National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[L] Evidence review for interventions to prevent re-bleeding

NICE guideline NG228

Methods, evidence and recommendations

November 2022

Final

National Institute for Health and Care Excellence

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Contents

1 Management of aneurysmal subarachnoid haemorrhage

Evidence review underpinning recommendations 1.2.4 and 1.2.6 and research recommendations in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of neurosurgical compared to endovascular interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?

1.2 Introduction

About half of the people who survive an aneurysmal subarachnoid haemorrhage will have a second bleed from the culprit aneurysm within the next few weeks, and the mortality from a second bleed exceeds 50%. The principal aim of treatment of aneurysmal subarachnoid haemorrhage is to secure the aneurysm and prevent re-bleeding.

The first treatment developed to prevent rebleeding was surgical clipping of the aneurysm. During clipping an opening is made in the person's skull at the appropriate location (craniotomy), the artery is identified and followed to the aneurysm, and a small metal clip is placed across the base of the aneurysm to seal it from the circulation.

More recently endovascular coiling was developed as a treatment for intracranial arterial aneurysms. During a coiling procedure, a catheter is passed through the circulation to the aneurysm. The aneurysm cavity is then packed with fine platinum coils, which disrupt the flow of blood inside the aneurysm and encourage occlusion of the aneurysm cavity with blood clot. Some coils have a coating that encourages thrombosis, and balloon- and stent-assisted coiling techniques have been developed to increase the number of coils that can be retained in the aneurysm cavity. Other novel endovascular techniques involve deployment of tubular mesh devices across the mouth of the aneurysm and woven endosaccular devices that expand within the aneurysm to fill and occlude the aneurysm cavity.

Aneurysms usually occur at arterial branch points, and the need to preserve all of the branches to avoid a stroke often determines the techniques that are most suitable for the person. The size and shape of the aneurysm, and the width of the opening between the aneurysm and artery (the aneurysm neck) also limit the available techniques for that individual.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm.
Interventions	• Neurosurgical clipping • Endovascular intervention such as: ○ coiling (e.g. bare platinum, coated platinum, balloon assisted, stent assisted)

	○ other endovascular device: bridge (e.g. intra-saccular occlusion devices), flow diversion (e.g. intrasaccular occlusion devices, flow diverters).
Comparisons	• To each other (across class and within class comparison)
Outcomes	CRITICAL: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) IMPORTANT • Subsequent subarachnoid haemorrhage • Return to daily activity • Length of hospital stay • Complications of intervention (any) • Need for retreatment
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

Twenty-six studies from 11 randomised controlled trials were included in the review,[8, 20, 21, 33, 36, 40, 70, 72, 73, 78, 85, 86, 90, 92-95, 112, 120-123, 125, 126, 132, 137] these are summarised in Table 2 below.

Evidence was found for neurosurgical clipping, endovascular coiling and flow diverter devices. The committee agreed it was appropriate to pool studies including bioactive coils for comparison between classes. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). No evidence was identified for this review for endovascular interventions of balloon or stent-assisted coiling, or intrasaccular devices i.e. WEB devices.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bairstow 2002[8]	**Neurosurgical Clipping** N=12 **Endovascular Coiling:** Gugliemi detachable platinum coil N=12 Follow-up: 12 months	Patients had subarachnoid haemorrhage due to intracranial aneurysms, suitable for either endovascular or neurosurgical treatment. (Copied from ISAT as specified by author) Australia	• Degree of disability • Length of stay	RCT
Coley 2012[33] Merged with: Molyneux 2012[93]	**Bare platinum coil** N=119 **Coated coil:** Cerecyte (polymer-loaded-Polyglycolic acid) coil N=114 Follow-up: 6 months	Patients aged between 18 and 70 years of age with a ruptured or unruptured intracranial aneurysm judged suitable for coil embolization; aneurysm <18 mm; aneurysm neck >2mm; ruptured aneurysm resulting in a good clinical grade, WFNS 1 or 2, or a UIA with an mRS score of zero to two; and within 30 days following aSAH. Mean age: 49.4 ±10.3 UK	• Mortality • Degree of disability • Subsequent aSAH • Complications • Length of stay	RCT Only ruptured aneurysm subset included for analysis.
Darsaut 2019[36]	**Neurosurgical Clipping** **N=55**	Patients aged ≥ 18; at least one intradural aneurysm, ruptured within the previous	• Degree of disability	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Endovascular Coiling: **N=48** Follow-up: 1 year	30 days, and considered appropriate for both surgical and endovascular management. Mean age: Clipping: 58.5 years; Coiling: 56.5 Canada & Spain		Interim analysis after 103 patients were recruited and analysed
Li 2012[78]	**Neurosurgical Clipping** N=92 **Endovascular Coiling:** no more information N=94 Follow-up: 1 year	Patients with acute aSAH, admitted to the Department of Neurosurgery Mean age: Coiling group 54.7±14.2, Clipping 53.7 ±13.8 China	• Mortality • Re-bleed • Adverse events	RCT
McDougall 2012[86] Merged with: Spetzler 2013[120] Spetzler 2015[122] Spetzler 2018[123] Spetzler 2020[121]	**Neurosurgical Clipping** N=239 **Endovascular Coiling:** no more information N=233 Follow-up: 10 years	Patients with Acute subarachnoid haemorrhage (SAH) Confirmed by CT scan or lumbar puncture Mean age: Clipping 53.1 ±12.8; Coiling 54.3 ±12 USA	• Modified Rankin score >2 • Re-bleeding • Re-intervention	RCT Results given for 1 year, 3 year,6 years and 10 years or hospitalisation/ discharge
McDougall 2014[85]	**Bare metal Coiling** N=119	The study population is 18–80 years of age with a single untreated, intracranial saccular aneurysm (4–	• Mortality • Re-bleeding • Re-intervention	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Matrix 2 coiling: a platinum coil modified with a polyglycolic/polylactic acid braid. N=109 Follow-up: 15 months	20mm;Hunt and Hess scale score, I–III; mRS score, 0–3), ruptured or unruptured, for which both polymer-modified coils and bare metal coils (BMCs) were treatment options and for which primary coiling treatment was planned to be completed during a single procedure. Mean age: Bare metal coiling 54.4 ±13.2 Matrix2: 55.7 ±11.6 USA		
Molyneux 2002[90] Merged with: Molyneux 2005[95] Molyneux 2009[94] Dorhout Mees 2012[40] Molyneux 2015[92]	**Neurosurgical Clipping** N=1070 **Endovascular Coiling:** detachable platinum coils N=1073 Follow-up: 10 years	Patients were eligible for the trial if:1. they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, with the preceding 28 days; 2. they had an intercranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; 3. they were in the clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; 4. they had an intracranial aneurysm that was judged	• Mortality • Modified Rankin Score • Re-bleeding	RCT Results given at 1 year, 5 years and 10 years

Study	Intervention and comparison	Population	Outcomes	Comments
		by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee. If a patient was not competent to give consent (because of his or her cognitive state), assent from relatives was obtained if the ethics committee regarded it as an acceptable alternative. Mean (range): Clipping 52 (18-84); Coiling 52 (18-87) United Kingdom		
Raymond 2017[112]	**Flow diverter device (EV3):** any flow diversion device, with or without coil embolization N= 39 **Best Standard Option (BSO)** N=39	All patients harbouring an aneurysm for which flow diversion was considered a promising treatment were eligible to participate. Mean age:	• Mortality • Modified Rankin Score • Adverse events	RCT BSO (best standard option) included observation, coil embolisation, parent vessel occlusion or clip placement. Standard treatment was selected

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 10 months	Flow diversion 59 ±12; BSO 57±11) Canada		according to clinical judgment at the time of enrolment but prior to randomization.
Taschner 2016[125] Merged with: Taschner 2018[126]	**Endovascular Coiling:** Coated platinum, HydroSoft/Hydroframe - hydrogel N=256 **Endovascular Coiling (Bare platinum)** N=257 Follow-up: 18 months	Patients presenting with a previously untreated cerebral aneurysm measuring 4–12 mm in maximal diameter (the maximum size for hydrogel coils at the outset of the trial) deemed to require endovascular coil embolization were eligible for inclusion if they were 18–75 years of age, were World Federation of Neurosurgeon (WFNS) grade 0–3, had anatomy such that endovascular occlusion was considered possible, had not previously been randomized into the trial, and the neuro-interventionalist was content to use either bare platinum or hydrogel coils. Mean age: Hydrogel: 52.9±12.6 (24–79); Bare Platinum: 54.1 ± 11.8 (21–82) France & Germany	• Mortality • Aneurysm reoccurrence • Adverse events • Re-intervention	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
Vanninen 1999[132] Merged with: Koivisto 2000[73] Koivisto 2002[72] Koivisto 2002[70]	**Neurosurgical Clipping** N=57 **Endovascular Coiling (Gugliemi detachable platinum coil)** N=52 Follow-up: 12 months	Patients with a ruptured aneurysm that was suitable for both surgical clipping and endovascular treatment Mean age range: Coiling: 49 (16 - 73); Clipping: 50 (14 - 75) Finland	• Mortality • Degree of disability	RCT
White 2008[137] Merged with: Brinjikji 2015[21] Brinjikji 2015[20]	**Endovascular Coiling (Coated platinum-hydrogel):** Hydrocoil N=249 **Endovascular Coiling (Bare platinum)** N=250 Follow-up: 18 months	Patients presenting with a previously untreated cerebral aneurysm measuring 2–25 mm in maximal diameter deemed to require endo-vascular treatment by the neurovascular team (typically comprising a neurosurgeon, neuro-interventionalist, plus or minus a neurologist) were eligible for inclusion if they were 18–75 years of age and not pregnant, were World Federation of Neurosurgeons (WFNS) grade 0–3,12 had anatomy such that endovascular occlusion was deemed possible, had not previously been randomized into the trial, and the neuro-interventionalist was content to use either bare platinum or hydrogel coils.	• Mortality rate • Degree of disability • Adverse events • Re-intervention	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
		Age range: <45: 158; 46-55: 143; >55: 198 United Kingdom		

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Neurosurgical clipping versus endovascular coiling

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Coiling	Risk difference with Clipping (95% CI)
Mortality (intraoperative or postoperative)	109 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.82 (0.17 to 19.53)	Moderate	
				19 per 1000	16 more per 1000 (from 16 fewer to 352 more)
Mortality at 3 months	109 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.91 (0.31 to 2.65)	Moderate	
				115 per 1000	10 fewer per 1000 (from 79 fewer to 190 more)
Mortality at 1 year	2413 (3 studies) 1 year	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.26 (0.98 to 1.61)	Moderate	
				106 per 1000	28 more per 1000 (from 2 fewer to 51 more)
Mortality at 5 years	2087 (1 study) 5 years	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.29 (1.02 to 1.63)	Moderate	
				107 per 1000	31 more per 1000 (from 2 more to 67 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Coiling	Risk difference with Clipping (95% CI)
Mortality at 10 years	1644 (1 study) 10 years	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.28 (1.04 to 1.56)	Moderate	
				167 per 1000	47 more per 1000 (from 7 more to 94 more)
Degree of disability (MRS ≤2) at 1 year scale 0-6; high score represents poor outcome	2118 (1 study)	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 0.9 (0.86 to 0.95)	Moderate	
				765 per 1000	77 fewer per 1000 (from 38 fewer to 107 fewer)
Degree of disability (MRS ≥2) at 1 year scale 0-6; high score represents poor outcome	76 (1 study) 1 year	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.23 (0.65 to 2.31)	Moderate	
				310 per 1000	71 more per 1000 (from 109 fewer to 406 more)
Degree of disability (MRS ≥3) at 1 year scale 0-6; high score represents poor outcome	2407 (2 studies) 1 year	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, imprecision, inconsistency	RR 1.46 (1.07 to 1.98)	Moderate	
				235 per 1000	96 more per 1000 (from 15 more to 205 more)
Degree of disability (MRS ≥3) at 3 years scale 0-6; high score represents poor outcome	295 (1 study) 3 years	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.51 (1 to 2.27)	Moderate	
				216 per 1000	110 more per 1000 (from 0 more to 274 more)
Degree of disability (MRS ≤2) at 5 years scale 0-6; high score represents poor outcome	2087 (1 study) 5 years	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 0.94 (0.87 to 1.01)	Moderate	
				599 per 1000	36 fewer per 1000 (from 78 fewer to 6 more)
Degree of disability (MRS ≥3) at 5 years scale 0-6; high score represents poor outcome	2087 (1 study) 5 years	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.14 (0.98 to 1.32)	Moderate	
				230 per 1000	32 more per 1000 (from 5 fewer to 74 more)
				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Coiling	Risk difference with Clipping (95% CI)
Degree of disability (MRS ≥3) at 6 years scale 0-6; high score represents poor outcome	365 (1 study) 6 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.15 (0.87 to 1.5)	339 per 1000	51 more per 1000 (from 44 fewer to 170 more)
Degree of disability (mRS ≥3) at 10 years scale 0-6; high score represents poor outcome	327 (1 study) 10 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.95 (0.75 to 1.21)	Moderate 339 per 1000	17 fewer per 1000 (from 85 fewer to 71 more)
Degree of disability (MRS ≤2) at 10years scale 0-6; high score represents poor outcome	1003 (1 study) 10 years	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.96 (0.9 to 1.02)	Moderate 819 per 1000	33 fewer per 1000 (from 82 fewer to 16 more)
Degree of disability (MRS ≥3) at 10years scale 0-6; high score represents poor outcome	1003 (1 study) 10 years	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.2 (0.93 to 1.53)	Moderate 181 per 1000	36 more per 1000 (from 13 fewer to 96 more)
Severe disability or vegetative state at (Glasgow outcome scale) 3 months	109 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.37 (0.41 to 4.58)	Moderate 77 per 1000	28 more per 1000 (from 45 fewer to 276 more)
Severe disability or vegetative state (Glasgow outcome scale) at 12 months	109 (1 study) 1 year	⊕⊕⊖⊖ LOW2 due to imprecision	RR 1.14 (0.32 to 4.02)	Moderate 77 per 1000	11 more per 1000 (from 52 fewer to 233 more)
Re-intervention at discharge	289 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.43 (0.14 to 1.33)	Moderate 64 per 1000	36 fewer per 1000 (from 55 fewer to 21 more)
Re-intervention at 3 months	109 (1 study) 3 months	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.55 (0.14 to 2.18)	Moderate 96 per 1000	43 fewer per 1000 (from 83 fewer to 113 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Coiling	Risk difference with Clipping (95% CI)
Re-intervention at 1 year	289 (1 study) 1 year	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 0.26 (0.11 to 0.62)	Moderate	
				147 per 1000	109 fewer per 1000 (from 56 fewer to 131 fewer)
New re-treatment at 3 years	281 (1 study) 3 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 0.07 (0 to 1.23)	Moderate	
				19 per 1000	18 fewer per 1000 (from 19 fewer to 4 more)
New re-treatment at 6 years	336 (1 study) 6 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RD 0 (-0.01 to 0.01)	Moderate	
				0 per 1000	0 fewer per 1000 (from 10 fewer to 10 more)
Re-bleeding during initial hospitalisation	289 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 0.59 (0.03 to 10.38)	Moderate	
				9 per 1000	4 fewer per 1000 (from 9 fewer to 77 more)
Re-bleeding at 1 year	2618 (3 studies) 1 year	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.82 (0.57 to 1.19)	Moderate	
				47 per 1000	8 fewer per 1000 (from 20 fewer to 9 more)
New re-bleeding at 3 years	281 (1 study) 3 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RD 0 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)
New re-bleeding at 6 years	336 (1 study) 6 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RD 0 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)
Re-bleeding at 1 to 10 years	1644 (1 study) 10 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.55 (0.27 to 1.12)	Moderate	
				26 per 1000	12 fewer per 1000 (from 19 fewer to 3 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Coiling	Risk difference with Clipping (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. When a single study reported zero events in both arms, imprecision was measured by sample size: No imprecision - sample size >350, serious imprecision – sample size >70 to ≤350, very serious imprecision - sample size ≤70. 3 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, subgroup analysis not possible; <2 studies per subgroup.					

Table 4: Clinical evidence summary: Coated coil versus bare platinum coil

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Bare platinum coil	Risk difference with Coated coil (95% CI)
Mortality (24 hours)	233 (1 study) 24 hours	⨁⨁⨀⨀ LOW2 due to imprecision	Peto OR 7.79 (0.48 to 125.35)	Moderate	
				0 per 1000	20 more per 1000 (from 10 fewer to 50 more)
Mortality 14 days	484 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.99 (0.29 to 3.38)	Moderate	
				21 per 1000	0 fewer per 1000 (from 15 fewer to 50 more)
Mortality 3 months	499 (1 study) 3 months	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.81 (0.61 to 5.32)	Moderate	
				20 per 1000	16 more per 1000 (from 8 fewer to 86 more)
Mortality (6-18 months)	905 (3 studies) 6-18 months	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.03 (0.46 to 2.29)	Moderate	
				9 per 1000	0 more per 1000 (from 5 fewer to 12 more)
				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Bare platinum coil	Risk difference with Coated coil (95% CI)
Degree of disability (MRS ≤2) at 3-18 months scale 0-6; high score represents poor outcome	720 (2 studies) 3-18 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 0.97 (0.92 to 1.03)	887 per 1000	9 fewer per 1000 (from 61 fewer to 43 more)
Degree of disability (MRS ≥3) at 6 months scale 0-6; high score represents poor outcome	221 (1 study) 6 months	⨁⨁⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 3.08 (0.33 to 29.18)	Moderate	
				28 per 1000	30 more per 1000 (from 17 fewer to 280 more)
Subsequent SAH at 3-18 months	918 (3 study) 3-18 months	⨁⨁⨁⨀ MODERATE 2 due to imprecision	RR 0.77 (0.52 to 1.15)	Moderate	
				112 per 1000	23 fewer per 1000 (from 50 fewer to 18 more)
Need for re-intervention at 3-18 months	1183 (3 studies) 3-18 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 0.64 (0.43 to 0.96)	Moderate	
				44 per 1000	16 fewer per 1000 (from 25 fewer to 2 fewer)
Procedure related adverse events	1216 (3 studies)	⨁⨀⨀⨀ VERY LOW1,2, 3 due to risk of bias, imprecision, inconsistency	RR 1.07 (0.73 to 1.58)	Moderate	
				341 per 1000	24 more per 1000 (from 92 fewer to 198 more)
Adverse events	484 (1 study)	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 5.55 (2.18 to 14.14)	Moderate	
				21 per 1000	96 more per 1000 (from 25 more to 276 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, unexplained by subgroup analysis

Table 5: Clinical evidence summary: Flow diverter versus coiling

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Coiling	Risk difference with Flow diverter (95% CI)
Mortality at ~9.8 months	78 (1 study) 9.8 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.67 (0.12 to 3.77)	Moderate	
				77 per 1000	25 fewer per 1000 (from 68 fewer to 213 more)
Degree of disability (MRS ≥3) at ~9.8 months scale 0-6; high score represents poor outcome	78 (1 study) 9.8 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.5 (0.27 to 8.49)	Moderate	
				51 per 1000	25 more per 1000 (from 37 fewer to 382 more)
Complications (stroke +any SAE complication) at ~9.8 months	78 (1 study)	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.11 (0.51 to 2.43)	Moderate	
				231 per 1000	25 more per 1000 (from 113 fewer to 330 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded by 1 because the majority of the evidence included an indirect population, intervention or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

See appendix F for full GRADE tables.

Table 6: Evidence not suitable for GRADE analysis: Coated coils compared to bare platinum coils

Outcome	Study (no. of participants)	Risk of bias	Comparison (bare platinum) results	Intervention (coated) results	*P* value
Length of stay	Coley 2012[33] (233)	Low	Median (IQR): 7 days (3-11)	Median (IQR): 6 days (3-11)	0.54

Table 11: Evidence not suitable for Grade analysis: Clipping compared to Endovascular coiling

Outcome	Study (no. of participants)	Risk of bias	Comparison (Neurosurgical clipping) results	Intervention (Endovascular coiling) results	*P* value
Modified Rankin score scale 0-6; high score represents poor outcome	Bairstow 2002 (24)	High	Median: 2	Median: 0.5	n/a
Length of stay	Bairstow 2002 (24)	High	Median: 22 days	Median: 11.5days	n/a

1.5 Economic evidence

1.5.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review[139]. This is summarised in the health economic evidence profile below (Table 7) and the health economic evidence table in Appendix H:.

1.5.2 Excluded studies

Two health economic studies relating to this review question were identified but were selectively excluded due to the availability of more applicable evidence[30,75]. This is listed in Appendix I:, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Summary of studies included in the economic evidence review

Table 7: Health economic evidence profile: Neurosurgical clipping vs endovascular coiling

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Wolstenholme 2008[139] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	Within-RCT analysis (Molyneux 2005[95]) • Population: UK subsample of ISAT trial. • Two comparators: 1. Neurosurgical clipping 2. Endovascular coiling • Follow-up: 2 years	2-1: saves £1,228	n/a	n/a	n/a

Abbreviations: RCT= randomised controlled trial
(a) Resource use data (2002-2004) and unit costs (2004) may not reflect current NHS context. Health outcomes not reported.
(b) Time horizon may not be sufficient to capture all cost differences. Within-trial analysis and so does not reflect full body of available evidence.

1.5.4 Unit costs

Unit costs have been provided below to aid consideration of cost effectiveness. The procedural cost of clipping and coiling are available in Table 8.

Table 8: UK costs of non-elective neurosurgical clipping and endovascular coiling

Description	Average cost (a)
Neurosurgical clipping	
Clipping of aneurysm of cerebral artery in people 19 years and older [NHS Reference cost codes: AA50A-C, AA51A-D, AA52A-D]	£13,940
Clipping of aneurysm of cerebral artery in people 18 years and under [NHS Reference cost codes: AA50D-F, AA51E-G, AA52E-G]	£14,168
Endovascular coiling	
Percutaneous Transluminal Embolisation of intracranial and extracranial aneurysms [NHS Reference cost codes: YA01Z, YA02A-B, YA03A-C]	£9,942

Source: NHS Reference Costs 2018/19[100]
(a) *Weighted by activity*

The cost of coils is not included in the procedural cost of coiling as these are high-cost tariff-excluded devices. The average costs of coils, per unit is summarised in Table 9.

Table 9: UK cost of coils

Description	Cost Range	Average Cost
Coils manufactured by Microvention	£395 - £685	£545
Coils manufactured by Johnson & Johnson	£390 - £800	£729
Coils manufactured by Medtronic Limited	£438 - £1,500	£617
Coils manufactured by Penumbra Europe GMBH	£395 - £1,000	£630
Coils manufactured by Stryker UK LTD	£400 - £620	£614

Source: NHS Supply Chain Catalogue July 2020 [99]*. All costs exclude VAT.*

There will be further additional equipment costs for stent or balloon-assisted coiling. Flow diverters can also be used in conjunction with coiling, and less commonly as a standalone procedure. The procedure cost for the use of flow diverters is the same procedure cost as that of endovascular coiling presented in Table 8. The unit cost of flow diverter devices is presented in Table 10.

Table 10: UK cost of flow diverters

Description	Cost
Flow diverter, manufactured by Medtronic Limited	£10,450
Flow diverter, manufactured by Johnson & Johnson	£12,500
Flow diverter, manufactured by Selamedical UK LTD	£9,950
Flow diverter, manufactured by Stryker UK LTD	£9,945

Source: NHS Supply Chain Catalogue 2020 [99] *, all costs exclude VAT.*

1.6 Evidence statements

1.6.1 Clinical evidence statements

Three outcomes from *2* studies were not suitable for inclusion in the GRADE summary tables.

One study reported that there was no statistically significant difference in median length of stay between people having coated coils compared to bare platinum coils. (n=233, low risk of bias).

A second study reported that there was an apparent benefit in median degree of disability (as measured by mRS) and median length of stay with endovascular coiling compared to neurosurgical clipping, although statistical significance was not reported. (n=24, high risk of bias)

1.6.2 Health economic evidence statements

- One comparative cost analysis found that neurosurgical clipping was more costly than endovascular coiling for treating ruptured aneurysms in people with subarachnoid haemorrhage (cost difference: £1,228). This analysis was assessed as partially applicable with potentially serious limitations.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee considered the critical outcomes for decision making to be mortality and degree of disability (modified Rankin scale, Glasgow outcome scale). Subsequent subarachnoid haemorrhage, length of hospital stay, complications of intervention (adverse events), and need for re-intervention were considered to be important outcomes.

No evidence was identified for health and social-related quality of life outcomes.

1.7.1.2 The quality of the evidence

The quality of evidence that was suitable for GRADE analysis ranged from very low to high. Most of the evidence was graded at low quality. This was mostly due to outcome imprecision and risk of bias, often due to high risk of selection and attrition bias. Outcomes which were not suitable for GRADE analysis were considered to be at low to high risk of bias.

The committee noted that relatively few 'poor grade' patients (typically characterised by the aneurysmal subarachnoid haemorrhage resulting in unconsciousness and/or needing ventilation for more than 48 hours) were enrolled in the studies reviewed; for example in ISAT 88% of patients were assessed as good grade WFNS 1 or 2. The committee agreed that this raised uncertainty about management of 'poor grade' patients.

The committee also noted that studies comparing neurosurgical clipping versus endovascular intervention will only include patients who were deemed suitable for either clipping or coiling. Some patients will be regarded as better suited to one intervention or another and will not have been recruited to comparative studies. The committee acknowledged that availability of neuro-radiologists, their experience in coiling techniques and the reducing experience amongst vascular neurosurgeons may also have affected judgements about suitability of techniques. This may have affected who was recruited to trials over time and was noted as a potential selection bias in the review of evidence.

The committee considered that the quality of the evidence was not sufficient on its own to determine the clinical effectiveness of endovascular coiling compared with neurosurgical clipping. The committee therefore made a recommendation balancing the low quality evidence available and group consensus.

The quality and quantity of evidence available for newer intervention techniques to prevent rebleeding were too low for the committee to make a clinical recommendation on these practices. Therefore, the committee agreed to make a research recommendation; assessing the clinical and cost effectiveness of novel endovascular interventions, for example, intra-saccular devices, extra-aneurysmal endolumenal devices (see Appendix J:).

The committee also noted further research was needed to analyse what is the outcome if intervention to prevent rebleeding in people who present with or rapidly develop severe neurological deficits as a consequence of (see Appendix K).

1.7.1.3 Benefits and harms

Neurosurgical clipping versus endovascular coiling

Six studies reported mortality at different time points with low-quality evidence showing a clinically significant increase in rate of mortality at 3 months with endovascular coiling but a larger body of evidence suggested clinically important harm associated with neurosurgical clipping at 1 year, 5 years and 10 years. The committee noted the variation in direction of effect at different time points could be random, particularly with the low quantity of data at some time-points and statistical imprecision of the data.

Multiple studies reported degree of disability (categorised as a modified Rankin Scale of 0-2 or 3-5) from discharge to 10 years. This was very low to moderate quality evidence and showed a slightly increased risk of more severe disability (mRS ≥3) with neurosurgical clipping. However, this difference in risk between intervention groups was only found to be clinically significant when reported at 3 years. Two studies reported severe disability using the Glasgow outcome scale at 3 months and 12 months and found no clinically important difference when comparing neurosurgical clipping with endovascular coiling.

Re-treatment of the target aneurysm was reported by 4 studies in two trials. The committee reviewed the low quality evidence and agreed that there was a clinically important benefit in one trial of neurosurgical clipping to reduce the need for re-treatment measured at 1 year follow-up. This difference was not clinically significant at 3 months in another trial. The committee noted that patients may consider the risk of re-treatment a significant factor, as this would result in another general anaesthetic and further hospital stay.

Three studies reported re-bleeding at different time points but there was no clinically important difference for re-bleeding between endovascular coiling and neurosurgical clipping.

Coated coil versus bare platinum coil

The committee discussed the evidence on bioactive (coated) coils versus bare platinum coils. The committee noted that endovascular coils can be modified with bioactive agents such as polyglycolic acid or Hydrogel, which are designed to improve aneurysm occlusion rates. The biological plausibility of such technologies relates to the volume of aneurysmal sac filling, increasing clot formation within the aneurysmal sac or clot integrity.

Mortality was reported by 5 studies at different time points. Although there was an apparent clinically significant benefit of bioactive coils for mortality measured at 3 months there was no clinically significant difference between the 2 interventions for mortality reported at 14 days and mortality at 6-18 months. There was a suggestion of a clinical harm of bioactive coils for mortality at 24 hours. When assessing the evidence for degree of disability (MRS ≤2) and (MRS ≥3) at 3-18 months the committee agreed that there was no evidence of a clinically important difference between interventions. The committee also agreed that there were no clinically important differences in subsequent subarachnoid haemorrhage, need for re-intervention, procedure-related adverse events, or adverse events when comparing coated coils with bare platinum coils. The committee did however consider that the coating on coils promotes thrombosis which is expected to help treat the aneurysm. The committee

considered that this may also allow for fewer coils to be used, with greater packing density compared to bare-platinum coils. The committee noted that the types of coil used in current practice varied, and that the extent of benefits and harms of coated coils is still unclear. The committee highlighted this as an area for further research and made a research recommendation for the use of novel endovascular interventions.

Flow diverter versus coiling

There was evidence available from one study on flow diverter devices versus the best standard alternative (included observation, coil embolization, parent vessel occlusion or clip placement). Mortality at 9.8 months showed a clinically significant reduction with flow diverter compared to an alternative. The same trial reported degree of disability (MRS ≥3) and complications at 9.8 months. There was no clinically important difference for either outcome between the 2 interventions. The committee highlighted that all evidence for this comparison was of very low quality and insufficient to make any positive recommendation. Given the uncertainty around the potential benefits and harms of flow diverting devices, this area too was included in a recommendation for further research.

Committee discussion

The committee discussed the evidence on neurosurgical clipping versus endovascular coiling, and on novel neurointerventional techniques. The committee agreed that suitability for interventional treatment depends on the patient's clinical condition and on the anatomy of the ruptured arterial aneurysm. The committee also agreed by consensus that if interventional treatment to secure the aneurysm is an option following aSAH, both neurosurgical clipping and endovascular coiling will reduce risk of mortality, rebleeding, and neurological deficit compared to medical management.

The committee acknowledged that interventional treatment may not be suitable for some people with aSAH, including those whose clinical condition is poor (for example patients with severe neurological deficit, impaired consciousness, or requirement for ventilatory support). The costs of non-interventional medical care and long-term nursing and rehabilitation costs were not adequately described but are likely to be considerable in this population. The committee therefore agreed that the treatment options for people with aSAH should include neurosurgical clipping, endovascular coiling and medical management. The committee emphasized that medical management should include monitoring to detect changes in the person's clinical condition and suitability for interventional treatment.

The committee accepted that there was little clinically significant difference in the benefits and harms between endovascular coiling and neurosurgical clipping, although a small amount of evidence suggested that endovascular coiling might be more beneficial for patient outcome and risk of rebleeding. The committee agreed that endovascular coiling is less invasive and consequently potentially safer than neurosurgical clipping. The committee concluded that endovascular coiling is the preferred interventional treatment to secure the ruptured aneurysm, but if endovascular coiling is not suitable neurosurgical clipping may be an alternative option.

On the basis of the evidence and their consensus the committee recommended that a neuroradiologist and neurosurgeon discuss the options for managing a person with a ruptured intracranial arterial aneurysm, taking account of the person's clinical condition, the characteristics of the aneurysm, and the amount and pattern of subarachnoid blood. The committee agreed that the neurosurgeon and neuroradiologist should agree and document a preferred treatment plan from the options of endovascular coiling, neurosurgical clipping and medical management (with monitoring to detect changes in clinical condition and suitability for interventional treatment). The committee highlighted that healthcare professionals should refer to NICE's interventional procedures guidance on coil embolisation of ruptured intracranial aneurysms and endovascular insertion of an intrasaccular wire-mesh blood-flow

disruption device for intracranial aneurysms for more guidance on endovascular procedures for ruptured intracranial aneurysms.

The committee were aware that SAH severity scores are used in clinical practice to guide decisions about suitability of people with aSAH for interventional treatment. The committee were concerned that the quantity and quality of evidence for the use of SAH severity scores does not support this practice and agreed treatment decisions should be based on a more holistic assessment. The committee therefore recommended that a SAH severity score should not be used in isolation to determine the suitability of any management option for a person with aSAH.

The committee also recommended that if interventional treatment to secure the aneurysm is an option, endovascular coiling should be offered, but neurosurgical clipping should be offered if endovascular coiling is not suitable. The committee made a consensus recommendation that the proposed treatment plan and any alternative treatment options should be discussed with the person, and their family or carers if appropriate, so that a final treatment plan can be agreed and documented.

The committee agreed a research recommendation to determine the best intervention for people with major neurological deficit caused by aneurysmal subarachnoid haemorrhage.

1.7.2 Cost effectiveness and resource use

One economic evaluation was identified for inclusion in this review comparing surgical clipping to endovascular coiling in people with aneurysmal subarachnoid haemorrhage. This comparative cost analysis was undertaken using resource use data prospectively gathered from the UK population in the International Subarachnoid Aneurysm Trial (ISAT) over 2 years. This analysis found that overall endovascular coiling is less costly than neurosurgical clipping, saving £1,228 per patient.

The study showed that when directly comparing the intervention costs, endovascular coiling was more expensive than surgical clipping. However, as the length of hospital stay was longer for people undergoing surgical clipping, largely due to a greater number of days in a rehabilitation clinic, overall surgical clipping became more costly for the first episode of care. Conversely, the follow up costs for endovascular coiling were found to be greater than those for neurosurgical clipping due to a greater number of check angiograms and repeat procedures in the coiling group. The committee noted that in the study follow up imaging in the coiling group was much more frequent than current practice, probably because the procedure was still relatively new, and clinicians wanted to confirm that the coils had successfully occluded the aneurysm. The committee also considered that the increased cost of follow up in the coiling group may be due to the higher mortality rate in the clipping group, although the effect of this is likely to be small.

The committee discussed that the 2 year time horizon of this analysis may be too short to reflect the true cost difference between neurosurgical clipping and noted that the 95% confidence intervals reported in the cost analysis indicate uncertainty in the estimate of cost saving (-£3,119 to £786).

It was noted that the study did not collect information on the use of long-term nursing and informal care. The committee considered that this cost is likely to be higher for neurosurgical clipping as there is a greater risk of having a mRS score greater than 3 and therefore a greater risk of severe disability requiring long term care.

The committee acknowledged that the relative costs of equipment and procedural time and follow up will have changed significantly since these data were published and are therefore unlikely to reflect current NHS activity.

The NHS reference costs associated with neurosurgical clipping (£13,940 in adults, £14,168 in children) and endovascular coiling (£9,942) were presented. Of note, the HRG code for neurosurgical clipping is a code which includes a number of procedures of which one is clipping, therefore the cost presented is an average of these various procedures. The committee noted that between four and eight coils may be required for a typical coiling procedure and the unit cost of coils is between £545 and £729 per unit (mean cost £627). The total cost of coiling is estimated to be between £12,450 (using 4 coils) and £14,957 (using 8 coils). The committee noted that the larger the aneurysm the greater number of coils required. The committee also highlighted that operators commonly use multiple coil systems to treat an aneurysm (for example, a combination of Stryker, Medtronic, and Microvention coils may be used for one single procedure). This is primarily due to different coil properties but can also be because of stock availability and the compatibility with other equipment. In addition, they noted there may be variation between centres and operators in terms of coils utilised which may impact costs. Based on the procedure and device costs presented above neurosurgical clipping and endovascular coiling appear to be similar in cost, however differences in resource use such as longer length of stay observed for neurosurgical clipping and the greater follow up and/or re-intervention required for coiling are not captured.

The committee also considered the difference in quality of life between the 2 interventions. It considered that quality of life was likely to be lower in the neurosurgical clipping group due to the greater degree of disability suggested in the clinical evidence. The committee also acknowledged that there is likely to be a decrease in quality of life associated with re-intervention, even if only temporarily. The clinical evidence indicates re-intervention is more likely with endovascular coiling, although this is highly uncertain. However, as mortality and the degree of disability were significantly higher in the neurosurgical clipping group, the committee considered that QALYs would likely be higher for endovascular coiling. The committee agreed that when considering all the costs of coiling (procedure, devices, greater follow-up and/or re-intervention required), coiling is likely to be more expensive than clipping however a greater QALY gain is expected and therefore overall coiling is likely to be more cost effective than clipping.

No published economic evaluations comparing different endovascular techniques or surgical techniques were identified for inclusion in this review. The committee discussed that coated coils are more costly than platinum coils, but as the clinical benefit of coated coils was uncertain, it agreed not to make a recommendation about the type of coil that should be used. It was noted that stent-assisted or balloon-assisted coiling would incur additional costs, and the use of these assist devices varies significantly between aneurysms. The unit costs of flow diverters were presented, these range between £9,945 and £12,500. This cost is in addition to the procedure cost (£9,942). The committee also noted the use of intrasaccular devices such as the Woven EndoBridge (WEB) device is an alternative to clipping, coiling, and flow diverters and this would also incur additional significant costs.

Overall, there was insufficient evidence to make a recommendation specifically around the use of flow diverters, WEB devices, stent or balloon-assisted coiling, or the use of coated coils. The committee did make a research recommendation around the clinical and cost effectiveness of these novel endovascular techniques.

The committee do not expect there to be a significant resource impact as a result of the recommendations, as endovascular coiling of ruptured aneurysms is currently common practice.

1.7.3 Other factors the committee took into account

The committee noted that a neurosurgical team is the usual first point of referral for patients with confirmed or suspected aneurysmal subarachnoid haemorrhage. Informal discussion between a neuro-radiologist and a neurosurgeon about treatment strategy forms part of current practice and the requirement to document this discussion is unlikely to add a

significant cost burden. The treatment options would be discussed with the patient and documented in the treatment plan. The committee recognised this is good practice and recommended that a neuroradiologist and a neurosurgeon should discuss the options for managing the culprit aneurysm, and document a proposed treatment plan from endovascular coiling, neurosurgical clipping or medical management and follow-up monitoring. The committee recognised that neuroanaesthetists and neurointensivists are key members of the multidisciplinary team caring for patients with aSAH and may participate in the clinical decision making.

The committee noted that if the patient does not have capacity to participate in decision making family members or carers would be approached. The committee made a consensus recommendation to discuss the proposed management treatment plan and any alternative options with the person, and their family or carers if appropriate, then agree and document a final management treatment plan. In some circumstances the neurosurgical team may need to act in the best interest of the patient and make the decision on treatment if family or carers are not available to prevent delays.

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Appendices

Appendix A: Review protocols

Table 11: Review protocol: Management of subarachnoid haemorrhage

ID	Field	Content
0.	PROSPERO registration number	CRD42019132413
1.	Review title	What is the clinical and cost effectiveness of neurosurgical compared to endovascular interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?
2.	Review question	What is the clinical and cost effectiveness of neurosurgical compared to endovascular interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?
3.	Objective	To determine which intervention to prevent rebleed following subarachnoid haemorrhage is the most clinically and cost-effective.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language only The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
7.	Intervention/Exposure/Test	• Neurosurgical clipping • Endovascular intervention such as: ○ coiling (e.g. bare platinum, coated platinum, balloon assisted, stent assisted)

ID	Field	Content
		○ other endovascular device: bridge (e.g. WEB, intra-saccular occlusion devices), flow diversion (e.g. pipeline device).
8.	Comparator/Reference standard/Confounding factors	Comparators: • To each other (across class and within class comparison)
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to daily activity • Length of hospital stay • Complications of intervention (any) • Need for retreatment Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
14.	Data extraction (selection and coding)	• EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. • EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

ID	Field	Content	
		• Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • Subgroups will be investigated separately if meta-analysed results show heterogeneity.	
17.	Analysis of sub-groups	Subgroups (if heterogeneity): • Grade ○ Good grade ○ Bad grade • Location of aneurysm (as reported by study) • Characteristic of aneurysm (as reported by study) ○ Size e.g. large, small ○ Neck width e.g. normal, wide	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date	3 February 2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SAH@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be		

ID	Field	Content	
		documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage, aneurysm, clipping, coiling	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

Table 12: Health economic review protocol

Review question	All questions where health economic evidence applicable
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[98] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will decide based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

This literature search strategy was used for the following review;

- What is the clinical and cost effectiveness of neurosurgical compared to endovascular interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[98]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 26 June 2020	Exclusions Randomised controlled trials Systematic review studies

Database	Dates searched	Search filter used
		Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	limit 27 to English language
29.	Embolization, Therapeutic/
30.	(coil* or hydrocoil* or Guglielmi* or GDC*).ti,ab.
31.	endovascular procedures/
32.	(((neuroendovascular or endovascular or intrasaccular or intra-saccular) adj3 (treatment* or intervention* or procedure* or therap* or device* or surgery)) or EVT).ti,ab.
33.	blood vessel prosthesis implantation/
34.	vascular surgical procedures/
35.	blood vessel prosthesis/

36.	emboli?at*.ti,ab.
37.	(clip* or microsurg*).ti,ab.
38.	Neurosurgery/
39.	neurosurgical procedures/
40.	(web or woven endobridge* or bridg*).ti,ab.
41.	((flow adj (diver* or disrupt*)) or FRED or pipeline).ti,ab.
42.	or/29-41
43.	28 and 42
44.	Epidemiologic studies/
45.	Observational study/
46.	exp Cohort studies/
47.	(cohort adj (study or studies or analys* or data)).ti,ab.
48.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
49.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
50.	Controlled Before-After Studies/
51.	Historically Controlled Study/
52.	Interrupted Time Series Analysis/
53.	(before adj2 after adj2 (study or studies or data)).ti,ab.
54.	exp case control study/
55.	case control*.ti,ab.
56.	Cross-sectional studies/
57.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	or/44-57
59.	Meta-Analysis/
60.	exp Meta-Analysis as Topic/
61.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
62.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
63.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
64.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
65.	(search* adj4 literature).ab.
66.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
67.	cochrane.jw.
68.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
69.	or/59-68
70.	randomized controlled trial.pt.
71.	controlled clinical trial.pt.
72.	randomi#ed.ti,ab.
73.	placebo.ab.
74.	randomly.ti,ab.
75.	Clinical Trials as topic.sh.
76.	trial.ti.
77.	or/70-76

78.	43 and (58 or 69 or 77)

Embase (Ovid) search terms

1.	*subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
25.	23 not 24
26.	limit 25 to English language
27.	exp artificial embolization/
28.	(coil* or hydrocoil* or Guglielmi* or GDC*).ti,ab.
29.	exp endovascular surgery/
30.	(((neuroendovascular or endovascular or intrasaccular or intra-saccular) adj3 (treatment* or intervention* or procedure* or therap* or device* or surgery)) or EVT).ti,ab.
31.	blood vessel transplantation/
32.	vascular surgery/
33.	exp aneurysm surgery/
34.	blood vessel prosthesis/
35.	emboli?at*.ti,ab.
36.	(clip* or microsurg*).ti,ab.
37.	neurosurgery/
38.	(web or woven endobridge* or bridg*).ti,ab.
39.	((flow adj (diver* or disrupt*)) or FRED or pipeline).ti,ab.

40.	or/27-39
41.	26 and 40
42.	Clinical study/
43.	Observational study/
44.	family study/
45.	longitudinal study/
46.	retrospective study/
47.	prospective study/
48.	cohort analysis/
49.	follow-up/
50.	cohort*.ti,ab.
51.	49 and 50
52.	(cohort adj (study or studies or analys* or data)).ti,ab.
53.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
54.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
55.	(before adj2 after adj2 (study or studies or data)).ti,ab.
56.	exp case control study/
57.	case control*.ti,ab.
58.	cross-sectional study/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/42-48,51-59
61.	random*.ti,ab.
62.	factorial*.ti,ab.
63.	(crossover* or cross over*).ti,ab.
64.	((doubl* or singl*) adj blind*).ti,ab.
65.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
66.	crossover procedure/
67.	single blind procedure/
68.	randomized controlled trial/
69.	double blind procedure/
70.	or/61-69
71.	systematic review/
72.	meta-analysis/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/71-80

82.	41 and (60 or 70 or 81)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#3.	(SAH or aSAH):ti,ab
#4.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Embolization, Therapeutic] explode all trees
#8.	(coil* or hydrocoil* or Guglielmi* or GDC*):ti,ab
#9.	MeSH descriptor: [Endovascular Procedures] explode all trees
#10.	(((neuroendovascular or endovascular or intrasaccular or intra-saccular) near/3 (treatment* or intervention* or procedure* or therap* or device* or surgery)) or EVT):ti,ab
#11.	MeSH descriptor: [Blood Vessel Prosthesis Implantation] explode all trees
#12.	MeSH descriptor: [Vascular Surgical Procedures] explode all trees
#13.	MeSH descriptor: [Blood Vessel Prosthesis] explode all trees
#14.	emboli?at*:ti,ab
#15.	(clip* or microsurg*):ti,ab
#16.	MeSH descriptor: [Neurosurgery] explode all trees
#17.	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#18.	(web or woven endobridge* or bridg*):ti,ab
#19.	((flow next (diver* or disrupt*)) or FRED or pipeline):ti,ab
#20.	(or #7-#19)
#21.	#6 and #20

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to subarachnoid haemorrhage population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003 – 23 June 2020	Exclusions Health economics studies
Embase	2003 – 23 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 23 June 2020 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.

42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

Embase (Ovid) search terms

1.	subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.

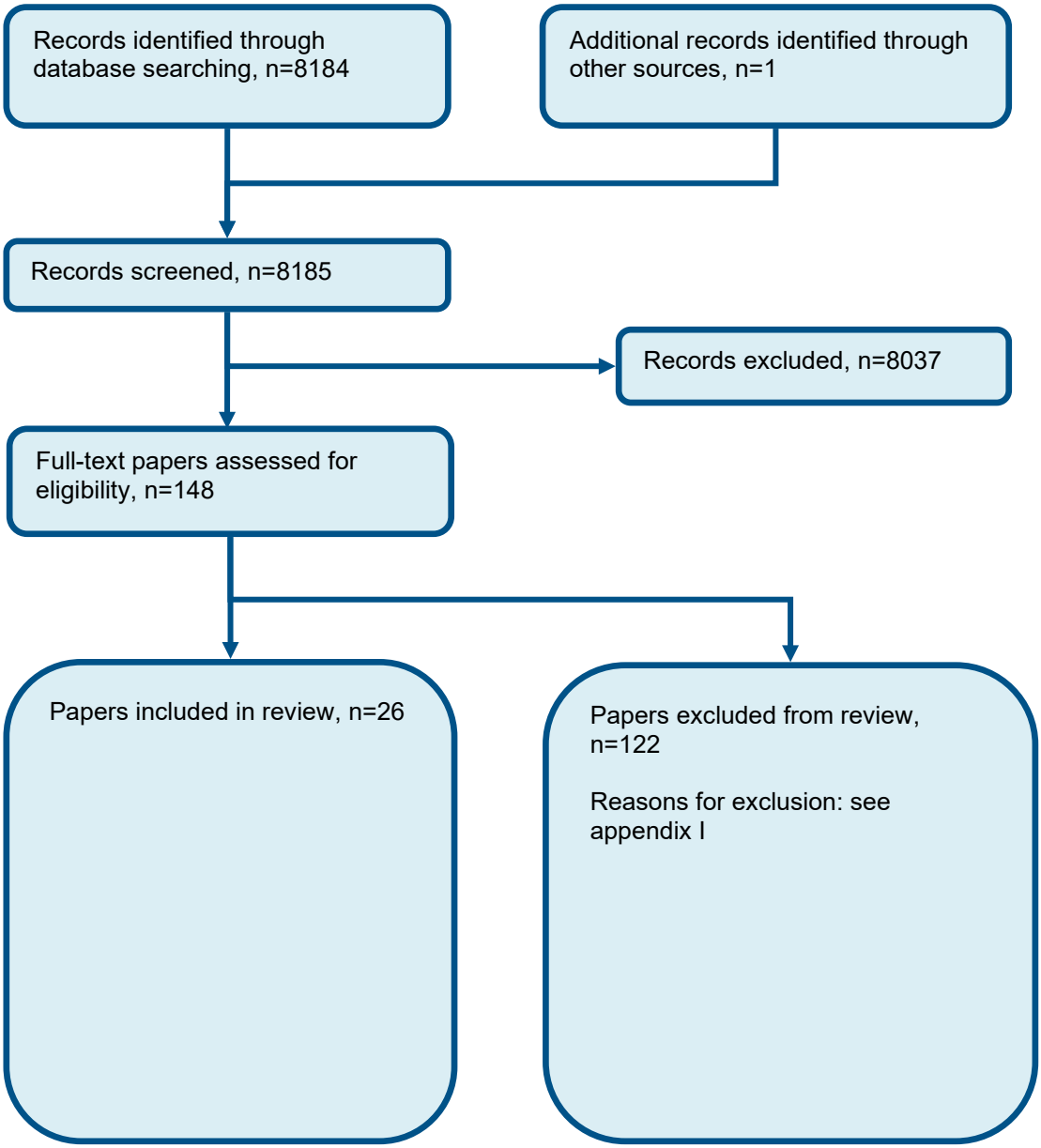
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Subarachnoid Hemorrhage EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#3.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)))
#4.	((SAH or aSAH))
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Aneurysm EXPLODE ALL TREES
#7.	((aneurysm* or hematoma* or haematoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Intracranial Aneurysm EXPLODE ALL TREES
#10.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (aneurysm* or hematoma* or haematoma*)))
#11.	#9 OR #10
#12.	MeSH DESCRIPTOR Aneurysm, ruptured
#13.	(((ruptur* or weak* or brain or trauma*) adj3 (aneurysm* or hematoma* or haematoma*)))
#14.	#12 OR #13
#15.	(#5 or #8 or #11 or #14)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of interventions to prevent rebleeding



Appendix D: Clinical evidence tables

Study	Bairstow 2002[8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=24)
Countries and setting	Conducted in Australia; Setting: Royal Perth Hospital
Line of therapy	1st line
Duration of study	Intervention time: not specified
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had subarachnoid haemorrhage due to intracranial aneurysms, suitable for either endovascular or neurosurgical treatment. (copied from ISAT as specified by author)
Exclusion criteria	not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Other: not specified. Gender (M:F): not specified. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear 2. Characteristic of aneurysm: Not stated / Unclear 3. Location of aeurysm: Not stated / Unclear
Indirectness of population	Serious indirectness
Interventions	(n=12) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. Neurosurgical clipping. Duration long term. Concurrent medication/care: NA. Indirectness: No indirectness (n=12) Intervention 2: Endovascular intervention - Coiling. Endovascular coiling. Duration long term. Concurrent medication/care: NA. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROSURGICAL CLIPPING versus ENDOVASCULAR COILING Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Modified Rankin score at 12 month post discharge ; Median, Comments: Neurosurgical clipping - 2 Endovascular coiling - 0.5); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: treatment not possible; Group 2 Number missing: 0 Protocol outcome 2: Length of stay - Actual outcome: Total post procedure length of stay at postoperatively to discharge; Median days, Comments: Neurosurgical clipping - 22 days Endovascular coiling - 11.5 days); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: treatment not possible; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Complications of intervention ; Need for re-intervention

Study	Mcdougall 2014[85]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=626)
Countries and setting	Conducted in USA; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention time + follow up: 455 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The study population included subjects 18–80 years of age with a single untreated, intracranial saccular aneurysm (4–20mm;Hunt and Hess scale score, I–III; mRS score, 0–3), ruptured or unruptured, for which both polymer-modified coils and bare metal coils (BMCs) were treatment options and for which primary coiling treatment was planned to be completed during a single procedure.
Exclusion criteria	not specified
Recruitment/selection of patients	Twenty-six of the 43 investigational sites were located in the United States. Due to the wide variability in the rate of patient recruitment among centres, large-volume centres were closed to enrolment after 60 patients were recruited to avoid having the recruitment dominated by a small number of large-volume centres.
Age, gender and ethnicity	Age - Mean (SD): BMC 54.4 (13.2); Matrix2 55.7(11.6). Gender (M:F): BMC 104/211 Matrix2 82/229. Ethnicity: not specified
Further population details	1. aSAH grade: Not stated / Unclear 2. Characteristic of aneurysm: Not stated / Unclear 3. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=109) Intervention 1: Endovascular intervention – Coiling (polylactic acid biopolymer-modified coils). Patients were randomized in blocks of 2 and 4, stratified by target aneurysm rupture status and hospital site, to ensure equal distribution of those elements between the trial arms. Patients

	randomized to Matrix2 of Matrix2 were to be treated with 75%total length of coils composed. Duration intervention time. Concurrent medication/care: n/a. Indirectness: No indirectness; Indirectness comment: Matrix coil (n=119) Intervention 2: Endovascular intervention - Coiling. Patients were randomized in blocks of 2 and 4, stratified by target aneurysm rupture status and hospital site, to ensure equal distribution of those elements between the trial arms. patients randomized to BMC group were treated with BMC coils. Duration intervention time. Concurrent medication/care: n/a. Indirectness: No indirectness; Indirectness comment: BMC Comments: Guglielmi detachable coil
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING versus COILING Protocol outcome 1: Mortality - Actual outcome: mortality at 455 days after the surgery; Group 1: 1/109, Group 2: 0/119 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Subsequent subarachnoid haemorrhage - Actual outcome: bleeding or rebleeding at 455 days after the surgery; Group 1: 1/109, Group 2: 2/119 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Need for re-intervention - Actual outcome: need for re-intervention at 455 days after the surgery; Group 1: 0/109, Group 2: 1/119 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Return to daily activity (e.g. work) ; Complications of intervention ; Length of stay

Study (subsidiary papers)	Coley 2012[33] (Molyneux 2012[93])
Study type	RCT
Number of studies (number of participants)	(n=249)
Countries and setting	Conducted in United Kingdom; Setting: UK hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ages between 18 and 70 years of age with a ruptured or unruptured intracranial aneurysm judged suitable for coil embolization; aneurysm <18 mm (the maximum size for Cerecyte coils at the outset of the trial); aneurysm neck >2mm; ruptured aneurysm resulting in a good clinical grade, WFNS 1 or 2, or a UIA with an mRS core of zero to two; capable of providing their own consent; and within 30 days following an SAH.
Exclusion criteria	A lack of consent or they could not provide their own consent; they were in a poor clinical grade, WFNS 3–5 following SAH, or mRS 3–5 with a UIA; they were unwilling or unlikely to return for follow-up angiography; the aneurysm size was >18 mm; and 5) there was a planned use of a stent during treatment.
Recruitment/selection of patients	patients planning to undergo endovascular coiling recruited
Age, gender and ethnicity	Age - Mean (SD): 49.4 (10.3). Gender (M:F): 88/145. Ethnicity:
Further population details	1. aSAH grade: Good grade 2. Characteristic of aneurysm: (aneurysm neck >2mm). 3. Location of aneurysm:
Indirectness of population	No indirectness
Interventions	(n=119) Intervention 1: Endovascular intervention - Coiling (bare platinum). Bare platinum coils. Duration n/a. Concurrent medication/care: Not reported. Indirectness: No indirectness

	(n=114) Intervention 2: Endovascular intervention - Coiling (coated platinum). Cerecyte coil (polymer-loaded- Polyglycolic acid or containing additional, polylactic-coglycolic acid fibre). Duration n/a. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Micrus Endovascular Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING (BARE PLATINUM) versus COILING (COATED PLATINUM)

Protocol outcome 1: Mortality
- Actual outcome: Death at 6 months (or first follow-up); Group 1: 1/112, Group 2: 3/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: mRS 0 at 6 months (or first follow-up); Group 1: 62/112, Group 2: 64/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5
- Actual outcome: mRS 1 at 6 months (or first follow-up); Group 1: 43/112, Group 2: 31/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5
- Actual outcome: mRS 2 at 6 months (or first follow-up); Group 1: 5/112, Group 2: 8/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5
- Actual outcome: mRS 3 at 6 months (or first follow-up); Group 1: 0/112, Group 2: 2/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5
- Actual outcome: mRS 4 at 6 months (or first follow-up); Group 1: 1/112, Group 2: 1/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5
- Actual outcome: mRS 5 at 6 months (or first follow-up); Group 1: 0/112, Group 2: 0/109
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5

Protocol outcome 3: Subsequent subarachnoid hemorrhage

- Actual outcome: Aneurysm rupture at 24 hours; Group 1: 5/119, Group 2: 8/114 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Complications of intervention - Actual outcome: Procedural adverse events at 24 hours; Group 1: 13/119, Group 2: 21/114 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Need for retreatment - Actual outcome: Retreatment (pre follow-up) at 6 months (median); Number of patients needing retreatment, Comments: Cerecyte Coils - 17 out of 22 Bare Platinum - 8 out of 230 p value 0.064); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5 - Actual outcome: Retreatment (post follow-up angiogram) at first follow up; Number of patients needing retreatment after first follow up angiogram, Comments: Cerecyte coil - 10 out of 215 needing retreatment Bare Platinum - 4 out of 218 needing retreatment); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 5 Protocol outcome 6: Length of stay - Actual outcome: Length of stay at 24 hours; p: 0.54, Comments: Median (IQR) Cerecyte: 6 (3–11); Bare platinum: 7 (3–11)); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health and social quality of life; Return to daily activity (e.g. work)

Study	Raymond 2017[112]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Canada; Setting: There were 3 Canadian centres that participated in the study: Notre Dame Hospital of the Centre Hospitalier de l'Université de Montréal, the Ottawa Hospital, and the Mackenzie Health Sciences Centre of the University of Alberta Hospital.
Line of therapy	Not applicable
Duration of study	Intervention time + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	All patients harbouring an aneurysm for which flow diversion was considered a promising treatment were eligible to participate.
Exclusion criteria	1) severe allergy, intolerance, or bleeding disorder that precluded dual antiplatelet regimens; 2) absolute contraindication to endovascular treatment or anaesthesia; or 3) inability to provide consent. All patients signed an informed consent form.
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): Flow diversion 59 (12); BSO 57(11). Gender (M:F): Flow diversion 7/32; BSO 5/34. Ethnicity: not specified
Further population details	1. aSAH grade: Not stated / Unclear 2. Characteristic of aneurysm: Not stated / Unclear 3. Location of aneurysm: (Proximal carotid BSO 28 Flow Diversion 26; Other anterior BSO 4 Flow 6; Posterior circulation BSO 7 Flow 7).
Indirectness of population	Serious indirectness: BSO (best standard option) included observation, coil embolization, parent vessel occlusion or clip placement. Standard treatment was selected according to clinical judgment at the time of enrolment but prior to randomization.
Interventions	(n=39) Intervention 1: Endovascular intervention - Flow diverter (e.g. pipeline device – EV3) . Standard local procedures were followed. Any arterial (not intra-aneurysmal) flow-diverting devices

	were permitted. Duration intervention time. Concurrent medication/care: not specified. Indirectness: No indirectness (n=39) Intervention 2: Endovascular intervention - Coiling. Standard treatment was selected according to clinical judgment at the time of enrolment but prior to randomization. Duration intervention time. Concurrent medication/care: not specified. Indirectness: Serious indirectness; Indirectness comment: 25 patients received coiling; 10 PVO; 10 observation
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLOW DIVERTER (E.G. PIPELINE DEVICE) versus COILING Protocol outcome 1: Mortality - Actual outcome: mortality at mean follow up 9.8 (3.9) months; Group 1: 2/39, Group 2: 3/39 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: modified Rankin scale 3-5 at mean follow up 9.8 (3.9) months; Group 1: 3/39, Group 2: 2/39 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Complications of intervention - Actual outcome: stroke +any SAE or complication at mean follow up 9.8 (3.9) months; Group 1: 10/39, Group 2: 9/39 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health and social quality of life; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Need for re-intervention ; Length of stay

Study (subsidiary papers)	White 2008[137] (Brinjikji 2015[20], Brinjikji 2015[21])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=499)
Countries and setting	Conducted in United Kingdom; Setting: Department of Neuroradiology (P.M.W., R.J.S.), Western General Hospital, Edinburgh, UK; University of Edinburgh Neurosciences Trials Unit (P.M .W., S.C.L.), Edinburgh, UK; Walton Centre for Neurosurgery and Neurology (H.N.), Liverpool, UK; Leeds General Infirmary (T.G.), Leeds, UK; and Department of Neuroradiology (A.G.), Newcastle General Hospital, Newcastle, UK
Line of therapy	1st line
Duration of study	Intervention + follow up: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with a previously untreated cerebral aneurysm measuring 2–25 mm in maximal diameter deemed to require endovascular treatment by the neurovascular team (typically comprising a neurosurgeon, neuro-interventionalist, plus or minus a neurologist) were eligible for inclusion if they were 18–75 years of age and not pregnant, were World Federation of Neurosurgeons (WFNS) grade 0–3,12 had anatomy such that endovascular occlusion was deemed possible, had not previously been randomized into the trial, and the neuro-interventionalist was content to use either bare platinum or hydrogel coils.
Exclusion criteria	Patients were excluded if they had ☐1 aneurysm requiring treatment, unless the treatment was to be staged with only 1 aneurysm being treated at 1 sitting. All patients gave written informed consent, or if they could not consent for themselves, appropriate written assent was sought from their next of kin.
Recruitment/selection of patients	Patients presenting with a previously untreated cerebral aneurysm measuring
Age, gender and ethnicity	Age - Range: <45: 158; 46-55: 143; >55: 198. Gender (M:F): 149/350. Ethnicity:

Further population details	1. aSAH grade: Not stated / Unclear (WFNS 0 - 3). 2. Characteristic of aneurysm: Not stated / Unclear (Target Aneurysm size: 2-4.9mm - 83; 5-9.9mm - 288; 10 - 24.9mm - 128. Aneurysm shape: irregular (multilobulated) 153; not multilobulated 246). 3. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=249) Intervention 1: Endovascular intervention - Coiling (coated platinum- Hydrogel (The HydroCoil embolic system – MicroVention, Aliso Viejo, Calif)). Standard local procedures for the coiling of aneurysms were followed. The aim was to coil to angiographic occlusion whenever possible. Patient safety was the paramount consideration at all times. In the HydroCoil arm, for aneurysms 2–9.9 mm, it was recommended that HydroCoil constitute at least 50% of the total coil length deployed or□50% of the aneurysm packing achieved and that the total aneurysm packing should exceed 50%. For aneurysms ≥ 10 mm, it was recommended that HydroCoil should constitute at least two thirds of the total coil length deployed, or at least 70% of the aneurysm packing achieved, and the total aneurysm packing should exceed 40%. These recommendations were for guidance only and not a rigid requirement. Duration long term. Concurrent medication/care: NA. Indirectness: No indirectness (n=250) Intervention 2: Endovascular intervention - Coiling (bare platinum). Standard local procedures for the coiling of aneurysms were followed. The aim was to coil to angiographic occlusion whenever possible. Patient safety was the paramount consideration at all times. These recommendations were for guidance only and not a rigid requirement. Type of bare platinum coil were left entirely to the operator's discretion. . Duration long term. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The study was funded by MicroVention Terumo Incorporated, the manufacturers of the hydrogel coils. However, they have had no direct or indirect access to the data or source documents. The trial was sponsored (on behalf of the UK National Health Service) by Lothian Health University Hospitals Division. The sponsors had no part in data collection, analysis, or reporting. This was organized by the Steering Committee.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYDROGEL versus BARE PLATINUM

Protocol outcome 1: Mortality

- Actual outcome: Mortality rate at 0-3 months postoperatively; Group 1: 9/249, Group 2: 5/250 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Flawed, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS ≤2 at 3-18 months postoperatively; Group 1: 204/249, Group 2: 209/250; Comments: Subgroup analysis on irregular shape and dome/neck size combined to provide total cohort value. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Complications of intervention - Actual outcome: Procedure and disease related adverse events at postoperatively; Group 1: 155/249, Group 2: 176/250 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Flawed, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Need for re-intervention - Actual outcome: Re-intervention at 3-18 months postoperatively; Group 1: 6/249, Group 2: 11/250; Comments: Subgroup analysis on irregular shape and dome/neck size combined to provide total cohort value. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health and social quality of life; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage ; Length of stay

Study (subsidiary papers)	Molyneux 2002[90] (Dorhout Mees 2012[40], Molyneux 2009[94], Molyneux 2005[95], Molyneux 2015[92])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=2143)
Countries and setting	Conducted in United Kingdom; Setting: 43 neurological centres
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Patients were eligible for the trial if:1. they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, with the preceding 28 days; 2. they had an intercranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; 3. they were in the clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; 4. they had an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee. If a patient was not competent to give consent (because of his or her cognitive state), assent from relatives was obtained if the ethics committee regarded it as an acceptable alternative.
Exclusion criteria	Patients were not eligible if any of the following criteria were: 1. SAH occurred more than 28 days before randomization; 2 the patient was regarded as unsuitable for one or both treatments; consent was refused or 4. the patient was participating in another randomized clinical trial of a treatment for subarachnoid haemorrhage.
Recruitment/selection of patients	2143 patients with ruptured intracranial aneurysms were enrolled between 1994 and 2002
Age, gender and ethnicity	Age - Mean (range): Clipping 52 (18-84); coiling 52 (18-87). Gender (M:F): clipping 399/671; coiling 400/673. Ethnicity: not stated

Further population details	1. aSAH grade: Not stated / Unclear 2. Characteristic of aneurysm: Not stated / Unclear 3. Location of aneurysm: Not applicable (intracranial).
Indirectness of population	No indirectness
Interventions	(n=1070) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. neurosurgical clipping. Duration intervention time. Concurrent medication/care: not specified. Indirectness: No indirectness (n=1073) Intervention 2: Endovascular intervention - Coiling. detachable platinum coils. Duration intervention time. Concurrent medication/care: not specified. Indirectness: No indirectness
Funding	Academic or government funding (supported by grant from oxford regional health authority research and development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROSURGICAL CLIPPING versus COILING

Protocol outcome 1: Mortality
- Actual outcome: mortality (Rankin scale 6) at 1 year; Group 1: 105/1055, Group 2: 85/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: mortality (Rankin scale 6) at 5 years; Group 1: 144/1041, Group 2: 112/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27
- Actual outcome: mortality (Rankin scale 6) at 10 years; Group 1: 178/835, Group 2: 135/809
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 235; Group 2 Number missing: 264

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: modified Rankin scale- 0 no symptoms at 1 year; Group 1: 187/1055, Group 2: 260/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale (0-2 inclusive) at 1 year; Group 1: 729/1055, Group 2: 813/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale- 1 minor symptoms at 1 year; Group 1: 292/1055, Group 2: 301/1063

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale- 3 significant restriction in lifestyle at 1 year; Group 1: 141/1055, Group 2: 107/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale- 4 partly dependent at 1 year; Group 1: 42/1055, Group 2: 30/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale- 5 fully dependent at 1 year; Group 1: 38/1055, Group 2: 28/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale 2 some restriction in lifestyle at 1 year; Group 1: 250/1055, Group 2: 252/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale (3-6 inclusive) at 1 year; Group 1: 326/1055, Group 2: 250/1063
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10
- Actual outcome: modified Rankin scale- 0 no symptoms at 5 years; Group 1: 198/1041, Group 2: 264/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27
- Actual outcome: modified Rankin scale (0-2 inclusive) at 5 years; Group 1: 584/1041, Group 2: 626/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27
- Actual outcome: modified Rankin scale- 1 minor symptoms at 5 years; Group 1: 211/1041, Group 2: 217/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27
- Actual outcome: modified Rankin scale- 3 significant restriction in lifestyle at 5 years; Group 1: 93/1041, Group 2: 83/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness
- Actual outcome: modified Rankin scale- 4 partly dependent at 5 years; Group 1: 18/1041, Group 2: 24/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27
- Actual outcome: modified Rankin scale- 5 fully dependent at 5 years; Group 1: 18/1041, Group 2: 22/1046
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27

- Actual outcome: modified Rankin scale 2 some restriction in lifestyle at 5 years; Group 1: 175/1041, Group 2: 145/1046 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27 - Actual outcome: modified Rankin scale (3-6 inclusive) at 5 years; Group 1: 273/1041, Group 2: 241/1046 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27 - Actual outcome: modified Rankin scale (0-2 inclusive) at 10 years; Group 1: 370/472, Group 2: 435/531 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 235; Group 2 Number missing: 264 - Actual outcome: modified Rankin scale (3-5 inclusive) at 10 years; Group 1: 102/472, Group 2: 96/531 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 235; Group 2 Number missing: 264 Protocol outcome 3: Subsequent subarachnoid haemorrhage - Actual outcome: rebleeding at 1 year; Group 1: 39/1070, Group 2: 45/1073 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 10 - Actual outcome: rebleeding at more than 1 year; Group 1: 7/1070, Group 2: 17/1073 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 27 - Actual outcome: rebleeding at 10 years; Group 1: 12/1070, Group 2: 21/1073 Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 235; Group 2 Number missing: 264	
Protocol outcomes not reported by the study	Health and social quality of life; Return to daily activity (e.g. work) ; Complications of intervention ; Need for re-intervention ; Length of stay

Study	**ISAT - 2 trial: Darsaut 2019[36]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=103)

Countries and setting	Conducted in Multiple countries; Setting: two tertiary hospitals in Canada and two tertiary hospitals in Spain
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	age ≥ 18; at least one intradural aneurysm, ruptured within the previous 30 days, and considered appropriate for both surgical and endovascular management.
Exclusion criteria	Grade 5 SAH patients, for whom death or morbidity is considered likely; absolute contraindications to administration of contrast medium; associated AV malformation; or aneurysm located at the basilar apex for which surgical treatment is considered risky.
Recruitment/selection of patients	Patients admitted with an intradural aneurysm
Age, gender and ethnicity	Age - Other: Mean age: clipping: 58.5 years; coiling: 56.5 years. Gender (M:F): 35/68. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (WFNS 1: 46; 2: 27; 3: 9; 4: 18). 2. Characteristic of aneurysm: Not stated / Unclear (≤3mm: 22; 4 - 9mm: 59; ≥10mm: 22). 3. Location of aneurysm: (to be reported) (anterior circulation - 98; posterior circulation: 5).
Extra comments	. This analysis was performed after 103 patients were treated from November 2012 - July 2017 across the four centres.
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. Neurosurgical clipping (no further information provided). Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness (n=48) Intervention 2: Endovascular intervention - Coiling. Endovascular coiling (no further information provided). Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROSURGICAL CLIPPING versus COILING Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS ≥2 at 1 year; Group 1: 15/40, Group 2: 11/36; Comments: only patients with as treated analysis have been included Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15, Reason: lost to follow up , deaths and crossed over; Group 2 Number missing: 12, Reason: lost to follow up , deaths and crossed over	
Protocol outcomes not reported by the study	Mortality ; Health and social quality of life ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Complications of intervention ; Need for retreatment ; Length of stay

Study	Li 2012[78]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=186)
Countries and setting	Conducted in China; Setting: Department of Neurosurgery, Fengxian District Central Hospital (Branch Hospital of Shanghai Sixth People's Hospital), Shanghai Jiaotong University
Line of therapy	Not applicable
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	patients with acute aSAH, admitted to the Department of Neurosurgery
Exclusion criteria	not specified
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): Coiling group 54.7 (14.2), clipping 53.7 (13.8). Gender (M:F): coiling 68/32; clipping 62/28. Ethnicity: Chinese
Further population details	1. aSAH grade: Not stated / Unclear (Hunt and Hess scale 1-2 coiling (56) clipping (61); grade 3 coiling (30) clipping (23); grade 4-5 coiling (8) clipping (8)). 2. Characteristic of aneurysm: Not stated / Unclear 3. Location of aneurysm: Not applicable (ICA;MCA;ACA-AComA; BA-bifurcation;PCoA).
Indirectness of population	No indirectness
Interventions	(n=94) Intervention 1: Endovascular intervention - Coiling. In both groups, all surgeries were carried out by the same team, which was experienced in performing both surgical procedures. Two patients in the endovascular treatment group and four patients in the surgical treatment group were not treated for their ruptured aneurysm. Duration intervention. Concurrent medication/care: N/a. Indirectness: No indirectness (n=92) Intervention 2: Neurosurgical intervention - Neurosurgical clipping. In both groups, all

	surgeries were carried out by the same team, which was experienced in performing both surgical procedures. Two patients in the endovascular treatment group and four patients in the surgical treatment group were not treated for their ruptured aneurysm. Duration intervention. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING versus NEUROSURGICAL CLIPPING Protocol outcome 1: Mortality - Actual outcome: mortality at 1 year follow-up; Group 1: 10/94, Group 2: 14/92 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Subsequent subarachnoid haemorrhage - Actual outcome: rebleeding at 1 year follow-up; Group 1: 3/94, Group 2: 3/92 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Complications of intervention - Actual outcome: vasospasm at 1 year follow-up; Group 1: 22/94, Group 2: 34/92 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: cerebral infarction at 1 year follow-up; Group 1: 12/94, Group 2: 20/92 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Return to daily activity (e.g. work) ; Need for re-intervention ; Length of stay

Study (subsidiary papers)	Taschner 2016[125] (Taschner 2018[126])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=513)
Countries and setting	Conducted in France, Germany; Setting: GREAT is a French-German multi-centre, open-label, randomized controlled trial. Five hundred thirteen patients were randomized in 15 centres in France and 7 centres in Germany.
Line of therapy	1st line
Duration of study	Intervention + follow up: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with a previously untreated cerebral aneurysm measuring 4–12 mm in maximal diameter (the maximum size for hydrogel coils at the outset of the trial) deemed to require endovascular coil embolization were eligible for inclusion if they were 18–75 years of age, were World Federation of Neurosurgeon (WFNS) grade 0–3, had anatomy such that endovascular occlusion was considered possible, had not previously been randomized into the trial, and the neuro-interventionalist was content to use either bare platinum or hydrogel coils.
Exclusion criteria	Patients were excluded if they had >1 aneurysm requiring treatment, unless the treatment was to be staged with only 1 aneurysm being treated at one sitting. Written informed consent had to be obtained from patients with WFNS grades 0 and 1 prior to randomization. In patients presenting with subarachnoid haemorrhage, the consent process differed between the participating centres in France and Germany.
Recruitment/selection of patients	Patients with a previously untreated cerebral aneurysm measuring 4 - 12mm
Age, gender and ethnicity	Age - Mean (SD): Hydrogel: 52.9±12.6 (24–79); Bare Platinum: 54.1 ± 11.8 (21–82). Gender (M:F): 151/333. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (World Federation of Neurosurgeon (WFNS) grade 0 - 3). 2. Characteristic of aneurysm: Neck width (large) (Mean ±SD (range) Hydrogel: 3.5 ± 1.3 (1–8); Bare

	Platinum 3.6 ± 1.3 (2–9)). 3. Location of aneurysm: (to be reported) (Hydrogel: Anterior- 177; Posterior/other - 62; Missing - 4; Bare Platinum: Anterior - 182; Posterior/other - 56; Missing - 3).
Extra comments	patients were stratified by rupture status, was employed to ensure balance concerning the rupture status (recently ruptured [within 30 days] versus unruptured aneurysms) between the two arms of the study.
Indirectness of population	No indirectness
Interventions	(n=256) Intervention 1: Endovascular intervention - Coiling (coated platinum- HydroCoil (HydroSoft, HydroFrame [3D], MicroVention Inc., Tustin, CA)). In the hydrogel arm of the study, at least 50% of the total coil length deployed should constitute of hydrogel coils. Standard local procedures for the coiling of aneurysms were followed. Complete angiographic aneurysm occlusion was the goal. These recommendations were for guidance only and not a rigid requirement. Duration permanent. Concurrent medication/care: The antiplatelet and anticoagulation regimens were left to individual operator's discretion as part of the clinical practice at each centre. Indirectness: No indirectness Comments: Hydrogel Coils (Hydrosoft or HydroFrame) (n=257) Intervention 2: Endovascular intervention - Coiling (bare platinum). Any bare platinum coils were permitted, as were assist devices such as remodelling balloons or endovascular stents. Standard local procedures for the coiling of aneurysms were followed. Complete angiographic aneurysm occlusion was the goal. Duration permanent. Concurrent medication/care: The antiplatelet and anticoagulation regimens were left to individual operator's discretion as part of the clinical practice at each centre. Indirectness: No indirectness Comments: Bare platinum coils
Funding	Equipment / drugs provided by industry (The study was funded by MicroVention Inc., the manufacturers of the HydroSoft/HydroFrame coils. MicroVention Inc. supplied the electronic case report form for data entry.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYDROGEL versus BARE PLATINUM

Protocol outcome 1: Mortality
- Actual outcome: 14 day mortality at up to 14 days postoperatively; Group 1: 5/243, Group 2: 5/241; Comments: p value 0.99
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 16

- Actual outcome: Mortality (mRS score 6) at 6 OR 18 months follow up; Group 1: 7/226, Group 2: 10/230 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 27 Protocol outcome 2: Subsequent subarachnoid haemorrhage - Actual outcome: Major aneurysm reoccurrence (without re-intervention) at 6 OR 18 months follow up; Group 1: 28/226, Group 2: 42/230 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 27 Protocol outcome 3: Complications of intervention - Actual outcome: Any complications and adverse events at postoperatively; Group 1: 28/243, Group 2: 30/241; Comments: p value 0.77 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 16 - Actual outcome: Other procedure related adverse events at postoperatively; Group 1: 21/243, Group 2: 19/241 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 16 Protocol outcome 4: Need for re-intervention - Actual outcome: Re-intervention for aneurysm at 6 OR 18 months follow up; Group 1: 7/226, Group 2: 14/230 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 30; Group 2 Number missing: 27	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Return to daily activity (e.g. work) ; Length of stay

Study (subsidiary papers)	McDougall 2012[86] (Spetzler 2018[123], Spetzler 2013[120], Spetzler 2015[122], Spetzler 2020[121])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=500)
Countries and setting	Conducted in USA; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Inclusion Criteria: Acute subarachnoid haemorrhage (SAH) Confirmed by CT scan or lumbar puncture Age 18-80 years Ability to give informed consent (subject or legally authorized representative) No anatomic inclusions
Exclusion criteria	Exclusion Criteria: Traumatic subarachnoid haemorrhage Presents to hospital >14 days post-bleed SAH caused by other primary disease No anatomic exclusions
Recruitment/selection of patients	not specified

Age, gender and ethnicity	Age - Mean (SD): clipping 53.1 (12.8); coiling 54.3 (12). Gender (M:F): Clipping group 72/166; coiling 67/166. Ethnicity: not specified
Further population details	1. aSAH grade: Not applicable (Hunt & Hess grade clipping 2.6(1.1); coiling 2.6(1.1)). 2. Characteristic of aneurysm: Not applicable (mean size of aneurysm in mm Clipping 6.8 (4.1); coiling 6.6 (4)). 3. Location of aneurysm: Not applicable (CLIPPING (posterior circulation 38, anterior circulation 174, angiography negative 26, other n/a) COILING (posterior circulation 32, anterior circulation 169, angiography negative 31, other 1)).
Extra comments	COMORBIDITIES: clipping group (diabetes 20, hypertension 103, smoking 147, cocaine 21, methamphetamines 17) coiling group diabetes 17, hypertension 104, smoking 145, cocaine 21, methamphetamines 20)
Indirectness of population	No indirectness
Interventions	(n=239) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. Subjects randomized to surgical therapy received treatment from one of two neurosurgeon's expert in surgery for ruptured aneurysms. Duration intervention time. Concurrent medication/care: n/a. Indirectness: Serious indirectness; Indirectness comment: Inability to perform or complete the assigned therapy resulted in crossing over to the other treatment modality when the alternative treatment provided a viable option. 4 patients in the Clipping group (205 patients assigned to clipping were treated by clipping, 4 crossed to coiling, 26 Angiography Neg patients admitted with SAH for which no source was identified, 3 not treated because of death), (n=233) Intervention 2: Endovascular intervention - Coiling. Subjects randomized to endovascular therapy were treated by one of two neurosurgical experts in such treatment. All endovascular treatments will be accomplished using accepted techniques. Duration intervention time. Concurrent medication/care: n/a. Indirectness: Serious indirectness; Indirectness comment: Coiling group (124 treated by coiling, 74 crossed over to clipping, 3 dead, 31 - Angiography Neg)
Funding	Academic or government funding (St. Joseph's Hospital and Medical Centre, Phoenix)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROSURGICAL CLIPPING versus COILING Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Modified Rankin scale (score >2) at 1 year; Group 1: 61/180, Group 2: 20/109; Comments: patients assigned to clipping group received clipping, patients assigned to coiling group received coiling	

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 59; Group 2 Number missing: 124
- Actual outcome: Modified Rankin scale (score >2) at 3 years; Group 1: 60/184, Group 2: 24/111; Comments: includes patients seen at 1 year but not at 3 years
patients assigned to clipping group received clipping, patients assigned to coiling group received coiling
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 55; Group 2 Number missing: 122
- Actual outcome: Modified Rankin scale (score >2) at 6 years; Group 1: 73/188, Group 2: 60/177; Comments: outcome by assigned treatment groups
Includes patients seen at the 1- and 3-year follow-ups, but not at the 6-year follow-up; it does not include patients no longer in the study and patients who could not be contacted at the 1-, 3-, and 6-year follow-ups.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 51; Group 2 Number missing: 56
- Actual outcome: Modified Rankin scale (score >2) at 10 years; Group 1: 73/164, Group 2: 76/163; Comments: Includes patients seen at the 1-, 3-, or 6-year follow-up but not at the 10-year follow-up; it does not include patients no longer in the study or
those who could not be contacted at the 1-, 3-, 6-, and 10-year follow-ups.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed ; Group 1 Number missing: 76; Group 2 Number missing: 69

Protocol outcome 2: Subsequent subarachnoid haemorrhage
- Actual outcome: rebleeding at 1 year; Group 1: 0/180, Group 2: 0/109
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 59; Group 2 Number missing: 124
- Actual outcome: rebleeding at 3 years; Group 1: 0/175, Group 2: 0/106; Comments: includes patients seen at 1 year but not at 3 years
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low,

Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 64; Group 2 Number missing: 127
- Actual outcome: rebleeding at 6 years; Group 1: 0/174, Group 2: 0/162
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 65; Group 2 Number missing: 71
- Actual outcome: rebleeding at DURING INITIAL HOSPITALISATION; Group 1: 1/180, Group 2: 1/109
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 59; Group 2 Number missing: 124

Protocol outcome 3: Need for retreatment
- Actual outcome: retreatment at 1 year; Group 1: 7/180, Group 2: 16/109
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 59; Group 2 Number missing: 124
- Actual outcome: retreatment at 3 years; Group 1: 0/175, Group 2: 2/106
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 64; Group 2 Number missing: 127
- Actual outcome: retreatment at 6 years ; Group 1: 0/174, Group 2: 0/162
Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number missing: 65; Group 2 Number missing: 71
- Actual outcome: retreatment at discharge; Group 1: 5/180, Group 2: 7/109
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: None, Comments: number of analysed patients is a number of patients actually treated by clipping or coiling therefore numbers of patients randomised differ from numbers of patients analysed; Group 1 Number

missing: 59; Group 2 Number missing: 124	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Return to daily activity (e.g. work) ; Complications of intervention ; Length of stay

Study (subsidiary papers)	Vanninen 1999[132] (Koivisto 2002[70], Koivisto 2002[72], Koivisto 2000[73])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=109)
Countries and setting	Conducted in Finland; Setting: University Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with a ruptured aneurysm that was considered to be suitable for both surgical clipping and endovascular treatment
Exclusion criteria	≥75 years; bleeding for more than 3 days before the procedure; presence of a large haematoma necessitating surgery; presence of a mass effect causing a neurological deficit; previous surgery for the ruptured aneurysm.
Recruitment/selection of patients	all patients admitted to the university hospital because of primary subarachnoid haemorrhage were evaluated as potential candidates for the study
Age, gender and ethnicity	Age - Mean (range): Coiling: 49 (16 - 73); Clipping: 50 (14 - 75). Gender (M:F): 51/58. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (HH Grade I - II: 67; HH Grade III: 26; HH Grade IV-V: 16). 2. Characteristic of aneurysm: Size (small) (mean size: coiling - 6 (2-14) mm; clipping - 7 (2-15)mm). 3. Location of aneurysm: (to be reported) ((anterior circulation) MCA: 19; ACA: 55; ICA: 24 (posterior circulation) 11).
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. a standard micro-surgical method was used for clipping of the aneurysm neck with a Sugita or Aesculap clip. If feasible, the aneurysm was opened, coagulated or both. Duration long term. Concurrent medication/care: All patients received corticosteroids and mannitol. Indirectness: No indirectness

	(n=52) Intervention 2: Endovascular intervention - Coiling. Once catheterization had been achieved, the sac was filled with Gugliemi detachable coils (GDC-10, GDC-10 soft or GDC-10 2 diameter) which can be electrolytically detached. complete occlusion of the aneurysmal sac was always attempted. The largest coil, which was selected according to measured aneurysm diameter, was positioned first to form a basketlike frame in the aneurysm. The smaller coils were then sequentially delivered into the aneurysm until the lumen was completely occluded and flow inside the aneurysm, as well as the secondary pouch, was arrested. If the size or of the selected coil proved to be unsuitable, the GDC system allowed removal of the coil and repositioning of the mesh to an optimal position. Duration long term. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENDOVASCULAR COILING versus NEUROSURGICAL CLIPPING

Protocol outcome 1: Mortality
- Actual outcome: Mortality at intraoperative or immediately postoperative; Group 1: 1/52, Group 2: 2/57
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: Mortality (Glasgow Outcome Scale) at 3 months; Group 1: 6/52, Group 2: 6/57
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness
- Actual outcome: Severe disability or Vegetative state (Glasgow Outcome Scale) at 3 months; Group 1: 4/52, Group 2: 6/57
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness
- Actual outcome: Severe disability or Vegetative state (Glasgow Outcome Scale) at 12 months; Group 1: 4/52, Group 2: 5/57
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness
- Actual outcome: Mortality (Glasgow Outcome Scale) at 12 months; Group 1: 7/52, Group 2: 9/57
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Need for re-intervention - Actual outcome: Re-intervention at immediately postoperative up to 3 months; Group 1: 5/52, Group 2: 3/57 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health and social quality of life; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage ; Complications of intervention ; Length of stay

Appendix E: Forest plots

E.1 Neurosurgical clipping versus endovascular coiling

Figure 2: Mortality (intraoperative or postoperative)

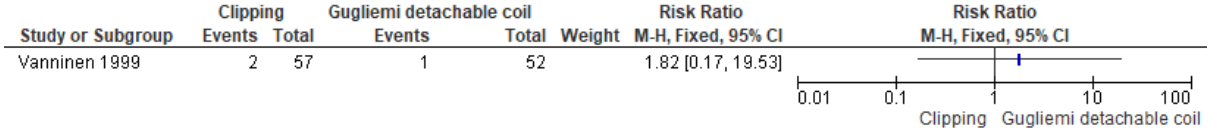


Figure 3: Mortality at 3 months

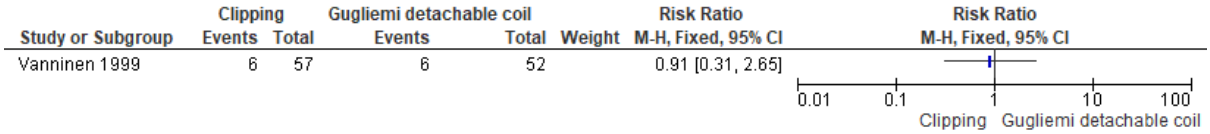


Figure 4: Mortality at 1 Year

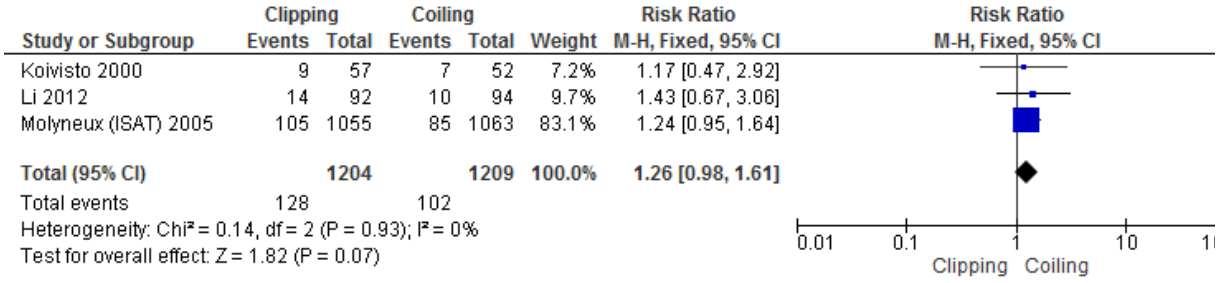


Figure 5: Mortality at 5 years

Figure 6: Mortality at 10 years

Figure 7: Modified Rankin scale ≤2 at 1 year. Scale 0-6; high score represents poor outcome

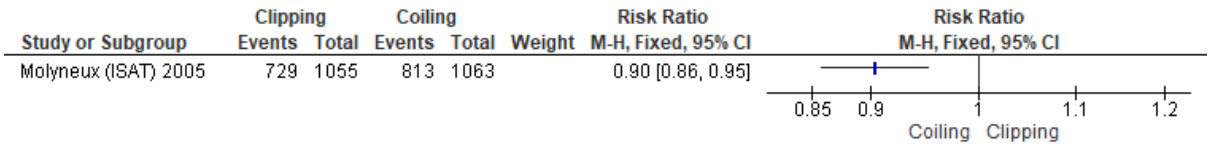


Figure 8: Modified Rankin scale ≥2 at 1 year. Scale 0-6; high score represents poor outcome

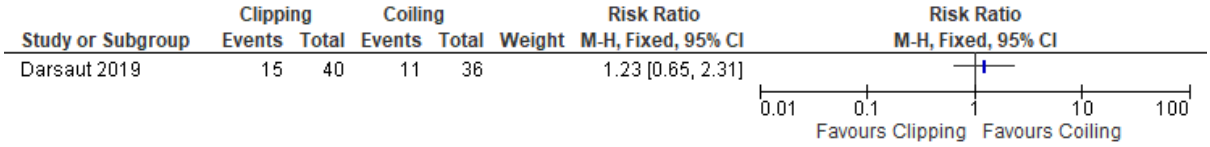


Figure 9: Modified Rankin scale ≥3 at 1 year. Scale 0-6; high score represents poor outcome

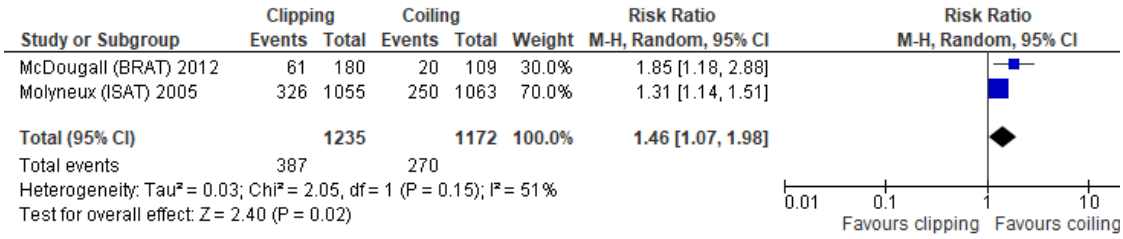


Figure 10: Modified Rankin scale ≥3 at 3 year. Scale 0-6; high score represents poor outcome

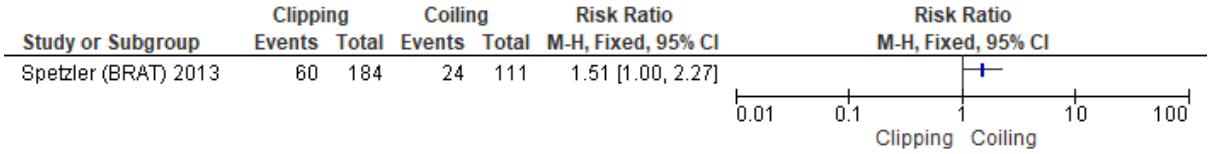


Figure 11: Modified Rankin scale ≤2 at 5 years. Scale 0-6; high score represents poor outcome

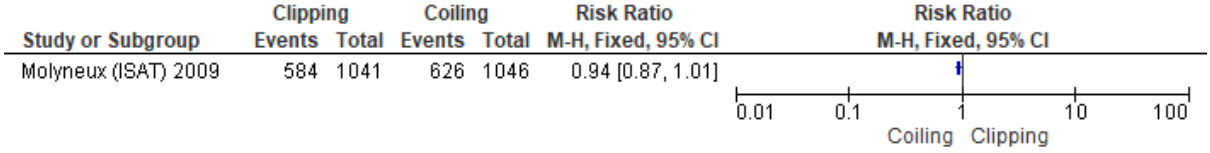


Figure 12: Modified Rankin scale ≥3 at 5 years. Scale 0-6; high score represents poor outcome

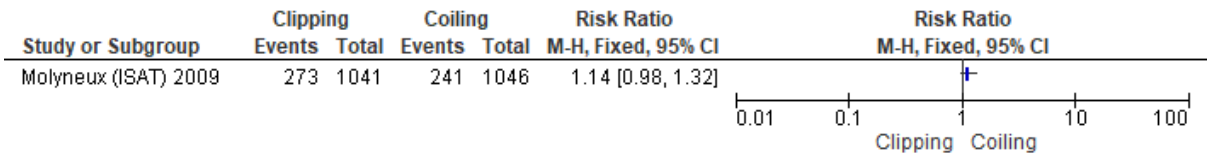


Figure 13: Modified Rankin scale ≥3 at 6 year. Scale 0-6; high score represents poor outcome

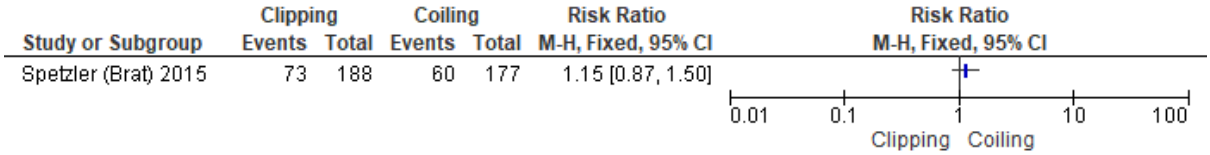


Figure 14: Modified Rankin scale ≥3 at 10 year. Scale 0-6; high score represents poor outcome

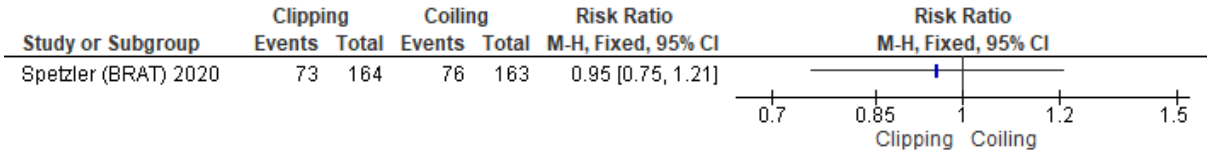


Figure 15: Modified Rankin scale ≤2 at 10 years. Scale 0-6; high score represents poor outcome

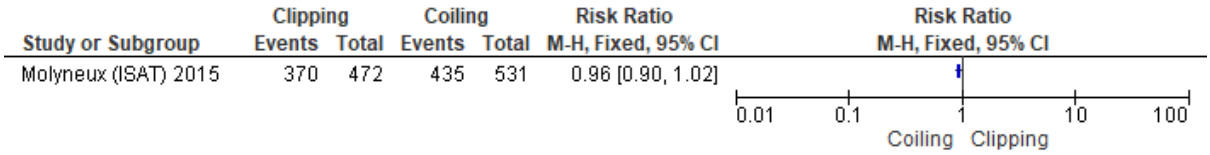


Figure 16: Modified Rankin scale ≥3 at 10 years. Scale 0-6; high score represents poor outcome

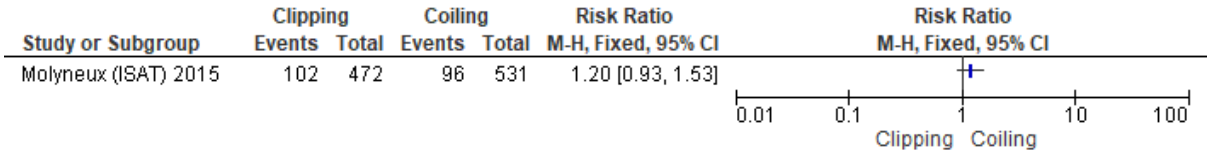


Figure 17: Severe disability or vegetative state (Glasgow outcome scale) at 3 months

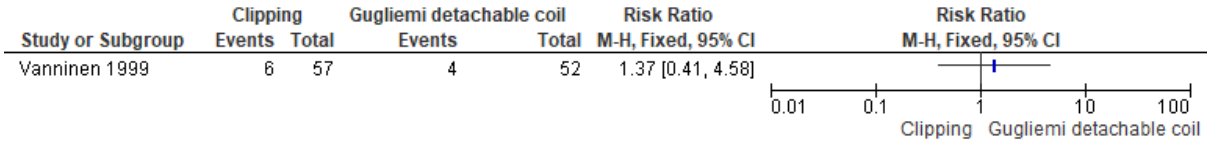


Figure 18: Severe disability or vegetative state (Glasgow outcome scale) at 12 months

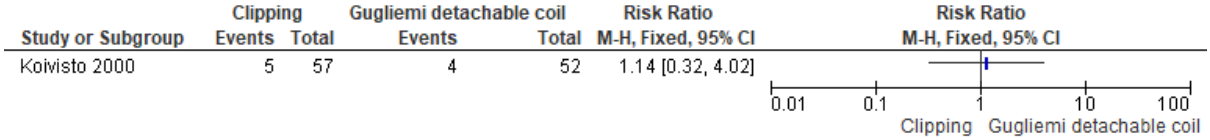


Figure 19: Re-intervention at discharge

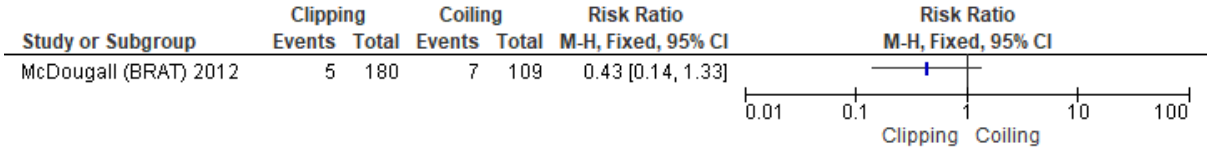


Figure 20: Re-intervention at 3 months

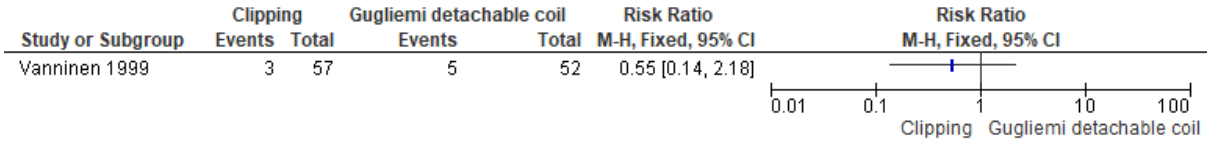


Figure 21: Re-intervention at 1 year

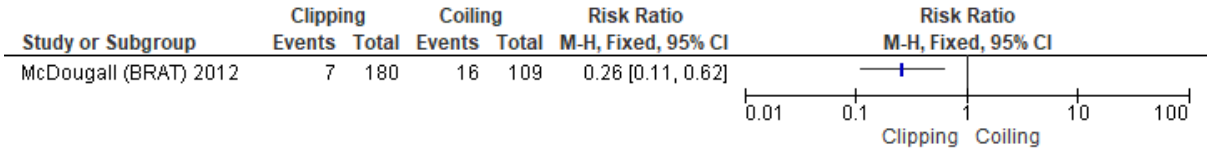


Figure 22: New re-intervention at 3 years

Figure 23: New re-intervention at 6 years

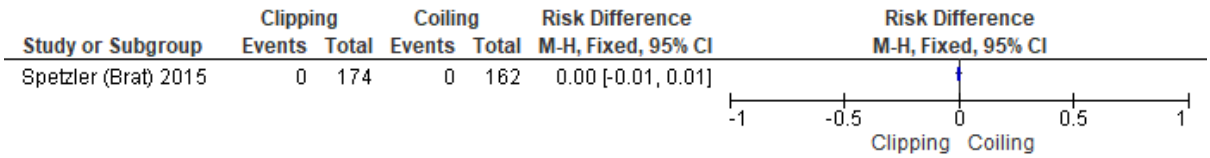


Figure 24: Rebleed during hospitalisation

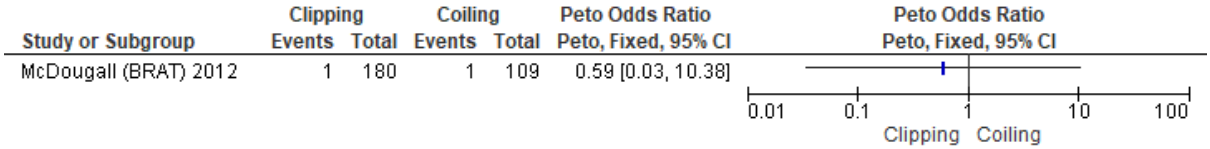


Figure 25: Rebleed at 1 year

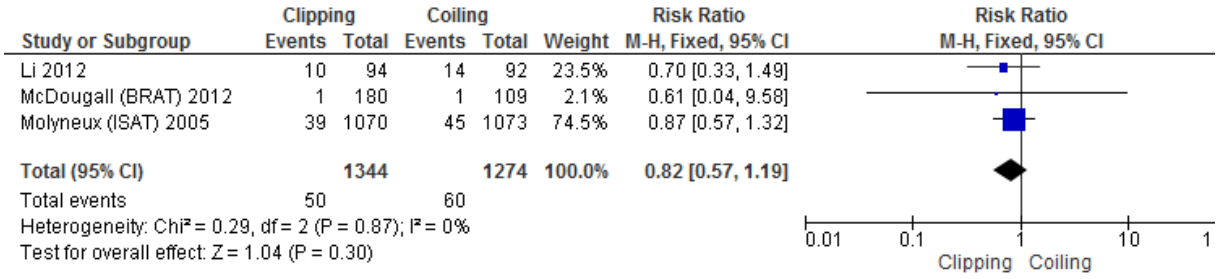


Figure 26: New rebleed at 3 years

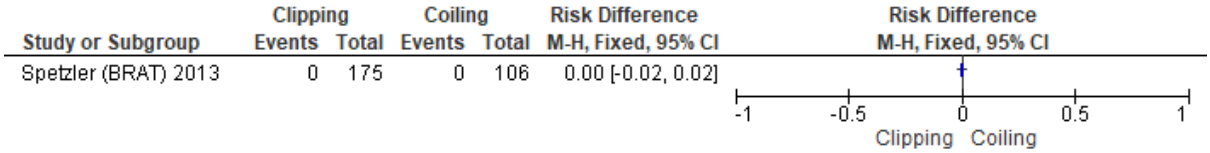


Figure 27: New rebleed at 6 years

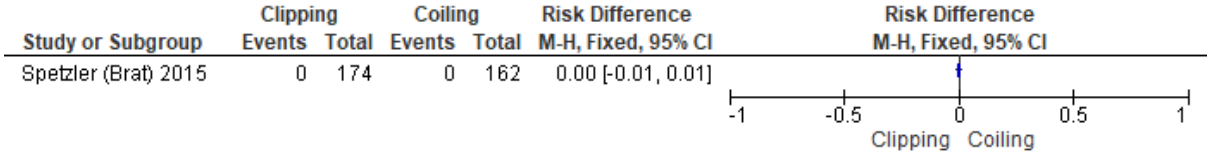
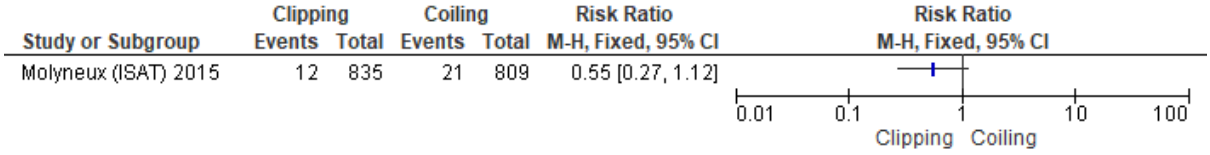


Figure 28: Rebleed at 1 to 10 years



E.2 Coated coil versus bare platinum coil

Figure 29: Mortality at 24 hours

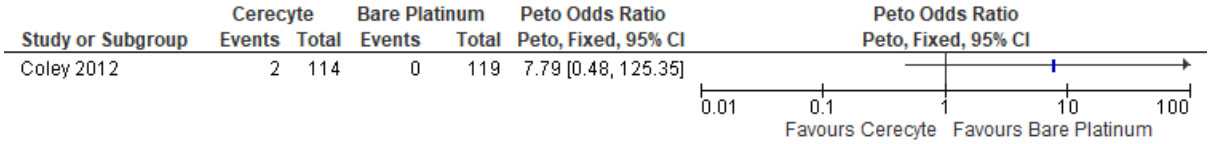


Figure 30: Mortality at 14 days

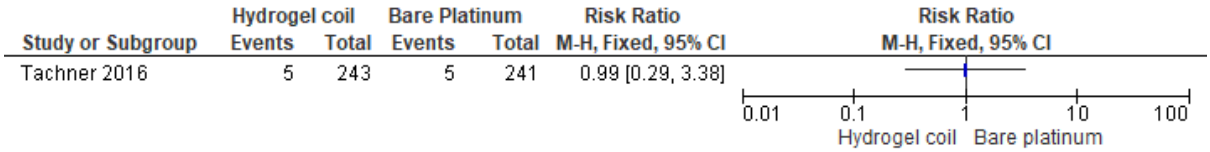


Figure 31: Mortality at 3 months

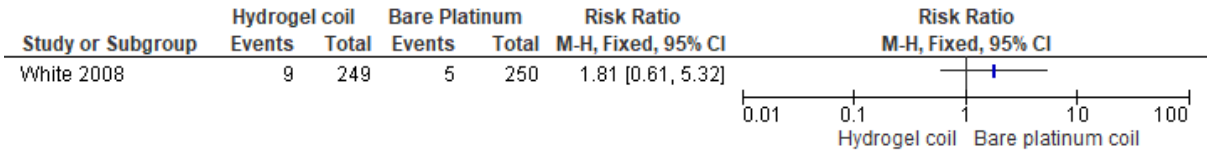


Figure 32: Mortality at 6-18 months

Figure 33: Modified Rankin scale ≤2 at from 3 to 18 months. Scale 0-6; high score represents poor outcome

Figure 34: Modified Rankin scale ≥3 3 to 18 months. Scale 0-6; high score represents poor outcome

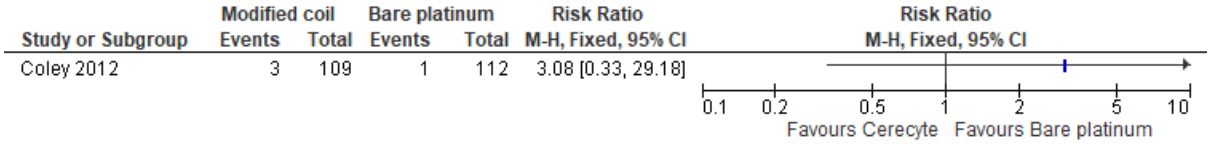


Figure 35: Subsequent aSAH

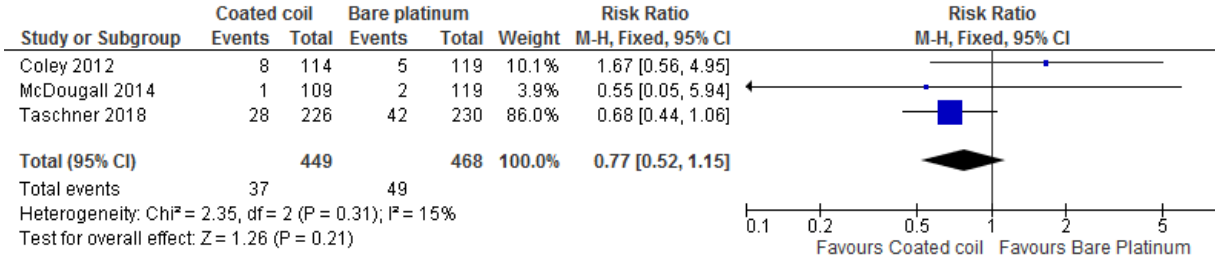


Figure 36: Need for re-intervention at 3-18 months

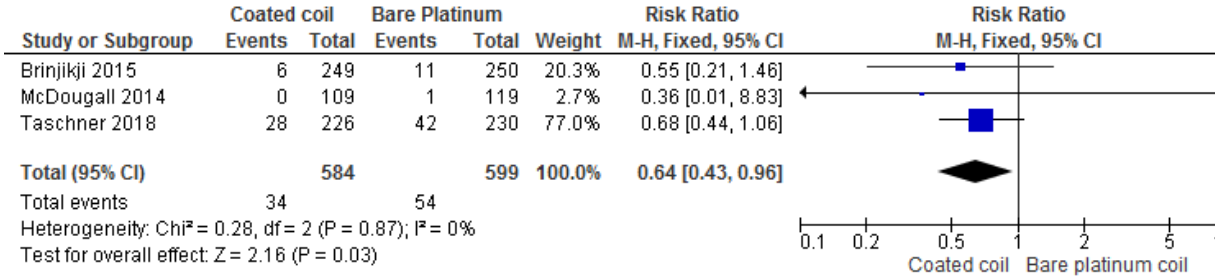


Figure 37: Procedure related adverse events

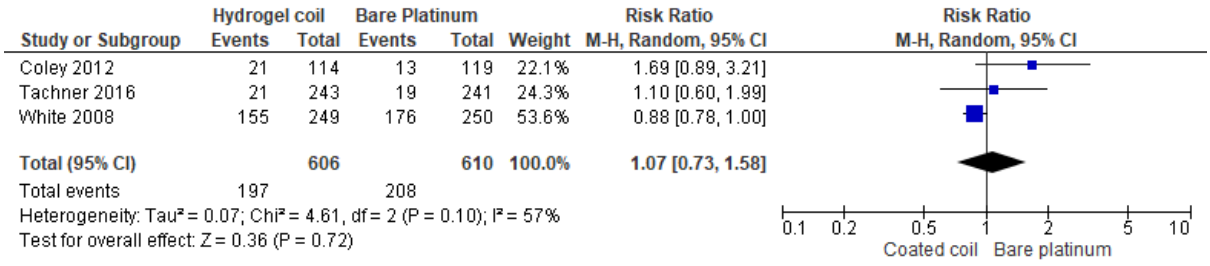
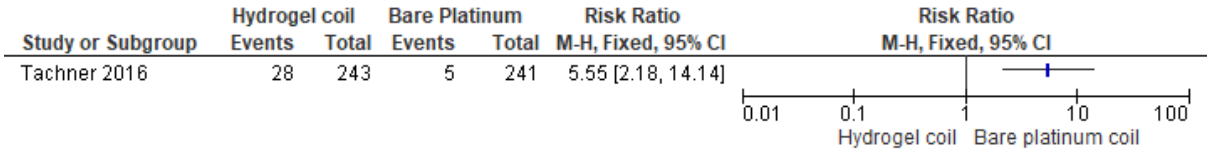


Figure 38: Adverse events



E.3 Flow diverter versus coiling

Figure 39: Mortality at 10 months

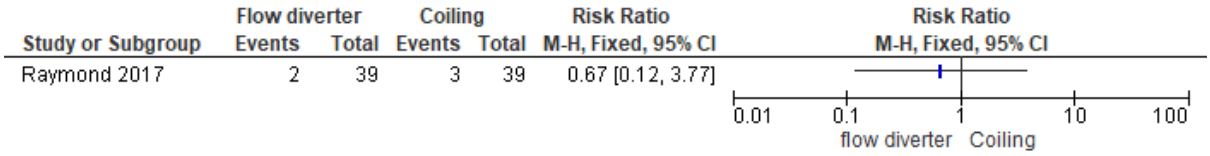


Figure 40: Modified Rankin scale ≥3 at 10 months. Scale 0-6; high score represents poor outcome

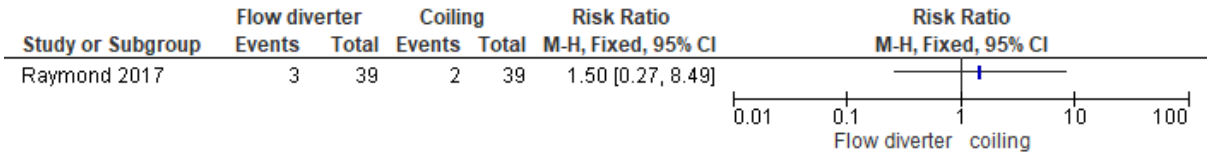
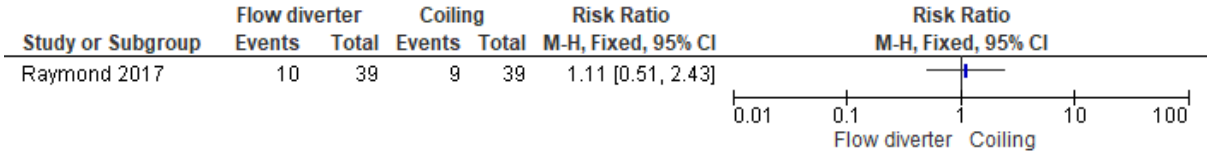


Figure 41: Complications at 10 months (stroke or any other serious adverse events)



Appendix F: GRADE tables

Table 15: Clinical evidence profile: Neurosurgical clipping versus endovascular coiling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clipping	Coiling	Relative (95% CI)	Absolute		
Mortality (intraoperative or postoperative)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/57 (3.5%)	1.9%	RR 1.82 (0.17 to 19.53)	16 more per 1000 (from 16 fewer to 352 more)	⊕⊕OO LOW	CRITICAL
Mortality 3 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/57 (10.5%)	11.5%	RR 0.91 (0.31 to 2.65)	10 fewer per 1000 (from 79 fewer to 190 more)	⊕⊕OO LOW	CRITICAL
Mortality at 1 year (follow-up mean 1 years)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	128/1204 (10.4%)	8.4%	RR 1.26 (0.98 to 1.61)	28 more per 1000 (from 2 fewer to 65 more)	⊕⊕OO LOW	CRITICAL
Mortality at 5 years (follow-up mean 5 years)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	144/1041 (13.8%)	10.7%	RR 1.29 (1.02 to 1.63)	31 more per 1000 (from 2 more to 67 more)	⊕⊕OO LOW	CRITICAL
Mortality at 10 years (follow-up mean 10 years)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	178/835 (21.3%)	16.7%	RR 1.28 (1.04 to 1.56)	47 more per 1000 (from 7 more to 94 more)	⊕⊕OO LOW	CRITICAL
Modified Rankin scale 0 - 2 at 1 year												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	none	none	729/1055 (69.1%)	76.5%	RR 0.9 (0.86 to 0.95)	77 fewer per 1000 (from 38 fewer to 107 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin scale ≥2 at 1 year												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[2]	none	15/40 (37.5%)	31%	RR 1.23 (0.65 to 2.31)	71 more per 1000 (from 109 fewer to 406 more)	⊕⊕OO LOW	CRITICAL
Modified Rankin scale 3-6 inclusive at 5 years (follow-up mean 1 years)												
2	randomised trials	serious[1]	serious[3] inconsistency	no serious indirectness	serious[2]	none	387/1235 (31.3%)	23.5%	RR 1.46 (1.07 to 1.98)	96 more per 1000 (from 15 more to 205 more)	⊕OOO VERY LOW	CRITICAL
Modified Rankin scale (>2) at 3 years (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60/184 (32.6%)	21.6%	RR 1.51 (1 to 2.27)	110 more per 1000 (from 0 more to 274 more)	⊕OOO VERY LOW	CRITICAL
Modified Rankin scale 0-2 inclusive at 5 years (follow-up mean 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	584/1041 (56.1%)	59.9%	RR 0.94 (0.87 to 1.01)	36 fewer per 1000 (from 78 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin scale 3-6 inclusive at 5 years (follow-up mean 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	273/1041 (26.2%)	23%	RR 1.14 (0.98 to 1.32)	32 more per 1000 (from 5 fewer to 74 more)	⊕⊕OO LOW	CRITICAL

Modified Rankin scale (>2) at 6 years (follow-up mean 6 years)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73/188 (38.8%)	33.9%	RR 1.15 (0.87 to 1.5)	51 more per 1000 (from 44 fewer to 170 more)	⊕OOO VERY LOW	CRITICAL
Modified Rankin scale (>2) at 10 years (follow-up mean 10 years)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	76/163 (46.6%)	44.5%	RR 0.95 (0.75 to 1.21)	22 fewer per 1000 (from 111 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
Modified Rankin scale 0 - 2 inclusive at 10years (follow-up mean 10 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	370/472 (78.4%)	81.9%	RR 0.96 (0.9 to 1.02)	33 fewer per 1000 (from 82 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin scale 3-6 inclusive at 10years (follow-up mean 10 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	102/472 (21.6%)	18.1%	RR 1.2 (0.93 to 1.53)	36 more per 1000 (from 13 fewer to 96 more)	⊕⊕OO LOW	CRITICAL
Severe disability or vegetative state (Glasgow outcome scale) 3 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/57 (10.5%)	7.7%	RR 1.37 (0.41 to 4.58)	28 more per 1000 (from 45 fewer to 276 more)	⊕⊕OO LOW	CRITICAL
Severe disability or vegetative state (Glasgow outcome scale) 12 months (follow-up mean 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/57 (8.8%)	7.7%	RR 1.14 (0.32 to 4.02)	11 more per 1000 (from 52 fewer to 233 more)	⊕⊕OO LOW	CRITICAL
Re-treatment at discharge												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/180 (2.8%)	6.4%	RR 0.43 (0.14 to 1.33)	36 fewer per 1000 (from 55 fewer to 21 more)	⊕OOO VERY LOW	IMPORTANT
Re-intervention (3 months) (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/57 (5.3%)	9.6%	RR 0.55 (0.14 to 2.18)	43 fewer per 1000 (from 83 fewer to 113 more)	⊕⊕OO LOW	IMPORTANT
Re-treatment at 1 year (follow-up mean 1 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	none	none	7/180 (3.9%)	14.7%	RR 0.26 (0.11 to 0.62)	109 fewer per 1000 (from 56 fewer to 131 fewer)	⊕⊕OO LOW	IMPORTANT
Re-treatment at 3 years (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/175 (0%)	1.9%	Peto OR 0.07 (0 to 1.23)	18 fewer per 1000 (from 19 fewer to 4 more)	⊕OOO VERY LOW	IMPORTANT
Re-treatment at 6 years (follow-up mean 6 years)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious2	none	0/174 (0%)	0%	RD 0 (-0.01, 0.01)	0 fewer per 1000 (from 10 fewer to 10 more)	⊕OOO VERY LOW	IMPORTANT
Re-bleeding during initial hospitalisation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/180 (0.56%)	0.9%	Peto OR 0.59 (0.03 to 10.38)	4 fewer per 1000 (from 9 fewer to 77 more)	⊕OOO VERY LOW	IMPORTANT
Re-bleeding at 1 year (follow-up mean 1 years)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/1344 (3.6%)	4.2%	RR 0.82 (0.57 to 1.2)	8 fewer per 1000 (from 20 fewer to 9 more)	⊕⊕OO LOW	IMPORTANT

Re-bleeding at 3 years (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/175 (0%)	0%	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
Re-bleeding at 6 years (follow-up mean 6 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/174 (0%)	0%	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
Re-bleeding at 1 to 10 years (follow-up mean 10 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/1070 (1.1%)	2%	RR 0.57 (0.28 to 1.16)	9 fewer per 1000 (from 14 fewer to 3 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. When a single study reported zero events in both arms imprecision was measured by sample size: No imprecision - sample size >350, serious imprecision – sample size >70 to ≤350, very serious imprecision - sample size ≤70.
[3] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, subgroup analysis not possible; <2 studies per subgroup.

Table 16: Clinical evidence profile: Coated coil versus bare platinum coil

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Coated coil**	**Bare platinum coil**	**Relative (95% CI)**	**Absolute**		
Mortality (24 hours) (follow-up mean 24 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/114 (1.8%)	0%	Peto OR 7.79 (0.28 to 125.35)	-	⊕⊕OO LOW	CRITICAL
Mortality 14 days post operatively												

1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/243 (2.1%)	2.1%	RR 0.99 (0.29 to 3.38)	0 fewer per 1000 (from 15 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Mortality 3 months post surgery (follow-up mean 3 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/249 (3.6%)	2%	RR 1.81 (0.61 to 5.32)	16 more per 1000 (from 8 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Mortality 6 or 18 months post surgery (follow-up mean 6-18 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/444 (2.5%)	2.4%	RR 1.03 (0.46 to 2.29)	1 more per 1000 (13 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (MRS ≤2) (follow-up mean 6 months)												
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307/358 (85.8%)	0.9%	RR 0.99 (0.93 to 1.05)	0 fewer per 1000 (from 1 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (MRS ≥3) (follow-up mean 6 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/109 (2.8%)	0.89%	RR 3.08 (0.33 to 29.18)	30 more per 1000 (from 17 fewer to 280 more)	⊕OOO VERY LOW	CRITICAL
Subsequent SAH (follow-up range 3-18 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	49/469 (10.4%)	8.2%	RR 0.77 (0.52 to 1.15)	23 fewer per 1000 (from 50 fewer to 18 more)	⊕⊕⊕O MODERATE	IMPORTANT
Need for re-intervention (3-18 months) (follow-up mean 3-18 months)												
3	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/599 (2.4%)	5.8	RR 0.64 (0.43 to 0.96)	23 fewer per 1000 (from 50 fewer to 18 more)	⊕⊕OO LOW	IMPORTANT
Procedure related adverse events (follow-up mean 24 hours)												

3	randomised trials	Serious[1]	serious inconsistency	no serious indirectness	serious[2]	none	197/606 (32.5%)	34.1%	RR 1.07 (0.73 to 1.58)	24 more per 1000 (from 92 fewer to 198 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	none	none	28/243 (11.5%)	2.1%	RR 5.55 (2.18 to 14.14)	96 more per 1000 (from 25 more to 276 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, unexplained by subgroup analysis

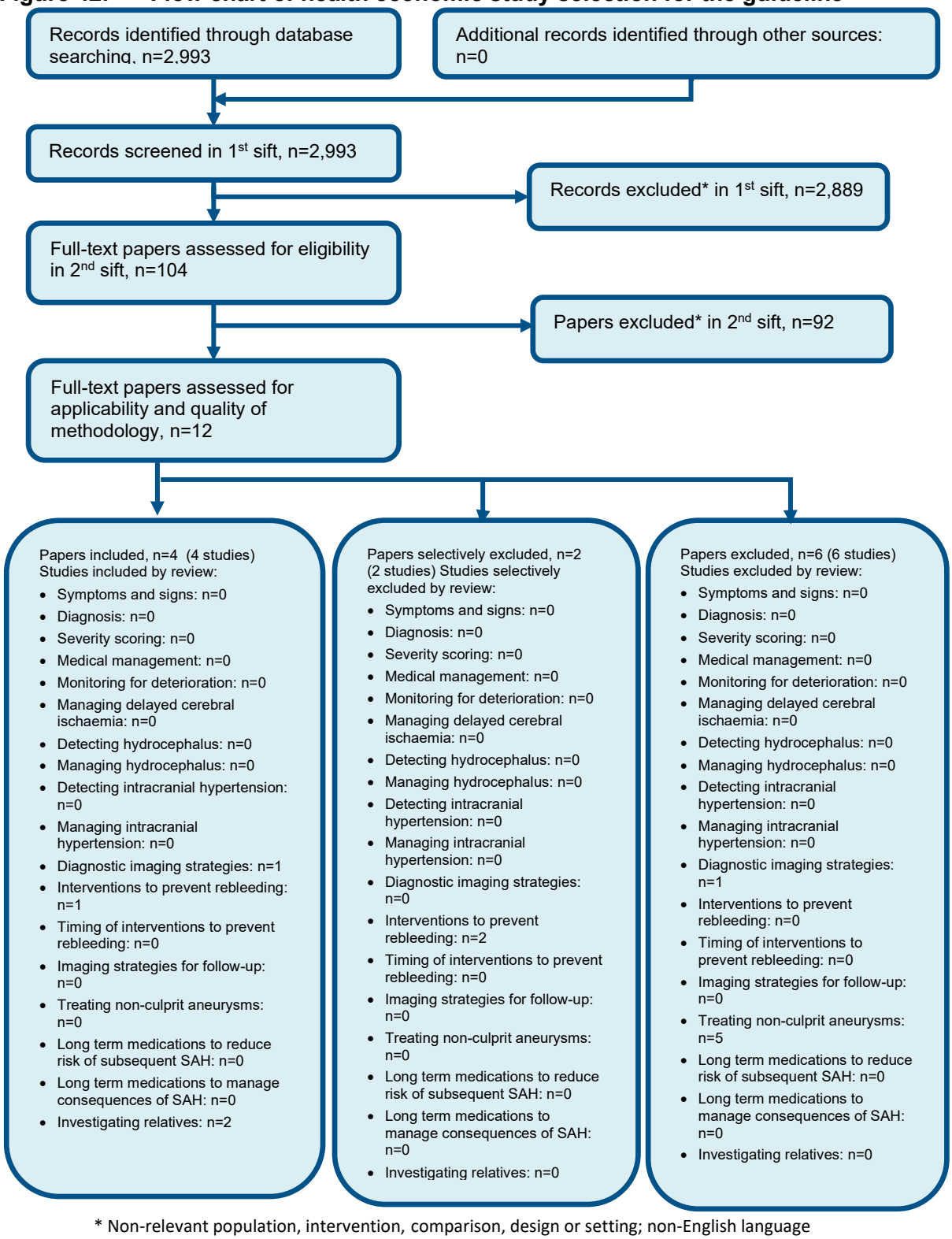
Table 17: Clinical evidence profile: Flow diverter versus coiling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Flow diverter**	**Coiling**	**Relative (95% CI)**	**Absolute**		
Mortality (mean follow up 9.8 months) (follow-up mean 9.8 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness[3]	very serious[2]	none	2/39 (5.1%)	7.7%	RR 0.67 (0.12 to 3.77)	25 fewer per 1000 (from 68 fewer to 213 more)	⊕OOO VERY LOW	CRITICAL
Modified Rankin scale 3-5(mean follow up 9.8 months) (follow-up mean 9.8 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness[3]	very serious[2]	none	3/39 (7.7%)	5.1%	RR 1.5 (0.27 to 8.49)	25 more per 1000 (from 37 fewer to 382 more)	⊕OOO VERY LOW	CRITICAL
complications (stroke +any SAE complication) (mean follow up 9.8 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness[3]	very serious[2]	none	10/39 (25.6%)	23.1%	RR 1.11 (0.51 to 2.43)	25 more per 1000 (from 113 fewer to 330 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 because the majority of the evidence included an indirect population, intervention or indirect outcomes, or by 2 increments because the majority of the evidence included a very indirect population or outcomes

Appendix G: Health economic evidence selection

Figure 42: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

Study	Wolstenholme 2008[139]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CC **Study design:** Within-RCT analysis **Approach to analysis:** Resource use data prospectively collected alongside RCT[89]. A detailed observational study at one centre was also undertaken to identify more detailed costing of each procedure with regards to number and type of staff involved, equipment and consumables. Questionnaire to remaining centres to indicate local practice with regards to resource use. Unit costs applied. **Perspective:** UK NHS **Follow-up:** 2 years **Treatment effect duration:** n/a **Discounting:** Costs: 3.5% ; Outcomes: n/a	**Population:** UK subsample of ISAT. **Patient characteristics:** N = 1,644 Start age: NR Male: NR **Intervention 1:** Neurosurgical clipping (n=835) **Intervention 2:** Endovascular coiling (n=809)	**Total costs (mean per patient):** Intervention 1: £20,330 Intervention 2: £19,102 Incremental (2−1): -£1,228 (95% CI: (-£3,119 to £786); p=NR) ***Cost breakdown (mean per patient):*** *Intervention cost for first episode of care:* *Intervention 1: £3,146* *Intervention 2: £4,520* *Overall cost for first episode of care:* *Intervention 1: £19,339* *Intervention 2: £16,935* *Follow-up costs in first year (including further procedures):* *Intervention 1: £837* *Intervention 2: £1,483* *Follow-up costs from 1-2 years:* *Intervention 1: £131* *Intervention 2: £613* **Currency & cost year:** 2004 UK pounds **Cost components incorporated:** Type and number of hospitalisations and procedures, procedure duration, number of coils, length of stay in ICU and general wards, hospital readmissions, follow up angiography/imaging, staff time, equipment and consumables.	n/a	n/a **Analysis of uncertainty:** None.

Data sources
Health outcomes: n/a **Quality-of-life weights:** n/a **Cost sources:** Unit costs of health and social care, PSSRU 2004; Department of Health, 2005; NHS reference costs, 2004.
Comments
Source of funding: Pilot phase of study supported by a grant from Oxford Regional Health Authority Research and Development. The main trial was supported by grants from: Medical Research Council, UK; Programme Hospitalier de Recherche Clinique, French Ministry of Health sponsored by Assistance Publique-Hopitaux de Paris; Candian Institutes of Health Research; Stroke Association, UK. **Limitations:** Resource use data (2002-2004) and unit costs (2004) may not reflect current NHS context. Health outcomes not reported.Time horizon may not be sufficient to capture all costs. Within-trial analysis and so does not reflect full body of available evidence. **Other:** None.
Overall applicability:[a] Partially applicable **Overall quality:**[b] Potentially serious limitations

Abbreviations: CC=comparative-costing analysis; NR= not reported; years; n/a=not applicable; PSSRU= Personal Social Services Research Unit.
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 18: Studies excluded from the clinical review

Study	Exclusion reason
Abi-Aad 2018[1]	Incorrect study design- trial protocol only
Acioly 2019[2]	Incorrect study design / population – non comparative study / ruptured and unruptured aneurysms
Agnoletto 2019[3]	Systematic review – references checked
Ahmed 2013[4]	Incorrect study design – nonrandomized study
Ahmed 2019[5]	Systematic review – references checked
Ahn 2006[6]	Inappropriate study design / comparison – non comparative study of interventions for aneurysms with nerve palsy
Anon 2016[7]	Incorrect intervention – comparison of clipping and coiling via haemodynamic changes
Barbarite 2016[9]	Systematic review - references checked
Bechan 2016[10]	Inappropriate comparison – ruptured compared to unruptured complications
Bekelis 2015[12]	Incorrect study design – nonrandomized study
Bekelis 2017[11]	Incorrect study design – nonrandomized study
Bendok 2020[13]	Incorrect population – majority of participants with unruptured aneurysms. Data from a direct population (with ruptured aneurysms) already available.
Berro 2019[14]	Incorrect study design – nonrandomized study
Boogaarts 2014[15]	Systematic review - not relevant to review question or unclear PICO
Brilstra 1999[16]	Citation only
Brilstra 1999[18]	Systematic review - not relevant to review question or unclear PICO
Brilstra 2002[17]	Systematic review: appropriate papers already included
Brilstra 2004[19]	Inappropriate population – unruptured aneurysm
Britz 2005[22]	Inappropriate study design – editorial
Broeders 2016[23]	Systematic review - relevant studies included
Brunken 2009[24]	Paper not available
Brzegowy 2019[25]	Incorrect study design – nonrandomized study
Cagnazzo 2018[26]	Paper not available
Campi 2007[27]	Inappropriate study design / comparison - re-intervention after surgery for ruptured cerebral aneurysms including cross over
Chalouhi 2012[28]	Incorrect study design – nonrandomized study
Chang 2019[29]	Not in English
Chen 2019[31]	Incorrect population – mixed ruptured and unruptured population
Cloutier 2017[32]	Inappropriate comparison - comparison of different sized coils
Crocker 2008[34]	Incorrect study design – assessment of neurosurgical team

Darsaut 2012[35]	Systematic review _references checked
De Oliveira 2007[37]	Systematic review_- references checked
Dengler 2016[38]	Systematic review – references checked (papers already included)
Deutsch 2018[39]	Incorrect study design – nonrandomized study
Dorhout Mees 2012[41]	Inappropriate comparison – timing of intervention (ISAT trial data)
Egeto 2018[42]	Systematic review - references checked (study designs inappropriate)
Engele 2019[43]	Systematic review – references checked
Falk Delgado 2017[44]	Systematic review - references checked
Falk Delgado 2017[45]	Systematic review - references checked (study designs inappropriate)
Feng 2016[47]	Systematic review - references checked
Feng 2019[46]	Incorrect study design – nonrandomized study
Fotakopoulos 2017[48]	Systematic review- references checked
Gaetani 1998[49]	Inappropriate study design - no useable outcomes
Gero Escapa 2015[50]	Incorrect study design – nonrandomized study
Ghostine 2016[51]	Inappropriate study design - study protocol
Goertz 2019[52]	Incorrect study design – nonrandomized study
Gory 2019[53]	Incorrect study design – nonrandomized study
Gross 2019[54]	Incorrect population – unruptured aneurysms only
Guimond 2012[55]	Systematic review - references checked
Hart 2011[56]	Inappropriate study design – no useable outcomes (includes ISAT data)
Hong 2014[57]	Systematic review - references checked
Huang 2016[58]	Inappropriate population – intracranial wide necked aneurysms
Hubner 2000[59]	Incorrect study design – abstract
Hulsbergen 2019[60]	Systematic review – references checked
Ikawa 2020[61]	Systematic review – references checked
Izquierdo 1996[62]	Paper not in English
Johnston 2004[63]	Citation only
Johnston 2009[64]	Citation only
Kabbasch 2019[65]	Incorrect study design / population – non comparative study / ruptured and unruptured aneurysms
Kaku 2007[66]	Incorrect study design – non comparative study
Kanamaru 2015[67]	Systematic review - references checked
Kato 2005[68]	Incorrect study design – nonrandomized study
Kiselev 2018[69]	Incorrect population – complex intracranial cavernous aneurysms
Koivisto 1997[71]	Incorrect study design – abstract
Kotowski 2012[74]	Systematic review - references checked
Kurogi 2018[75]	Incorrect study design – economic paper
Lanzino 2013[76]	Systematic review - references checked
Li 2013[77]	Systematic review - references checked

Lindgren 2019[79]	Incorrect study design – nonrandomized study
Linfante 2009[80]	Incorrect study design – nonrandomized study
Liu 2018[81]	Inappropriate population – unruptured aneurysms
Luo 2019[82]	Systematic review – references checked
Lv 2019[83]	Incorrect study design – nonrandomized study
Mascitelli 2019[84]	Incorrect study design – ad hoc study of a small population of aneurysm (included from BRAT study)
Meyer 2010[87]	Incorrect study design – nonrandomized study
Mokin 2020[88]	Incorrect study design – nonrandomized study
Molyneux 1998[91]	Paper not available
Molyneux 2002[89]	Duplicate paper
Mortimer 2016[96]	Incorrect study design – nonrandomized study
Munich 2019[97]	Incorrect study design – nonrandomized study
O'Neill 2017[101]	Systematic review - references checked
Ota 2019[102]	Incorrect study design – nonrandomized study
Park 2015[103]	Incorrect study design – nonrandomized study
Petr 2017[104]	Systematic review - references checked
Phan 2016[105]	Systematic review - references checked
Pierot 2020[106]	Incorrect study design / population – nonrandomized study/ ruptured and unruptured aneurysms
Pierot 2020[107]	Incorrect study design – no relevant outcomes
Poncyljusz 2015[108]	Inappropriate population – unruptured aneurysms
Proust 2020[109]	Incorrect study design – nonrandomized study
Qureshi 2007[110]	Systematic review - references checked
Raja 2008[111]	Systematic review - references checked
Raymond 2008[115]	Inappropriate study design - study protocol
Raymond 2014[114]	Inappropriate population – majority unruptured aneurysms
Raymond 2017[113]	Inappropriate population – majority unruptured aneurysms
Sauvigny 2019[116]	Incorrect study design – nonrandomized study
Shao 2019[117]	Systematic review – references checked
Shen 2019[118]	Incorrect study design – nonrandomized study
Silva 2017[119]	Systematic review - references checked
Sweid 2018[124]	Incorrect study design – nonrandomized study
Tjoumakaris 2007[127]	Citation only
Turk 2014[128]	Inappropriate study design - study protocol
Upchurch 2005[129]	Inappropriate study design - conference abstract
Van der Schaaf 2005[130]	Systematic review - references checked
Van der Schaaf 2006[131]	Systematic review - references checked
Wadd 2015[133]	Inappropriate study design – no relevant outcomes
Wang 2016[134]	Incorrect study design – nonrandomized study
White 2004[135]	Inappropriate study design - no relevant outcomes

White 2011[136]	Inappropriate study design -no relevant outcomes
Wiebers 2006[138]	Inappropriate study design - commentary article
Xia 2017[140]	Systematic review – references checked
Xue 2018[141]	Systematic review – references checked
Zhang 2018[144]	Inappropriate study design - no relevant outcomes
Zhang 2019[142]	Incorrect study design – nonrandomized study
Zhang 2019[143]	Systematic review – references checked
Zhang 2019[145]	Systematic review – references checked
Zhao 2017[146]	Incorrect study design – nonrandomized study
Zhao 2019[147]	Incorrect study design – nonrandomized study
Zheng 2017[148]	Systematic review – references checked
Zhou 2016[149]	Incorrect study design – nonrandomized study
Zijlstra 2016[150]	Systematic review – references checked
Zubair Tahir 2009[151]	Incorrect study design – nonrandomized study

I.2 Excluded health economic studies

Studies that meet the review protocol population and interventions, and the economic study inclusion criteria but have not been included in the review based on applicability and/or methodological quality are summarised below with reasons for exclusion.

Table 19: Studies excluded from the health economic review

Reference	Reason for exclusion
Chang 2016[30]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis[139] was available, this study was selectively excluded.
Kurogi 2018[75]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was available, this study was selectively excluded.

Appendix J: Research recommendations

J.1 New endovascular interventions

Research question: What is the clinical and cost effectiveness of novel endovascular techniques and devices such as coated coils, endoluminal flow diverters, and intrasaccular devices to treat aneurysmal subarachnoid haemorrhage?

Why this is important:

Endovascular treatment of ruptured brain aneurysms with coils is known to be effective and marginally safer than treatment by surgical clipping. Since early clinical use, incomplete aneurysm treatment, aneurysm recurrence and rebleeding from the treated aneurysm have been recognised as potential limitations of coil technology. Over the last 25 years, coils have been modified in various ways to improve aneurysm packing (% filling by coil) or aneurysm healing. More recently other techniques and devices have been developed to supplement (e.g. balloon or stent-assisted coiling), or replace coiling (e.g. flow diverting stents or intra-saccular aneurysm devices).

Aneurysm coiling was widely adopted in practice based on RCT evidence of clinical benefit. Subsequent second-generation coil technologies were also evaluated against 'bare platinum' coils in RCTs. By contrast, evolving generations of stents and intra-aneurysmal devices have been evaluated in animal models and clinical case series, generally with demonstration of safety, but without reliable comparison with alternative treatments.

Several of these devices were developed for a specific role, such as treatment of fusiform aneurysms or bifurcation aneurysms with a wide neck, but their use in clinical practice has diversified as experience and operator views about utility, risk and efficacy have evolved.

Evaluation of evidence related to efficacy of devices is confounded by variation in selection criteria, clinical characteristics and management protocols between study populations.

Novel technologies generally also add significant cost to aneurysm treatment compared with aneurysm coiling alone. While some aneurysms cannot be treated effectively by coils alone, this should not detract from efforts to identify the most clinically and cost effective ways to treat intracranial arterial aneurysms within a population.

Criteria for selecting high-priority research recommendations:

PICO question	RCTs should be undertaken to assess the clinical and cost-effectiveness of novel intra- or extra-aneurysmal devices with conventional aneurysm coiling or clipping. Such trials could include comparison of: • An intra-saccular device (other than coils) vs. aneurysm coiling • An intra-saccular device (including coils) vs. an extra-aneurysmal endoluminal device • Any device delivered endovascularly vs. surgical clipping. Population: Adults (over 16 years old) presenting with SAH caused by a brain aneurysm (< 10mm), suitable for treatment with either approach proposed in the trial. (If appropriate patients could be stratified to facilitate evaluation of populations with culprit/ruptured and non-culprit/unruptured aneurysms.) Intervention/comparison: prospective randomised controlled trials to compare a novel technique or device with standard treatment with coiling or clipping.

	Outcome(s): Mortality, health-related quality of life, procedure related adverse events, aneurysm occlusion, clinical outcome (mRS at 28 days and 3 months), aneurysm recurrence at 6 months, aneurysm rebleeding.
Importance to patients or the population	Randomised trials are needed to establish the clinical and cost-effectiveness of novel techniques and devices relative to standard treatments such as coiling and clipping. The results of such trials will help to ensure that patients are offered the most appropriate treatment for the management of ruptured and unruptured intracranial arterial aneurysms.
Relevance to NICE guidance	Rigorous evaluation of new devices will inform future versions of NICE Interventional Procedures Guidance (such as IPG658) and future versions of this guideline.
Relevance to the NHS	New devices have been used for aneurysm treatment either to supplement or replace aneurysm coiling for some time. For some devices there is weak evidence of equivalent efficacy and improved safety compared with coiling. New devices are comparatively expensive and broad adoption of such technology without demonstration of superior clinical and cost effectiveness could have significant budgetary implications for the NHS. Some devices enable aneurysm treatment in approximately half the time taken for aneurysm coiling. This may improve access for other time-critical procedures delivered in interventional neuroradiology, including mechanical thrombectomy (MT) for acute stroke due to large vessel occlusion.
National priorities	The potential for new treatment options to shorten aneurysm treatment procedure times may improve access to biplane angiography equipment for mechanical thrombectomy patients (https://www.longtermplan.nhs.uk/areas-of-work/stroke/).
Current evidence base	Limited evidence of clinical effectiveness. Limited RCT evidence, no RCTs for some novel devices. See https://www.nice.org.uk/guidance/ipg658.
Equality	No equality issues
Study design	Randomised controlled trial(s).
Timeframe	2 years as the novel techniques are increasingly being used in practice and this time-frame should allow for sufficient follow-up to measure efficacy.
Feasibility	Such trials are feasible and of high priority as routine use of novel devices unsupported by RCT evidence undermines equipoise and willingness of clinicians to offer randomisation to patients. A study based in Canada has similar objectives. (https://clinicaltrials.gov/ct2/show/NCT03936647).
Other comments	There is enthusiasm to recruit to such trials. It is likely that recruitment rates would be reasonable, particularly from centres that have been slow adopters of a new technology.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

Appendix K: Research recommendations

K.1 Interventions for major neurological deficit

Research question: What is the outcome of intervention to prevent rebleeding in people who present with or rapidly develop severe neurological deficits as a consequence of acute aneurysmal subarachnoid haemorrhage?

Why this is important:

The principal aim of treatment of aneurysmal subarachnoid haemorrhage is to secure the ruptured aneurysm and prevent re-bleeding. Clinical research on treatments to prevent rebleeding have generally excluded people who present with or rapidly develop severe neurological deficit, including prolonged loss of consciousness. The prognosis for people with such severe neurological complications is poor and many will die or survive with major disability, resulting in substantial costs for rehabilitation and long-term nursing care. There is limited evidence on the use of interventions to prevent rebleeding in this population and no widely accepted guidance.

Criteria for selecting priority research recommendations:

PICO question	Population: Adults (16 and older) presenting with established or rapidly developing major neurological deficit as a consequence of an aneurysmal subarachnoid haemorrhage prior to interventions to prevent rebleeding. Intervention/comparison(s): • Neurosurgical or neuroradiological intervention to secure the aneurysm and prevent rebleeding within 48 hours of symptom onset • Medical therapy (no neurosurgical or neuroradiological intervention to secure the aneurysm and prevent rebleeding within 48 hours of symptom onset) Outcome(s): • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Early rebleed before aneurysm treatment or subsequent subarachnoid haemorrhage (if managed conservatively) • Return to daily activity • Length of hospital stay • Complications of intervention (any) • Need for retreatment
Importance to patients or the population	Little evidence was found for people who present with or rapidly develop major neurological deficit after an aneurysmal subarachnoid haemorrhage. The committee agreed there is considerable uncertainty about how this population should be managed and research is required to improve decision-making for these patients.
Relevance to NICE guidance	Current guidance recommends management of aneurysmal SAH to prevent rebleeding for a general population of patients who present with the condition. However, the role of intervention in patients with major neurological deficit is uncertain and clinicians may prefer a trial of medical therapy in the first instance, potentially denying patients effective treatment. The costs of long-term nursing care and rehabilitation of people who have a major neurological deficit after an aneurysmal subarachnoid haemorrhage can also be considerable and the cost-efficacy of interventional treatment in this population has not been established. There is currently no guidance specifically for this population.
Relevance to the NHS	It is expected that improved guidance on interventions to prevent rebleeding in patients with major neurological deficit would reduce variation in practice, improve patient outcome and potentially reduce long-term costs for the NHS.
National priorities	This question is not relevant to a national priority area.
Current evidence base	The committee noted that relatively few patients with major neurological deficit were enrolled in the studies reviewed; for example, in the

	International Subarachnoid Aneurysm Trial (ISAT) 88% of patients were assessed as good grade WFNS 1 or 2.
Equality	No equality issues
Study design	New evidence should be developed using a registry-based study design.
Timeframe	New research could be conducted over 3-5 years to allow for sufficient data collection and follow-up of participants.
Feasibility	The research is considered to be feasible. The committee noted that currently many clinicians may not be in equipoise about the management of patients with major neurological deficit and a RCT in this area currently may not be feasible. The committee added that a registry-based study could inform practice and potentially allow a subsequent RCT to be completed.
Importance	• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.