National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[P] Evidence review for non-culprit aneurysms

NICE guideline NG228

Methods, evidence and recommendations

November 2022

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National Institute for Health and Care Excellence

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Contents

1 Managing non-culprit aneurysms

Evidence review underpinning recommendations 1.4.5 to 1.4.7 in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of different options for managing non-culprit aneurysms in adults with a confirmed aneurysmal subarachnoid haemorrhage?

1.2 Introduction

Approximately 20% of people with aneurysmal SAH will have multiple aneurysms on vascular imaging at the time of the index bleed, including the ruptured aneurysm and one or more 'non-culprit' aneurysms. In some cases, it may be difficult to identify the ruptured aneurysm and treatment of multiple aneurysms may be appropriate. After successful treatment of a ruptured aneurysm, de novo non-culprit aneurysms are also recognised on follow-up imaging in around 0.5% of cases per annum.

Non-culprit aneurysms are at risk of future rupture, causing recurrent subarachnoid haemorrhage. This review assesses evidence for the clinical and cost effectiveness of options to manage non-culprit aneurysms in people with aneurysmal SAH.

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 with identified non-culprit 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. WEB, intra-saccular occlusion devices), flow diversion (e.g. pipeline device).

Comparisons	• To each other (across class and within class comparison) • To no treatment / conservative (medical) management
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) • Subsequent subarachnoid haemorrhage • Complications of treatment allocation IMPORTANT: • Return to daily activity
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered, starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

Twenty-five studies from 19 randomised controlled trials and cohorts were included in the review,[3, 27, 31, 32, 37, 40, 50, 60, 63, 73, 78, 87, 91, 98, 103, 104, 125, 126, 130-132, 138-141] these are summarised in Table 2 below. Four of these were randomly controlled trials and 15 were cohort studies. Evidence from observational studies was only considered for inclusion where no evidence for the critical outcomes of the evidence review was available from RCTs, or if the RCT evidence included for review included an indirect population and the evidence from a non-randomised study provided outcome data from a direct population. Observational data was also only considered if outcome adjustment was performed for the key confounder of patient age or if intervention and comparison groups were matched for this key confounder. Where both randomised trials and non-randomised studies (NRS) of an intervention were identified and both were included in the review, results of these were presented separately. A number of studies included three intervention groups and provided outcome data for multiple comparisons. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

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 G:.

1.4.2 Excluded studies

See the excluded studies list in Appendix J:.

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
Interventional therapy (neurosurgical or endovascular) versus conservative management for non-culprit aneurysms				
Towgood 2005[130]	**Conservative management:** UIA remained untreated. N=23 **Intervention management:** UIA treated by clipping (19 cases) or endovascular coiling (7 cases) N=26 Follow up: 6 months	Patients aged >15 years with at least one UIA which may or may not be symptomatic, and may have had previous SAH that had been treated at an earlier time. Mean age (SD): Untreated : 50 years (10.9) Treated: 48.7 years (10.8) New Zealand	• Quality of life	History of SAH: Untreated group – 48% Treated group – 62% Cohort study Confounding factors: Groups matched for age
Neurosurgical clipping versus conservative management				
Ishibashi 2013[60]	**Conservative management:** No intervention. Patients treated conservatively were scheduled for consultation and 3D-CTA follow-up every 6 months. N=741 **Intervention management:** 325 patients with 369 UIAs were treated either with endovascular surgery (EVS), microsurgical clipping (MC), or both: 287 patients with 315 UIAs (85.4%) with EVS only, 29	Patients with UIAs referred to study institution were prospectively included. Mean age (range): 59.2 years (17-89) Japan	• Mortality • Degree of disability • Subsequent SAH	66 unruptured intracranial aneurysm (UIA) were associated with a history of SAH from a separate aneurysm; of these, 30 were observed and 36 were treated. Cohort study Confounding factors: Groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
	patients with 32 UIAs (8.7%) with MC only, and 9 patients with multiple aneurysms received both EVS and MC. N=325 Follow up: ~23 months			
Jang 2011[63]	**Conservative management:** The observation group visited outpatient clinic annually to observe the change of shape of dome and size of aneurysms with computed tomography angiography until loss to follow up. N=28 **Neurosurgical clipping:** Surgical clipping. Aneurysms on the middle cerebral artery were more frequently treated by clipping. N=56 ***Endovascular coiling:*** *Coil embolization. Aneurysms on the vertebral artery-basilar artery were more frequently treated by coiling.* *N=25* Follow up: 1 year	Patients aged 65 years and older diagnosed with unruptured intracranial aneurysms (UIAs). Mean age: 72 years South Korea	• Mortality • Degree of disability	No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
ISUIA: Mahaney 2014[3] Wiebers 1998[140] Wiebers 2003[141]	**Conservative management:** Patients untreated for UIA N=1691 **Neurosurgical clipping:** A surgical procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment. N=1917 ***Endovascular coiling:*** *An endovascular procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment.* *N=451* Follow up: 1 year	People with at least 1 saccular UIA of at least 2 mm in maximum diameter confirmed by cerebral arteriography, with mRS of ≤2. Mean age (SD): No surgery: 55.2 years(13.1) Clipping: 51.5 years (11.4) Coiling: 53.7 years (13.1) USA	• Mortality • Degree of disability • Subsequent SAH	Study separated age groups. These categories were grouped for this analysis. Some patients had other aneurysms presenting with SAH in the past; these aneurysms were required to be definitively treated prior to enrolment in the study. This subgroup is used for comparison of clipping and coiling. Prospective cohort study Confounding factors: Groups matched for age
O'Donnell 2019[98]	**Conservative management:** Conservatively managed/untreated. N=57 **Neurosurgical clipping:** Microsurgical repair N=112 Follow up: 1 year	Patients with recently diagnosed UIA referred to the neurosurgery team. Mean age (SD): Conservative: 58 years (15) Surgical: 53 years (11) Australia	• Quality of life • Degree of disability	Excluded if treated by endovascular technique No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age
Tsukahara 2002[131] Tsukahara 2005[132]	**Conservative management:** Natural course observed without intervention.	Patients with unruptured cerebral aneurysms.	• Degree of disability • Subsequent SAH	No reference to previous or concurrent SAH

Study	Intervention and comparison	Population	Outcomes	Comments
	N=181 **Neurosurgical clipping:** Craniotomy N=472 ***Endovascular coiling:*** *Coil embolization* *N=31* Follow up: 6 months	Age: <50 years: 105; 51-60 years: 172; 61-70 years: 218; 71-80 years: 109; >81 years: 11 Japan/Switzerland		Cohort study Confounding factors: Groups matched for age
Endovascular coiling versus conservative management				
Ge 2017[40]	**Conservative management:** The refusal of endovascular treatment resulted in conservative treatment. N=35 **Endovascular coiling:** Endovascular treatment included conventional simple coiling and stent-assisted coiling. Stents were used for wide-neck aneurysms that were defined as having a dome-to-neck ratio <2 and irregularly shaped aneurysms. N=44 Follow up: 18 months	Consecutive cases of unruptured basilar tip aneurysms Mean age (SD): 37.3 years (10.6) China	• Mortality • Degree of disability • Subsequent SAH	All patients had no SAH history. Cohort study Confounding factors: Groups matched for age
Ishibashi 2013[60]	**Conservative management:** No intervention. Patients treated conservatively were	Patients with UIAs referred to study institution were prospectively included.	• Mortality • Degree of disability • Subsequent SAH	66 unruptured intracranial aneurysm (UIA) were associated with a history of SAH from a

Study	Intervention and comparison	Population	Outcomes	Comments
	scheduled for consultation and 3D-CTA follow-up every 6 months. N=741 **Intervention management:** 325 patients with 369 UIAs were treated either with endovascular surgery (EVS), microsurgical clipping (MC), or both: 287 patients with 315 UIAs (85.4%) with EVS only, 29 patients with 32 UIAs (8.7%) with MC only, and 9 patients with multiple aneurysms received both EVS and MC. N=325 Follow up: ~23 months	Mean age (range): 59.2 years (17-89) Japan		separate aneurysm; of these, 30 were observed and 36 were treated. Cohort study Confounding factors: Groups matched for age
Jang 2011[63]	**Conservative management:** The observation group visited outpatient clinic annually to observe the change of shape of dome and size of aneurysms with computed tomography angiography until loss to follow up. N=28 **Endovascular coiling:** Coil embolization. Aneurysms on the vertebral artery-basilar artery were more frequently treated by coiling.	Patients aged 65 years and older diagnosed with unruptured intracranial aneurysms (UIAs). Mean age: 72 years South Korea	• Mortality • Degree of disability	No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
	N=25 ***Neurosurgical clipping:*** *Surgical clipping. Aneurysms on the middle cerebral artery were more frequently treated by clipping.* *N=56* Follow up: 1 year			
ISUIA: Mahaney 2014[3] Wiebers 1998[140] Wiebers 2003[141]	**Conservative management:** Patients untreated for UIA N=1691 **Endovascular coiling:** An endovascular procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment. N=451 ***Neurosurgical clipping:*** *A surgical procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment.* *N=1917* Follow up: 1 year	People with at least 1 saccular UIA of at least 2 mm in maximum diameter confirmed by cerebral arteriography, with mRS of ≤2. Mean age (SD): No surgery: 55.2 years(13.1) Clipping: 51.5 years (11.4) Coiling: 53.7 years (13.1) USA	• Mortality • Degree of disability • Subsequent SAH	Study separated age groups. These categories were grouped for this analysis. Some patients had other aneurysms presenting with SAH in the past; these aneurysms were required to be definitively treated prior to enrolment in the study. This subgroup is used for comparison of clipping and coiling. Prospective cohort study Confounding factors: Groups matched for age
Tsukahara 2002[131] Tsukahara 2005[132]	**Conservative management:** Natural course observed without intervention. N=181	Patients with unruptured cerebral aneurysms. Age:	• Degree of disability • Subsequent SAH	No reference to previous or concurrent SAH Cohort study

Study	Intervention and comparison	Population	Outcomes	Comments
	Neurosurgical clipping: Craniotomy N=472 ***Endovascular coiling:*** *Coil embolization* *N=31* Follow up: 6 months	<50 years: 105; 51-60 years: 172; 61-70 years: 218; 71-80 years: 109; >81 years: 11 Japan/Switzerland		Confounding factors: Groups matched for age
Neurosurgical versus endovascular intervention				
CURES: Darsaut 2017[32]	**Neurosurgical clipping:** Surgical clipping. N=66 **Endovascular coiling:** Endovascular coiling. N=70 Technical details left to the individual operators. Follow up: 1 year	Independent (modified Rankin Scale (mRS) score of ≤2) patients 18 years and older with any intradural saccular UIAs 3–25 mm in maximal cross-sectional diameter were offered participation if they had at least 10 years of life expectancy. Considered suitable for either clipping or coiling. Mean age (SD): 57 years (7) Canada	• Mortality • Degree of disability • Subsequent aSAH • Complications	History of previous SAH from another aneurysm: 14(7&7)/136 RCT
ISUIA: Mahaney 2014[3] Wiebers 1998[140]	**Endovascular coiling:** An endovascular procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment.	People with at least 1 saccular UIA of at least 2 mm in maximum diameter confirmed by cerebral	• Mortality • Degree of disability • Subsequent SAH	Study separated age groups. These categories were grouped for this analysis.

Study	Intervention and comparison	Population	Outcomes	Comments
Wiebers 2003[141]	N=451 **Neurosurgical clipping:** A surgical procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment. N=1917 ***Conservative management:*** *Patients untreated for UIA* *N=1691* Follow up: 1 year	arteriography, with mRS of ≤2. Mean age (SD): No surgery: 55.2 years(13.1) Clipping: 51.5 years (11.4) Coiling: 53.7 years (13.1) USA		Some patients had other aneurysms presenting with SAH in the past; these aneurysms were required to be definitively treated prior to enrolment in the study. This subgroup is used for comparison of clipping and coiling. Prospective cohort study Confounding factors: Groups matched for age
Kunz 2013[78]	**Neurosurgical clipping:** Microsurgical clipping. N=44 **Endovascular coiling:** Coil embolization. N=22 Follow up: 1 year	Patients were eligible if they had at least one UIA, whether or not they had symptoms. Patients may have had a previous ruptured aneurysm at another location that was micro-surgically or endovascularly obliterated. Mean age (SD): 52.4 years (10.5) Germany	• Complications	Subgroup of people with previous SAH from another aneurysm used for analysis Cohort study Confounding factors: Groups matched for age
Bioactive coil versus bare platinum coil				
Coley 2012[31] Molyneux 2012[87]	**Endovascular coiling (bare platinum coil):** N=131	Patients ages between 18 and 70 years of age with a ruptured or unruptured	• Mortality • Degree of disability • Complications	Only unruptured aneurysm subset included for analysis. RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Endovascular coiling (bioactive coil): Cerecyte (polyglycolic acid) coated coil N=133 Follow up: 6 months	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		
GREAT: Taschner 2016[125] Taschner 2018[126]	**Endovascular coiling (bioactive coil):** Coated platinum, HydroSoft/Hydroframe (Hydrogel coating) N=132 **Endovascular coiling (bare platinum)** N=129 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 neurointerventionalist was content to use either bare platinum or hydrogel coils.	• Mortality • Degree of disability	Only unruptured aneurysm subset included for analysis. Subset of incidental aneurysm – no rupture within 30 days. RCT

Study	Intervention and comparison	Population	Outcomes	Comments
		Mean age: Hydrogel: 52.9±12.6 (24–79); Bare Platinum: 54.1 ± 11.8 (21–82) France & Germany		
HELPS: White 2008[139] White 2011[138]	**Endovascular coiling (bioactive platinum):** Hydrocoil (Hydrogel coating) 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, neurointerventionalist, 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 neurointerventionalist was content to use either bare platinum or hydrogel coils. Age range: <45: 158; 46-55: 143;	• Mortality rate • Degree of disability • Subsequent SAH	Only unruptured aneurysm subset included for analysis. Subset of incidental aneurysm – no rupture within 30 days. RCT

Study	Intervention and comparison	Population	Outcomes	Comments
		>55: 198 United Kingdom		
Stent assisted coil versus bare platinum coil				
Frontera 2014[37]	**Stent-assisted coil (SAC):** Self-expanding stents were used. All patients received stent placement followed by coiling during a single procedure. Stents were deployed under roadmap guidance. After confirming the stent position with a follow-up angiogram, coil embolization of the aneurysm was performed using either Gugliemi detachable coils or Orbit coils. N=47 **Endovascular coiling:** Gugliemi detachable coils or Orbit coils were deployed through a standard microcatheter approach to pack the aneurysm. N=33 Follow up: 1 year	Unruptured cerebral aneurysm, attempted aneurysm repair using stent assisted coiling, coiling alone or surgical clipping, presence of at least one digital subtraction angiogram following aneurysm repair and age ≥18 years. Median age (range): SAC: 58 years (42-78) Coil: 55 years (31-78) USA	• Mortality • Complication	Clipping arm not included in analysis. Cohort study Confounding factors: Groups matched for age
Hetts 2014[50]	**Stent-assisted coil:** Neuroform stent and either platinum bare metal coils or polymer modified coils. N=137	Subjects 18–80 years of age with a baseline mRS score of 0–3 who had a single documented, untreated, unruptured intracranial aneurysm (4–20 mm) for	• Mortality • Degree of disability • Subsequent aSAH • Complications	No reference to previous or concurrent SAH Cohort study

Study	Intervention and comparison	Population	Outcomes	Comments
	Endovascular coiling: Platinum bare metal coils or polymer modified coils without a stent. N=224 Follow up: 1 year	which both polymer modified coils and platinum bare metal coils were treatment options and for which primary coiling treatment was planned to be completed during a single procedure. Mean age: 56.7 years USA		Confounding factors: Groups matched for age
Balloon assisted coil versus bare platinum coil				
Pierot 2009[104]	**Bare-platinum coil:** Endovascular coiling (standard treatment). N=325 **Balloon-assisted coil:** Balloon assisted coiling (remodelling technique) N=222 Follow up unclear.	Unruptured intracranial aneurysm ≤15mm. Mean age (SD): 51 years (11.1) France/Canada	• Mortality • Complications	No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age
Balloon assisted coil versus stent-assisted coil				
Peterson 2014[103]	**Stent-assisted coiling:** Stent-assisted coiling. N=71 **Balloon-assisted coil:** Balloon-assisted coiling.	People with unruptured aneurysms treated endovascularly with an adjunct device. USA	• Complications	No reference to previous or concurrent SAH Cohort study Confounding factors:

Study	Intervention and comparison	Population	Outcomes	Comments
	N=35 Follow up: 1 year			Groups matched for age
Flow diverter (PED) versus neurosurgical clipping				
Kim 2014[73]	**Neurosurgical clipping:** Microsurgical clipping. N=21 **Pipeline embolization device:** Flow diverter (pipeline embolization device). N=23 ***Stent-assisted coiling:*** *Stent-assisted coiling.* *N=38* Follow up: 2 to 60 months	All patients with unruptured ICA aneurysms. Mean age: Clipping: 48.2 years; Coiling: 55.9 years; PED: 53.2 years	• Degree of disability • Complications	No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age
Flow diverter (PED) versus endovascular coiling				
Chalouhi 2013[27]	**Pipeline embolization device:** Pipeline embolization. The number of stents deployed and the adjunctive use of coils was left to the operator's discretion. The pipeline embolization device (PED) procedure was stopped when any amount of stasis was seen inside the aneurysm. Placement of additional PEDs was considered at follow-up if the	Patients with unruptured, large or giant (≥10 mm) aneurysms treated with PED or coiling. Mean age (SD): PED: 60.7 years (12.7); Coil: 60.3 years (10.6) USA	• Mortality • Degree of disability • Complications	No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
	aneurysm remained unchanged, despite treatment. N=40 **Endovascular coiling:** Coiling was interrupted when the aneurysm was completely occluded or when no additional coils could be deployed. 67 (56%) were treated with conventional coiling, 52 (43%) with stent-assisted coiling, and 1 (1%) with balloon-assisted coiling. N=120 Follow up: 15 months			
Kim 2014[73]	**Stent-assisted coiling:** Stent-assisted coiling. N=38 **Pipeline embolization device:** Flow diverter (pipeline embolization device). N=23 ***Neurosurgical clipping:*** *Microsurgical clipping.* *N=21* Follow up: 2 to 60 months	All patients with unruptured ICA aneurysms. Mean age: Clipping: 48.2 years; Coiling: 55.9 years; PED: 53.2 years	• Degree of disability • Complications	No reference to previous or concurrent SAH Cohort study Confounding factors: Groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
Narata 2019[91]	**Stent-assisted coiling:** Stent-assisted coiling. N=41 **Flow diverter device:** Flow diverter stent. N=113 Follow up: 3 months	Patients with unruptured intracranial aneurysms treated with a stent and under dual antiplatelet therapy with aspirin and ticagrelor. Mean age (SD): 53 years (12) France	• Mortality • Complications	Patients with ruptured aneurysm excluded from study. No reference to previous SAH. Cohort study Confounding factors: Groups matched for age

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: Interventional therapy (neurosurgical clipping or endovascular coiling) versus conservative management for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative management	Risk difference with interventional therapy (95% CI)
Quality of life (SF-36) Scale from: 0 to 100.	37 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf-36) in the control groups was 56.3	The mean quality of life (sf-36) in the intervention groups was 13.8 higher (1.18 lower to 28.78 higher)

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 because the majority of the evidence included an indirect population

Table 4: Clinical evidence summary: Neurosurgical clipping versus conservative management for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative management	Risk difference with neurosurgical clipping (95% CI)
Mortality	4324 (3 studies) 1 years	⨁⊖⊖⊖ VERY LOW1,23 due to risk of bias, indirectness, imprecision	Peto OR 0.62 (0.34 to 1.14)	Moderate	
				17 per 1000	6 fewer per 1000 (from 11 fewer to 2 more)
Quality of life (SF-36: Physical) Scale from: 0 to 100.	113 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf-36: physical) in the control groups was 50	The mean quality of life (sf-36: physical) in the intervention groups was 2 higher (1.24 lower to 5.24 higher)
Quality of life (SF-36: Mental) Scale from: 0 to 100.	113 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean quality of life (sf-36: mental) in the control groups was 50	The mean quality of life (sf-36: mental) in the intervention groups was 1 lower (5.13 lower to 3.13 higher)
mRS 3-5 Scale 0-6; high score represents poor outcome	4240 (2 studies) 1 years	⨁⨁⊖⊖ LOW1,3 due to risk of bias, indirectness	RR 5.74 (3.92 to 8.52)	Moderate	
				14 per 1000	66 more per 1000 (from 41 more to 105 more)
mRS >1 Scale 0-6; high score represents poor outcome	141 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	Peto OR 4.77 (1.05 to 21.73)	Moderate	
				0 per 1000	80 more per 1000 (from 20 more to 150 more)
Subsequent aneurysm haemorrhage	4261 (2 studies) 1 years	⨁⊖⊖⊖ VERY LOW1,3, 4, due to risk of bias, inconsistency, indirectness	Peto OR 0.13 (0.07 to 0.23)	Moderate	
				38 per 1000	33 fewer per 1000 (from 29 fewer to 35 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative management	Risk difference with neurosurgical clipping (95% CI)

1 Downgraded because the majority of the evidence included an indirect population
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 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
4 Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, subgroup analysis not possible as <2 studies per subgroup.

Table 5: Clinical evidence summary: Endovascular coiling versus conservative management for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative management	Risk difference with endovascular coiling (95% CI)
Mortality	3159 (4 studies) 1 years	⨁⊖⊖⊖ VERY LOW1,2,4 due to indirectness, imprecision, risk of bias	RR 0.6 (0.31 to 1.13)	Moderate	
				44 per 1000	18 fewer per 1000 (from 30 fewer to 6 more)
mRS 3-5 Scale 0-6; high score represents poor outcome	3106 (3 studies) 1 years	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to inconsistency, imprecision, indirectness, risk of bias	RR 1.26 (0.36 to 4.34)	Moderate	
				18 per 1000	5 more per 1000 (from 30 fewer to 60 more)
Subsequent aneurysm haemorrhage	2427 (3 studies) 1 years	⨁⊖⊖⊖ VERY LOW1,2,4 due to indirectness, imprecision, risk of bias	RR 0.57 (0.28 to 1.17)	Moderate	
				61 per 1000	26 fewer per 1000 (from 44 fewer to 10 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conservative management	Risk difference with endovascular coiling (95% CI)

1 Downgraded because the majority of the evidence included an indirect population
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.
4 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.

Table 6: Clinical evidence summary: Neurosurgical clipping versus endovascular coiling intervention for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endovascular coiling	Risk difference with neurosurgical clipping (95% CI)
Mortality	134 (1 RCT) at discharge	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	RR 1.06 (0.07 to 16.62)	Moderate	
				14 per 1000	1 more per 1000 (from 13 fewer to 219 more)
	368 (1 NRS) at one year	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	Peto OR 3.1 (0.04 to 243.83	0 per 1000	10 more per 1000 (from 30 fewer to 40 more)
mRS 3-5 Scale 0-6; high score represents poor outcome	134 (1 RCT) at discharge	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	RR 1.06 (0.07 to 16.62)	Moderate	
				14 per 1000	3 more per 1000 (from 40 fewer to 672 more)
	368 (1 NRS) at one year	⨁⊖⊖⊖ VERY LOW1,2 due to indirectness, imprecision	Peto OR 3.11 (0.09 to 110.34)	0 per 1000	10 more per 1000 (from 20 fewer to 40 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endovascular coiling	Risk difference with neurosurgical clipping (95% CI)
Neurological deterioration	134 (1 study) at discharge	⨁⨁⨀⨀ LOW1,2 due to indirectness, imprecision	RR 2.43 (1.07 to 5.51)	Moderate	
				101 per 1000	144 more per 1000 (from 7 more to 456 more)
Subsequent aneurysm haemorrhage	104 (1 study) 1 years	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.12 (0.07 to 17.47)	Moderate	
				18 per 1000	2 more per 1000 (from 17 fewer to 296 more)
Complication: failure to treat aneurysm	104 (1 study) 1 years	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 0.37 (0.04 to 3.48)	Moderate	
				55 per 1000	35 fewer per 1000 (from 53 fewer to 136 more)
Complication: Intraoperative aneurysm rupture or periprocedural ischemia	66 (1 study) 1 years	⨁⨀⨀⨀ VERY LOW1,3 due to imprecision, risk of bias	RR 3 (0.38 to 23.4)	Moderate	
				46 per 1000	91 more per 1000 (from 28 fewer to 1000 more)

1 Downgraded because the majority of the evidence included an indirect population
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 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

Table 7: Clinical evidence summary: Bioactive coil versus bare platinum coil for non-culprit aneurysms

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 bioactive coil (95% CI)
Mortality				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 bioactive coil (95% CI)
	746 (3 studies) 6-18 months	⨁⨀⨀⨀ VERY LOW1,2 due to indirectness, imprecision	RR 0.82 (0.24 to 2.81)	17 per 1000	3 fewer per 1000 (from 13 fewer to 31 more)
mRS 3-5 Scale 0-6; high score represents poor outcome	746 (3 studies) 6-18 months	⨁⨁⨀⨀ LOW1,2 due to indirectness, imprecision	RR 1.77 (0.85 to 3.67)	Moderate	
				27 per 1000	21 more per 1000 (from 4 fewer to 72 more)
Subsequent aneurysm haemorrhage	234 (1 study) 18 months	⨁⨁⨁⨁ HIGH	RD 0 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 more per 1000 (from 20 fewer to 20 more)
Procedural complications	487 (2 studies) 6-18 months	⨁⨀⨀⨀ VERY LOW1,2 due to indirectness, imprecision	RR 1.02 (0.65 to 1.6)	Moderate	
				135 per 1000	3 more per 1000 (from 47 fewer to 81 more)

1 Downgraded because the majority of the evidence included an indirect population
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: Stent assisted coil versus bare platinum coil for non-culprit aneurysms

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 stent assisted coil (95% CI)
Mortality	330 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, indirectness	RD 0.00 (-0.03 to 0.03)	Moderate	
				20 per 1000	0 more per 1000 (from 30 fewer to 30 more)
mRS greater than baseline				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 stent assisted coil (95% CI)
Scale 0-6; high score represents poor outcome	330 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.49 (0.78 to 2.83)	84 per 1000	41 more per 1000 (from 18 fewer to 154 more)
Subsequent aneurysm haemorrhage	361 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	Peto OR 0.2 (0 to 11.33)	Moderate	
				5 per 1000	4 fewer per 1000 (from 5 fewer to 49 more)
Complications of treatment allocation	441 (2 studies) 1 year	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision	RR 1.52 (0.65 to 3.53)	Moderate	
				39 per 1000	20 more per 1000 (from 14 fewer to 99 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 because the majority of the evidence included an indirect population
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: Balloon assisted coil versus bare platinum coil for non-culprit aneurysms for non-culprit aneurysms

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 balloon-assisted coil (95% CI)
Mortality	547 (1 study) unclear	⨁⊖⊖⊖ VERY LOW1,2,3 due to indirectness, imprecision, risk of bias	RR 1.46 (0.3 to 7.19)	Moderate	
				9 per 1000	4 more per 1000 (from 6 fewer to 56 more)

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 balloon-assisted coil (95% CI)
Complications of treatment allocation	547 (1 study)	⨁⊖⊖⊖ VERY LOW1,2,3 due to indirectness, imprecision, risk of bias	RR 1.09 (0.67 to 1.75)	Moderate	
				108 per 1000	10 more per 1000 (from 36 fewer to 81 more)

1 Downgraded because the majority of the evidence included an indirect population
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 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

Table 10: Clinical evidence summary: Balloon assisted coil versus stent-assisted coil for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with stent assisted coil	Risk difference with balloon-assisted coil (95% CI)
Complications of treatment allocation	106 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW1,2,3 due to indirectness, imprecision, risk of bias	Peto OR 0.21 (0.03 to 1.42)	Moderate	
				0 per 1000	70 fewer per 1000 (from 140 fewer to 0 more)

1 Downgraded because the majority of the evidence included an indirect population
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 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

Table 11: Clinical evidence summary: Flow diverter (PED) versus neurosurgical clipping for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with neurosurgical clipping	Risk difference with PED (95% CI)
mRS 3-5 Scale 0-6; high score represents poor outcome	44 (1 study) 6-14 months	⨁⊖⊖⊖ VERY LOW1,3 due to indirectness, risk of bias	RD 0 (-0.08 to 0.08)	Moderate	
				0 per 1000	0 more per 1000 (from 80 fewer to 80 more)
Procedure-related complications	44 (1 study) 6-14 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to indirectness, imprecision, risk of bias	RR 1.10 (0.42 to 2.87)	Moderate	
				261 per 1000	26 more per 1000 (from 151 fewer to 488 more)

1 Downgraded because the majority of the evidence included an indirect population
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 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.

Table 12: Clinical evidence summary: Flow diverter (PED) versus endovascular coiling for non-culprit aneurysms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endovascular coiling	Risk difference with PED (95% CI)
Mortality	295 (2 studies) 3-15 months	⨁⊖⊖⊖ VERY LOW1,2,3,4 due to inconsistency, indirectness, imprecision	Peto OR 2.28 (0.31 to 16.83)	Moderate	
				12 per 1000	15 more per 1000 (from 8 fewer to 158 more)
mRS 3-5 Scale 0-6; high score represents poor outcome	202 (2 studies) 8-23 months	⨁⊖⊖⊖ VERY LOW2,3,4 due to risk of bias, indirectness, imprecision	RR 0.81 (0.2 to 3.25)	Moderate	
				50 per 1000	9 fewer per 1000 (from 40 fewer to 113 more)
Procedure-related complications				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endovascular coiling	Risk difference with PED (95% CI)
	365 (3 studies) 3-23 months	⨁⊖⊖⊖ VERY LOW1,3,4 due to indirectness, imprecision, risk of bias	RR 1.33 (0.64 to 2.8)	73 per 1000	24 more per 1000 (from 26 fewer to 131 more)

1 Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, subgroup analysis not possible as <2 studies per subgroup.
2 Downgraded because the majority of the evidence included an indirect population
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 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

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

Five health economic studies relating to this question were identified but excluded due to a combination of limited applicability and methodological limitations[44, 55, 74, 149 38]. These are listed in Appendix J:, with reasons for exclusion given.

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

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 13: UK costs of elective neurosurgical clipping and endovascular coiling

Description	Average cost (a)
Clipping of aneurysm of cerebral artery in people 19 years and older [NHS Reference cost codes: AA50A-C, AA51A-D, AA52A-D]	£10,114
Clipping of aneurysm of cerebral artery in people 18 years and under [NHS Reference cost codes: AA50D-F, AA51E-G, AA52E-G]	£9,843
Percutaneous Transluminal Embolisation of intracranial and extracranial aneurysms [NHS Reference cost codes: YA01Z, YA02A-B, YA03A-C]	£5,909

Source: NHS Reference Costs 2018/19[94]
(a) Weighted by activity

Table 14: UK costs of conservative management

Description	Average cost
Computerised tomography scan with pre and post contrast [NHS Reference cost code: RD22Z]	£97
Neurosurgery consultant led outpatient follow up appointment [NHS Reference cost code: WF01A,150]	£167

Source: NHS Reference Costs 2018/19[94]

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee highlighted that the primary goal of intervention is to prevent future rupture of an aneurysm. Subsequent subarachnoid haemorrhage was considered to be a critical outcome, along with mortality, health and social-related quality of life, degree of disability (modified Rankin scale, Glasgow outcome scale) and complication of treatment. Return to daily activity was considered to be an important outcome.

No evidence was identified for return to daily activity.

1.6.1.2 The quality of the evidence

The evidence compared several different techniques to each other and some to conservative management. The sizes and locations of aneurysms are considered important in risk of future rupture but these were inconsistently or poorly described in the available studies.

The majority of evidence was graded at very low quality. This was mostly due to a risk of bias with the inclusion of non-randomised cohort studies with increased risk of selection bias and confounding bias. The observational data included demonstrated that participants were matched for the key confounder of age but none of the outcome evidence was adjusted to account for age or any other potentially confounding factors. The evidence comparing neurosurgical or endovascular to conservative management, stent-assisted coils to bare platinum coils (with no stent-assistance), balloon-assisted coils to bare platinum coils (with no balloon-assistance), and balloon-assisted coils compared to stent-assisted coils were all observational studies. RCT evidence was available for comparisons of neurosurgical clipping and endovascular coiling, and bioactive coil and bare platinum coil.

There was a high level of uncertainty due to significant statistical imprecision for most outcomes of the included studies. This was indicated by wide-ranging confidence intervals crossing the thresholds which demonstrate clinical significance, with which the committee would typically judge if an intervention shows benefit or harm. The committee noted that the small size of some studies and the low event rate of outcomes likely contributed towards this imprecision and reduced the overall quality of outcome data.

The evidence review intended to focus on people who have had an aneurysmal subarachnoid haemorrhage and also have a non-culprit aneurysm. However almost all of the studies in the review included populations who only had an un-ruptured aneurysm found incidentally with no previous or concurrent aneurysmal subarachnoid haemorrhage. Current knowledge of the natural history of aneurysms that subsequently rupture is drawn from these observational studies. The committee therefore wished to consider this evidence and agreed that it should inform the discussions regarding lifetime risk of aneurysm rupture and subsequent treatment options for non-culprit aneurysms. The committee acknowledged that people with a history of aneurysmal subarachnoid haemorrhage are recognised as having an increased risk of further aneurysm rupture compared to people with no history of subarachnoid haemorrhage. The quality of the evidence was therefore downgraded for indirectness due the potential difference in risk of aneurysm rupture.

For the comparison of clipping and endovascular coiling, 1 RCT and 2 non-randomised studies were reviewed. The observational data was reviewed alongside the RCT evidence given the indirectness of the RCT data, and the availability of observational data including a direct population.

The committee acknowledged the evidence was largely of low quality and from an indirect population and did not allow them to recommend a specific type of treatment for non-culprit lesions.

The committee considered it important to patients to include recommendations for non-culprit aneurysms in the guideline since this is an important issue for patients and agreed to make recommendations using informal consensus based on their experience.

The committee acknowledged this is a challenging area to conduct research. Given the importance of treating the ruptured aneurysm early after aneurysmal subarachnoid haemorrhage to secure the aneurysm and prevent rebleeding, limiting the risk of morbidity and mortality, the committee agreed that it would be uncommon for any un-ruptured aneurysms to be treated at the initial procedure. As such, the committee made a consensus recommendation and did not make any further research recommendations specifically for the management of non-culprit aneurysms. The committee highlighted that the intention for treatment of un-ruptured aneurysms found in patients with aneurysmal subarachnoid

haemorrhage is to provide life-long protection from a subsequent rupture. Evidence that could better predict rupture on the basis of aneurysmal location and other characteristics would better direct treatment in this area. In addition, good quality evidence on the treatment modalities available to prevent rupture of non-culprit aneurysms is lacking. The committee noted that the research recommendation made on the evaluation of risk stratification tools to estimate the risk of subsequent aneurysmal subarachnoid haemorrhage within the risk of subsequent SAH evidence review (see evidence review N, Appendix H) would also include a population who had non-culprit aneurysms and inform this area. Similarly, the research recommendation made on the effectiveness of novel endovascular techniques and devices within the interventions to prevent rebleeding evidence review would also be applicable to people with non-culprit aneurysms.

1.6.1.3 Benefits and harms

The aim of managing non-culprit lesions is to prevent future aSAH and associated death and disability and to balance this benefit with potential harm of an intervention. The findings were not consistent across studies and the low quality of the evidence made using the evidence to judge between benefits and harms difficult.

The evidence available suggested a benefit for treatment over conservative management. One study comparing either clipping or coiling to conservative management found a clinically important benefit of intervention for patient quality of life as measured by SF-36 at 6 months post-intervention, although this evidence was from a small study and was assessed to be very low quality.

Four studies showed clinically significantly lower mortality rates with coiling compared to conservative management. However, there was no clinically significant difference in the same studies between coiling and conservative management for neurological status (as measured by mRS) or risk of subsequent aneurysm haemorrhage.

Evidence from 3 studies showed no clinically important difference between groups receiving clipping or conservative management for overall mortality. The differences seen between clipping and conservative management for quality of life (mental), neurological status (as measured by mRS) and risk of subsequent aneurysm haemorrhage were also not clinically significant. The committee recognised that clipping provided a clinically important benefit over conservative management for quality of life (physical) but noted the very low quality of the evidence.

The evidence available showed no clear benefit or harm between clipping and coiling. One RCT and 2 non-randomised studies compared the safety and efficacy of clipping to endovascular coiling. Evidence from the RCT showed a benefit of coiling for likelihood of postoperative neurological deterioration (mRS reduced following intervention). Summated evidence from the 3 studies showed no difference between interventions for mortality, poor postoperative neurological status (mRS 3-5), subsequent aneurysm rupture or complication of intervention.

The evidence from 6 RCTs comparing bioactive coils to bare-platinum coils showed no clinically important difference between interventions for mortality, poor postoperative neurological status (as indicated by mRS 3-5), subsequent aneurysm rupture or complication of intervention. The committee noted that the included studies reviewed the differing technologies of coated coils, including Matrix and Cerecyte coils, and first- and second-generation hydrogel coils. The committee noted that second generation hydrogel coils are more commonly used in current practice but agreed that evidence could be pooled for comparison to bare-platinum coils.

The committee discussed the findings from cohort studies comparing stent-assisted coils to bare platinum coils (with no stent-assistance), balloon-assisted coils to bare platinum coils (with no balloon-assistance), and balloon-assisted coils compared to stent-assisted coils,

respectively. The evidence presented suggested no clinically important difference between interventions for mortality, poor postoperative neurological status (mRS 3-5), subsequent aneurysm rupture or complication of intervention.

Evidence from 1 study comparing a flow diverting device to neurosurgical clipping showed no significant difference between groups for poor postoperative neurological status (mRS 3-5) or complication of intervention. The committee noted a benefit of coiling for mortality in studies comparing flow diverting devices to endovascular coiling. Evidence also suggested no difference between interventions for poor postoperative neurological status (mRS 3-5) or complication of intervention.

The committee added that estimated lifetime rupture risk of an unruptured aneurysm is considered to be influenced by aneurysm location and increase with aneurysm size. Although this information was not captured by the evidence review, the committee agreed that these aneurysm characteristics should be considered alongside the potential benefits and harms of interventions for non-culprit aneurysms (as presented by the low quality evidence available). The committee were aware that non-culprit aneurysms can enlarge over time, and there was consensus that in selected patients whose aneurysm has grown to a large size, coiling and clipping may prevent rupture and significant harms associated with this.

The committee also noted that conservative management can negatively impact a person's quality of life due to anxiety over the possibility that they may have another subarachnoid haemorrhage. On the other hand, any intervention involves procedural risk, including the risks of general anaesthesia and rupture of a previously stable aneurysm.

There was not enough good evidence to enable the committee to recommend a specific management option for non-culprit aneurysms. Based on their experience, the committee made a consensus recommendation that a multidisciplinary team (MDT) that includes a neuroradiologist and a neurosurgeon should evaluate the options for managing non-culprit aneurysms, including endovascular coiling, neurosurgical clipping or conservative management and follow-up monitoring. Based on the committee's experience of evaluating the options for managing a non-culprit aneurysm, the MDT would take into account factors such as the size and location of the aneurysm, the estimated lifetime risk of the aneurysm rupturing, the estimated risk of each treatment option and the person's preferences.

1.6.2 Cost effectiveness and resource use

No published economic evaluations were identified for inclusion in this review; therefore unit costs were presented to the committee to aid consideration of cost effectiveness.

The committee discussed that conservative management would usually include ongoing monitoring of the aneurysm with a MR angiogram to detect any changes in the aneurysm size or shape. The committee discussed that the frequency of this would usually be determined by a multidisciplinary team (MDT) involving neuroradiology and neurosurgical opinion and taking account of the estimated lifetime risk of rupture. An outpatient consultation with a suitably qualified healthcare professional would then be required to discuss the MDT opinion and to determine the patient's preferred management strategy.

The committee acknowledged that intervention is initially much more costly than conservative management but long-term surveillance also carries costs. In addition, the effectiveness of a long-term surveillance strategy is currently uncertain due to the unpredictability of aneurysm rupture, and therefore conservative management may not prevent future rupture of an aneurysm. If the aneurysm were to rupture and cause a subsequent subarachnoid haemorrhage, this will incur the high cost of emergency treatment, and potentially also a decrease in quality of life due to significant disability or death. Due to this uncertainty in clinical and cost-effectiveness of follow-up strategies, a weaker recommendation for

conservative management and follow-up monitoring as an option for the management of non-culprit aneurysms was made.

Overall, the committee discussed that the probability of a non-culprit aneurysm rupturing is relatively low. Therefore, it is unlikely that treating all non-culprit aneurysms will be a cost-effective strategy, and so made a recommendation that intervention for a non-culprit aneurysm should be considered taking into consideration the estimated lifetime risk of rupture, comorbidities and patient preference.

1.6.3 Other factors the committee took into account

The initial decision on whether to treat or not is based on multiple factors. The committee considered that a MDT including neuroradiologist and neurosurgeon should evaluate options taking into account the size and location of the aneurysm, the lifetime risk of rupture, the risk of each treatment option and individual patient preference and co-morbidities. The options need to be explained and discussed with the patient and their family. As such, the committee recommended that the proposed management plan and any alternative options should be discussed with the person with a SAH (and their family or carers as appropriate).

The committee also acknowledged that awareness of the presence of an unruptured aneurysm may adversely impact a person with subarachnoid haemorrhage, and emphasized the importance of support from a suitably qualified healthcare professional. Patient's will differ in their attitude to risk and their general health status and other morbidities will influence the suitability of an intervention for each individual. The committee noted that rupture risk tools are currently used by clinicians to evaluate the growth of an aneurysm and risk of subsequent rupture to help inform these discussions.

The committee recognised that there is variation in surveillance protocols for people with non-culprit aneurysms, and inconsistent thresholds of lifetime risk at which intervention is offered and accepted by people with non-culprit aneurysms. This will be related to individual patient choice and the committee agreed that such discussions and decisions are vital for ongoing care.

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149. Zweifel C, Sacho RH, Tymianski R, Radovanovic I, Tymianski M. Safety, efficacy, and cost of surgery for patients with unruptured aneurysms deemed unsuitable for endovascular therapy. Acta Neurochirurgica. 2015; 157(12):2061-2070; discussion 2070

Appendices

Appendix A: Review protocols

Table 15: Review protocol: Managing non-culprit aneurysms

ID	Field	Content
0.	PROSPERO registration number	CRD42019132508
1.	Review title	What is the clinical and cost effectiveness of different options for managing non-culprit aneurysms in adults with a confirmed aneurysmal subarachnoid haemorrhage?
2.	Review question	What is the clinical and cost effectiveness of different options for managing non-culprit aneurysms in adults with a confirmed aneurysmal subarachnoid haemorrhage?
3.	Objective	To determine which intervention to manage non-culprit aneurysms 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 with identified non-culprit 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) ○ 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) • To no treatment/conservative (medical) management
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, 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	
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) • Subsequent subarachnoid haemorrhage • Complications of treatment allocation
13.	Secondary outcomes (important outcomes)	• Return to daily activity 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) • 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): • Detection: ○ at time of initial intervention for culprit aneurysm ○ during follow-up • Age: ○ <60 years ○ >60 years • Comorbidity: ○ Diabetes

<table>
<tr><td></td><td></td><td colspan="3">
○ Hypertension
○ Pulmonary disease
○ Myocardial disease
○ Cerebrovascular disease
• Size (as reported by studies):
○ Small
○ Large
• Location (as reported by studies)
</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3"></td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">3 February 2021</td></tr>
<tr><td rowspan="8">23.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☑</td><td>☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☑</td><td>☑</td></tr>
<tr><td>Data analysis</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail
SAH@nice.org.uk

5e Organisational affiliation of the review</td></tr>
</table>

		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 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; non-culprit anuerysm	
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 16: 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.[92] **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 different options for managing non-culprit aneurysms in adults with a confirmed aneurysmal subarachnoid haemorrhage?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[92]

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 17: 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 Observational studies

Database	Dates searched	Search filter used
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 18: 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

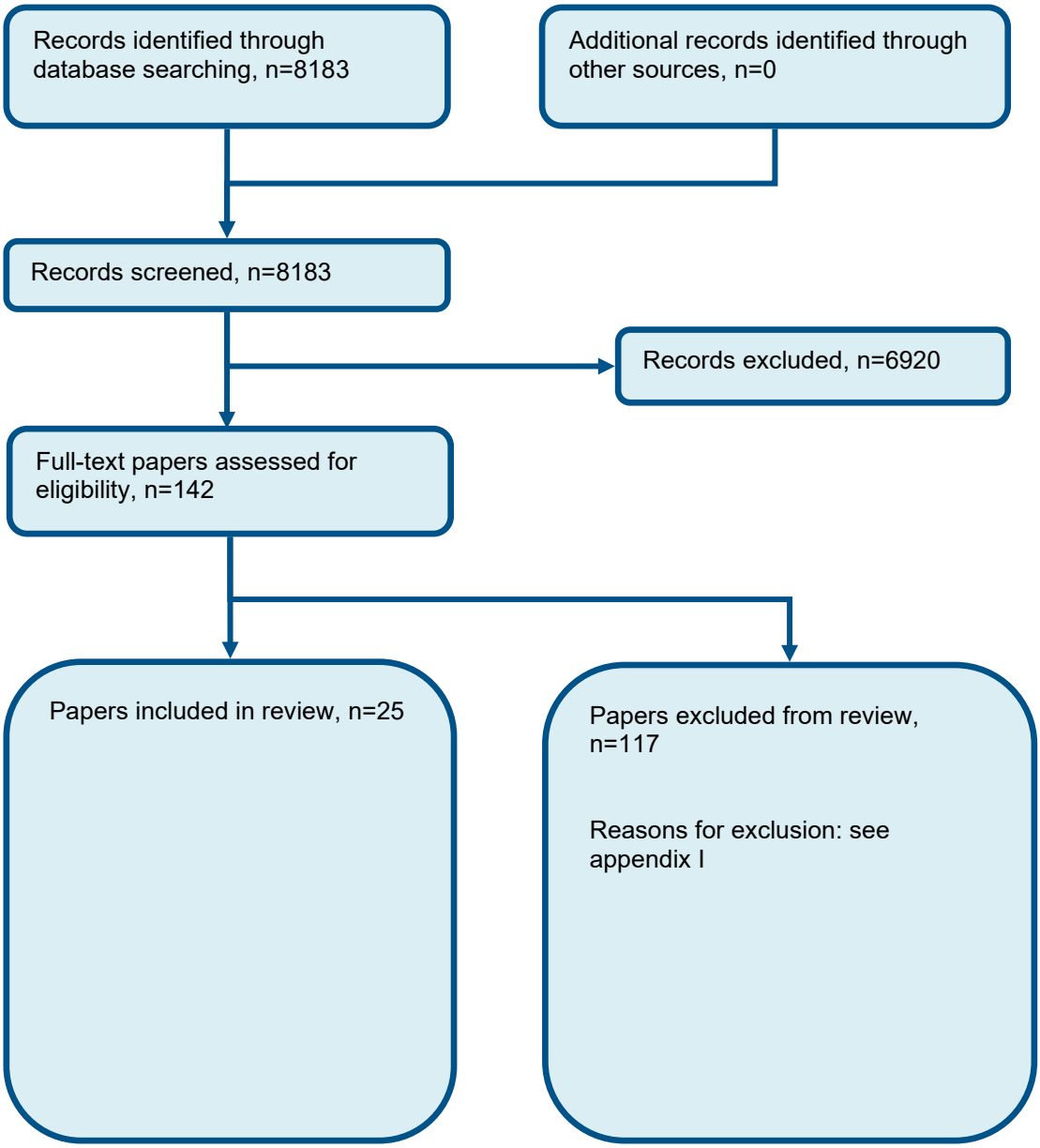
39.	24 and 38

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 non-culprit aneurysms



Appendix D: Clinical evidence tables

Study (subsidiary papers)	Mahaney 2014[3] (Wiebers 2003[141], Wiebers 1998[140])
Study type	Cohort study
Number of studies (number of participants)	(n=4059)
Countries and setting	Conducted in USA; Setting: Centres in the USA, Canada, and Europe
Line of therapy	Not applicable
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	People with at least 1 saccular UIA of at least 2 mm in maximum diameter confirmed by cerebral arteriography.
Exclusion criteria	Patients with a neurologically devastating prior haemorrhage. Patients in whom the sole UIA was previously manipulated by wrapping, packing, coil placement, proximal arterial ligation, bypass, balloon occlusion, or clip placement before entry into the study were not eligible. Patients with a history of intracranial haemorrhage from an unrepaired underlying structural lesion, primary intracerebral haemorrhage (without an underlying structural lesion), or SAH from an undetermined origin were excluded from the study. Patients with a malignant brain tumour were also excluded from the study.
Recruitment/selection of patients	Eligible patients from centres recruited
Age, gender and ethnicity	Age - Other: No surgery: 55.2 years (13.1); Clipping: 51.5 years (11.4); Coiling: 53.7 years (13.1). Gender (M:F): Not reported. n/a
Further population details	1. Age: <65 years 2. Characteristic of aneurysm: Size (small) (<7mm: 865; 7-12mm: 485; 13-24mm: 209; 25+mm: 57). 3. Comorbidity: (to be reported) (History of ischemic heart disease: 7%; History of hypertension: 41%). 4. Location of aneurysm: (to be reported) (ICA:~25%; MCA:~25%; PCA:~15%;

	Other (cavernous sinus, ACA, BA)). 5. Point of detection: Not stated / Unclear (Subset with previous SAH, outcome data not separated).
Extra comments	Some patients had other aneurysms presenting with SAH in the past; these aneurysms were required to be definitively treated prior to enrolment in the study.
Indirectness of population	Serious indirectness: History of SAH/ no history of SAH: 42/451, 320/1917, 615/1691
Interventions	(n=1917) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. A surgical procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment.. Duration n/a. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=451) Intervention 2: Endovascular intervention - Coiling. An endovascular procedure to treat at least 1 intracranial aneurysm was scheduled within 30 days of enrolment.. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness (n=1691) Intervention 3: No treatment/conservative management - No treatment. Patients untreated for UIA. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Academic or government funding (National Institute of Neurological Disorders and Stroke, NIH.)

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

Protocol outcome 1: Mortality
- Actual outcome: Surgery-related death at 1 year; Group 1: 2/326, Group 2: 0/42
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, 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: mRS ≥3 (or haemorrhage) at 1 year; Group 1: 3/326, Group 2: 0/42
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROSURGICAL CLIPPING versus NO TREATMENT

Protocol outcome 1: Mortality
- Actual outcome: Fatality at 1 year; Group 1: 18/1917, Group 2: 22/1691
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, 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: mRS ≥3 (or haemorrhage) at 1 year; Group 1: 176/1917, Group 2: 27/1691
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Subsequent subarachnoid haemorrhage
- Actual outcome: Haemorrhage at 1 year; Group 1: 4/1917, Group 2: 27/1691
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING versus NO TREATMENT

Protocol outcome 1: Mortality
- Actual outcome: Fatality at 1 year; Group 1: 6/451, Group 2: 22/1691
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, 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: mRS ≥3 (or haemorrhage) at 1 year; Group 1: 23/451, Group 2: 27/1691
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Subsequent subarachnoid haemorrhage
Risk of bias: All domain – Very high, Selection bias – High, Confounding bias – High, 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 ; Complications of treatment ; Return to daily activity (e.g. work)

Study	Chalouhi 2013[27]
Study type	Cohort study
Number of studies (number of participants)	(n=160)
Countries and setting	Conducted in USA
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 15 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with unruptured, large or giant (≥10 mm) aneurysms treated with PED or coiling were identified.
Exclusion criteria	patients treated with PED were significantly older, had significantly larger aneurysms, and had aneurysms that were more likely to be fusiform in morphology. As there were significant differences between patients treated with PED and coils, fusiform aneurysms (more treated with PED) and anterior communicating artery aneurysms (none treated with PED) were eliminated
Recruitment/selection of patients	Records from database
Age, gender and ethnicity	Age - Mean (SD): PED: 60.7 (12.7); Coil: 60.3 (10.6). Gender (M:F): 24/136.
Further population details	1. Age: <65 years 2. Characteristic of aneurysm: Size (large) (>10mm). 3. Comorbidity: Not stated / Unclear 4. Location of aneurysm: (to be reported) (Carotis ophthalmic: 49; Carotid cavernous: 23; Vertebrobasilar: 24; Paraclinoid: 38; MCA: 8; Posterior communicating: 17; Petrous: 1). 5. Point of detection: Not stated / Unclear
Indirectness of population	Serious indirectness: No reference to previous or concurrent SAH
Interventions	(n=40) Intervention 1: Endovascular intervention - Flow diverter (e.g. pipeline device) . The number of stents deployed and the adjunctive use of coils was left to the operator’s discretion. The PED procedure was interrupted (i.e., no additional devices were placed) when any amount of stasis was

	seen inside the aneurysm. The expansion of the PED was documented under fluoroscopy or with additional DynaCT/Xpert computed tomography angiography at the operator's discretion. Inadequate vessel wall apposition was remedied with Gateway balloon (Boston Scientific, Fremont, CA) angioplasty when needed. Placement of additional PEDs was considered at follow-up if the aneurysm remained unchanged, despite treatment.. Duration n/a. Concurrent medication/care: Treatment was performed with an initial 100-U/kg heparin bolus and maintenance of activated clotting time of 2× the patient's baseline intraoperatively. Heparin was discontinued at the conclusion of the procedure. Dual antiplatelet therapy was continued for ≥6 months after the procedure.. Indirectness: No indirectness (n=120) Intervention 2: Endovascular intervention - Coiling (stent assisted). Coiling was interrupted when the aneurysm was completely occluded or when no additional coils could be deployed. Stent-assisted coiling was typically performed using the microcatheter jailing technique in which the stent is deployed after the aneurysm is microcatheterized but before coil deployment.. Duration n/a. Concurrent medication/care: Coiling was performed with an initial 100 U/kg of heparin bolus and maintenance of activated clotting time of 2× the patient's baseline intraoperatively.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIPELINE DEVICE versus COILING (STENT ASSISTED)

Protocol outcome 1: Mortality
- Actual outcome: Mortality at Median follow-up: PED 8 months; coil 15 months; Group 1: 1/38, Group 2: 0/103
Risk of bias: All domain – Very High, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 17

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: mRS ≥3 at Median follow-up: PED 8 months; coil 15 months; Group 1: 2/38, Group 2: 6/103
Risk of bias: All domain – Very High, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 17

Protocol outcome 3: Complications of treatment - Actual outcome: Procedure-related complications at n/a; Group 1: 3/40, Group 2: 9/120; Comments: Procedure-related complications occurred in 3 (7.5%) patients (1 ischemic event, and 1 contralateral and 1 ipsilateral distal haemorrhage) in the PED group. In the coil group, there were 9 (7.5%; P=1) overall procedure-related complications (8 thromboembolic or ischemic events and 1 cranial nerve palsy) Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, 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 ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work)

Study (subsidiary papers)	Coley 2012[31] (Molyneux 2012[87])
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 month
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 a 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.
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). 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: Endovascular intervention - Coiling (bare platinum) versus Endovascular intervention - Coiling (coated platinum). Protocol outcome 1: Mortality - Actual outcome: Mortality; Group 1: 1/119, Group 2: 0/123 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 - Actual outcome: Degree of disability (mRS 3-5).; Group 1: 4/119, Group 2: 0/123 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: Complications - Actual outcome: Procedural complications.; Group 1: 15/133, Group 2: 12/131 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)

Study	CURES trial: Darsaut 2017[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=136)
Countries and setting	Conducted in Canada; Setting: Four Canadian and one European centres
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with UIAs eligible for both endovascular and surgical repair. Independent (modified Rankin Scale (mRS) score of ≤2) patients 18 years and older with any intradural saccular UIAs 3–25 mm in maximal cross-sectional diameter were offered participation if they had at least 10 years of life expectancy.
Exclusion criteria	Aneurysms were excluded if they were thought to require endovascular flow diversion or parent vessel occlusion, with or without a bypass.
Recruitment/selection of patients	eligible patients recruited from centre
Age, gender and ethnicity	Age - Mean (SD): 57 (7). Gender (M:F): 42/94
Further population details	1. Age: <65 years 2. Characteristic of aneurysm: Size (medium) (Mean (range): surgical 8.7mm (3-20); 8.2mm (3-23)). 3. Comorbidity: (to be reported) (Hypertension: 65; Smoker: 56;). 4. Location of aneurysm: (to be reported) (Anterior circulation 131; posterior 5). 5. Point of detection: Not applicable
Indirectness of population	Serious indirectness: History of previous SAH from another aneurysm: 14 (7&7)/136
Interventions	(n=66) Intervention 1: Neurosurgical intervention - Neurosurgical clipping. Surgical clipping. Duration n/a. Concurrent medication/care: technical details left to the individual operators.. Indirectness: No indirectness (n=70) Intervention 2: Endovascular intervention - Coiling. Endovascular coiling. Duration n/a.

	Concurrent medication/care: technical details left to the individual operators.. Indirectness: No indirectness
Funding	Academic or government funding (Funded by the CIHR (MOP 119554) and sponsored by the Centre Hospitalier de l'Université de Montréal.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROSURGICAL CLIPPING versus COILING Protocol outcome 1: Mortality - Actual outcome: Mortality at discharge; Group 1: 1/65, Group 2: 1/69 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: 1; Group 2 Number missing: 1 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 discharge; Group 1: 3/65, Group 2: 3/65 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: 1; Group 2 Number missing: 1 - Actual outcome: neurological deficit at discharge; Group 1: 16/65, Group 2: 7/69 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: 1; Group 2 Number missing: 1 Protocol outcome 3: Subsequent subarachnoid haemorrhage - Actual outcome: Intracranial haemorrhage during first-year FU at 1 year; Group 1: 1/49, Group 2: 1/55 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: 17; Group 2 Number missing: 15 Protocol outcome 4: Complications of treatment - Actual outcome: Failure to treat aneurysm with allocated modality at 1 year; Group 1: 1/49, Group 2: 3/55 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: 17; Group 2 Number missing: 15	
Protocol outcomes not reported by the study	Health and social quality of life ; Return to daily activity (e.g. work)

Study	Frontera 2014[37]
Study type	Cohort study
Number of studies (number of participants)	(n=116)
Countries and setting	Conducted in USA; Setting: Study medical centre
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	unruptured cerebral aneurysm, attempted aneurysm repair using SAC, coiling alone or surgical clipping, presence of at least one digital subtraction angiogram following aneurysm repair and age ≥18 years.
Exclusion criteria	not reported
Recruitment/selection of patients	consecutive patients
Age, gender and ethnicity	Age - Median (range): SAC: 58 (42-78) Coil: 55 (31-78). Gender (M:F): 11/69.
Further population details	1. Age: <65 years 2. Characteristic of aneurysm: Size (large) (Median (range): SAC 9mm (5-25); Coiling 6.8mm (3-20)). 3. Comorbidity: Not stated / Unclear 4. Location of aneurysm: (to be reported) (Anterior/posterior: SAC 37/9; Coiling 26/7). 5. Point of detection: Not applicable
Indirectness of population	Serious indirectness: No reference of concurrent or previous SAH
Interventions	(n=47) Intervention 1: Endovascular intervention - Coiling (stent assisted). From 2003 to 2006, Neuroform (Stryker) self-expanding stents were preferentially used and from 2007 to 2010 Enterprise (Cordis) self-expanding stents were used. All patients received clopidogrel 75 mg orally four times a day and aspirin 325 mg orally four times a day beginning a minimum of 5 days prior to the procedure. During the procedure 4000 U intravenous heparin was administered and redosed throughout the case at 1000 U every hour. All patients received stent placement followed by coiling during a single procedure. Stents were deployed under roadmap guidance. After confirming the stent position with a follow-up angiogram, coil embolization of the aneurysm was performed using

	either Gugliemi detachable coils (Boston Scientific, Massachusetts, USA) or Orbit coils (Codman, Massachusetts, USA). Patients were instructed to continue a combination of clopidogrel 75 mg four times a day and aspirin 325 mg four times a day for a minimum of 6 weeks followed by aspirin 81 mg four times daily alone indefinitely.. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness (n=33) Intervention 2: Endovascular intervention - Coiling. Intravenous heparin was administered during the procedure as above and either Gugliemi detachable coils or Orbit coils were deployed through a standard microcatheter approach to pack the aneurysm. In some cases where a branch artery at the aneurysm base needed protection, balloon-assisted coil embolization using a hyperglide balloon (eV3, Plymouth, Minnesota, USA) was used during embolization.. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING (STENT ASSISTED) versus COILING

Protocol outcome 1: Mortality
- Actual outcome: mortality at discharge; Group 1: 0/47, Group 2: 0/33
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Complications of treatment
- Actual outcome: peri-procedural rupture at discharge; Group 1: 1/47, Group 2: 0/33
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, 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 ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work)

Study	Ge 2017[40]
Study type	Cohort study
Number of studies (number of participants)	(n=79)
Countries and setting	Conducted in China; Setting: Hospital in China
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 34 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	consecutive cases of unruptured basilar tip aneurysms
Exclusion criteria	Not reported
Recruitment/selection of patients	consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 57.3 (10.6). Gender (M:F): 27/52.
Further population details	1. Age: <65 years 2. Characteristic of aneurysm: Size (medium) (8.2mm +/- 4.4mm). 3. Comorbidity: Not stated / Unclear 4. Location of aneurysm: (to be reported) (basilar tip aneurysms). 5. Point of detection: Not applicable
Indirectness of population	Serious indirectness: All of these cases had no SAH history
Interventions	(n=44) Intervention 1: Endovascular intervention - Coiling (stent assisted). Endovascular treatment included conventional simple coiling and stent-assisted coiling. Stents were used for wide-neck aneurysms that were defined as having a dome-to-neck ratio <2 and irregularly shaped aneurysms.. Duration n/a. Concurrent medication/care: Antiplatelet therapy consisted of clopidogrel 75 mg/day and aspirin 100 mg/day for at least three days before implantation of stents. During procedures, a bolus of heparin was administered using 3000 IU, and then 1000IU per hour. After procedures, patients who were treated by stent-assisted coiling received clopidogrel therapy (75 mg/d) for four to six weeks and aspirin therapy (100 mg/d) for at least six months.. Indirectness: No indirectness

	(n=35) Intervention 2: No treatment/conservative management - Conservative management. The refusal of endovascular treatment resulted in conservative treatment. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Academic or government funding (National Natural Science Foundation of China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING (STENT ASSISTED) versus CONSERVATIVE MANAGEMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 18.1 months for conservative, 29.5 for treated; Group 1: 4/42, Group 2: 6/32
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Differing lengths of follow-up between groups; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: mRS ≥3 at 18.1 months for conservative, 29.5 for treated; Group 1: 5/42, Group 2: 7/32
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Study reports no. mRS ≤2 ; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcome 3: Subsequent subarachnoid haemorrhage
- Actual outcome: Subarachnoid haemorrhage at 18.1 months for conservative, 29.5 for treated; Group 1: 5/42, Group 2: 6/31
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Differing lengths of follow-up between groups; Group 1 Number missing: 2; Group 2 Number missing: 3

Protocol outcomes not reported by the study	Health and social quality of life ; Complications of treatment ; Return to daily activity (e.g. work)

Study (subsidiary papers)	GREAT trial: 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 multicentre, 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 neurointerventionalist 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.
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). 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: Endovascular intervention - Coiling (bare platinum) versus Endovascular intervention - Coiling (coated platinum).

Protocol outcome 1: Mortality
- Actual outcome: Mortality; Group 1: 2/136, Group 2: 1/134
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 - Actual outcome: Degree of disability (mRS 3-5).; Group 1: 2/136, Group 2: 1/134 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	Mortality ; Health and social quality of life ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Subsequent subarachnoid haemorrhage ; Complications of treatment ; Return to daily activity (e.g. work)

Study (subsidiary papers)	HELPS trial: White 2008[139] (White 2011[138])
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, neurointerventionalist, 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 neurointerventionalist 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.
Age, gender and ethnicity	Age - Range: <45: 158; 46-55: 143; >55: 198. Gender (M:F): 149/350.
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	Serious indirectness: No reference to concurrent SAH
Interventions	(n=249) Intervention 1: Endovascular intervention - Coiling (coated 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. 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: Endovascular intervention - Coiling (bare platinum) versus Endovascular intervention - Coiling (coated platinum). Protocol outcome 1: Mortality - Actual outcome: Mortality; Group 1: 1/117, Group 2: 2/117	

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 - Actual outcome: Degree of disability (mRS 3-5).; Group 1: 12/117, Group 2: 9/117 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: Rebleed - Actual outcome: Subsequent aneurysm haemorrhage.; Group 1: 0/117, Group 2: 0/117 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 4: Complications - Actual outcome: Procedural complications.; Group 1: 18/109, 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 ;	
Protocol outcomes not reported by the study	Mortality ; Health and social quality of life ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Subsequent subarachnoid haemorrhage ; Complications of treatment ; Return to daily activity (e.g. work)

Study	Hetts 2014[50]
Study type	Cohort study
Number of studies (number of participants)	(n=361)
Countries and setting	Conducted in USA; Setting: No reference to previous or concurrent SAH
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	subjects 18–80 years of age with a baseline mRS score of 0–3 who had a single documented, untreated, unruptured intracranial aneurysm (4–20 mm) for which both polymer modified coils and platinum bare metal coils were treatment options and for which primary coiling treatment was planned to be completed during a single procedure.
Exclusion criteria	Patients with ruptured aneurysms in the MAPS trial were excluded from our current analysis, consisting of 6 patients treated with stent-coiling and 201 patients treated with coiling.
Recruitment/selection of patients	Post-hoc analysis of MAPS trial
Age, gender and ethnicity	Age - Mean (SD): 56.7. Gender (M:F): 84/277.
Further population details	1. Age: <65 years 2. Characteristic of aneurysm: Neck width (large) (Average neck: stent 4.7mm; coil 3.5mm). 3. Comorbidity: Not stated / Unclear 4. Location of aneurysm: Not stated / Unclear 5. Point of detection: Not applicable
Indirectness of population	No indirectness
Interventions	(n=137) Intervention 1: Endovascular intervention - Coiling (stent assisted). Neuroform stent and either platinum bare metal coils or polymer modified coils. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness

	(n=224) Intervention 2: Endovascular intervention - Coiling. Platinum bare metal coils or polymer modified coils without a stent. Duration n/a. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Study funded by industry (Stryker Neurovascular and its predecessor Boston Scientific Neurovascular.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COILING (STENT ASSISTED) versus COILING

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 1 year; Group 1: 3/128, Group 2: 4/202
Risk of bias: All domain – Very High, Selection bias – High, Confounding bias – High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 22

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: mRS worse than baseline at 1 year; Group 1: 16/128, Group 2: 17/202
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 22

Protocol outcome 3: Subsequent subarachnoid haemorrhage
- Actual outcome: Delayed bleed at 1 year; Group 1: 0/137, Group 2: 1/224
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

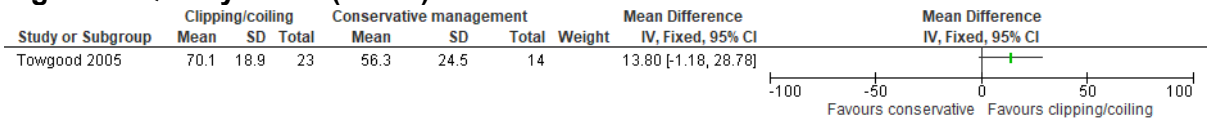
Protocol outcome 4: Complications of treatment
- Actual outcome: Peri-procedural serious adverse events at n/a; Group 1: 9/137, Group 2: 10/224
Risk of bias: All domain - Very High, Selection bias – High, Confounding bias – High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, 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)

Appendix E: Forest plots

E.1 Interventional therapy (neurosurgical clipping or endovascular coiling) versus conservative management

Figure 2: Quality of life (SF-36)



E.2 Neurosurgical clipping versus conservative management

Figure 3: Mortality (1 year)

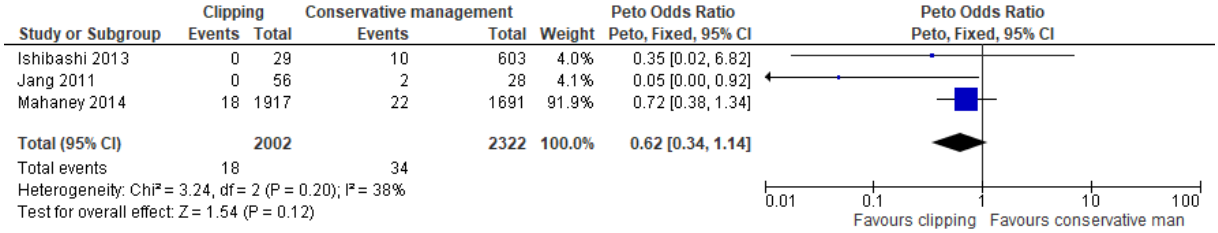


Figure 4: Quality of life (SF-36: Physical)

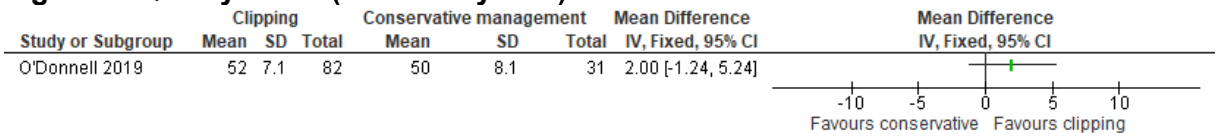


Figure 5: Quality of life (SF-36: Mental)

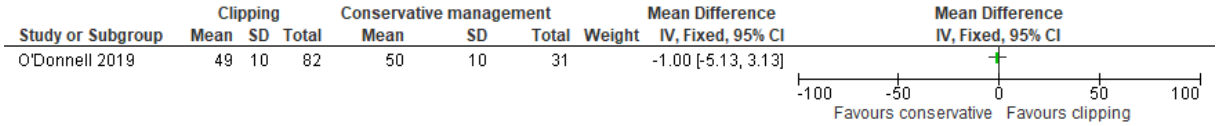


Figure 6: Degree of disability (mRS 3-5). Scale 0-6; high score represents poor outcome

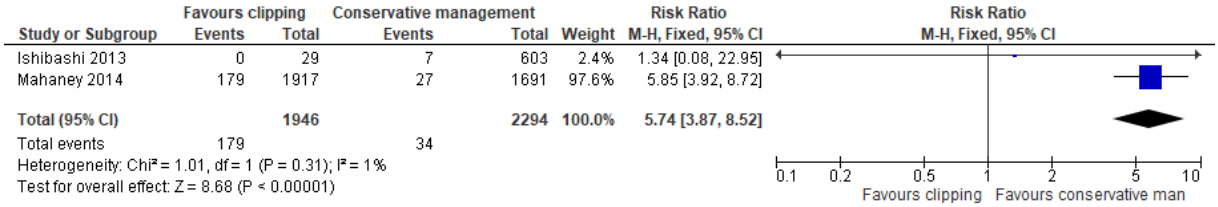


Figure 7: Degree of disability (mRS >1). Scale 0-6; high score represents poor outcome

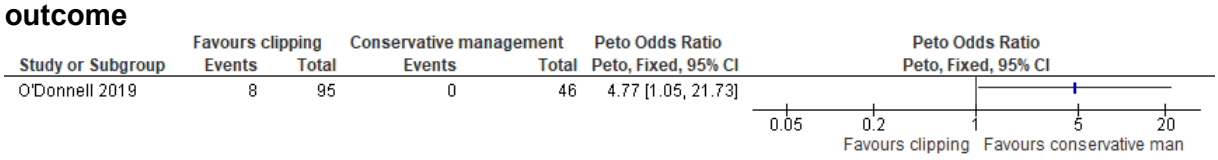
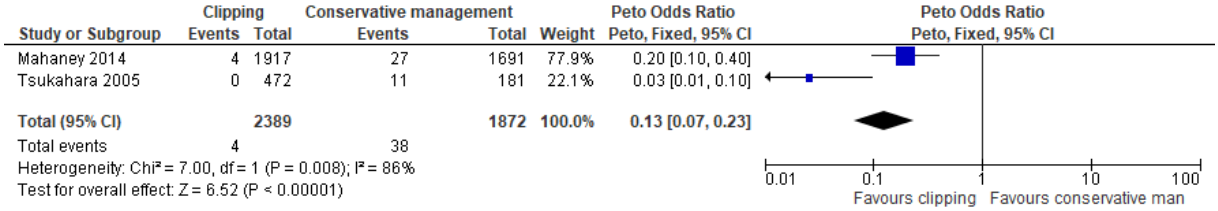


Figure 8: Subsequent aneurysm haemorrhage



E.3 Endovascular coiling versus conservative management

Figure 9: Mortality (1 year)

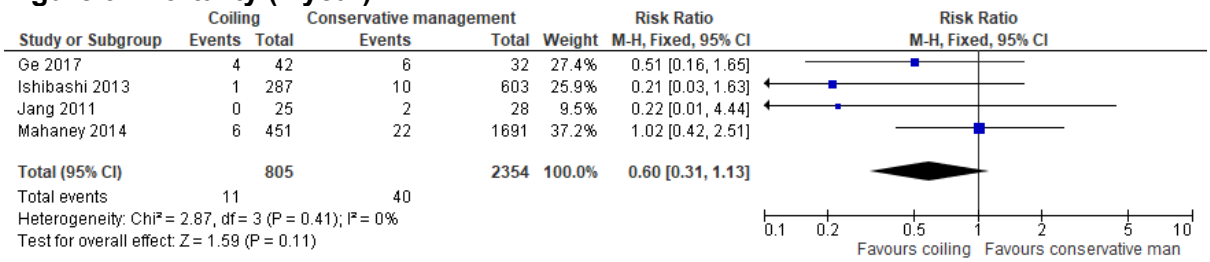


Figure 10: Degree of disability (mRS 3-5). Scale 0-6; high score represents poor outcome

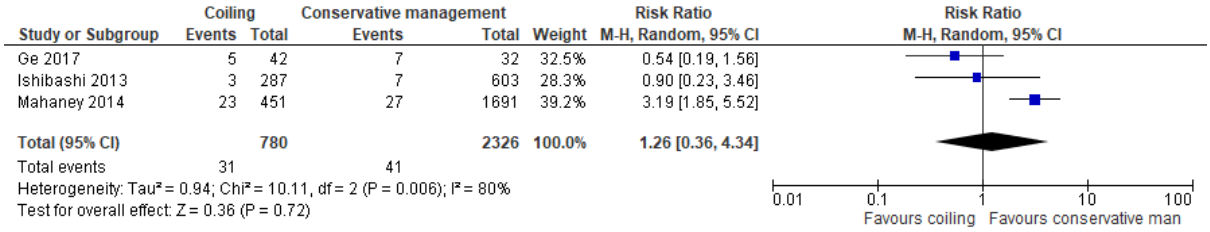
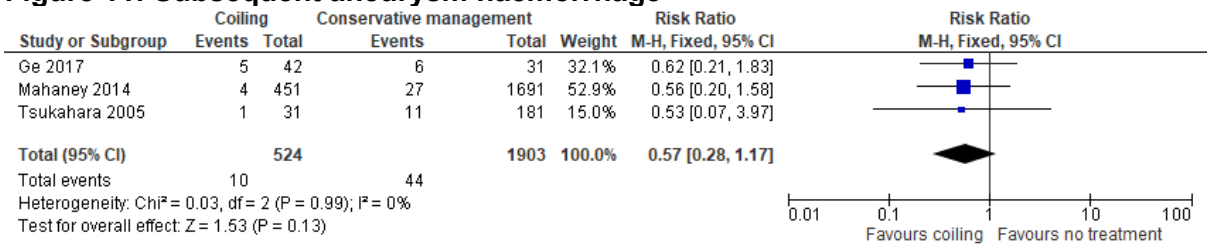


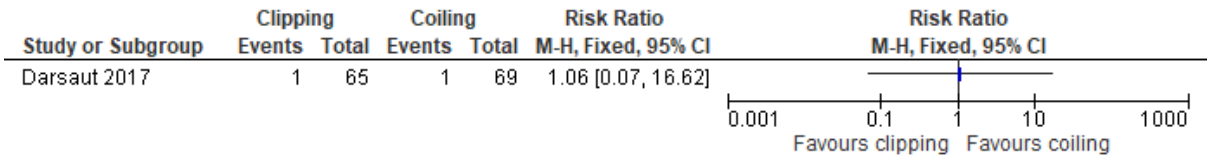
Figure 11: Subsequent aneurysm haemorrhage



E.4 Neurosurgical versus endovascular intervention

Figure 12: Mortality (1 year)

RCT data



NRS data

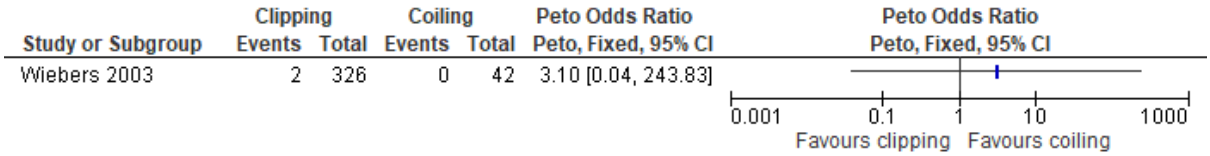
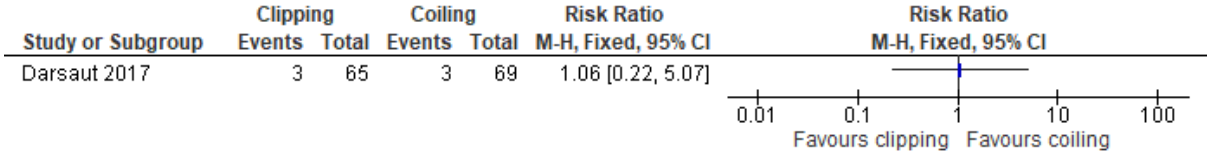


Figure 13: Degree of disability (mRS 3-5). Scale 0-6; high score represents poor outcome

RCT data



NRS data

Figure 14: Degree of disability (neurological deterioration)

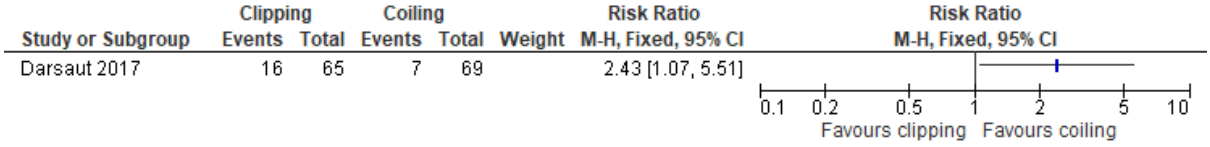


Figure 15: Subsequent aneurysm haemorrhage

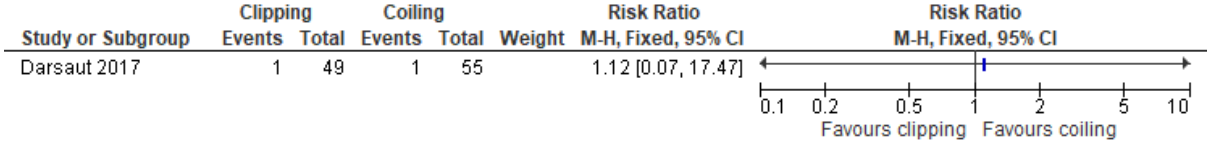


Figure 16: Procedural complications: Failure to treat aneurysm

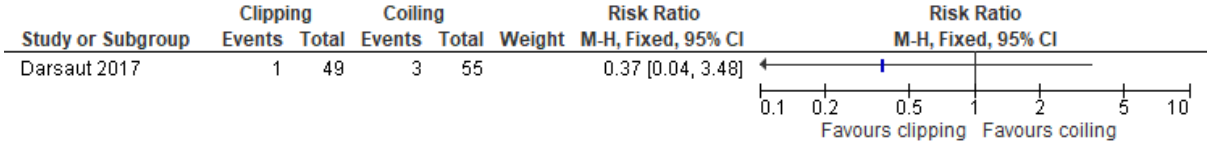
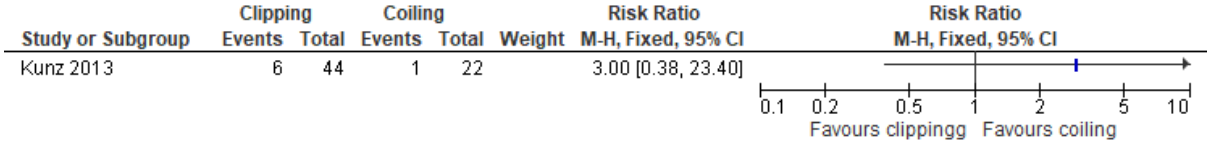


Figure 17: Procedural complication: Intraoperative aneurysm rupture or periprocedural ischemia



E.5 Bioactive coil versus bare platinum coil

Figure 18: Mortality (6-18 months)

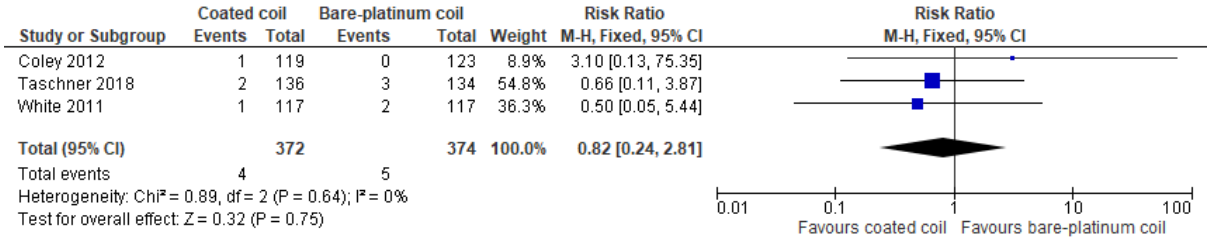


Figure 19: Degree of disability (mRS 3-5). Scale 0-6; high score represents poor outcome

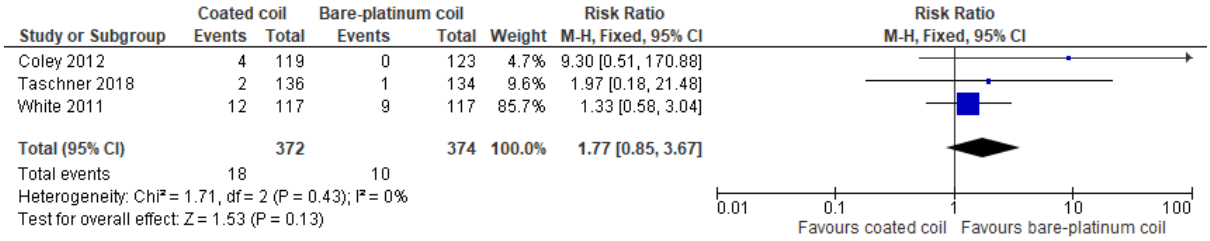


Figure 20: Subsequent aneurysm haemorrhage

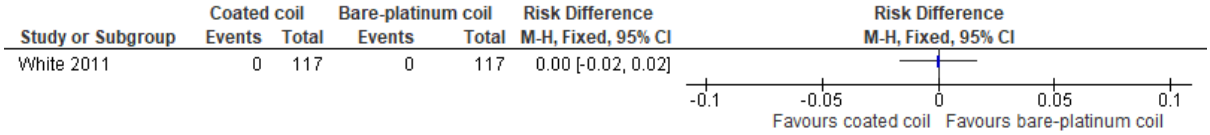
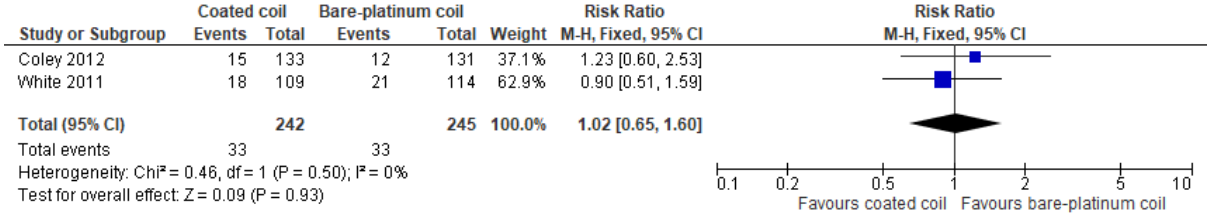


Figure 21: Procedural complications



E.6 Stent assisted coil versus bare platinum coil

Figure 22: Mortality

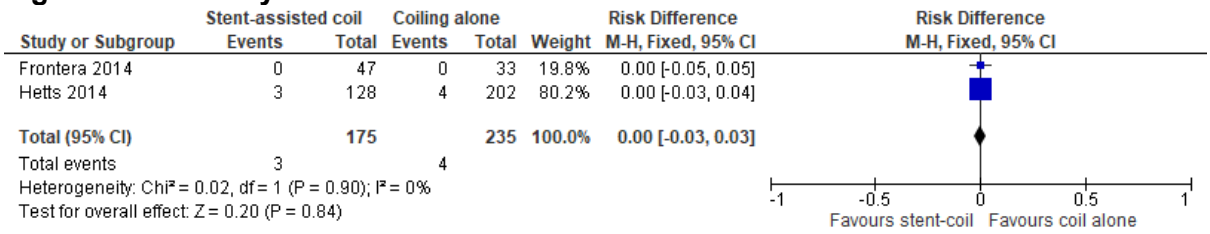


Figure 23: Degree of disability (mRS greater than baseline). Scale 0-6; high score represents poor outcome

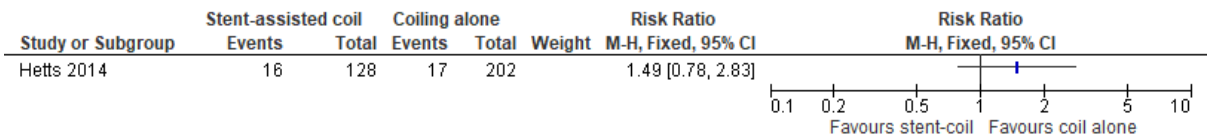


Figure 24: Subsequent aneurysm haemorrhage

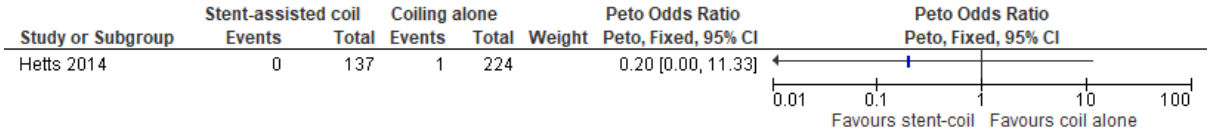
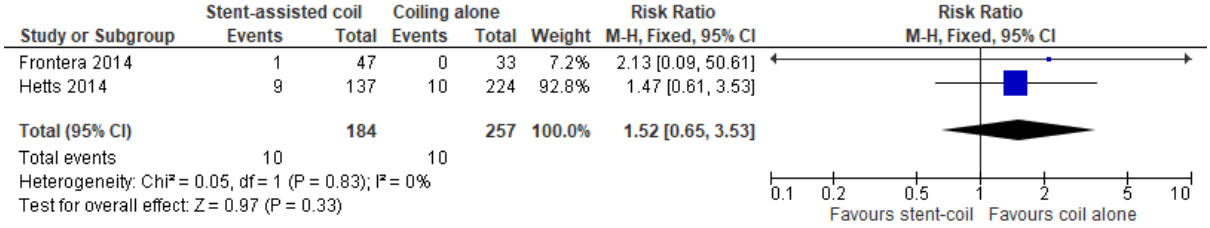


Figure 25: Procedural complications



E.7 Balloon assisted coil versus bare platinum coil

Figure 26: Mortality

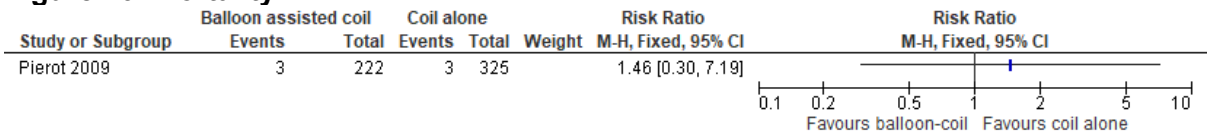
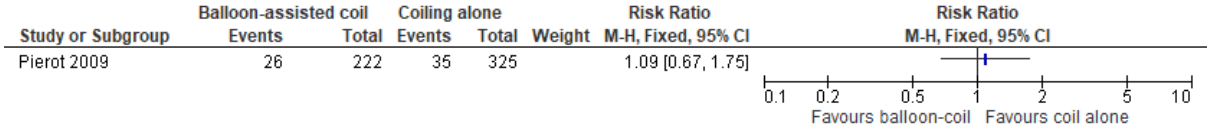
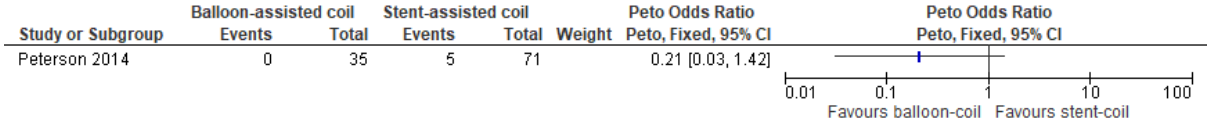


Figure 27: Procedural complications



E.8 Balloon assisted coil versus stent-assisted coil

Figure 28: Procedural complications



E.9 Flow diverter (PED) versus neurosurgical clipping

Figure 29: Degree of disability (mRS 3-5). Scale 0-6; high score represents poor outcome

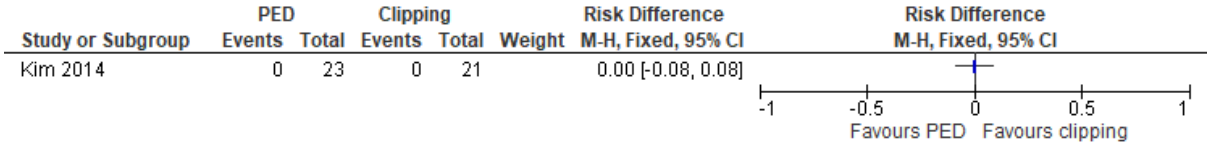
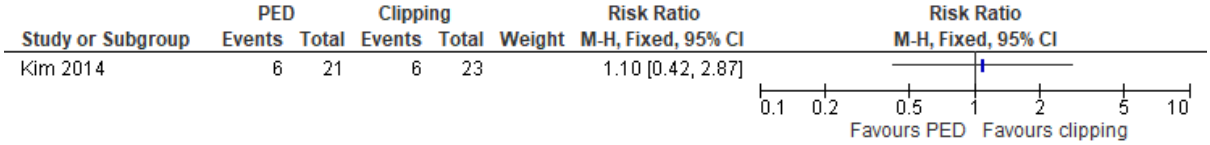


Figure 30: Procedural complications



E.10 Flow diverter (PED) versus endovascular coiling

Figure 31: Mortality

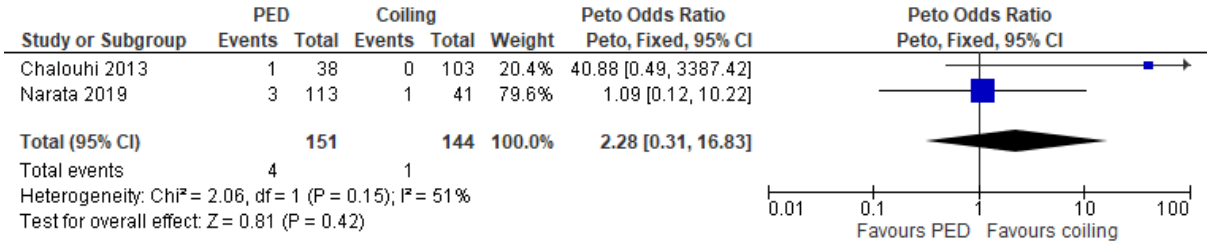
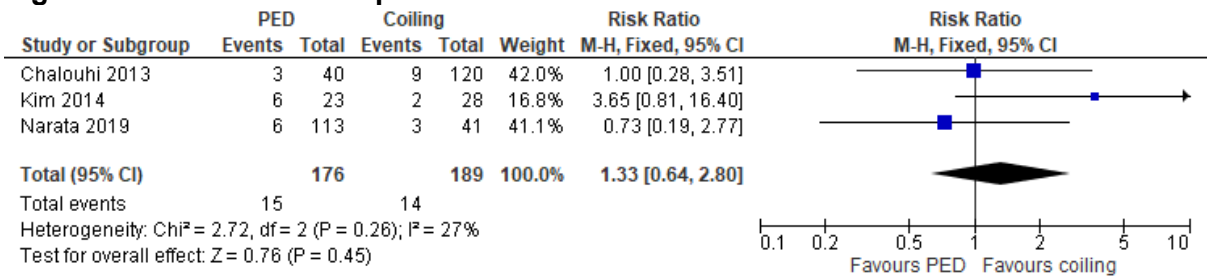


Figure 32: Degree of disability (mRS 3-5). Scale 0-6; high score represents poor outcome

Figure 33: Procedural complications



Appendix F: Minimal Important Difference for continuous outcomes

Table 19: Minimal important differences: Interventional therapy (neurosurgical or endovascular) versus conservative management for non-culprit aneurysms

Outcomes	Minimally important difference (MID)
Quality of life (SF-36) Scale from: 0 to 100.	12.25

Table 20: Minimal important differences: Neurosurgical clipping versus conservative management for non-culprit aneurysms

Outcomes	Minimally important difference (MID)
Quality of life (SF-36: Physical) Scale from: 0 to 100.	2†
Quality of life (SF-36: Mental) Scale from: 0 to 100.	3†

†Published MIDs (not median of control group)

Appendix G: GRADE tables

Table 21: Clinical evidence profile: Interventional therapy (neurosurgical clipping or endovascular coiling) versus conservative management for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clipping/coiling versus conservative management	Control	Relative (95% CI)	Absolute		
Quality of life (SF-36) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	observational studies[1]	very serious[2]	no serious inconsistency	serious[4]	serious[3]	none	23	14	-	MD 13.8 higher (1.18 lower to 28.78 higher)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence was from studies with observational/non-randomised study design.
[2] 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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded because the majority of the evidence included an indirect population

Table 22: Clinical evidence profile: Neurosurgical clipping versus conservative management for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neurosurgical clipping versus conservative management	Control	Relative (95% CI)	Absolute		
Mortality (follow-up mean 1 years)												

3	observational studies[1]	very serious[4]	no serious inconsistency	serious[2]	serious[3]	none	18/2002 (0.9%)	1.7%	OR 0.62 (0.34 to 1.14)	6 fewer per 1000 (from 11 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36: Physical) (follow-up 1 years; range of scores: 0-100; Better indicated by higher values)												
1	observational studies[1]	very serious[4]	no serious inconsistency	serious[2]	serious[3]	none	82	31	-	MD 2 higher (1.24 lower to 5.24 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF-36: Mental) (follow-up 1 years; range of scores: 0-100; Better indicated by higher values)												
1	observational studies[1]	very serious[4]	no serious inconsistency	serious[2]	serious[3]	none	82	31	-	MD 1 lower (5.13 lower to 3.13 higher)	⊕OOO VERY LOW	CRITICAL
mRS 3-5 (follow-up mean 1 years)												
2	observational studies[1]	very serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	179/1946 (9.2%)	1.4%	RR 5.74 (3.92 to 8.52)	42 more per 1000 (from 29 more to 58 more)	⊕⊕OO LOW	CRITICAL
mRS >1 (follow-up 1 years)												
1	observational studies[1]	very serious[4]	no serious inconsistency	serious[2]	serious[3]	none	8/95 (8.4%)	0%	OR 4.77 (1.05 to 21.73)	80 more per 1000 (from 20 more to 150 more)	⊕OOO VERY LOW	CRITICAL
Subsequent aneurysm haemorrhage (follow-up 1 years)												
2	observational studies[1]	very serious[4]	serious[5]	serious[2]	no serious imprecision	none	4/2389 (0.17%)	3.8%	OR 0.13 (0.07 to 0.23)	33 fewer per 1000 (from 29 fewer to 35 fewer)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence was from studies with observational/non-randomised study design.
[2] Downgraded because the majority of the evidence included an indirect population
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] 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
[5] Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 23: Clinical evidence profile: Endovascular coiling versus conservative management for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endovascular coiling versus conservative management	Control	Relative (95% CI)	Absolute		
Mortality (follow-up mean 1 years)												
4	observational studies[1]	very serious[5]	no serious inconsistency	serious[2]	serious[3]	none	11/805 (1.4%)	4.4%	RR 0.6 (0.31 to 1.13)	18 fewer per 1000 (from 30 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL
mRS 3-5 (follow-up mean 1 years)												
3	observational studies	very serious[5]	serious[4]	serious[2]	serious[3]	none	31/780 (4%)	1.8%	RR 1.26 (0.28 to 4.34)	18 more per 1000 (from 13 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
Subsequent aneurysm haemorrhage (follow-up mean 1 years)												
3	observational studies[1]	very serious[5]	no serious inconsistency	serious[2]	serious[3]	none	10/524 (1.9%)	6.1%	RR 0.57 (0.28 to 1.17)	26 fewer per 1000 (from 44 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 2 increments if the majority of the evidence was from studies with observational/non-randomised study design.
[2] Downgraded because the majority of the evidence included an indirect population
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[5] 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

Table 24: Clinical evidence profile: Neurosurgical versus Endovascular intervention for non-culprit aneurysms

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neurosurgical clipping versus endovascular coiling	Control	Relative (95% CI)	Absolute		
Mortality (follow-up at discharge) *RCT data*												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/65 (1.5%)	1.5%	RR 1.06 (0.07 to 16.62)	1 more per 1000 (from 14 fewer to 234 more)	⊕OOO VERY LOW	CRITICAL
Mortality (follow-up at 1 year) *NRS data*												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	2/326 (0.61%)	0%	Peto OR 3.1 (0.04 to 243.83)	1 more per 1000 (from 13 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
mRS 3-5 (follow-up at discharge) *RCT data*												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/65 (4.6%)	4.4%	RR 1.06 (0.22 to 5.07)	3 more per 1000 (from 34 fewer to 179 more)	⊕OOO VERY LOW	CRITICAL
mRS 3-5 (follow-up at 1 year) *NRS data*												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/326 (0.92%)	0%	Peto OR 3.11 (0.09 to 110.34)	10 more per 1000 (from 30 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Neurological deterioration (follow-up at discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	16/65 (24.6%)	10.1%	RR 2.43 (1.07 to 5.51)	144 more per 1000 (from 7 more to 456 more)	⊕⊕OO LOW	
Subsequent aneurysm haemorrhage (follow-up 1 years)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	1/49 (2%)	1.8%	RR 1.12 (0.07 to 17.47)	2 more per 1000 (from 17 fewer to 296 more)	⊕OOO VERY LOW	CRITICAL
Complication: failure to treat aneurysm (follow-up 1 years)												

1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	1/49 (2%)	5.5%	RR 0.37 (0.04 to 3.48)	35 fewer per 1000 (from 53 fewer to 136 more)	⊕OOO VERY LOW	CRITICAL
Complication: IAR or ischemia												
1	observational studies	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/44 (13.6%)	4.55%	RR 3 (0.38 to 23.4)	91 more per 1000 (from 28 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded because the majority of the evidence included an indirect population
[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 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

Table 25: Clinical evidence profile: Bioactive coil versus bare platinum coil for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bioactive coil versus bare platinum coil**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 6-18 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	4/372 (1.1%)	1.7%	RR 0.82 (0.24 to 2.81)	3 fewer per 1000 (from 13 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
mRS 3-5 (follow-up 6-18 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	18/372 (4.8%)	0.8%	OR 1.85 (0.86 to 3.99)	7 more per 1000 (from 1 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Subsequent aneurysm haemorrhage (follow-up 18 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/117 (0%)	0%	RD 0 (-0.02 to 0.02)	0 more per 1000 (from 20 fewer to 20 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Procedural complications (follow-up 6-18 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	33/242 (13.6%)	13.5%	RR 1.02 (0.65 to 1.6)	3 more per 1000 (from 47 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded because the majority of the evidence included an indirect population
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Clinical evidence profile: Stent assisted coil versus bare platinum coil for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stent assisted coil versus bare platinum coil**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 1 years)												
1	observational studies[1]	very serious[2]	no serious inconsistency	serious[3]	none	none	3/128 (2.3%)	2%	RD 0.00 (-0.03 to 0.03)	0 more per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
mRS worse than baseline (follow-up 1 years)												
1	observational studies[1]	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	16/128 (12.5%)	8.4%	RR 1.49 (0.78 to 2.83)	41 more per 1000 (from 18 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Subsequent aneurysm haemorrhage (follow-up 1 years)												
1	observational studies[1]	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	0/137 (0%)	0.5%	Peto OR 0.2 (0 to 11.33)	4 fewer per 1000 (from 5 fewer to 49 more)	⊕OOO VERY LOW	CRITICAL

Complications of treatment allocation (follow-up 1 years)												
2	observational studies[1]	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	10/184 (5.4%)	3.9%	RR 1.52 (0.65 to 3.53)	20 more per 1000 (from 14 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence was from studies with observational/non-randomised study design.
[2] 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
[3] Downgraded because the majority of the evidence included an indirect population
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence profile: Balloon assisted coil versus bare platinum coil for non-culprit aneurysms for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Balloon-assisted coil versus bare platinum coil**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up unclear)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/222 (1.4%)	0.9%	RR 1.46 (0.3 to 7.19)	4 more per 1000 (from 6 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Complications of treatment allocation												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	26/222 (11.7%)	10.8%	RR 1.09 (0.67 to 1.75)	10 more per 1000 (from 36 fewer to 81 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 because the majority of the evidence included an indirect population
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 28: Clinical evidence profile: Balloon assisted coil versus stent-assisted coil for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stent assisted coil versus balloon-assisted coil	Control	Relative (95% CI)	Absolute		
Complications of treatment allocation (follow-up 1 years)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/71 (7%)	0%	OR 4.72 (0.71 to 31.58)	-	⊕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 because the majority of the evidence included an indirect population
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 29: Clinical evidence profile: Flow diverter (PED) versus neurosurgical clipping for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PED versus neurosurgical clipping	Control	Relative (95% CI)	Absolute		
mRS 3-5 (follow-up 6-14 months)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/23 (0%)	0%	RD 0 (-0.08 to 0.08)	0 more per 1000 (from 80 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Procedure-related complications (follow-up 6-14 months)												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	6/21 (28.6%)	26.1%	RR 1.10 (0.42 to 2.87)	26 more per 1000 (from 151 fewer to 488 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 because the majority of the evidence included an indirect population
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

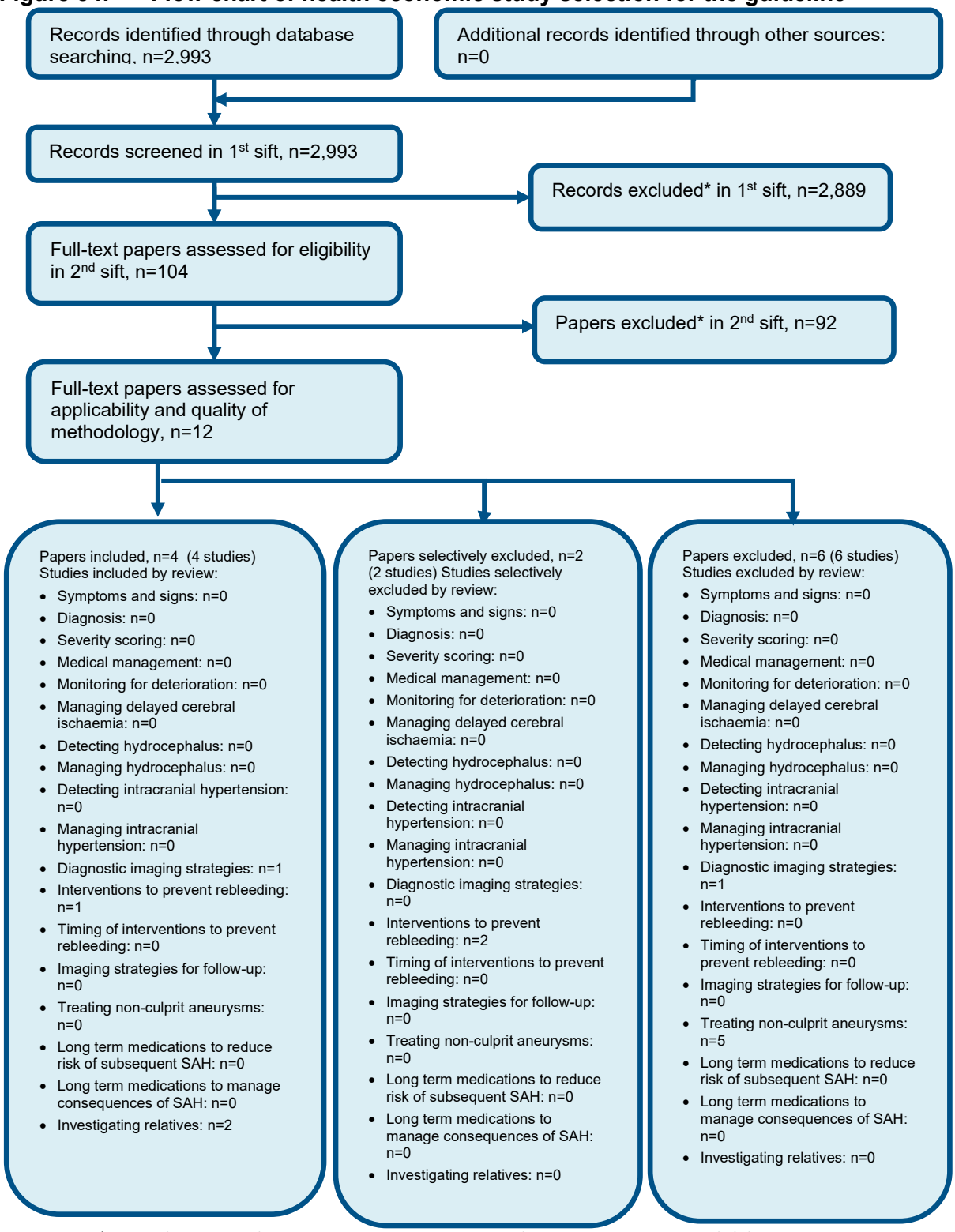
Table 30: Clinical evidence profile: Flow diverter (PED) versus endovascular coiling for non-culprit aneurysms

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PED versus endovascular coiling	Control	Relative (95% CI)	Absolute		
Mortality (follow-up 3-15 months)												
2	observational studies[1]	very serious[5]	serious[2]	serious[3]	very serious[4]	none	4/151 (2.6%)	1.2%	Peto OR 2.28 (0.31 to 16.83)	15 more per 1000 (from 8 fewer to 158 more)	⊕OOO VERY LOW	CRITICAL
mRS 3-5 (follow-up 8-23 months)												
2	observational studies[1]	very serious[5]	no serious inconsistency	serious[3]	very serious[4]	none	2/61 (3.3%)	5%	RR 0.81 (0.2 to 3.25)	9 fewer per 1000 (from 40 fewer to 113 more)	⊕OOO VERY LOW	CRITICAL
Procedure-related complications (follow-up 3-23 months)												
3	observational studies[1]	very serious[5]	no serious inconsistency	serious[2]	very serious[4]	none	15/176 (8.5%)	7.3%	RR 1.33 (0.64 to 2.8)	24 more per 1000 (from 26 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence was from studies with observational/non-randomised study design.
[2] Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, subgroup analysis not possible as <2 studies per subgroup.
[3] Downgraded because the majority of the evidence included an indirect population
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[5] 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

Appendix H: Health economic evidence selection

Figure 34: Flow chart of health economic study selection for the guideline



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

Appendix I: Health economic evidence tables

None.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 31: Studies excluded from the clinical review

Reference	Reason for exclusion
Aboukais 2014[1]	Indirect population/study design; evidence from direct population/RCT already included
Abud 2010[2]	Inappropriate study design – non comparative
Algra 2019[4]	Systematic review – references checked
Alreshidi 2018[5]	Systematic review - references checked
Alshekhlee 2010[6]	Indirect population/study design; evidence from direct population/RCT already included
Arena 2017[7]	Indirect population/study design; evidence from direct population/RCT already included
Asaid 2017[8]	Systematic review - references checked
Barbarite 2016[9]	References checked - included studies incorrect study design
Bechan 2016[10]	Inappropriate review population – ruptured compared to unruptured aneurysm
Bekelis 2017[11]	Indirect population/study design; evidence from direct population/RCT already included
Bendok 2020[12]	Indirect population; evidence from direct population already included
Benech 2014[13]	Inappropriate comparison – clipping techniques
Beretta 2004[14]	Inappropriate comparison - ruptured compared to unruptured aneurysm
Berro 2019[15]	Indirect population/study design; evidence from direct population/RCT already included
Bhatia 2019[16]	Systematic review - references checked
Blackburn 2014[17]	Systematic review - references checked
Bonares 2014[18]	Systematic review - references checked
Borggrefe 2016[19]	Inappropriate study design – non comparative
Brennan 2000[20]	Inappropriate study design – literature review
Briganti 2012[21]	Inappropriate comparison – silk embolization compared to pipeline embolization
Brilstra 2004[22]	Indirect population/study design; evidence from direct population/RCT already included
Brinjikji 2011[23]	Indirect population/study design; evidence from direct population/RCT already included
Brundl 2016[24]	Inappropriate review population – internal carotid artery aneurysm
Brzegowy 2019[25]	Indirect population/study design; evidence from direct population/RCT already included
Cagnazzo 2020[26]	Inappropriate population – dissecting and cavernous aneurysms
Choxi 2011[28]	Indirect population/study design; evidence from direct population/RCT already included
Chung 2016[29]	Indirect population/study design; evidence from direct population/RCT already included
Chyatte 2001[30]	Inappropriate study design – non comparative

Reference	Reason for exclusion
Darsaut 2011[33]	Inappropriate study design - review protocol
Dasenbrock 2020[34]	Indirect population/study design; evidence from direct population/RCT already included
Ernst 2019[35]	Inappropriate study design – Review of medical findings by neurointerventional radiologists
Fukuda 2020[38]	Indirect population/study design; evidence from direct population/RCT already included
Ge 2016[39]	Inappropriate review population – saccular aneurysm of vertebrobasilar artery
Ghandehari 2011[41]	Inappropriate paper retracted
Gillani 2016[42]	Inappropriate comparison – risk factors for complications of aneurysm
Gonzalez 2004[43]	Inappropriate study design – non comparative
Guan 2017[45]	Inappropriate comparison
Hackenberg 2018[46]	Indirect population/study design; evidence from direct population/RCT already included
Hagen 2019[47]	Indirect population/study design; evidence from direct population/RCT already included
Hammer 2016[48]	Inappropriate review population – risk factors for complications of aneurysm
Harland 2020[49]	Indirect population/study design; evidence from direct population/RCT already included
Higashida 2007[51]	Indirect population/study design; evidence from direct population/RCT already included
Hoh 2009[52]	Indirect population/study design; evidence from direct population/RCT already included
Hoh 2011[53]	Indirect population/study design; evidence from direct population/RCT already included
Hokari 2013[54]	Inappropriate study design – non comparative
Huo 2013[57]	Inappropriate study design – non comparative
Huang 2019[56]	Indirect population/study design; evidence from direct population/RCT already included
Hwang 2012[58]	Systematic review - references checked
Inamasu 2014[59]	Indirect population/study design; evidence from direct population/RCT already included
Ishii 2017[61]	Inappropriate review population – SAH excluded
Jalbert 2015[62]	Indirect population/study design; evidence from direct population/RCT already included
Jeon 2016[64]	Inappropriate comparison – clipping techniques
Johnston 2004[65]	Citation only
Johnston 1999[66]	Indirect population/study design; evidence from direct population/RCT already included
Johnston 2001[67]	Indirect population/study design; evidence from direct population/RCT already included
Juvela 2004[68]	Inappropriate study design – literature review
Kai 2011[69]	Inappropriate population – vertebral artery dissecting aneurysm
Kang 2020[70]	Systematic review - references checked
Kato 2001[71]	Inappropriate comparison – clinicopathological correlation for clipping versus coiling
Kim 2011[72]	Inappropriate study design – non comparative

Reference	Reason for exclusion
Kim 2018[75]	Indirect population/study design; evidence from direct population/RCT already included
Krisht 2006[76]	Inappropriate analysis – use of data already included (ISUIA)
Kumar 2007[77]	Inappropriate intervention – classification of aneurysm
Lad 2013[79]	Indirect population/study design; evidence from direct population/RCT already included
Maira 2019[80]	Indirect population/study design; evidence from direct population/RCT already included
Malhotra 2018[81]	Inappropriate outcome – Health economics data
Marchan 2008[82]	Indirect population/study design; evidence from direct population/RCT already included
McAuliffe 2012[83]	Inappropriate study design – non comparative
McKissock 1965[84]	Inappropriate population – ruptured aneurysms
Meckel 2011[85]	Inappropriate study design; review population – non comparative / ruptured aneurysm
Mihalea 2018[86]	Inappropriate study design – non comparative
Morgan 2016[88]	Inappropriate comparison – risk factors for complications of aneurysms
Mori 2018[89]	Inappropriate study design – non comparative
Moscato 2013[90]	Inappropriate study design – non comparative
Nguyen 2007[93]	Inappropriate comparison – ruptured versus unruptured aneurysm
Nii 2018[95]	Inappropriate comparison – braded stent versus expandable stent
Niskanen 2005[96]	Indirect population/study design; evidence from direct population/RCT already included
O'Donnell 2018[97]	Inappropriate review population – unruptured AVM
Ogilvy 2019[99]	Indirect population/study design; evidence from direct population/RCT already included
Oh 2015[100]	Inappropriate comparison – location of bleed
Pala 2019[101]	Inappropriate review population – unruptured versus general population
Pereira-Filho 2014[102]	Inappropriate study design – non comparative
Pietrantonio 2017[105]	Indirect population/study design; evidence from direct population/RCT already included
Preiss 2012[106]	Indirect population/study design; evidence from direct population/RCT already included
Raftopoulos 2003[107]	Indirect population/study design; evidence from direct population/RCT already included
Raymond 2008[108]	Inappropriate study design – critical appraisal of ISUIA
Regli 2002[109]	Indirect population/study design; evidence from direct population/RCT already included
Reza Rezvani 2011[110]	Inappropriate population – ruptured aneurysm
Ross 2005[111]	Inappropriate study design – non comparative
Roy 2001[112]	Inappropriate study design – non comparative
Ruan 2015[113]	Systematic review - references checked
Satow 2020[114]	Indirect population/study design; evidence from direct population/RCT already included
Schwedt 2011[115]	Inappropriate study design – non comparative
Silva 2018[116]	Indirect population/study design; evidence from direct population/RCT already included

Reference	Reason for exclusion
Singh 2002[117]	Inappropriate study design – non comparative
Smith 2015[118]	Systematic review - references checked
Solheim 2006[119]	Indirect population/study design; evidence from direct population/RCT already included
Song 2015[120]	Indirect population/study design; evidence from direct population/RCT already included
Starke 2015[121]	Inappropriate intervention - dual microcatheter vs stent assisted coil
Steiger 1999[122]	Inappropriate review population
Stetler 2017[123]	Inappropriate comparison – risk factors for complications of intervention
Takao 2007[124]	Inappropriate outcome – health economics study
Terada 2005[127]	Inappropriate study design – non comparative
Towgood 2005[129]	Inappropriate review population – unruptured aneurysm compared to controls (no aneurysm)
Toccaceli 2020[128]	Systematic review – references checked
Tsutsumi 1999[133]	Inappropriate study design – non comparative
Venkatesh 2000[134]	Inappropriate review population – infective aneurysm haemorrhage
Vergouwen 2018[135]	Inappropriate study design – review protocol
Vindlacheruvu 2005[136]	Inappropriate outcome – life expectancy with intervention
Wali 2017[137]	Inappropriate outcome – health economics study
Xin 2019[142]	Systematic review – references checked
Xin 2019[143]	Systematic review – references checked
Yan 2019[144]	Indirect population/study design; evidence from direct population/RCT already included
Yang 2019[145]	Indirect population/study design; evidence from direct population/RCT already included
Yeung 2012[146]	Inappropriate study design – non comparative
Zacharia 2011[147]	Indirect population/study design; evidence from direct population/RCT already included
Zhang 2018[148]	Indirect population/study design; evidence from direct population/RCT already included
Zweifel 2015[149]	Indirect population/study design; evidence from direct population/RCT already included

J.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 32: Studies excluded from the health economic review

Reference	Reason for exclusion
Familiari 2015[36]	Excluded due to a combination of applicability and methodological limitations. Unclear if the study population had had a previous subarachnoid haemorrhage. Retrospective analysis of Italian and German resource use and unit costs from three centres between

Reference	Reason for exclusion
	2004 and 2014 may not reflect the current NHS context. No discounting applied. No health outcomes reported..
Fukuda 2020[38]	Excluded due to a combination of applicability and methodological limitations. Patients were excluded from the study if they had received any treatment for unruptured intracranial aneurysms in the past five years, or if they had a history of subarachnoid or cerebral haemorrhage. Retrospective cohort analysis of Japanese total healthcare expenditures between 2015 and 2018 and may not reflect the NHS context. Total healthcare expenditure was reported instead of SAH related healthcare expenditures. No health outcomes reported.
Horcajadas 2018[55]	Excluded due to a combination of applicability and methodological limitations. Unclear if the study population had had a previous subarachnoid haemorrhage. Retrospective cohort analysis of Spanish resource use and unit costs from a single hospital between 2010 and 2015 and may not reflect the current NHS context. No discounting applied. QALYs not estimated. No controlling for confounders undertaken in the analysis.
Kim 2015[74]	Excluded due to a combination of applicability and methodological limitations. Retrospective analysis of South Korean resource use and unit costs from a single hospital between 2011 and 2014 and may not reflect the current NHS context. Length of follow-up unclear and no discounting applied. No health outcomes reported.
Zweifel 2015[149]	Excluded due to a combination of applicability and methodological limitations. Less than 20% of the study population had had a previous subarachnoid haemorrhage. Prospective analysis of Canadian resource use and unit costs between 2007 and 2012 from a single hospital may not reflect the current NHS context. Length of follow-up and whether discounting was applied is unclear. QALYs not estimated.