text) No date restrictions																													
Population	People undergoing surgery for a confirmed unruptured abdominal aortic aneurysm Subgroups: fitness for surgery, age, sex, comorbidities (including cardiovascular disease, renal disease, COPD, obesity), ethnicity																													
Intervention	<p>Elective standard (on-IFU) EVAR for infrarenal and juxtarenal abdominal aortic aneurysms</p> <p>Elective complex EVAR for infrarenal, juxtarenal and suprarenal abdominal aortic aneurysms, including:</p> <p>fenestrated EVAR</p> <p>EVAR with chimneys</p> <p>EVAR with snorkels</p> <p>branched grafts</p> <p>'CHIMPS' (CHIMneys, Periscopes, Snorkels)</p> <p>infrarenal devices used for juxtarenal AAA – that is, off-IFU use of standard devices</p> <p>Open repair</p> <p>Non-surgical intervention</p> <p>Summary:</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th>No surgery</th> <th>Open repair</th> <th>Standard (on-IFU) EVAR</th> <th>Off-IFU use of standard EVAR</th> <th>Other complex EVAR</th> </tr> </thead> <tbody> <tr> <td>Infrarenal</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td>Iliac-branched only</td> </tr> <tr> <td>Juxtarenal</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> </tr> <tr> <td>Suprarenal / 'type IV'</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">✓</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">✓</td> </tr> </tbody> </table>							No surgery	Open repair	Standard (on-IFU) EVAR	Off-IFU use of standard EVAR	Other complex EVAR	Infrarenal	✓	✓	✓	✓	Iliac-branched only	Juxtarenal	✓	✓	✓	✓	✓	Suprarenal / 'type IV'	✓	✓	-	-	✓
	No surgery	Open repair	Standard (on-IFU) EVAR	Off-IFU use of standard EVAR	Other complex EVAR																									
Infrarenal	✓	✓	✓	✓	Iliac-branched only																									
Juxtarenal	✓	✓	✓	✓	✓																									
Suprarenal / 'type IV'	✓	✓	-	-	✓																									
Comparator	Each other																													

Review question 12	<p>The original question was: What is the effectiveness of EVAR compared to open repair surgery in reducing morbidity and mortality in people with unruptured abdominal aortic aneurysms?</p> <p>The committee agreed to retrospectively change the question to: What are the relative benefits and harms of EVAR, open surgical repair and non-surgical management in people with unruptured abdominal aortic aneurysms?</p>
Outcomes	<p>Mortality/survival</p> <p>Peri- and post-operative complications</p> <p>Successful exclusion of the aneurysm, aneurysm rupture, or further aneurysm growth</p> <p>Need for reintervention</p> <p>Quality of life</p> <p>Resource use, including length of hospital or intensive care stay, and costs</p>
Other criteria for inclusion / exclusion of studies	<p>Exclusion:</p> <p>Non-English language</p> <p>Abstract/non-published</p>
Baseline characteristics to be extracted in evidence tables	<p>Age</p> <p>Sex</p> <p>Size of aneurysm</p> <p>Comorbidities</p>
Search strategies	See Appendix B
Review strategies	<p>i i) Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.</p> <p>The update of Paravastu et al's 2014 Cochrane review (ongoing at the time of protocol development) comparing endovascular and open surgical repair of unruptured AAAs will be used as the RCT evidence base for infrarenal AAAs in people who are considered 'fit for surgery'</p> <p>Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All key findings from evidence will be presented in GRADE profiles.</p> <p>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.</p> <p>i and ii) All key findings will be summarised in evidence statements.</p>
Key papers	<p>Sharath Chandra Paravastu, V, Rubaraj Jayarajasingam, Rachel Cottam, Simon J. Palfreyman, Jonathan A. Michaels, and Steven M. Thomas. Endovascular repair of abdominal aortic aneurysm. Cochrane Database of Systematic Reviews (1), 2014 – SYSTEMATIC REVIEW; included papers:</p> <ul style="list-style-type: none"> • ACE • DREAM • EVAR 1 • EVAR 2 • OVER

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 12

Paravastu SC, Jayarajasingam R, Cottam R et al. (2014) Endovascular repair of abdominal aortic aneurysm. *Cochrane Database Syst Rev*;(1): CD004178. doi: 10.1002/14651858.CD004178.pub2.

Medline Strategy, searched 15th August 2017

Database: Ovid MEDLINE(R) 1946 to August Week 1 2017

Search Strategy:

- 1 Aortic Aneurysm, Abdominal/
- 2 (aneurysm* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort* or spontan* or juxtarenal* or juxta-renal* or juxta renal* or paraarenal* or para-renal* or para renal* or suprarenal* or supra renal* or supra-renal* or short neck* or short-neck* or shortneck* or visceral aortic segment*)).tw.
- 3 (AAA or cAAA).tw.
- 4 or/1-3
- 5 exp Stents/

Medline Strategy, searched 15th August 2017**Database: Ovid MEDLINE(R) 1946 to August Week 1 2017****Search Strategy:**

```

6  Vascular Surgical Procedures/ or Blood Vessel Prosthesis/ or Blood Vessel Prosthesis
   Implantation/
7  (blood adj4 vessel* adj4 (transplant* or graft* or implant*)).tw.
8  (endovasc* or endostent* or endograft* or EVAR* or Palmaz or stent* or graft*).tw.
9  (endovascular* adj4 aneurysm* adj4 repair*).tw.
10 (endovascular* adj4 aort* adj4 repair*).tw.
11 or/5-10
12 4 and 11
13 Aortic Aneurysm, Abdominal/su [Surgery]
14 12 or 13
15 (complex or fenestrat* or branched or chimney* or snorkel* or periscope* or sandwich* or
   CHIMPS).tw.
16 14 and 15
17 (FEVAR or F-EVAR or BEVAR or B-EVAR or BREVAR or BR-EVAR or CHEVAR or CH-
   EVAR or Co-EVAR or CoEVAR or Co-FEVAR or CoFEVAR).tw.
18 (complex adj4 EVAR*).tw.
19 17 or 18
20 16 or 19
21 animals/ not humans/
22 20 not 21
23 limit 22 to english language

```

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/

```

Medline Strategy

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

Quality of life

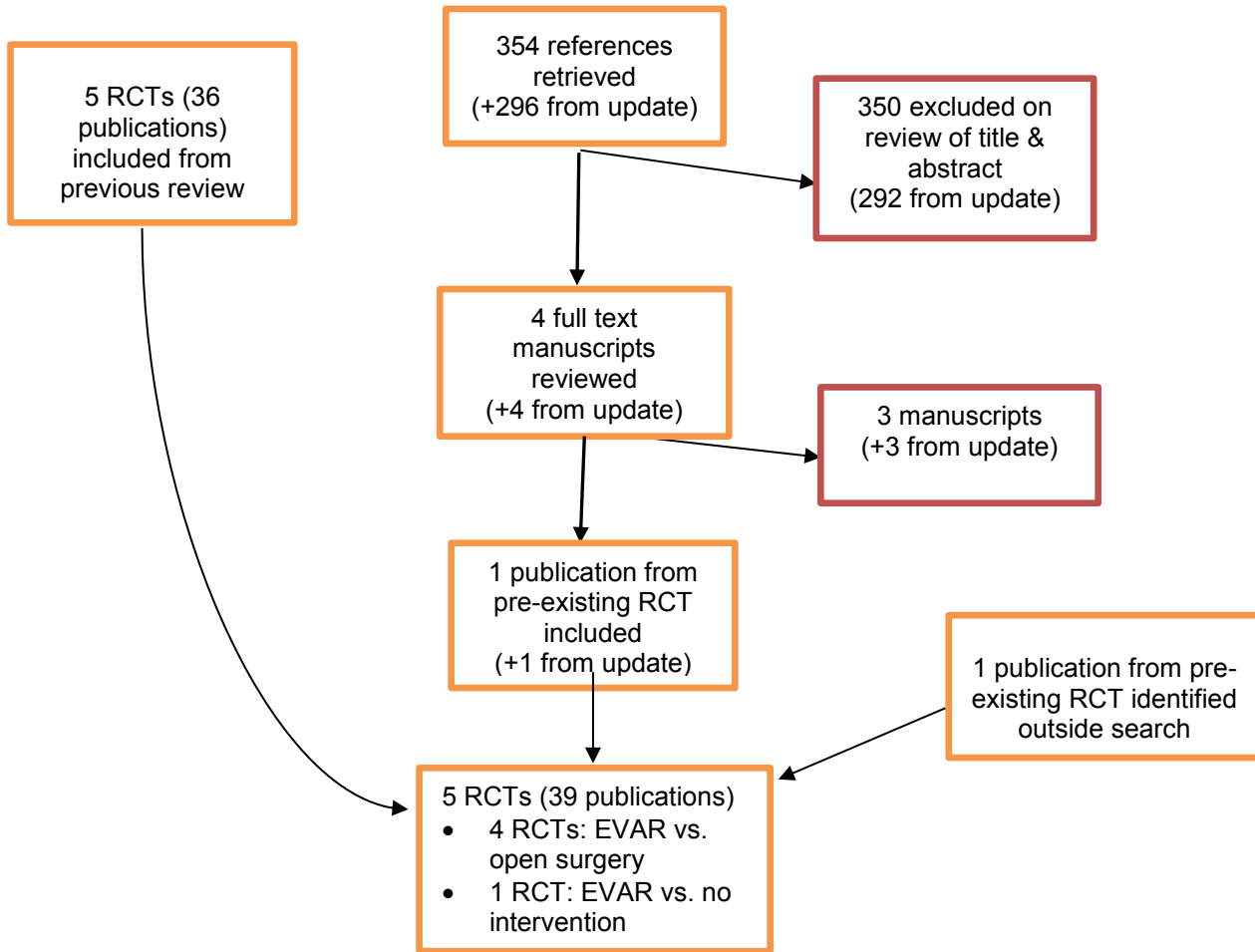
- 1 "Quality of Life"/
- 2 quality of life.tw.
- 3 "Value of Life"/
- 4 Quality-Adjusted Life Years/
- 5 quality adjusted life.tw.
- 6 (qaly* or qald* or qale* or qtime*).tw.
- 7 disability adjusted life.tw.
- 8 daly*.tw.
- 9 Health Status Indicators/
- 10 (sf36 or sf 36 or short form 36 or shortform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

Medline Strategy

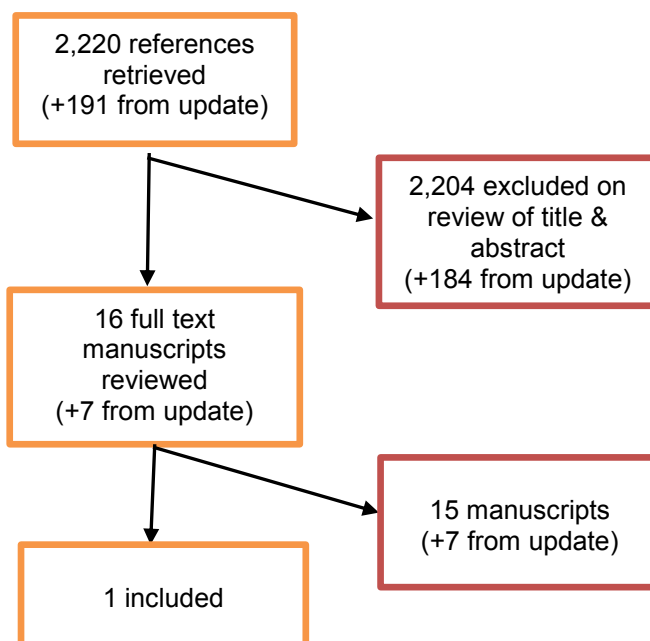
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble*.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix C – Clinical evidence study selection

Cochrane systematic review update search



Complex EVAR versus open surgery study selection



Appendix D – Clinical evidence tables

Standard EVAR compared with open surgical repair of simple AAA

Full citation	Paravastu SC, Jayarajasingam R, Cottam R et al. (2014) Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev;(1): CD004178. doi: 10.1002/14651858.CD004178.pub2.
Study details	<p>Study type: systematic review</p> <p>Location: UK</p> <p>Aim: to assess the effectiveness of EVAR versus conventional open surgical repair in individuals with AAA considered fit for surgery, and EVAR versus best medical care in those considered unfit for surgery, and EVAR versus best medical care for those considered unfit for surgery</p> <p>Study dates: literature searched for publications up to January 2013</p> <p>Follow-up: 30 days, up to 4 years, and up to 8 years</p> <p>Sources of funding: this study was supported by funding from the UK National Institute of Health Research (NIHR)</p>
Participants	<p>Population: patients with unruptured AAA, diagnosed by ultrasound or computed tomography, in whom surgical treatment was indicated</p> <p>Sample size: 4 RCTs including 2,745 participants</p> <p>Inclusion criteria: RCTs comparing EVAR with open surgical repair in individuals with unruptured AAAs that were considered fit for surgery</p> <p>Exclusion criteria: studies with inadequate data or studies that used an inadequate randomisation technique (not specified). Additionally, studies assessing complex and hybrid endovascular techniques (including fenestrated EVAR) were excluded.</p>
Methods	<p>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.</p>
Intervention	EVAR using any type of endovascular device

Full citation	Paravastu SC, Jayarajasingam R, Cottam R et al. (2014) Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev;(1): CD004178. doi: 10.1002/14651858.CD004178.pub2.
Comparison	Open surgical repair (for people in whom surgery was considered suitable), or best medical care (for people in whom surgery was not considered suitable)
Outcomes measures	All-cause mortality, aneurysm-related mortality, endograft-related complications, major complications, minor complications, and quality of life. Assessed at the following time points: 30 days, up to 4 years up to 8 years.
Study Appraisal using AMSTAR (Assessing the Methodological Quality of Systematic Reviews)	<ol style="list-style-type: none"> 1. Was an 'a priori' design provided? Yes 2. Was there duplicate study selection and data extraction? Yes 3. Was a comprehensive literature search performed? Yes 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? Yes 5. Was a list of studies (included and excluded) provided? Yes 6. Were the characteristics of the included studies provided? Yes 7. Was the scientific quality of the included studies assessed and documented? Yes 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? Yes 9. Were the methods used to combine the findings of studies appropriate? Yes 10. Was the likelihood of publication bias assessed? Yes 11. Was the conflict of interest included? Yes <p>Overall risk of bias: Low Directness: directly applicable</p>

Studies included in the systematic review by Paravastu et al.

Full citation	ACE trial (results reported in multiple publications outlined in the Cochrane systematic review)
Study details	<p>Study type: multicentre, non-blinded, randomised controlled trial</p> <p>Location: France</p> <p>Aim: to assess the results of EVAR and of open surgery in relatively good-risk patients presenting with an asymptomatic abdominal aortic or aorto-iliac aneurysm</p> <p>Study dates: 2003 to 2008</p> <p>Follow-up: up to 4 years</p> <p>Sources of funding: not reported</p>
Participants	<p>Population: patients with asymptomatic unruptured abdominal aortic or aorto-iliac aneurysm</p> <p>Sample size: 299; 99% male</p> <p>Inclusion criteria: men with AAA >5 cm in men and women with AAA >4.5 cm were included. Furthermore patients with common iliac artery aneurysms >3.0 cm, an aneurysm upper neck free of major thrombus or calcification, ≥1.5 cm length and angle between the neck, the axis of the aneurysm <60° and iliac arteries compatible with the introducer sheath were included</p> <p>Exclusion criteria: previous AAA surgery, a ruptured aneurysm, a mycotic aneurysm, severe iodine allergy and life expectancy <6 months, or patients graded as category 3 using the SVS/AAVS classification system</p> <p>Baseline characteristics:</p> <p>Mean age: EVAR group, 68.9 years; Open surgery group, 70.0 years</p> <p>Sex: EVAR group, 100% male; Open surgery group, 98% male</p> <p>Mean aneurysm diameter: EVAR group, 55.2 mm; Open surgery group, 55.6 mm</p> <p>Diabetes: EVAR group, 13.3%; Open surgery group, 19.5%</p> <p>Hypertension: EVAR group, 66.0%; Open surgery group, 63.8%</p> <p>Hyperlipidaemia: EVAR group, 68.7%; Open surgery group, 65.8%</p> <p>Carotid artery disease: EVAR group, 8.0%; Open surgery group, 8.1%</p> <p>Renal insufficiency: EVAR group, 14.0%; Open surgery group, 10.1%</p> <p>Pulmonary disease: EVAR group, 19.3%; Open surgery group, 28.2%</p>
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	All-cause mortality, major adverse events (myocardial infarction, permanent stroke, permanent haemodialysis, major amputation, paraplegia and bowel infarction), vascular reinterventions and minor complications

Full citation	ACE trial (results reported in multiple publications outlined in the Cochrane systematic review)
Risk of bias assessment (from the Cochrane review)	<ol style="list-style-type: none">1. Random sequence generation (selection bias): Low risk – A clinical research unit performed randomisation by centre2. Allocation concealment (selection bias): Low risk – Treatment allocation was notified less than 24 hours to the investigator3. 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 measured4. Blinding of outcome assessment (detection bias): Unclear – It is unclear whether assessors were blinded5. Incomplete outcome data (attrition bias): Low risk – Authors presented results based using an intention-to treat approach and presented final follow up results. All participants were accounted for.6. Selective reporting (reporting bias): Low risk – All pre-specified outcomes were reported7. Other bias: Low risk – none identified <p>Overall risk of bias: Low Directness: directly applicable</p>

Full citation	DREAM trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches van Schaik T G, Yeung KK, Verhagen HJ et al. (2017) Long-term survival and secondary procedures after open or endovascular repair of abdominal aortic aneurysms. European Journal of Vascular and Endovascular Surgery 54 (5), 671
Study details	Study type: multicentre, non-blinded, randomised controlled trial Location: Netherlands Aim: to assess the differences in results of conservative EVAR and open surgical treatment of unruptured AAA Study dates: 2000 to 2003 Follow-up: up to 15 years Sources of funding: the trial was funded by a grant from the Netherlands National Health Insurance Council.
Participants	Population: patients with unruptured AAA Sample size: 351; 91% male Inclusion criteria: men with AAA >5 cm in men and women with AAA >4.5 cm were included. Furthermore patients with common iliac artery aneurysms >3.0 cm, an aneurysm upper neck free of major thrombus or calcification, ≥1.5 cm length and angle between the neck, the axis of the aneurysm <60° and iliac arteries compatible with the introducer sheath were included Exclusion criteria: a ruptured aneurysm, a mycotic aneurysm, presence of anatomical variations, connective tissue disease, history of organ transplant, or life expectancy <2 years Baseline characteristics: Mean age: EVAR group, 70.7 years; Open surgery group, 69.6 years Sex: EVAR group, 93% male; Open surgery group, 90% male Mean aneurysm diameter: not reported Comorbidities: not reported
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	All-cause mortality, aneurysm-related mortality, complications and reintervention rates
Risk of bias assessment (from	1. Random sequence generation (selection bias): Low risk – Randomisation was performed centrally with the use of a computer-generated permuted block sequence and stratified according to study centre in blocks of 4 patients 2. Allocation concealment (selection bias): Low risk – Allocation concealment was performed appropriately

<p>Full citation</p>	<p>DREAM trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches van Schaik T G, Yeung KK, Verhagen HJ et al. (2017) Long-term survival and secondary procedures after open or endovascular repair of abdominal aortic aneurysms. European Journal of Vascular and Endovascular Surgery 54 (5), 671</p>
<p>the Cochrane review)</p>	<p>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 – Outcome assessors were blinded to group allocations 5. Incomplete outcome data (attrition bias): Low risk – Analysis was performed using an intention-to-treat basis 6. Selective reporting (reporting bias): Low risk – All pre-specified outcomes were reported 7. Other bias: Low risk – none identified Overall risk of bias: Low Directness: directly applicable</p>

Full citation	EVAR1 trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches Patel R, Sweeting MJ, Powell JT et al. (2016) Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet. 388(10058):2366-2374.
Study details	Study type: multicentre, non-blinded, randomised controlled trial Location: UK Aim: to assess the efficacy of EVAR in the treatment of AAA in terms of mortality, quality of life, durability and cost-effectiveness Study dates: 1999 to 2004 Follow-up: up to 15 years Sources of funding: the trial was funded by the National Health Service Research and Development Health Technology Assessment Programme
Participants	Population: patients with unruptured AAA Sample size: 1,252; 91% male Inclusion criteria: patients ≥ 60 years with AAA ≥ 5.5 cm in diameter were included Exclusion criteria: contraindications for surgery Baseline characteristics: Mean age: EVAR group, 74.1 years; Open surgery group, 74.0 years Sex: EVAR group, 90.3% male; Open surgery group, 90.1% male Mean aneurysm diameter: EVAR group, 64.0 mm; Open surgery group, 65.0 mm Diabetes: EVAR group, 9.8%; Open surgery group, 11.0% Cardiac disease: EVAR group, 41.8%; Open surgery group, 43.0%
Intervention	EVAR
Comparison	Open surgical repair
Outcomes measures	All-cause mortality, aneurysm-related mortality, complications and reintervention rates
Risk of bias assessment	1. Random sequence generation (selection bias): Low risk – Participants were randomised to groups on a 1:1 basis using randomly permuted block sizes constructed using STATA. Randomisation is stratified by centre and was performed centrally. 2. Allocation concealment (selection bias): Low risk – Allocation was performed only after all baseline data were recorded

Full citation	EVAR1 trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches Patel R, Sweeting MJ, Powell JT et al. (2016) Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet. 388(10058):2366-2374.
	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): Unclear – It is unclear whether assessors were blinded 5. Incomplete outcome data (attrition bias): Low risk – Analysis was performed using an intention-to-treat basis and all participants were accounted for 6. Selective reporting (reporting bias): Low risk – All pre-specified outcomes were reported 7. Other bias: Low risk – none identified Overall risk of bias: Low Directness: directly applicable

Full citation	OVER trial (results reported in multiple publications outlined in the Cochrane systematic review)
Study details	<p>Study type: multicentre, non-blinded, randomised controlled trial</p> <p>Location: USA</p> <p>Aim: to compare postoperative outcomes after EVAR and open repair</p> <p>Study dates: 2002 to 2008</p> <p>Follow-up: 8 years</p> <p>Sources of funding: this study was supported by the United States' Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development</p>
Participants	<p>Population: patients with unruptured AAA</p> <p>Sample size: 881; 99% male</p> <p>Inclusion criteria: patients with AAA ≥ 5 cm, an iliac aneurysm (associated with an AAA) ≥ 3 cm, an AAA ≥ 4.5 cm which had increased in size by ≥ 0.7 cm in 6 months, an AAA ≥ 4.5 cm which had increased in size by ≥ 1 cm in 12 months, an AAA ≥ 4.5 cm that was considered saccular (a portion of the circumference of the aorta at the level of the aneurysm is considered normal) or an AAA ≥ 4.5 cm that was associated with distal embolism were included</p> <p>Exclusion criteria: previous AAA repair, a ruptured aneurysm or likelihood of poor compliance to the study protocol</p> <p>Baseline characteristics:</p> <p>Mean age: EVAR group, 69.6 years; Open surgery group, 70.5 years</p> <p>Sex: EVAR group, 99.3% male; Open surgery group, 99.5% male</p> <p>Mean aneurysm diameter: EVAR group, 57.0mm; Open surgery group, 57.0 mm</p> <p>Coronary artery disease: EVAR group, 39.2%; Open surgery group, 42.3%</p> <p>Myocardial infarction: EVAR group, 23.6%; Open surgery group, 25.2%</p> <p>Coronary revascularization: EVAR group, 35.8%; Open surgery group, 35.0%</p> <p>Cerebrovascular disease: EVAR group, 15.1%; Open surgery group, 16.0%</p> <p>Hypertension: EVAR group, 78.2%; Open surgery group, 75.5%</p> <p>Claudication: EVAR group, 14.9%; Open surgery group, 18.5%</p> <p>Diabetes: EVAR group, 22.5%; Open surgery group, 22.9%</p> <p>COPD: EVAR group, 28.4%; Open surgery group, 30.4%</p>
Intervention	EVAR
Comparison	Open surgical repair

Full citation	OVER trial (results reported in multiple publications outlined in the Cochrane systematic review)
Outcomes measures	All-cause mortality, aneurysm-related mortality, complications and reintervention rates
Risk of bias assessment	<ol style="list-style-type: none">1. Random sequence generation (selection bias): Low risk – Randomisation was performed by 'permuted block design'2. Allocation concealment (selection bias): Low risk – Allocation was performed only after all baseline data were recorded3. 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 measured4. Blinding of outcome assessment (detection bias): Low risk – Outcomes were adjudicated by a blinded outcomes assessment committee5. Incomplete outcome data (attrition bias): Low risk – Analysis was performed using an intention-to-treat basis and all participants were accounted for6. Selective reporting (reporting bias): Low risk – All pre-specified outcomes were reported7. Other bias: Low risk – none identified <p>Overall risk of bias: Low Directness: directly applicable</p>

Complex EVAR compared with open surgical repair of juxtarenal aneurysms

Full citation	Donas Konstantinos P, Eisenack Markus, Panuccio Giuseppe, Austermann Martin, Osada Nani, and Torsello Giovanni (2012) The role of open and endovascular treatment with fenestrated and chimney endografts for patients with juxtarenal aortic aneurysms. Journal of vascular surgery 56, 285-90
Study details	<p>Study type: non-randomised comparative study</p> <p>Location: Germany</p> <p>Aim: to compare endovascular techniques (fenestrated and chimney approaches) for treating juxtarenal AAAs with open surgical repair</p> <p>Study dates: January 2008 to December 2010</p> <p>Follow-up: mean of 15.2 months</p> <p>Sources of funding: self-funded study performed at a University hospital</p>
Participants	<p>Population: patients with primary degenerative juxtarenal AAAs defined as complex AAAs with a short infrarenal necks (<9 mm) or aneurysmal extension to the inter-renal aorta</p> <p>Sample size: 90; 92% male</p> <p>Inclusion criteria: patients less than 68 years who were considered physiologically fit were included in the open repair group. Another indication for open repair was the coexistence of accessory polar renal arteries with evidence of significant kidney perfusion. Patients considered high-risk for open repair due to the presence of more than 3 cardiovascular comorbidities were included in the fenestrated-EVAR (f-EVAR) or chimney-EVAR (c-EVAR) groups. Patients that met the following criteria were included in the c-EVAR group: symptomatic aneurysms, aneurysms that displayed rapid eccentric growth (greater than 0.5 cm per year), aneurysms that had at least a 15 mm distance between the target vessel for chimney grafts and the upper aortic branch, a patent left subclavian artery, absence of severe kinking of the descending aorta, extensive thrombus in the aortic arch and juxtarenal segment, aneurysms with involvement of less than 2 aortic side branches. Any patients that did not meet criteria for inclusion in the c-EVAR group were assigned to the f-EVAR group.</p> <p>Exclusion criteria: Patients with persistent type I endoleaks after conventional EVAR, proximal para-anastomotic pseudoaneurysms after open repair, or ruptured, mycotic, or inflammatory juxtarenal AAAs were excluded</p> <p>Baseline characteristics:</p> <p>Mean age: c-EVAR group, 74.5; f-EVAR group, 73.7 years; Open surgery group, 71.2 years</p> <p>Sex: c-EVAR group, 90% male; f-EVAR group, 100% male; Open surgery group, 87.1% male</p> <p>Mean aneurysm diameter: c-EVAR group, 62.0 mm; f-EVAR group, 65.0 mm; Open surgery group, 60.0 mm</p> <p>Cardiac comorbidities: c-EVAR group, 73.3%; f-EVAR group, 82.3%; Open surgery group, 29.0%</p> <p>Renal comorbidities: c-EVAR group, 23.3%; f-EVAR group, 17.2%; Open surgery group, 6.5%</p>

Full citation	Donas Konstantinos P, Eisenack Markus, Panuccio Giuseppe, Austermann Martin, Osada Nani, and Torsello Giovanni (2012) The role of open and endovascular treatment with fenestrated and chimney endografts for patients with juxtarenal aortic aneurysms. Journal of vascular surgery 56, 285-90
	Respiratory comorbidities: c-EVAR group, 33.3%; f-EVAR group, 37.9%; Open surgery group, 19.3% Previous aortic intervention: c-EVAR group, 36.6%; f-EVAR group, 27.6%; Open surgery group, 6.5% Previous myocardial infarction: c-EVAR group, 30%; f-EVAR group, 24.1%; Open surgery group, 0%
Intervention	c-EVAR, f-EVAR
Comparison	Open surgical repair
Outcomes measures	30-day mortality, deterioration of renal function, blood loss, transfusion requirements, the need for re-intervention, length of stay,
Risk of bias assessment (using ROBINS-I tool)	<ol style="list-style-type: none"> 1. Is there potential for confounding of the effect of intervention in this study? No 2. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? Patients were selected for different surgical interventions according to characteristics indicative of operative difficulty or fitness for surgery. 3. Do start of follow-up and start of intervention coincide for most participants? Yes 4. Were intervention groups clearly defined? Yes 5. Was the information used to define intervention groups recorded at the start of the intervention? Yes 6. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? No 7. Were there deviations from the intended intervention beyond what would be expected in usual practice? No 8. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome? 9. Were important co-interventions balanced across intervention groups? Unclear 10. Was the intervention implemented successfully for most participants? Yes 11. Did study participants adhere to the assigned intervention regimen? Yes 12. Were outcome data available for all, or nearly all, participants? Yes 13. Were participants excluded due to missing data on intervention status? No 14. Were participants excluded due to missing data on other variables needed for the analysis? No 15. Could the outcome measure have been influenced by knowledge of the intervention received? No – objective outcome measures were assessed

Full citation	Donas Konstantinos P, Eisenack Markus, Panuccio Giuseppe, Austermann Martin, Osada Nani, and Torsello Giovanni (2012) The role of open and endovascular treatment with fenestrated and chimney endografts for patients with juxtarenal aortic aneurysms. Journal of vascular surgery 56, 285-90
	<p>16. Were outcome assessors aware of the intervention received by study participants? Yes – it was not possible to blind outcome assessors; however, this is unlikely to affect study results</p> <p>17. Were the methods of outcome assessment comparable across intervention groups? Yes</p> <p>18. Were any systematic errors in measurement of the outcome related to intervention received? No</p> <p>19. Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within multiple outcome measurements within the outcome domain? No</p> <p>Overall risk of bias: moderate</p> <p>Directness: directly applicable</p>

EVAR vs no intervention for patients in whom open surgery is not considered appropriate

Full citation	EVAR 2 trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches Sweeting M J, Patel R, Powell J T, and Greenhalgh R M (2017) Endovascular Repair of Abdominal Aortic Aneurysm in Patients Physically Ineligible for Open Repair: Very Long-term Follow-up in the EVAR-2 Randomized Controlled Trial. Annals of Surgery. 24
Study details	<p>Study type: multicentre, non-blinded, randomised controlled trial</p> <p>Location: UK</p> <p>Aim: compare long-term total and aneurysm-related mortality in physically frail patients with AAA who were randomised to either early EVAR or no intervention</p> <p>Study dates: patients were recruited from September 1999 to August 2004</p> <p>Follow-up: mean of 12 years</p> <p>Sources of funding: this study was funded by the National Institute for Health Research Health Technology Assessment programme</p>
Participants	<p>Population: patients with large aneurysms in whom open surgical repair was considered inappropriate</p> <p>Sample size: 404; sex-specific proportions were not reported</p>

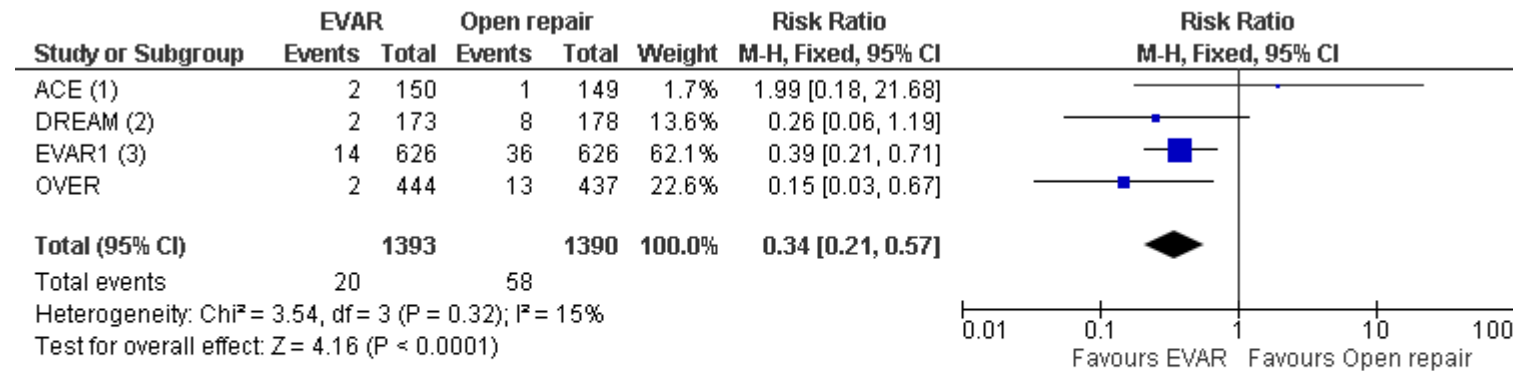
Full citation	EVAR 2 trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches Sweeting M J, Patel R, Powell J T, and Greenhalgh R M (2017) Endovascular Repair of Abdominal Aortic Aneurysm in Patients Physically Ineligible for Open Repair: Very Long-term Follow-up in the EVAR-2 Randomized Controlled Trial. Annals of Surgery. 24
	Inclusion criteria: patients over 60 years old with AAAs at least 5.5 cm in diameter (confirmed by computed tomography) who were considered physically ineligible for open repair, and anatomically suitable for EVAR, were included. The appropriateness of surgery was determined locally by the treating surgeon, radiologist, anaesthetist and cardiologist. Exclusion criteria: not reported Baseline characteristics: Mean age: EVAR group, 77.2 years; No repair group, 76.4 years Sex: EVAR group, 85.3% male; No repair group, 86.5% male Mean aneurysm diameter: EVAR group, 68.0 mm; No repair group, 67.0 mm Diabetes: EVAR group, 15.4%; No repair group, 14.1% History of cardiac disease: EVAR group, 67.0%; No repair group, 73.9%
Intervention	EVAR
Comparison	No intervention
Outcomes measures	All-cause mortality, aneurysm-related mortality, graft-related complications and graft-related re-interventions.
Risk of bias assessment (using Cochrane)	<ol style="list-style-type: none"> 1. Random sequence generation (selection bias): Low risk – Randomisation was performed appropriately, using randomly permuted block sizes. 2. Allocation concealment (selection bias): Low risk – Allocation was done only after all baseline data were recorded 3. Blinding of participants and personnel (performance bias): Unclear – Due to the nature of the interventions, it was not possible to blind participants and personnel 4. Blinding of outcome assessment (detection bias): Unclear risk – insufficient information was available 5. Incomplete outcome data (attrition bias): Low risk – reasonable rates of loss to follow-up, and reasons for losses were explained 6. Selective reporting (reporting bias): Low risk – Study reported on all predefined outcomes 7. Other bias: High risk – there was a considerably high rate of crossover between groups: 33.8% (70/207) patients in the no intervention were ended up being treated by EVAR during the trial. Authors analysed 4- and 8-year follow-up data using an intention-to-treat approach, which would not have taken crossover into account.

<p>Full citation</p>	<p>EVAR 2 trial (results reported in multiple publications outlined in the Cochrane systematic review) NB: a new publication was identified from update searches Sweeting M J, Patel R, Powell J T, and Greenhalgh R M (2017) Endovascular Repair of Abdominal Aortic Aneurysm in Patients Physically Ineligible for Open Repair: Very Long-term Follow-up in the EVAR-2 Randomized Controlled Trial. Annals of Surgery. 24</p>
	<p>Overall risk of bias: high risk for analyses performed at 4-and 8-year follow-up; low risk for analyses performed at 12-year follow-up because appropriate measures were taken to minimise bias due to crossover. Directness: directly applicable</p>

Appendix E – Forest plots

EVAR compared with open surgery for patients in whom open surgery is considered appropriate

Short-term all-cause mortality (30-day and in-hospital)



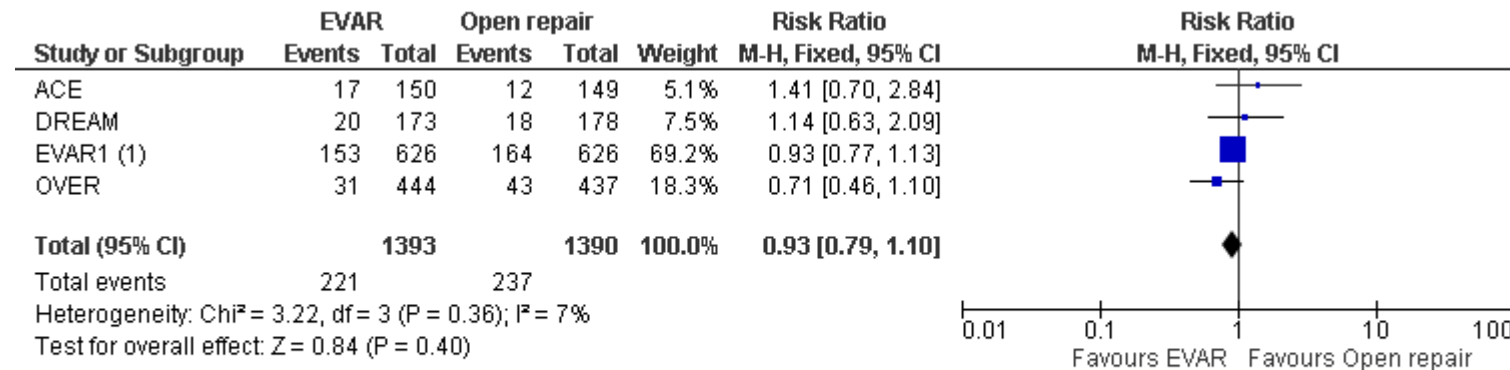
Footnotes

(1) One patient in OSR did not undergo surgery

(2) 2 in EVAR and 4 in OSR did not undergo surgery

(3) Of the 626 patients in each group, 12 in EVAR died prior to repair and 19 in OSR died before surgery and 5 refused surgery

All-cause mortality up to 4 years



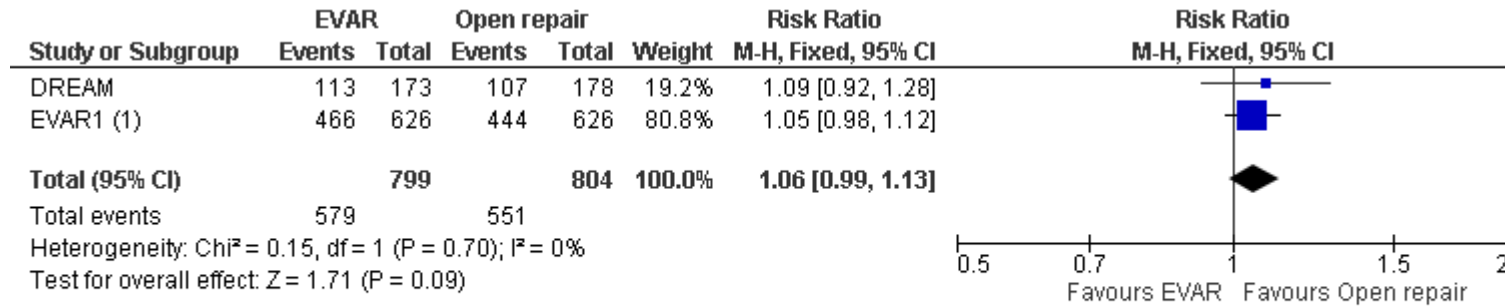
Footnotes

(1) Patients who died prior to intervention were included (Intention to treat analysis)

All-cause mortality up to 8 years



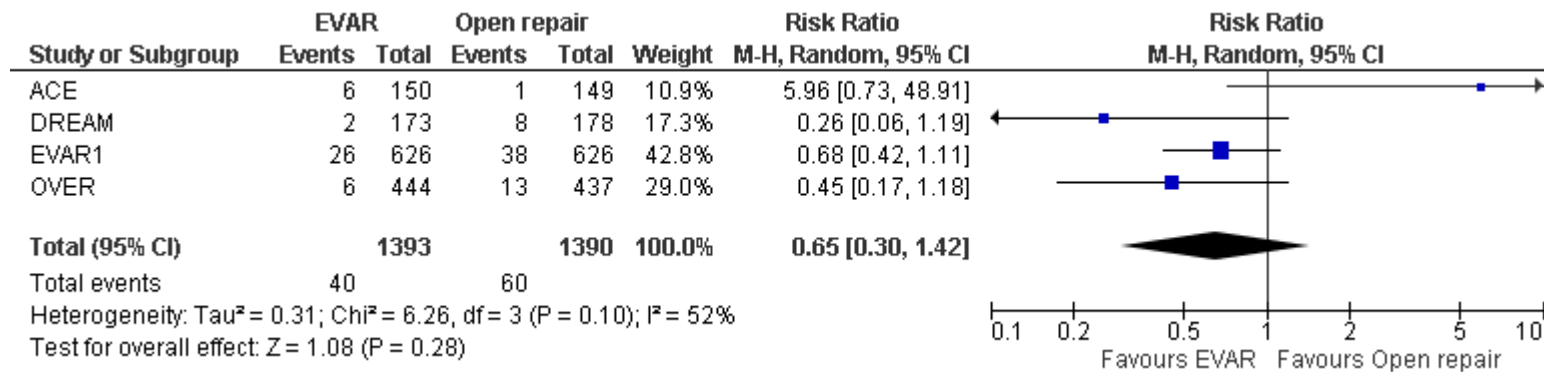
All-cause mortality up to 15 years



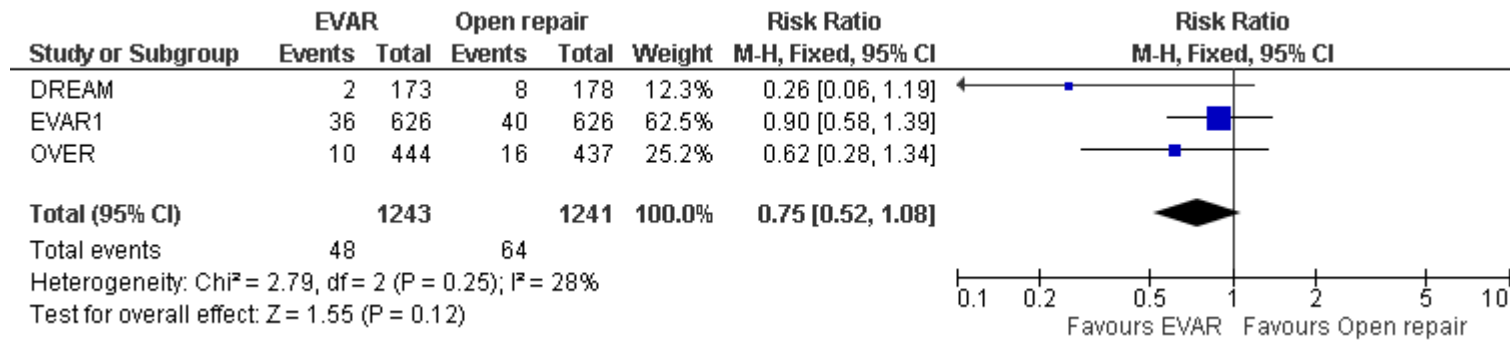
Footnotes

(1) Patients who died prior to intervention were included (Intention to treat analysis)

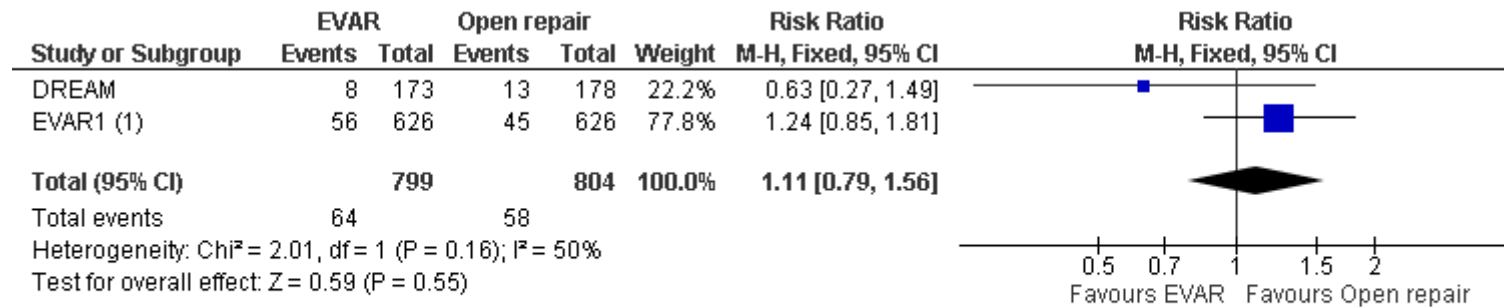
AAA-related mortality up to 4 years



AAA-related mortality up to 8 years



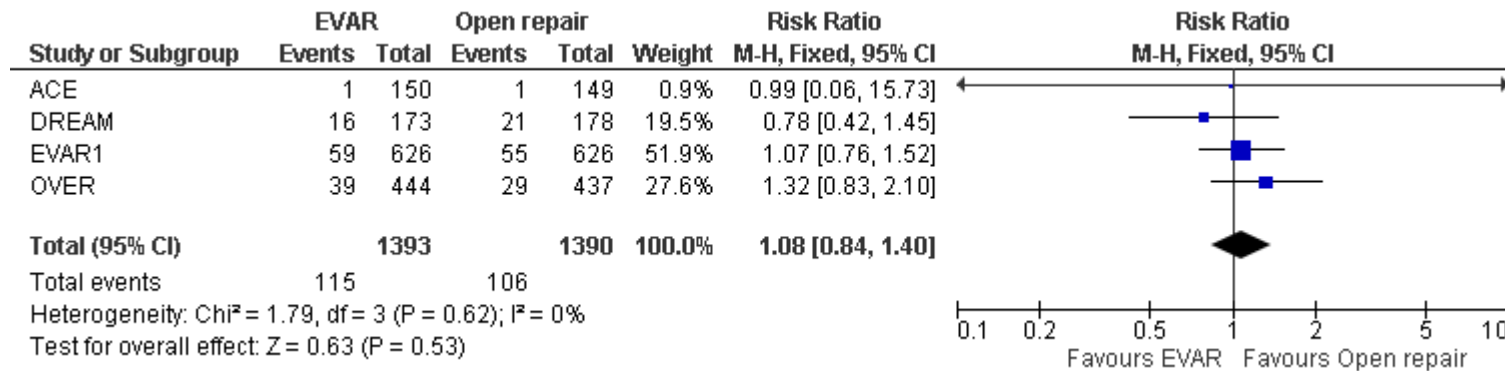
AAA-related mortality up to 15 years



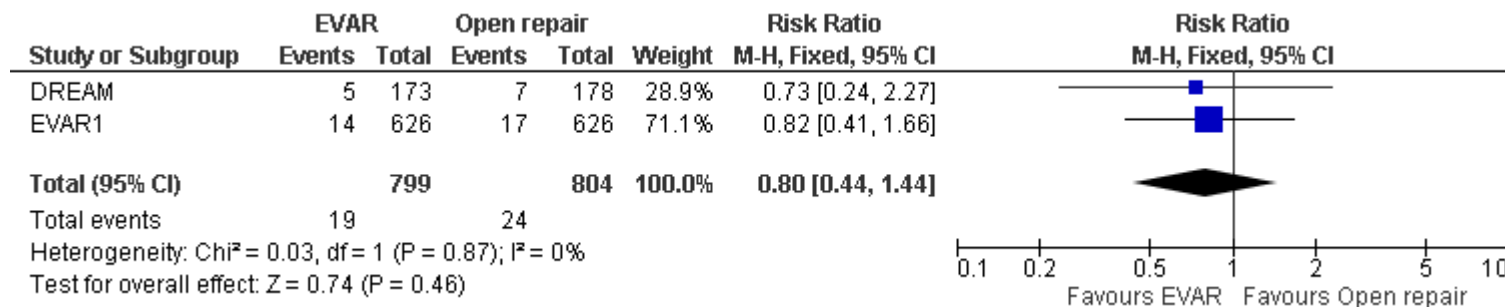
Footnotes

(1) Patients who died prior to intervention were included (Intention to treat analysis)

Cardiac-related mortality (follow-up not specified)



Stroke-related mortality (follow-up not specified)

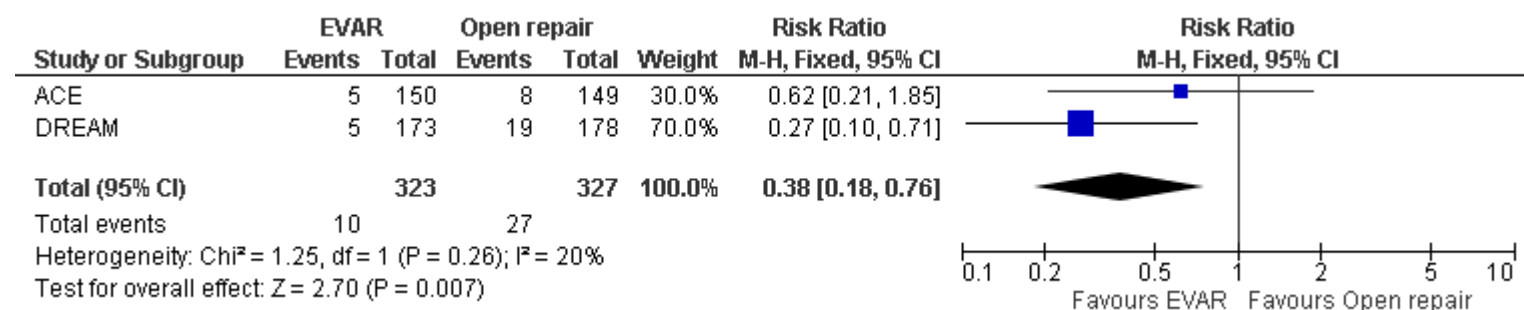
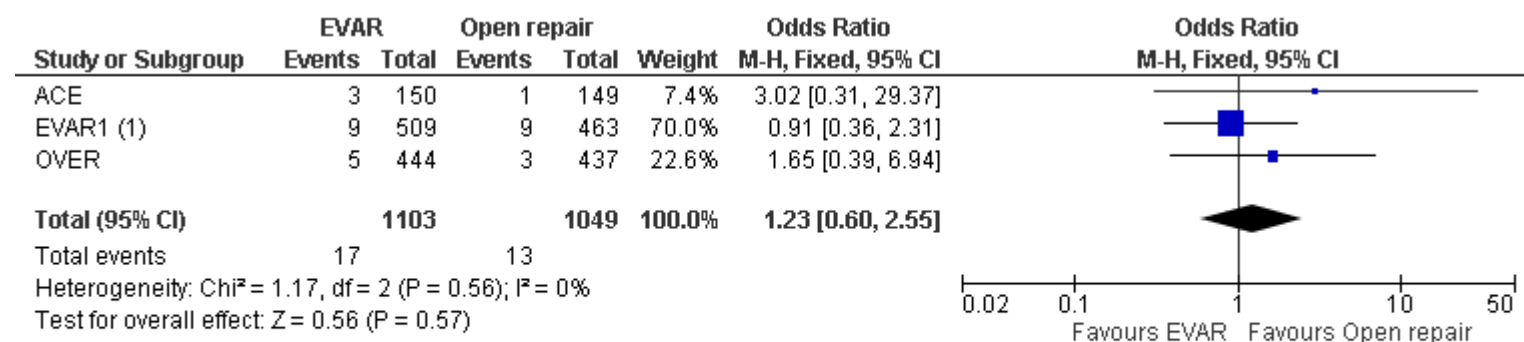


Pulmonary-related mortality (follow-up not specified)



Non-fatal stroke (follow-up not specified)

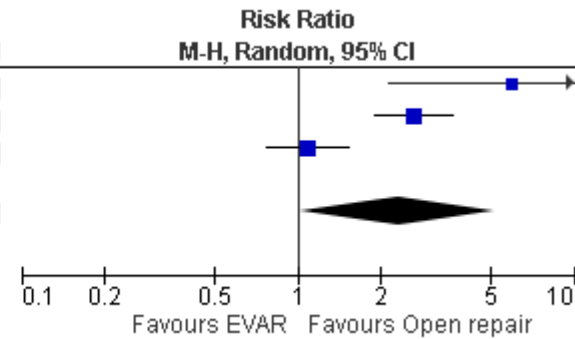


Pulmonary complications (follow-up not specified)**Renal complications (follow-up not specified)**Footnotes

(1) Renal failure was assessed based on annual GFR, hence only patients with minimum of one-year follow up were included.

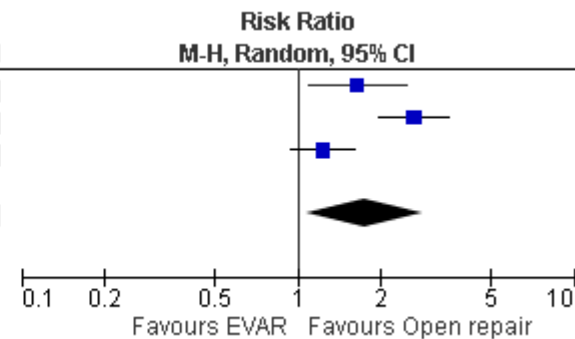
Need for reintervention up to 4 years

Study or Subgroup	EVAR		Open repair		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
ACE	24	150	4	149	24.3%	5.96 [2.12, 16.76]
EVAR1	121	626	46	626	38.0%	2.63 [1.91, 3.63]
OVER	61	444	55	437	37.7%	1.09 [0.78, 1.53]
Total (95% CI)		1220		1212	100.0%	2.30 [1.03, 5.18]
Total events	206		105			
Heterogeneity: Tau ² = 0.42; Chi ² = 19.03, df = 2 (P < 0.0001); I ² = 89%						
Test for overall effect: Z = 2.02 (P = 0.04)						

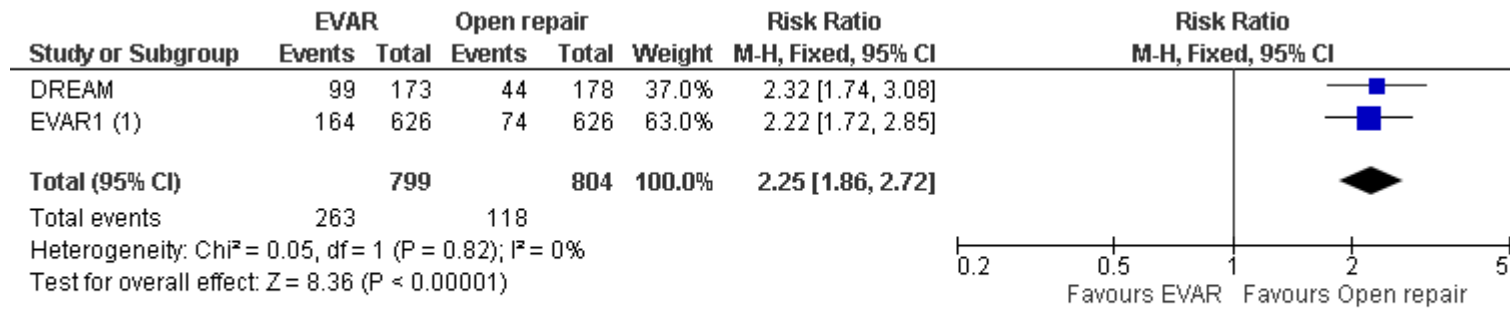


Need for reintervention up to 8 years

Study or Subgroup	EVAR		Open repair		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
DREAM	48	173	30	178	30.7%	1.65 [1.10, 2.47]
EVAR1	145	626	55	626	34.3%	2.64 [1.97, 3.52]
OVER	98	444	78	437	35.0%	1.24 [0.95, 1.61]
Total (95% CI)		1243		1241	100.0%	1.75 [1.07, 2.85]
Total events	291		163			
Heterogeneity: Tau ² = 0.16; Chi ² = 14.38, df = 2 (P = 0.0008); I ² = 86%						
Test for overall effect: Z = 2.25 (P = 0.02)						



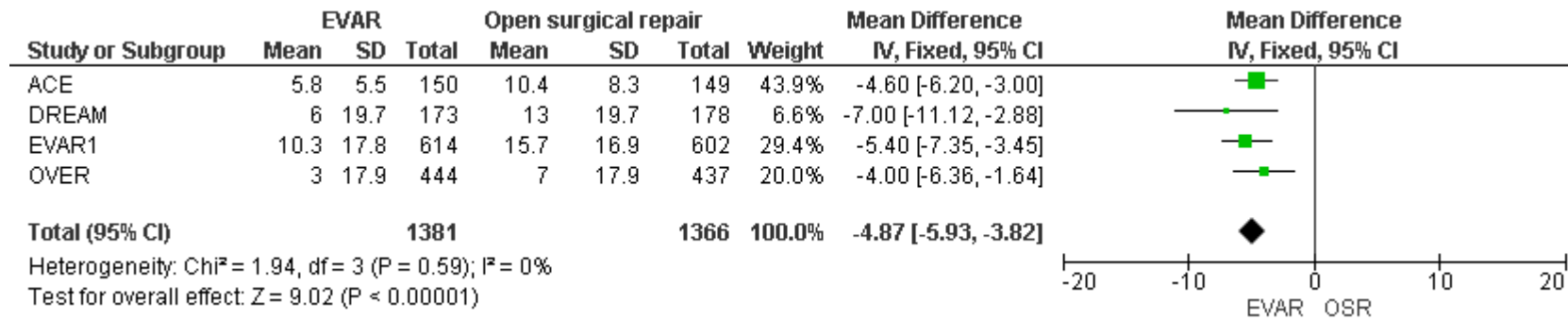
Need for reintervention up to 15 years



Footnotes

(1) Patients who died prior to intervention were included (Intention to treat analysis)

Length of stay



Appendix F – GRADE tables

EVAR compared with open surgery for patients in whom open surgery is considered appropriate

Mortality

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
All-cause mortality at 30 days or within hospital; effect sizes below 1 favour EVAR									
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Not serious	1,362	1,361	RR 0.34 (0.21, 0.57)	High
All-cause mortality up to 4 years; effect sizes below 1 favour EVAR									
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Serious ¹	1,393	1,390	RR 0.93 (0.79, 1.10)	Moderate
All-cause mortality up to 8 years; effect sizes below 1 favour EVAR									
3 (DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Not serious	1,243	1,241	RR 0.99 (0.89, 1.09)	High
All-cause mortality between 8 and 15 years; effect sizes below 1 favour EVAR									
1 EVAR1 trial	RCT	Not serious	Not serious	Not serious	Not serious	626	626	HR ^a 1.25 (1.00, 1.56) (Although 95% CI crosses 1 authors note this as a statistically significant result; p=0.048)	High
All-cause mortality up to 15 years; effect sizes below 1 favour EVAR									
2 (EVAR 1, DREAM trials)	RCTs	Not serious	Not serious	Not serious	Not serious	799	804	RR 1.06 (0.99, 1.13)	High
AAA-related mortality up to 4 years; 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	
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Serious ²	Very serious ³	1,393	1,390	RR 0.65 (0.30, 1.42)	Very low
AAA-related mortality up to 8 years; effect sizes below 1 favour EVAR									
4 (DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Serious ¹	1,243	1,241	RR 0.75 (0.52, 1.08)	Moderate
AAA-related mortality between 8 and 15 years; effect sizes below 1 favour EVAR									
1 EVAR1	RCT	Not serious	Not serious	Not serious	Not serious	626	626	HR ^a 5.82 (1.64, 20.65)	High
AAA-related mortality up to 15 years; effect sizes below 1 favour EVAR									
2 (EVAR 1, DREAM trials)	RCTs	Not serious	Not serious	Serious ²	Very serious ³	799	804	RR 1.11 (0.79, 1.56)	Very low
Cardiac-related mortality (follow-up not specified) ; effect sizes below 1 favour EVAR									
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Serious ¹	1,393	1,390	RR 1.08 (0.84, 1.40)	Moderate
Stroke-related mortality (follow-up not specified) ; effect sizes below 1 favour EVAR									
2 (DREAM & EVAR1 trials)	RCTs	Not serious	Not serious	Not serious	Very serious ³	799	804	RR 0.80 (0.44, 1.44)	Low
Pulmonary-related mortality (follow-up not specified) ; effect sizes below 1 favour EVAR									
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Serious ¹	1,243	1,241	RR 0.61 (0.41, 0.91)	Moderate

a. Hazard ratios were reported adjusting for age, sex, maximum aneurysm diameter, FEV1, log creatinine, statin use, BMI, smoking status, systolic blood pressure, and total cholesterol

1. Confidence interval crosses one line of a defined minimum clinically important difference (RR MID of 0.8 and 1.25), downgrade 1 level.

2. I² value between 33.3% and 66.7%, downgrade 1 level.

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

Endograft-related 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	
Any endograft complication (not specified)									
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Very serious ¹	Not serious	1,393	N/A	ACE: 27.3% (41/150) DREAM: 27.7% (48/173) EVAR1: 45.0% (282/626) OVER: 24.8% (110/444) Overall rate: 34.5%	Low
Endoleaks									
4 (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Very serious ¹	Not serious	1,296	N/A	ACE: 27.3% (41/150) DREAM: 11.7% (20/173) EVAR1: 22.3% (118/529) OVER: 24.8% (110/444) Overall rate: 22.3%	Low
Graft migration									
2 (DREAM & EVAR1 trials)	Systematic review (2 RCTs)	Not serious	Not serious	Not serious	Not serious	799	N/A	DREAM: 4.0% (7/173) EVAR1: 1.9% (12/444) Overall: 3.1% (15/617)	Low
1. Unexplained variation in complication rates reported across included studies, downgrade 2 levels.									

Other complications

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Non-fatal stroke (follow-up not reported); effect sizes below 1 favour EVAR									
3 (ACE, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Very serious ¹	1,220	1,212	RR 0.82 (0.52, 1.29)	Low
Pulmonary complications (follow-up not reported); effect sizes below 1 favour EVAR									
2 (ACE & DREAM trials)	RCTs	Not serious	Not serious	Not serious	Not serious	323	327	RR 0.38 (0.18, 0.76)	High
Renal complications (follow-up not reported); effect sizes below 1 favour EVAR									
3(ACE, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Very serious ¹	1,103	1,049	RR 1.23 (0.60, 2.55)	Low
Sexual dysfunction (follow-up not reported); effect sizes below 1 favour EVAR									
ACE trial	RCT	Not serious	Not serious	Not serious	Very serious ¹	150	148	RR 0.63 (0.25, 1.58)	Low
1. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MID of 0.8 and 1.25), downgrade 2 levels.									

Need for reintervention

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Any reintervention up to 4 years; effect sizes below 1 favour EVAR									
3 (ACE, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Very serious ¹	Serious ²	1,220	1,212	RR 2.30 (1.03, 5.18)	Very low
Any reintervention up to 8 years; effect sizes below 1 favour EVAR									
3v(DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Very serious ¹	Serious ²	1,243	1,241	RR 1.75 (1.07, 2.85)	Very low
Any reintervention between 8 and 15 years; effect sizes below 1 favour EVAR									
1 EVAR1	RCT	Not serious	Not serious	Not serious	Serious ³	264	282	HR ^a 1.51 (0.71, 3.19)	Moderate
Any reintervention up to 15 years; effect sizes below 1 favour EVAR									
2 (EVAR 1, DREAM trial)	RCT	Not serious	Not serious	Not serious	Not serious	799	804	RR 2.25 (1.86, 2.72)	High
AAA-related reintervention up to 15 years; effect sizes below 1 favour EVAR									
1 DREAM trial	RCT	Not serious	Not serious	N/A	Not serious	178	173	RR 6.66 (3.70, 12.5,)	High
Life threatening reintervention up to 15 years; effect sizes below 1 favour EVAR									
1 EVAR1	RCT	Not serious	Not serious	N/A	Not serious	302	300	HR ^a 2.09 (1.42, 3.08)	High
<p>a. Hazard ratios were reported adjusting for age, sex, maximum aneurysm diameter, FEV1, log creatinine, statin use, BMI, smoking status, systolic blood pressure, and total cholesterol</p> <p>1. I² value >66.7%, downgrade 2 levels.</p> <p>2. Confidence interval crosses one line of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 1 level.</p> <p>3. Non-significant result (95% CI crosses the line of no effect), downgrade 1 level.</p>									

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	
Mean changes in SF-36 Mental component scores at 2 years; effect sizes below 0 favour EVAR									
1 EVAR1 trial	RCT	Not serious	Not serious	N/A	Serious ¹	1,220	1,212	MD 0.92 (-0.39, 2.23)	Moderate
Mean changes in SF-36 physical component scores at 2 years; effect sizes below 0 favour EVAR									
1 EVAR1 trial	RCT	Not serious	Not serious	Not serious	Serious ¹	1,220	1,212	MD -0.20 (-1.59, 1.19)	Moderate
Mean changes in EQ-5D scores at 2 years; effect sizes below 0 favour EVAR									
1 EVAR1 trial	RCT	Not serious	Not serious	Not serious	Serious ¹	1,103	1,049	MD 0.01 (-0.01, 0.03)	Moderate
1. Non-significant result (95% CI 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 hospital stay; effect sizes below 0 favour EVAR									
4, (ACE, DREAM, EVAR1 & OVER trials)	RCTs	Not serious	Not serious	Not serious	Not serious	1,381	1,366	MD -4.87(-5.93, -3.82)	High

Complex EVAR compared with open surgical repair for patients with juxtarenal aneurysms

Mortality

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
30-day mortality; effect sizes below 1 favour EVAR									
1 Donas (2012)	Non-randomised controlled trial	Very serious ¹	Not serious	Not serious	Very serious ²	59	31	RR 0.11 (0.01, 2.16)	Very low
1. Patients were selected for different surgical interventions according to characteristics indicative of aneurysm anatomy complexity and fitness for surgery, downgrade 2 levels.									
2. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.									

Complications

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Need for persistent haemodialysis at 30 days; effect sizes below 1 favour EVAR									
1 Donas (2012)	Non-randomised controlled trial	Very serious ¹	Not serious	Not serious	Very serious ²	59	31	RR 0.11 (0.01, 2.16)	Very low
Pneumonia at 30 days; effect sizes below 1 favour EVAR									
1 Donas (2012)	Non-randomised controlled trial	Very serious ¹	Not serious	Not serious	Very serious ²	59	31	RR 0.18 (0.01, 4.24)	Very low
Stroke at 30 days; effect sizes below 1 favour EVAR									
1 Donas (2012)	Non-randomised controlled trial	Very serious ¹	Not serious	Not serious	Very serious ²	59	31	RR 0.18 (0.01, 4.24)	Very low
1. Patients were selected for different surgical interventions according to characteristics indicative of aneurysm anatomy complexity and fitness for surgery, downgrade 2 levels.									
2. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.									

Reintervention

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Need for reintervention; effect sizes below 1 favour EVAR									
1 Donas (2012)	Non-randomised controlled trial	Very serious ¹	Not serious	Not serious	Very serious ²	59	31	RR 2.10 (0.25, 18.00)	Very low
1. Patients were selected for different surgical interventions according to characteristics indicative of aneurysm anatomy complexity and fitness for surgery, downgrade 2 levels.									
2. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.									

Length of stay

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	Open repair	Summary of results	
Length of hospital stay; effect sizes below 0 favour EVAR									
1 Donas (2012)	Non-randomised controlled trial	Very serious ¹	Not serious	Not serious	Not serious	59	31	MD -3.70 (-4.86, -2.54)	Low
1. Patients were selected for different surgical interventions according to characteristics indicative of aneurysm anatomy complexity and fitness for surgery, downgrade 2 levels.									

EVAR vs no intervention for patients in whom open surgery is not considered appropriate

Mortality

No of studies	Design	Quality assessment				No of patients		Effect estimate	Quality
		Risk of bias	Indirectness	Inconsistency	Imprecision	EVAR	No intervention	Summary of results	
All-cause mortality at 6 months; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Serious ²	197	207	HR ^a 1.32 (0.68, 2.54)	Moderate
All-cause mortality at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Serious ²	197	207	HR ^a 1.02 (0.75, 1.37)	Low
All-cause mortality at 8 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Serious ²	197	207	HR ^a 0.96 (0.61, 1.51)	Low
All-cause mortality at 12 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Not serious	Not serious	Not serious	Serious ²	197	207	HR ^a 0.83 (0.65, 1.07)	Moderate
AAA-related mortality at 6 months; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Serious ²	197	207	HR ^a 1.78 (0.75, 4.21)	Low
AAA-related mortality at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Not serious	197	207	HR ^a 0.34 (0.16, 0.72)	Moderate
AAA-related mortality at 8 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Not serious	197	207	HR ^a 0.17 (0.04, 0.84)	Moderate
Fatal myocardial infarction at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Very serious ³	197	207	RR 0.74 (0.38, 1.42)	Very low
Stroke-related mortality at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Very serious ³	197	207	RR 1.75 (0.42, 7.23)	Very low

a. Hazard ratios were reported adjusting for age, sex, maximum aneurysm diameter, FEV1, log creatinine, statin use, BMI, smoking status, systolic blood pressure, and total cholesterol

1. Investigators analyses did not take into account a considerably high rate of crossover (34%) from the no intervention group to the EVAR group, downgrade 1 level.

2. Non-significant result (95% CI crosses the line of no effect), 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.

Endograft-related complications and 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 graft-related complication (including endoleak, infection, stenosis, migration, thrombosis rupture, and kinking)									
1 EVAR2 trial	RCT	Not serious	Not serious	Not serious	Not serious	197	N/A	49.2% (97/197)	High
Graft-related reinterventions									
1 EVAR2 trial	RCT	Not serious	Not serious	Not serious	Not serious	197	N/A	27.9% (55/197)	High

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	
Cardiovascular events (not specified) at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Serious ²	197	207	HR ^a 1.07 (0.60, 1.91)	Low
Non-fatal myocardial infarction at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Serious ²	197	207	RR 5.25 (1.17, 23.68)	Low
Non-fatal stroke at 4 years; effect sizes below 1 favour EVAR									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Very serious ³	197	207	RR 1.84 (0.55, 6.18)	Very low

a. Hazard ratios were reported adjusting for age, sex, maximum aneurysm diameter, FEV1, log creatinine, statin use, BMI, smoking status, systolic blood pressure, and total cholesterol

1. Investigators' analyses did not take into account a considerably high rate of crossover (34%) from the no intervention group to the EVAR group, downgrade 1 level.

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

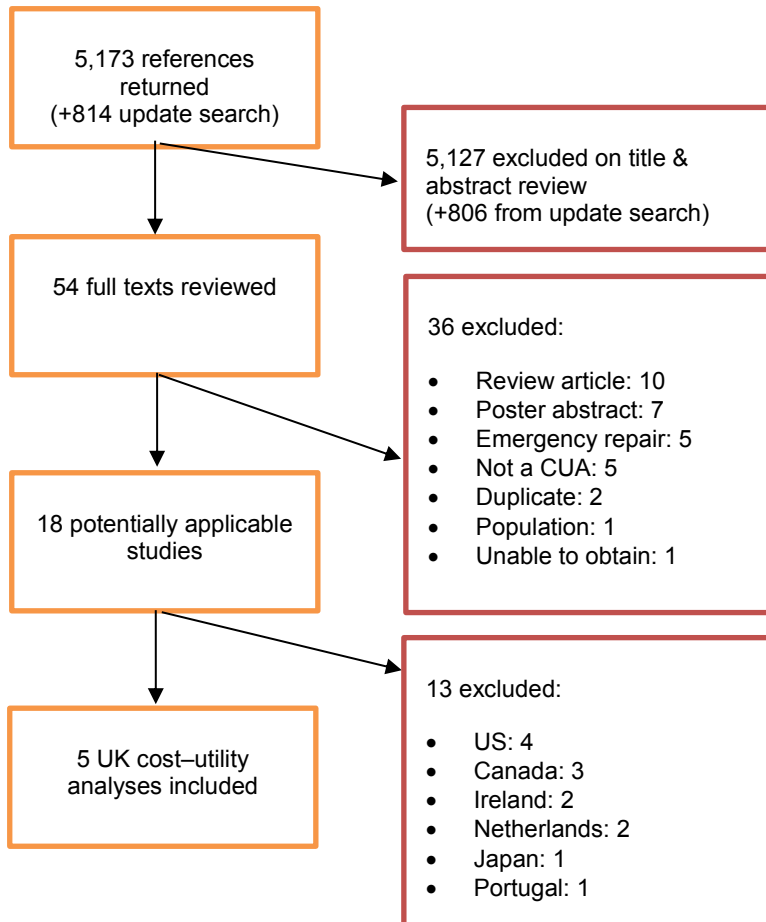
3. Confidence interval crosses two lines of a defined minimum clinically important difference (RR MIDs of 0.8 and 1.25), downgrade 2 levels.

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 scores at 2 years									

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 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Very serious ²	197	207	No difference between groups.	Very low
EQ-5D scores at 2 years									
1 EVAR2 trial	RCT	Serious ¹	Not serious	Not serious	Very serious ²	197	207	No difference between groups.	Very low
1. Investigators' analyses did not take into account a considerably high rate of crossover (34%) from the no intervention group to the EVAR group, downgrade 1 level. 2. Effect sizes and measures of dispersion were not reported, downgrade 2 levels.									

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (EVAR vs. OSR / no repair)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£)		
<p>Michaels et al. (2005) Decision tree model comparing EVAR with OSR (and EVAR with no repair). UK.</p>	<p><u>Effects:</u> EVAR-1 and DREAM studies for operative outcomes. NICE review of non-RCTs for other EVAR outcomes. <u>Costs:</u> Intervention, monitoring and reintervention. Tariff costs for primary procedure plus £4500 for EVAR. Other resource use from EUROSTAR registry and assumptions. <u>Utilities:</u> Short term recovery decrements (NR), followed by general age-related utility after successful repair.</p>	<p>Cohort: male, 70 years old, 5.5cm AAA.</p> <p>10-year time horizon. 3.5% discount rates. Price year 2003-04.</p> <p>No long-term CV events.</p> <p>General population life expectancy applied after successful repair.</p>	<p><u>EVAR vs. OSR</u> 11,449</p>	0.10	110,000	<p>‘The results of this analysis suggested that, in patients in whom conventional open repair would be an alternative, EVAR provided a slight additional benefit, but at a cost that would not normally be considered appropriate for funding by the NHS.’</p>	<p>EVAR ICER <£20,000 in ~0% of 1000 PSA model runs, compared with OSR.</p> <p>Base case result robust to scenario analyses (e.g. assuming £0 EVAR device cost: ICER >£50,000).</p>
<p>Partially applicable ^a</p>							
<p>Potentially serious limitations ^{b,c,d,e}</p>							

Key: EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; NR, not reported; OSR, open surgical repair; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

- a. Only considers infrarenal aneurysms.
- b. Relative effects only available for operative outcomes for EVAR vs. OSR comparison; no randomised data used for ‘unfit for OSR’ population.
- c. Successful repair effectively considered a ‘cure’ as patients return to general population life expectancy (long-term data not available at the time of analysis).
- d. Reintervention and complications (endoleak) only modelled for EVAR, and no long-term complications modelled.
- e. 10-year time horizon (15 in scenario analysis); shorter than lifetime, and current long-term EVAR-1 data suggest long-term survival differences.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (EVAR vs. OSR)			Conclusions	Uncertainty
			Cost (£) (95% CI)	Effect (QALYs) (95% CI)	ICER (£)		
<p>Epstein et al. (2008) Markov model comparing EVAR with OSR based on EVAR-1 patients and data. UK.</p> <p>Partially applicable ^a</p> <p>Potentially serious limitations ^{b,c,d}</p>	<p><u>Effects:</u> EVAR-1 study. <u>Costs:</u> EVAR-1 study, NHS reference costs and UK literature. <u>Utilities:</u> UK population norms (Kind et al. 1999), 1-month surgery morbidity (EVAR-1), cardiovascular conditions (UK literature).</p>	<p>2-year convergence of EVAR and OSR overall survival, despite 4-year aneurysm-related survival benefit for EVAR. 'Other cause' EVAR mortality catch-up factor applied in the model.</p> <p>Aneurysm-related readmissions modelled. Cardiovascular conditions were MI and stroke.</p> <p>Lifetime horizon, 3.5% discount rate applied to all outcomes.</p>	3,758 (2,439; 5,183)	-0.02 (-0.189; 0.165)	EVAR dominated	<p>'EVAR is unlikely to be cost-effective for all patients within collectively funded healthcare systems.'</p> <p>'EVAR may be cost-effective in a subpopulation of elderly patients fit for open surgery ... if patients maintain this early survival advantage over open surgery.'</p>	<p>EVAR ICER 1.2% likely to be ≤£20,000 per QALY gained.</p> <p>Various scenario analyses. Probability was 14.7% if OSR perioperative mortality was 8% (from 5%); and was 26.2% if the patient was aged 82 (from 74) and differences in cardiovascular event rates were omitted.</p>

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

- a. Only considers infrarenal aneurysms.
- b. Informed by early results from a single study.
- c. Unclear whether difference in aneurysm-related mortality over 4 years is extrapolated to lifetime.
- d. Potential conflict of interest.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (EVAR vs. OSR)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£)		
<p>Chambers et al. (2009) Markov model comparing EVAR with OSR. UK.</p> <p>Partially applicable ^a</p> <p>Potentially serious limitations ^{b,c,d}</p>	<p><u>Effects:</u> Baseline risk equations estimated using IPD from the EUROSTAR study. Relative effects from systematic review (EVAR-1 and DREAM).</p> <p><u>Costs:</u> Intervention, monitoring and readmission. Resource use from EVAR-1. Costs from EVAR-1 and UK sources.</p> <p><u>Utilities:</u> UK population norms (Kind et al. 1999), surgery-related decrements for 6 months (EVAR-1).</p>	<p>Lifetime horizon, 3.5% discount rates, Markov model. Price year 2007.</p> <p>Risk equations constructed to predict operative mortality, post-operative mortality, and readmission. Readmissions are AAA-related only. No long-term CV events.</p> <p>Non-AAA mortality converges after ~3 years. AAA-related mortality benefit of EVAR maintained. Rupture fatality rate assumed 100%.</p>	2,002	0.041	48,990	<p>'The base-case decision model found that EVAR is not cost-effective on average for patients who are fit for open surgery</p> <p>'If patients can be classified into good, average and poor operative risk, then for patients of most ages and aneurysm sizes, EVAR is cost-effective compared with open repair in patients of poor risk but not cost-effective in patients of good risk.'</p>	<p>EVAR ICER 26.1% likely to be ≤£20,000 per QALY gained. ICER is <£30,000 in patients with subjectively poor operative fitness. ICER <£20,000 where (1) EVAR sustained an overall survival benefit over OSR for the patient's lifetime and (2) unit cost of EVAR equal to OSR, follow-up costs lower and reintervention rates lower.</p> <p>ICER £21-22,000 if EVAR operative mortality odds ratio improved (from 0.35 to 0.25), and if overall mortality rates converge at 8 years (vs. 3 years).</p>

Key: CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; OSR, open surgical repair; QALY, quality-adjusted life year.

- a. Only considers infrarenal aneurysms.
- b. Relative effects largely drawn from a single study (EVAR-1).
- c. Impact of long-term non-aneurysm complications not captured by model.
- d. Assumption of maintained AAA-related mortality difference not supported by 15-year EVAR-1 study data.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (EVAR vs. OSR / no repair)			Conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£)		
Brown et al. (2012) Markov model comparing EVAR with OSR. Trial analysis comparing EVAR with no repair. UK.	Effects: EVAR-1 and EVAR-2 studies, including ITT analyses. Costs: Intervention, monitoring and readmission. Resource use from EVAR trials. Costs from trials and UK sources. In EVAR-2 analysis, costs not extrapolated beyond observed 8-year data. Utilities: EVAR-1 analysis: surgery-related decrements for 3 months (EVAR-1 analysis). EVAR-2 analysis: EQ-5D data from trial.	EVAR-1 analysis: Lifetime horizon. EVAR-2 analysis: 8-year analysis and lifetime analysis. 3.5% discount rates. Price year 2008-09. EVAR-1 model: Follow-up divided into first 6 months, 6 months to 4 years, 4 to 8 years, and 8 years onwards. AAA mortality converges after 8 years. Ongoing non-AAA mortality SMR of 1.1 vs. general population (based on EVAR-1 and UKSAT). EVAR-2 analysis: 2 analyses presented, 1 ITT (by randomised group) and 1 per protocol (excludes subjects who crossed over from 'no surgery' to intervention). No long-term CV events.	<u>EVAR-1</u> 3,521	-0.042	EVAR dominated	<u>EVAR-1</u> 'For patients with large AAA, who are deemed anatomically suitable for EVAR and anaesthetically fit for open repair, [EVAR] is a more costly treatment option [than OSR] and unlikely to be cost-effective in all patients.' <u>EVAR-2</u> 'For patients deemed anatomically suitable for EVAR but too unfit to for open repair, EVAR offers a long-term benefit in aneurysm mortality ... no benefits in quality of life and high rates of adverse events, complications and reinterventions after EVAR contribute to poor cost-effectiveness.'	<u>EVAR-1</u> EVAR ICER 1% likely to be ≤£20,000 per QALY gained compared with OSR. PSA mean costs: £3,519 (95% CI: 1,919 to 5,053). PSA mean QALYs: -0.032 (-0.117 to 0.096). Robust to univariate sensitivity analysis based on alternative clinical data (OVER) and modelling assumptions (Epstein 2008, NICE 2009). <u>EVAR-2</u> 0% and 3% of 1000 bootstrapped ICERs were ≤£20,000 (ITT analysis). Mean ICER of lifetime 'per protocol' analysis was £17,805 (61% ≤£20,000).
			<u>EVAR-2 8-years</u> 10,214	0.037	264,900		
			<u>Lifetime</u> 10,214	0.350	30,274		
Partially applicable ^a							
Potentially serious limitations ^{b,c,d}							

Key: CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OSR, open surgical repair; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; UKSAT, UK Small Aneurysm Trial.

- a. Only considers infrarenal aneurysms.
- b. Relative effects largely drawn from a single study for each analysis (EVAR-1 and EVAR-2), though these are the only studies to provide ITT data.
- c. Impact of long-term non-aneurysm complications not captured by model.
- d. Long-term costs not included in the EVAR-2 lifetime extrapolation.

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental (EVAR vs. OSR)			Conclusions	Uncertainty
			Cost (£) (95% CI)	Effect (QALYs) (95% CI)	ICER (£)		
Epstein et al. (2014) Markov model comparing EVAR with OSR based on 4 RCTs. UK. Partially applicable ^a Potentially serious limitations ^{b,c}	<u>Effects:</u> EVAR-1, ACE, DREAM and OVER studies. <u>Costs:</u> EVAR-1 (UK), ACE (France), DREAM (Netherlands) and OVER (US). Converted to 2009 UK pounds using purchasing power parities. <u>Utilities:</u> 3-month surgery morbidity (EVAR-1).	Model based on Epstein et al. (2008) EVAR-1 model. EVAR-1 8-year data used. Cardiovascular complications not modelled. 4 individual models, no synthesis of RCT data. Each analysis applies the relative survival (including convergence of curves), reintervention data and resource use from the relevant RCT. Lifetime horizon, 3.5% discount rate applied to all outcomes.	<u>EVAR-1</u> 4,014 (2,167; 5,942)	-0.02 (-0.19, 0.05)	EVAR dominated	'This economic analysis does not find that EVAR is cost-effective compared with open repair over the long term based on the EVAR-1, DREAM or ACE trials. EVAR does appear to be cost-effective over the long term based on the OVER trial.' EVAR ICER 0% likely to be <£20,000 in the base case EVAR-1, ACE and DREAM analyses, rising to 3% in a favourable scenario. EVAR ICER 91% likely to be <£20,000 in the base case OVER analysis, rising to 99% in a favourable scenario.	
			<u>ACE</u> 2,086 (1,526; 2,869)	-0.01 (-0.07, 0)	EVAR dominated		
			<u>DREAM</u> 3,181 (1,557; 4,986)	0 (-0.07, 0.05)	2,845,315		
			<u>OVER</u> -1,852 (-5,581; 2,097)	0.05 (-0.06, 0.13)	Dominant		

Key: CI, confidence interval; EVAR, endovascular aneurysm repair; ICER, incremental cost-effectiveness ratio; OSR, open surgical repair QALY, quality-adjusted life year; RCT, randomised controlled trial.

a. Only considers infrarenal aneurysms.

b. Each analysis informed by a single study; no synthesis of data.

c. EVAR-1 analysis is very similar to previous models (Epstein et al. 2008; Chambers et al. 2009; Brown et al. 2012); other analyses use non-UK resource use data.

Appendix J – Excluded studies

Clinical studies

No.	Study	Reason for exclusion
1	Belczak Sergio Quilici, Lanziotti Luiz, Botelho Yuri et al. (2014) Open and endovascular repair of juxtarenal abdominal aortic aneurysms: a systematic review. Clinics (Sao Paulo, and Brazil) 69, 641-6	Systematic review including studies that prospective and retrospective cohort studies. Individual studies were assessed to determine if they met inclusion criteria for this review question.
2	Bruen Kevin J, Feezor Robert J, Daniels et al. (2011) Endovascular chimney technique versus open repair of juxtarenal and suprarenal aneurysms. Journal of vascular surgery 53, 895-5	Authors collected data from patients who underwent EVAR and compared their results with retrospectively collected data from historical controls.
3	de Bruin , J L, Vervloet M G, Buimer M et al. (2013) Renal function 5 years after open and endovascular aortic aneurysm repair from a randomized trial. : John Wiley and Sons Ltd (Southern Gate, Chichester, West Sussex PO19 8SQ, United Kingdom)	Conference abstract.
4	Deery SE, Lancaster RT, Gubala AM et al. (2017) Early experience with fenestrated endovascular compared to open repair of complex abdominal aortic aneurysms in a high-volume open aortic center. Annals of vascular surgery	Retrospective cohort study design.
5	Di Xiao, Ye Wei, Liu Chang-Wei et al. (2013) Fenestrated endovascular repair for pararenal abdominal aortic aneurysms: a systematic review and meta-analysis. Annals of vascular surgery 27, 1190-200	Systematic review that assessed data from retrospective case series (single arm, non-comparative studies). Case series are not listed for inclusion in the review protocol.
6	Donas Konstantinos P, Torsello Giovanni, Pitoulis Georgios A et al. (2011) Surgical versus endovascular repair by iliac branch device of aneurysms involving the iliac bifurcation. Journal of vascular surgery 53, 1223-9	Retrospective cohort study design.
7	Donas Konstantinos P, Torsello Giovanni et al. (2012) Early outcomes for fenestrated and chimney endografts in the treatment of pararenal aortic pathologies are not significantly different: a systematic review with pooled data analysis. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 19, 723-8	Systematic review that assessed data from retrospective and prospective case series (single arm, non-comparative studies). Case series are not listed for inclusion in the review protocol.
8	Fanelli F (2017) Do the long-term outcomes of EVAR justify its generalised use? Cardiovascular and interventional radiology. Conference: cardiovascular	Conference abstract

No.	Study	Reason for exclusion
	and interventional radiological society of europe, and CIRSE 2017. Denmark 40(2 Supplement 1), S58-s59	
9	Gallitto E, Gargiulo M, Freyrie A et al. (2015) The endovascular treatment of juxta-renal abdominal aortic aneurysm using fenestrated endograft: early and mid-term results. The Journal of cardiovascular surgery ,	Case series
10	Gupta P K, Brahmabhatt R, Kempe K et al. (2017) Thirty-day outcomes after fenestrated endovascular repair are superior to open repair of abdominal aortic aneurysms involving visceral vessels. Journal of Vascular Surgery ,	Retrospective cohort study involving retrospective analysis of data from an American surgical registry.
11	Han Y, Zhang S, Zhang J et al. (2017) Outcomes of Endovascular Abdominal Aortic Aneurysm Repair in Octogenarians: Meta-analysis and Systemic Review. European Journal of Vascular and Endovascular Surgery.	Systematic review which included studies that employed multiple study designs. Individual studies were assessed to establish if they met criteria for inclusion in this NICE review.
12	Health Quality, and Ontario (2009) Fenestrated endovascular grafts for the repair of juxtarenal aortic aneurysms: an evidence-based analysis. Ontario health technology assessment series 9, 1-51	Systematic review including studies that employed various study designs. Individual studies were assessed to determine if they met inclusion criteria for this review question.
13	Katsargyris Athanasios, Oikonomou Kyriakos, Klonaris Chris et al. (2013) Comparison of outcomes with open, fenestrated, and chimney graft repair of juxtarenal aneurysms: are we ready for a paradigm shift? Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 20, 159-69	Systematic review that assessed data from retrospective and prospective case series (single arm, non-comparative studies). Case series are not listed for inclusion in the review protocol.
14	Lederle F A, Stroupe K T, Kyriakides T C, Ge L, and Freischlag J A (2016) Long-term Cost-effectiveness in the Veterans Affairs Open vs Endovascular Repair Study of Aortic Abdominal Aneurysm: a Randomized Clinical Trial.	Investigators performed secondary data analysis using data from a study (OVER trial) that is included in a systematic review identified as relevant to this review question. No additional relevant data was reported in this new publication.
15	Li Yue, Zhang Tao, Guo Wei et al. (2015) Endovascular chimney technique for juxtarenal abdominal aortic aneurysm: a systematic review using pooled analysis and meta-analysis. Annals of vascular surgery 29, 1141-50	Systematic review including studies that employed various study designs. Individual studies were assessed to determine if they met inclusion criteria for this review question.
16	Locham S S, Nejm B, Aridi H et al. (2017) Perioperative outcomes of patients undergoing fenestrated endovascular repair vs open repair of intact abdominal aortic aneurysms involving the visceral vessels: 10-year national study. Journal of the American	Conference abstract

No.	Study	Reason for exclusion
	College of Surgeons 225 (4 Supplement 1), S220	
17	Nordon I M, Hinchliffe R J, Holt P J et al. (2009) Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair--a systematic review. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 38, 35-41	Systematic review that assessed data from prospective and retrospective case series (single arm, non-comparative studies). Case series are not listed for inclusion in the review protocol.
18	Orr Nathan T, Davenport Daniel L, Minion David J, and Xenos Eleftherios S (2017) Comparison of perioperative outcomes in endovascular versus open repair for juxtarenal and pararenal aortic aneurysms: A propensity-matched analysis. Vascular 25, 339-345	Retrospective cohort study involving retrospective analysis of data from an American surgical registry.
19	Raux Maxime, Patel Virendra I, Cochennec Frederic et al. (2014) A propensity-matched comparison of outcomes for fenestrated endovascular aneurysm repair and open surgical repair of complex abdominal aortic aneurysms. Journal of vascular surgery 60, 858-4	Retrospective cohort study.
20	Sala-Almonacil VA, Zaragoza-Garcia JM, Ramirez-Montoya M et al. (2017) Fenestrated and chimney endovascular aneurysm repair versus open surgery for complex abdominal aortic aneurysms. The Journal of cardiovascular surgery 58(6), 801-813	Study employed a mixture of study designs: prospectively collected data of patients who underwent EVAR was compared against data from a historical cohort
21	Stather P W, Sidloff D, Dattani N et al. (2013) Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm.	Systematic review including studies that employed various study designs. Individual studies were assessed to determine if they met inclusion criteria for this review question.
22	Tsilimparis Nikolaos, Perez Sebastian, Dayama Anand et al. (2013) Endovascular repair with fenestrated-branched stent grafts improves 30-day outcomes for complex aortic aneurysms compared with open repair. Annals of vascular surgery 27, 267-73	Retrospective cohort study involving retrospective analysis of data from an American surgical registry.
23	Ultee Klaas H. J, Zettervall Sara L, Soden Peter A et al. (2017) Perioperative outcome of endovascular repair for complex abdominal aortic aneurysms. Journal of vascular surgery 65, 1567-1575	Retrospective cohort study involving retrospective analysis of data from an American surgical registry.
24	van Lammeren GW, Unlu C, Verschoor S et al. (2017) Results of open pararenal abdominal aortic aneurysm repair: single	Case series

No.	Study	Reason for exclusion
	centre series and pooled analysis of literature. <i>Vascular</i> 25(3), 234-241	
25	Yaoguo Yang, Zhong Chen, Lei Kou, and Yaowen Xiao (2017) Treatment of complex aortic aneurysms with fenestrated endografts and chimney stent repair: Systematic review and meta-analysis. <i>Vascular</i> 25, 92-100	Systematic review comparing 2 approaches of performing complex EVAR (fenestrated versus chimney endografts). The aim of this review question is to compare complex EVAR with open surgical repair or no intervention. Thus, comparisons between different types of complex EVAR are out of scope of this review question.

Economic studies

Study	Primary reason for exclusion
Selectively excluded	
Blackhouse et al. (2009). A cost-effectiveness model comparing endovascular repair to open surgical repair of abdominal aortic aneurysm in Canada. <i>Value in Health</i> , 12(2): 245-52.	Non-UK (Canada)
Bosch et al. (2002). Abdominal aortic aneurysms: cost-effectiveness of elective endovascular and open surgical repair. <i>Radiology</i> , 225(2): 337-44.	Non-UK (US)
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.	Interim results of Tarride et al. (2008)
Burgers et al. (2016). Cost-effectiveness of Elective Endovascular Aneurysm Repair Versus Open Surgical Repair of Abdominal Aortic Aneurysms. <i>Eur J Vasc Endovasc Surg</i> , 52: 29-40.	Non-UK (Netherlands)
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. <i>J Endovasc Ther</i> , 14: 763-76.	Non-UK (Republic of Ireland)
Lederle et al. (2016). Long-term cost-effectiveness in the veterans Affairs Open vs Endovascular Repair Study of aortic abdominal aneurysm: a randomised clinical trial. <i>JAMA Surg</i> , 151(12): 1139-1144.	Non-UK (US)
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. <i>Med Decis Mak</i> , 33(3): 437-50.	Non-UK (Canada)
Patel et al. (1999). The cost-effectiveness of endovascular repair versus open surgical repair of abdominal aortic aneurysms: a decision analysis model. <i>J Vasc Surg</i> , 29(6): 958-72.	Non-UK (US)
Prinssen et al. (2007). Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: Results of a randomized trial. <i>J Vasc Surg</i> , 46: 883-90.	Non-UK (Netherlands)
Sousa et al. (2014). Cost-effectiveness of the endovascular repair of abdominal aortic aneurysm in Portugal. <i>Angiol Cir Vasc</i> , 10(2): 41-8.	Non-UK (Portugal)
Sultan & Hynes (2011a). Clinical efficacy and cost per quality-adjusted life years of pararenal endovascular aortic aneurysm repair compared with open surgical repair. <i>J Endovasc Ther</i> , 18: 181-96.	Non-UK (Republic of Ireland)
Takayama (2017). A Cost-Utility Analysis of Endovascular Aneurysm Repair for Abdominal Aortic Aneurysm. <i>Ann Vasc Dis</i> , 10(3): 185-91.	Non-UK (Japan)

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. <i>J Vasc Surg</i> , 48: 779-87.	Non-UK (Canada)
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. <i>HTA</i> , 18(70).	Not a CUA
Badger et al. (2014). Endovascular treatment for ruptured abdominal aortic aneurysm (review). <i>Cochrane Database of Systematic Reviews</i> , 7.	Review article, no additional CUAs
Forbes et al. (2002). A cost-effectiveness analysis of standard versus endovascular abdominal aortic aneurysm repair. <i>J Can Chir</i> , 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. <i>The Lancet</i> , 365(9458): 2179-86.	Not a CUA
Hayes et al. (2010). Cost-effectiveness analysis of endovascular versus open surgical repair of acute abdominal aortic aneurysms based on worldwide experience. <i>J Endovasc Ther</i> , 17: 174-82.	Population (emergency repair)
Jonk et al. (2007). Cost-effectiveness of abdominal aortic aneurysm repair: a systematic review. <i>Int J Tech Assess Health Care</i> , 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. <i>J Endovasc Ther</i> , 14: 777-84.	Not a CUA
Kapma et al. (2014). Cost-effectiveness and cost-utility of endovascular versus open repair of ruptured abdominal aortic aneurysm in the Amsterdam Acute Aneurysm Trial. <i>Br J Surg</i> , 101(3): 208-15.	Population (emergency repair)
Lederle. (2009). Repair of nonruptured abdominal aortic aneurysm: a systematic review of randomized trials. <i>Vascular</i> , 17: S71.	Poster abstract
Lederle et al. (2012). Cost-effectiveness at two years in the VA open versus endovascular repair trial. <i>Eur J Vasc Endovasc Surg</i> , 44: 543-8.	Non-UK (US)
Luebke et al. (2014). Cost-effectiveness of endovascular versus open repair of acute complicated type B aortic dissections. <i>J Vasc Surg</i> , 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. <i>J Vasc Surg</i> , 61: 1331-9.	Review article, no additional CUAs
Medical Advisory Secretariat Ontario (2002). Endovascular repair of abdominal aortic aneurysm: an evidence-based analysis. <i>Ontario HTA Series</i> , 2(1).	Review article, no additional CUAs
Michaels et al. (2014). Long-term cost-effectiveness analysis of endovascular versus open repair for abdominal aortic aneurysms based on four randomized clinical trials. <i>Br J Surg</i> , 101(6): 632.	Commentary, no additional CUAs
Patel et al. (2000). The cost-effectiveness of repairing ruptured abdominal aortic aneurysms. <i>J Vasc Surg</i> , 32: 247-57.	Population (emergency repair)
Perras et al. (2009). Elective endovascular abdominal aortic aneurysm repair versus open surgery: a review of the clinical and cost-effectiveness.	Review article, no additional CUAs
Powell et al. (2015). Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial. <i>Eur Heart J</i> , 35: 2061-9.	Population (emergency repair)
Powell et al. (2017). Comparative clinical effectiveness and cost effectiveness of endovascular strategy v open repair for ruptured abdominal aortic aneurysm: three year results of the IMPROVE randomised trial. <i>BMJ</i> , 359.	Population (emergency repair)

Rollins et al. (2014). Mid-term cost-effectiveness analysis of open and endovascular repair for ruptured abdominal aortic aneurysm. <i>Br J Surg</i> , 101: 225-31.	Population (emergency repair)
Sala-Almonicil et al. (2017). Fenestrated and chimney endovascular aneurysm repair versus open surgery for complex abdominal aortic aneurysms. <i>J Cardiovasc Surg</i> , 58(6): 801-13.	Not a CUA.
Stroupe et al. (2012). Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm in the OVER trial. <i>J Vasc Surg</i> , 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. <i>BUMC Proceedings</i> , 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. <i>Vascular</i> , (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. <i>Vascular</i> , 17: S74.	Not found
Sultan & Hynes (2010a). Five-year experience with pararenal endovascular aortic repair (PEVAR) without fenestration: clinical efficacy, reintervention rates & cost-effectiveness. <i>J Vasc Surg</i> , 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. <i>J Vasc Surg</i> , 51(4): 1068-9.	Poster abstract
Sultan & Hynes (2010c)	Poster abstract
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. <i>Cardiovasc Interv Radiol</i> , 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. <i>JACC</i> , 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. <i>Br J Surg</i> , 102: 1229-39.	Review article, no additional CUAs
Tarride et al. (2011). Should endovascular repair be reimbursed for low risk abdominal aortic aneurysm patients? Evidence from Ontario, Canada. <i>Int J Vasc Med</i> , 2011.	Not a CUA
Taylor et al. (2012). EVAR is now cost effective and should replace open surgery for all suitable patients: con. <i>Cardiovasc Interv Radiol</i> , 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. <i>Vasc Endovasc Surg</i> , 50(3) 147-55.	Population (emergency repair)
Van Bochove et al. (2016). Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm. <i>J Vasc Surg</i> , 63(3): 827-38.	Review article, no additional CUAs
Weinkauff et al. (2017). Open versus endovascular aneurysm repair trial review. <i>Surgery</i> , 162(5): 974-78.	Duplicate of Lederle et al. (2016)
Wilt et al. (2006). Comparison of endovascular and open surgical repairs for abdominal aortic aneurysm. <i>Evid Rep Technol Assess</i> , 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 an unruptured AAA for whom open surgical repair is a suitable option?
Population	People undergoing elective surgery for unruptured abdominal aortic aneurysm Sub-grouped by: age, sex, comorbidities (including cardiovascular disease, renal disease, COPD, obesity) and ethnicity
Intervention(s)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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. Although EVAR has been shown to produce no long-term benefit over open surgical repair in people with unruptured infrarenal aneurysms, it is less clear whether this is the same in people with unruptured or ruptured juxtarenal, suprarenal type IV, and short-necked 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 unclear whether EVAR can improve long-term outcomes of people with complex aneurysm anatomies.
Current evidence base	A single non-randomised controlled trial assessing the efficacy of chimney- and fenestrated-EVAR in 90 people was identified from literature searches. The study reported no significant differences in 30-day mortality, complication, and reintervention rates between patients treated by complex EVAR and those who received open surgery. The results of this study, coupled with data from a new health economic model produced by NICE led the committee to conclude that complex EVAR yielded no benefit over open surgery in the short-term. The committee considered that longer-term evidence from large RCTs was needed to clarify the clinical utility of complex EVAR, and inform health economic modelling.
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.