National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[O] Evidence review for imaging strategies for follow-up

NICE guideline NG228

Methods, evidence and recommendations

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1 Imaging strategies for follow-up

Evidence review underpinning recommendation 1.4.4 in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of different imaging strategies for follow-up of adults with confirmed aneurysmal subarachnoid haemorrhage?

1.2 Introduction

Prior to the introduction of aneurysm coiling, long-term imaging follow-up for clipped brain aneurysms was uncommon. Aneurysm clipping was known to achieve complete aneurysm occlusion, as the aneurysm clip pinched the endothelial surfaces of the aneurysm wall together (the direct contact of biological surfaces resulting in healing across the aneurysm neck akin to scar formation).

In contemporary practice, imaging follow-up is not generally required after aneurysm clipping, but catheter angiography is arranged if there is concern about adequacy of clip placement, if there is a residual aneurysm after clipping, or if there is another known unruptured aneurysm that may require future treatment.

Technology that enabled endovascular treatment of brain aneurysms at a population level was developed in the early 1990s and evaluated primarily by the ISAT trial. Histological and angiographic evaluation of the results of early coiling treatments showed that aneurysm neck healing after treatment with coils was frequently incomplete, as the extent that reconstruction of the arterial wall occurs over a metal scaffold varies depending on a number of factors. Knowledge that aneurysm treatment with coiling may not result in complete aneurysm occlusion (when compared with aneurysm clipping) resulted in the evolution of imaging strategies to evaluate the immediate and longer-term results of endovascular aneurysm treatment.

In some cases where it is thought that follow-up imaging will not change patient management, either due to a low likelihood of further events in the patient's estimated life-time, or due to a very poor clinical outcome, patients are discharged from imaging surveillance.

This review was carried out to assess the clinical and cost-effectiveness of different follow-up imaging strategies for adults with confirmed 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.

Interventions	Follow up imaging strategy at:
	• <1 year
	  ○ 6-monthly follow-up
	  ○ Yearly follow-up
	• 1-2 years
	  ○ 6-monthly follow-up

	○ Yearly follow-up ○ Follow-up at >yearly intervals • >2-5 years ○ 6-monthly follow-up ○ Yearly follow-up ○ Follow-up at >yearly intervals
Comparisons	• To each other • No imaging follow up
Outcomes	Critical: • Mortality • Health and social-related quality of life (any validated score) • Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) • Complications of investigation (e.g. stroke, vascular injury) Important: • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Need for retreatment • Length of hospital stay (if rehospitalised)
Study design	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

No relevant clinical studies comparing follow up imaging strategies were identified.

See also the study selection flow chart in Appendix C:.

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.3 Summary of clinical studies included in the evidence review

No evidence was identified for this review.

1.4.4 Quality assessment of clinical studies included in the evidence review

No evidence was identified for this review.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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

1.5.3 Unit costs

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

Table 2: UK costs of imaging modalities for follow-up

Drug	Description	Average cost
Computerised Tomography Angiography	Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over [NHS Reference Cost code: RD21A]	£101
Magnetic Resonance Angiography	Magnetic Resonance Imaging Scan of One Area, with Pre and Post-Contrast, 19 years and over [NHS Reference Cost code: RD03Z]	£190
Digital Subtraction Angiography	Percutaneous Transluminal Arteriography, of Intracranial or Extracranial Blood Vessel (day case) [NHS Reference Cost code: YA11Z]	£1,448

Source: NHS Reference Cost 2018/19[83]

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 agreed that the intention of follow-up imaging is to monitor any non-culprit aneurysms, assess the status of previous interventions, and to help detect and manage any treatment complications. The committee considered critical outcomes for decision making to be mortality, health and social related quality of life, degree of disability or dependence in daily activities (e.g. Modified Rankin scale and patient reported outcome measures), and complications of investigation. The committee also considered subsequent subarachnoid haemorrhage, return to daily activity, complications of intervention, need for re-treatment, and length of hospital stay (if rehospitalised) to be important outcomes.

1.6.1.2 The quality of the evidence

No evidence was identified. As such, the committee used consensus to provide clinical recommendation to consider neuroimaging as part of a follow up strategy for some people depending on individual clinical need and risk factors.

Given the lack of evidence the committee discussed making a research recommendation on the optimal frequency, duration and indications for follow-up. This is a difficult area to study as decisions to carry out neuroimaging during follow-up of a patient are based on multiple

factors, such as perceived effectiveness of the initial treatment, estimated risk of aneurysm recurrence, actual aneurysm recurrence, patient age, the presence and estimated risk of associated aneurysms and comorbidities.

The committee agreed that an important first point is estimation of risk of subarachnoid haemorrhage and the research recommendation that they made on the development and evaluation of risk stratification tools to estimate the risk of subsequent aneurysmal subarachnoid haemorrhage within the evidence review in this guideline on the risk of subsequent SAH would inform indications for follow-up imaging (see evidence review N, Appendix H). They considered therefore that a separate research recommendation around follow up imaging was not appropriate at this time.

1.6.1.3 Benefits and harms

The committee agreed that there are benefits to follow-up imaging: assessment of the operative result and detection of aneurysm recurrence, identification of complications of SAH or treatment, and evaluation and surveillance of non-culprit, or de-novo aneurysms. Some of these are necessary for early patient management and the benefits will generally outweigh any harms. Following endovascular treatment, imaging follow-up is usually required to confirm that operative treatment has been effective and that on-going risks from the treated aneurysm are negligible and or remain low for the duration of follow-up. The main long-term harms from imaging relate to effects of ionising radiation as well as use of resources. The committee noted however that patients with treated aSAH are at risk of both aneurysm recurrence and formation of new aneurysm(s). The committee considered the evidence presented in evidence review N on the risk of subsequent SAH showing that the risk of rebleed or subsequent aSAH in people who receive endovascular or neurosurgical intervention is generally around 0.5% per annum, although this incidence rate varies between individual patients. These data also showed that the overall risk of subsequent SAH beyond 1-year post-ictus is closer to 0.1% per annum. People who have had aSAH can also benefit from reassurance of follow up imaging to help manage any anxiety and management of continuing symptoms such as headache.

The lack of evidence on both the clinical and cost effectiveness of follow-up strategies prevented the committee from making a strong recommendation. The committee therefore decided to make a consensus recommendation to consider neuroimaging as part of a follow up strategy for some people depending on individual clinical need and risk factors.

Individual clinical factors, and type and outcome of any neurointervention or neurosurgery may influence this risk and should inform any follow-up strategy.

The committee agreed that follow-up imaging can be done by MRA, which is the preferred modality as it avoids exposure to ionising radiation. CT angiography can also be used but involves ionising radiation and CT images may be degraded by artefact from aneurysm metal coils. Catheter angiography (DSA) also requires ionising radiation, is an invasive procedure associated with a small risk, and associated with additional cost compared with non-invasive alternatives (MRA, CTA). DSA is reserved for patients in whom MRA and CTA are contraindicated or not tolerated. In current practice the majority of patients are followed up with non-invasive MRA.

The committee therefore recommended that the choice of imaging follow-up technique will be at clinician discretion but should take account of the treatment method, presence of non-culprit aneurysm(s), perceived risk of further bleeding, risks of planned investigations and any subsequent interventions and patient preference.

1.6.2 Cost effectiveness and resource use

No published economic evaluations were identified or included in this review. Unit costs of different imaging modalities were presented to the committee, but the lack of clinical

evidence precluded assessment of the cost effectiveness of different follow up strategies. The committee made a consensus recommendation, which will not change current clinical practice or result in a resource impact to the NHS.

1.6.3 Other factors the committee took into account

The committee noted that current standard practice is to offer a follow-up appointment to patients at 6 months and at 2 years. There is no nationally agreed standard surveillance interval, and strategies will be individualised. Imaging strategies should take into account the accuracy and any associated risk of the test, as well as acceptability to the patient. The approach to imaging follow-up should weigh the impact of uncertainty on a patient's well-being and be responsive to patient wishes.

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Appendices

Appendix A: Review protocols

Table 3: Review protocol: Imaging strategies for follow-up

ID	Field	Content
0.	PROSPERO registration number	CRD42019153672
1.	Review title	What is the clinical and cost effectiveness of different imaging strategies for follow-up of adults with confirmed aneurysmal subarachnoid haemorrhage?
2.	Review question	What is the clinical and cost effectiveness of different imaging strategies for follow-up of adults with confirmed aneurysmal subarachnoid haemorrhage?
3.	Objective	To determine the clinical and cost effectiveness of imaging strategies for subarachnoid haemorrhage.
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 studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger. Strata: • If received intervention

		○ Clip following aSAH ○ Coil following aSAH • Treated conservatively (no clipping/coiling)
7.	Intervention/Exposure/Test	Follow up imaging strategy at: • <1 year ○ 6-monthly follow-up ○ Yearly follow-up • 1-2 years ○ 6-monthly follow-up ○ Yearly follow-up ○ Follow-up at >yearly intervals • >2-5 years ○ 6-monthly follow-up ○ Yearly follow-up ○ Follow-up at >yearly intervals Follow up intervention to include: • MR Angiography • DSA • CT angiography
8.	Comparator/Reference standard/Confounding factors	Comparators: • To each other • No imaging follow up
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Non- English language studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Review focused on the efficacy of imaging strategies at follow up, once the person with aSAH has been discharged.
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated score) • Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) • Complications of investigation (e.g. stroke, vascular injury) Outcomes will be captured at or after the point of imaging follow-up. Outcomes will therefore be grouped at <1 year, 1-2 years and >2-5 years

13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Need for retreatment • Length of hospital stay (if rehospitalised) Outcomes will be captured at or after the point of imaging follow-up. Outcomes will therefore be grouped at <1 year, 1-2 years and >2-5 years.
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. For Intervention reviews • 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. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be reported in full.		
17.	Analysis of sub-groups	Strata: • Received intervention ○ Clip following aSAH ○ coil following aSAH • Treated conservatively (no clipping/coiling) Subgroups (if heterogeneity): • Monitoring technique ○ MR Angiography ○ DSA ○ CT angiography		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date	3 February 2021		
23.		Review stage	Started	Completed

	Stage of review at time of this submission	Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SAH@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be 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; imaging; follow-up	
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 4: 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.[82] **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 imaging strategies for follow-up of adults with 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[82] 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 5: 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
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12	None

Database	Dates searched	Search filter used
	CENTRAL to 2020 Issue 6 of 12	

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.	Epidemiologic studies/
30.	Observational study/
31.	exp Cohort studies/
32.	(cohort adj (study or studies or analys* or data)).ti,ab.
33.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
34.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
35.	Controlled Before-After Studies/
36.	Historically Controlled Study/
37.	Interrupted Time Series Analysis/

38.	(before adj2 after adj2 (study or studies or data)).ti,ab.
39.	or/29-38
40.	exp case control study/
41.	case control*.ti,ab.
42.	or/40-41
43.	39 or 42
44.	Cross-sectional studies/
45.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
46.	or/44-45
47.	39 or 46
48.	39 or 42 or 46
49.	Meta-Analysis/
50.	exp Meta-Analysis as Topic/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(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.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-57
60.	randomized controlled trial.pt.
61.	controlled clinical trial.pt.
62.	randomi#ed.ti,ab.
63.	placebo.ab.
64.	randomly.ti,ab.
65.	Clinical Trials as topic.sh.
66.	trial.ti.
67.	or/60-66
68.	Magnetic Resonance Angiography/ or Angiography, Digital Subtraction/ or Computed Tomography Angiography/
69.	((magnetic resonance or digital subtraction or computed tomograph*) adj3 angiograph*).ti,ab.
70.	((MR or DS or CT) adj3 (angiograph* or angiogram*)).ti,ab.
71.	(MRA or DSA or CTA).ti,ab.
72.	or/68-71
73.	28 and 72 and (48 or 59 or 67)

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.	Clinical study/
28.	Observational study/
29.	family study/
30.	longitudinal study/
31.	retrospective study/
32.	prospective study/
33.	cohort analysis/
34.	follow-up/
35.	cohort*.ti,ab.
36.	34 and 35
37.	(cohort adj (study or studies or analys* or data)).ti,ab.
38.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
39.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
40.	(before adj2 after adj2 (study or studies or data)).ti,ab.
41.	or/27-33,36-40
42.	exp case control study/
43.	case control*.ti,ab.
44.	or/42-43
45.	41 or 44

46.	cross-sectional study/
47.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
48.	or/46-47
49.	41 or 48
50.	41 or 44 or 48
51.	random*.ti,ab.
52.	factorial*.ti,ab.
53.	(crossover* or cross over*).ti,ab.
54.	((doubl* or singl*) adj blind*).ti,ab.
55.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
56.	crossover procedure/
57.	single blind procedure/
58.	randomized controlled trial/
59.	double blind procedure/
60.	or/51-59
61.	systematic review/
62.	meta-analysis/
63.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
64.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
65.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
66.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
67.	(search* adj4 literature).ab.
68.	(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.
69.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
70.	cochrane.jw.
71.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
72.	or/61-70
73.	magnetic resonance angiography/ or computed tomographic angiography/ or digital subtraction angiography/
74.	((magnetic resonance or digital subtraction or computed tomograph*) adj3 angiograph*).ti,ab.
75.	((MR or DS or CT) adj3 (angiograph* or angiogram*)).ti,ab.
76.	(MRA or DSA or CTA).ti,ab.
77.	or/73-76
78.	26 and 77 and (50 or 60 or 72)

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: [Magnetic Resonance Angiography] this term only
#8.	MeSH descriptor: [Angiography, Digital Subtraction] this term only
#9.	MeSH descriptor: [Computed Tomography Angiography] this term only
#10.	((magnetic resonance or digital subtraction or computed tomograph*) near/3 angiograph*):ti,ab
#11.	((MR or DS or CT) near/3 (angiograph* or angiogram*)):ti,ab
#12.	(MRA or DSA or CTA):ti,ab
#13.	(or #7-#12)
#14.	#6 and #13

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 6: 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

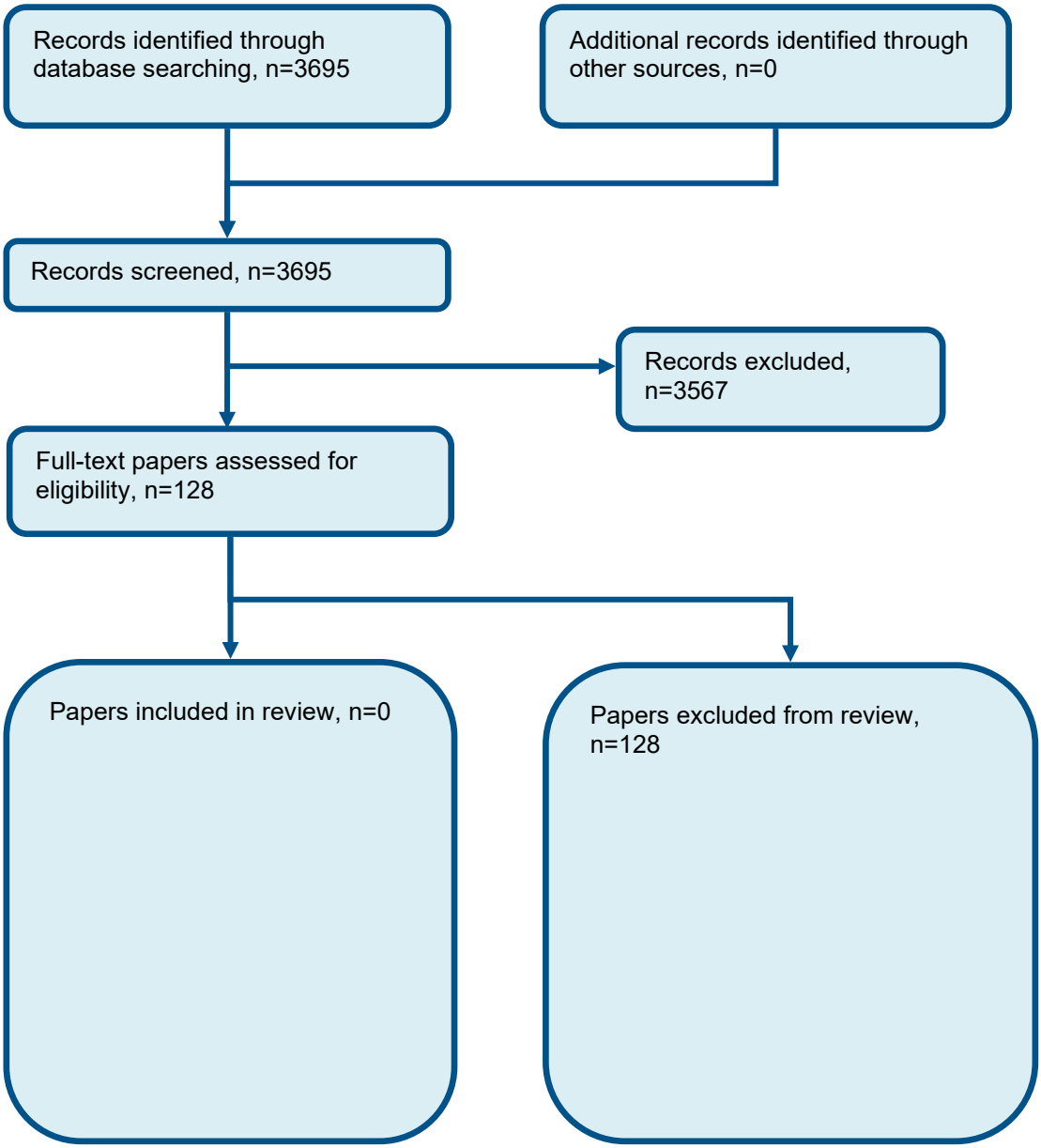
NHS EED and HTA (CRD) search terms

#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 imaging strategies for follow-up



Appendix D: Clinical evidence tables

No studies were included.

Appendix E: Forest plots

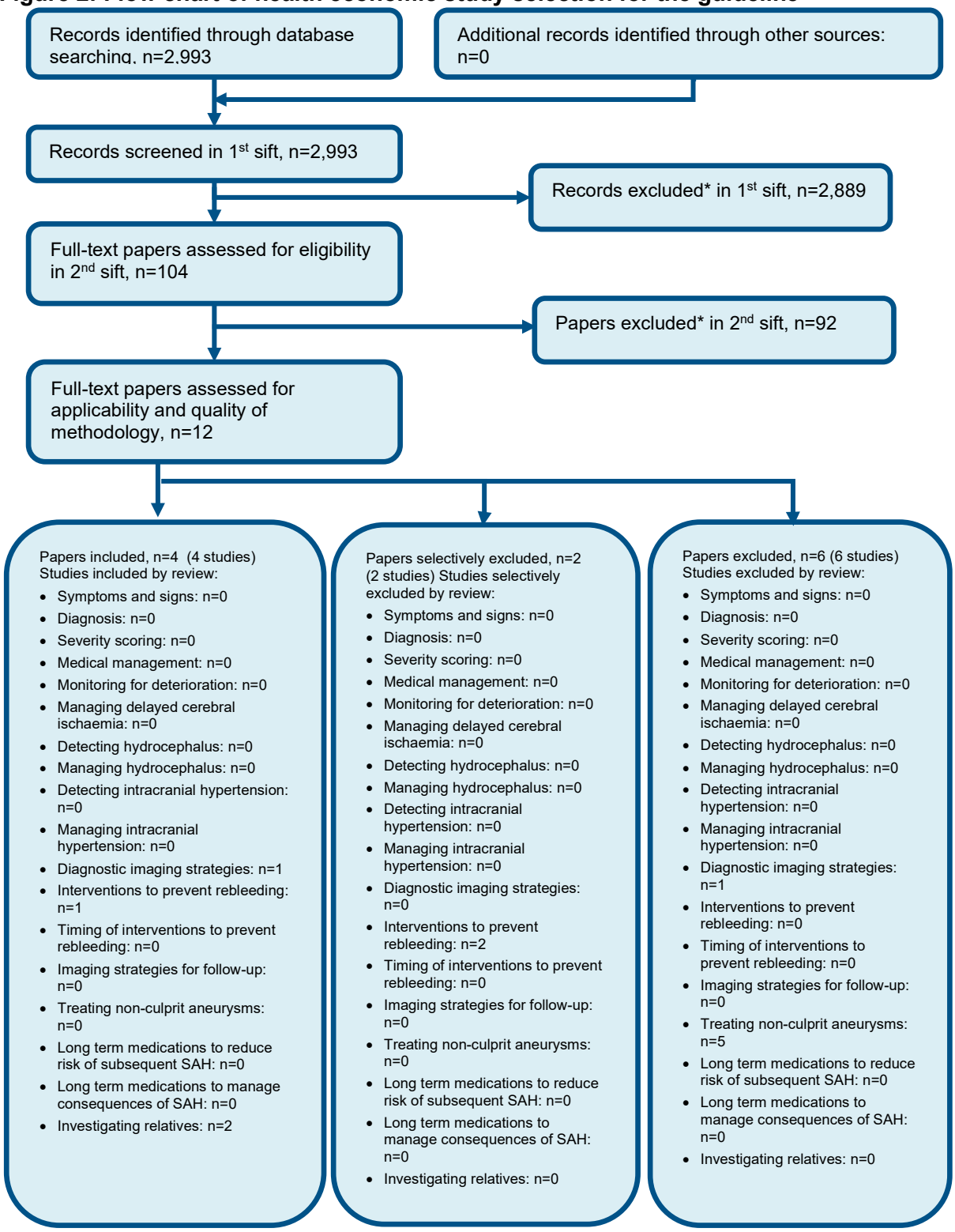
No studies were included.

Appendix F: GRADE tables

No studies were included.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Study	Exclusion reason
Aboukais 2015[1]	Not in English
Adeeb 2017[2]	Inappropriate population – ophthalmic segment aneurysm
Ahmed 2019[3]	Systematic review - references checked
Anzalone 2015[4]	Inappropriate study design – non comparative study
Arrese 2013[5]	Systematic review - references checked
Arthur 2019[6]	Inappropriate study design – non comparative study
Atasoy 2019[7]	Not review population - patients with unruptured aneurysms
Aydin 2012[9]	Inappropriate study design – non comparative study
Aydin 2019[8]	Not review population - patients with wide-necked complex bifurcation aneurysms (99 out of 102 unruptured)
Bakker 2014[10]	Systematic review - references checked
Bendok 2013[11]	Inappropriate study design – no relevant outcomes
Bor 2014[12]	Inappropriate population – relatives of people with SAH
Boussel 2008[13]	Inappropriate study design - no relevant outcomes
Bracard 2002[14]	Inappropriate comparison – single cohort studied at multiple time points
Bruneau 2011[15]	Inappropriate intervention – angiogram 10 years post intervention (no previous angiogram)
CBS Office of Statistics Netherlands 2000[16]	Paper not available
Chalouhi 2014[17]	Inappropriate study design - no relevant outcomes
Chen 2018[18]	Inappropriate comparison/No relevant outcomes – single cohort studied at multiple time points
Cho 2014[20]	Inappropriate study design - no relevant outcomes
Cho 2015[19]	Inappropriate study design - no relevant outcomes
Cloft 1999[21]	Inappropriate study design - no relevant outcomes
Cognard 2015[22]	Inappropriate study design / inappropriate population - no relevant outcomes/ all forms of aneurysm
Crawley 1999[23]	Inappropriate study design – theoretical models
David 1999[24]	Inappropriate study design – non comparative study
De Letter 1994[25]	Inappropriate comparison/ Inappropriate population – patching after carotid endarterectomy
Delgado Almandoz 2012[26]	Inappropriate study design - no relevant outcomes
Disney 1988[27]	Inappropriate study design – case series
Dorhout Mees 2007[28]	Systematic review - references checked
Flores 2019[29]	Systematic review - references checked
Fountas 2008[30]	Inappropriate comparison – no angiographic follow up
Fujimura 2017[31]	Inappropriate study design/inappropriate comparison – medication comparison
Gallas 2005[33]	Inappropriate study design – non comparative study
Gallas 2009[32]	Inappropriate study design – non comparative study

Study	Exclusion reason
Garg 2013[34]	Inappropriate intervention – no angiographic follow up
Gauvrit 2005[35]	Inappropriate study design - no relevant outcomes
Geng 2019[36]	Systematic review - references checked
Germano 2013[37]	Inappropriate comparison – MRA at follow up
Geyik 2013[38]	Inappropriate study design - no relevant outcomes
Ghogawala 2013[39]	Inappropriate population – carotid artery stenosis
Gibbs 2004[40]	Inappropriate population – people with polycystic kidney disease and SAH
Goksu 2015[41]	Inappropriate study design – non comparative study
Groden 2003[42]	Inappropriate study design – non comparative study
Hai 2009[43]	Inappropriate study design - no relevant outcomes
Hashimoto 2000[44]	Inappropriate study design / no relevant outcomes – non comparative study / no angiographic follow up results
Hassan 2012[45]	Inappropriate population – arterial dissection
Heller 2013[46]	Inappropriate study design - no relevant outcomes
Helthuis 2018[47]	Inappropriate study design / no relevant outcomes – case series
Hendryk 2004[48]	Inappropriate intervention – no angiographic follow up
Hijdra 1987[49]	Inappropriate study design - no relevant outcomes
Hop 1997[50]	Systematic review - references checked
Hosono 2002[51]	Inappropriate comparison - single photon emission CT (SPECT performed at 1 and 7 days after SAH)
Hussain 2009[52]	Inappropriate comparison- results of last follow up
Ji 2016[53]	Inappropriate study design – non comparative study
Juvela 1993[54]	Inappropriate population – unruptured aneurysms
Juvela 2001[55]	Inappropriate study design – non comparative study
Kalra 2015 [56]	Systematic review - references checked
Kannath 2019[57]	Inappropriate study design - non comparative study/case series
Kao 2018[58]	Not review population - patients with chronic carotid artery occlusion
Kapapa 2014[59]	Inappropriate study design – surveys and questionnaires
Kasner 1997[60]	Inappropriate population – arterial dissection
Kim 2018[63]	Inappropriate study design – non comparative study
Kim 2018[62]	Inappropriate study design – non comparative study
Kim 2019[61]	Not review population - patients with unruptured aneurysms
King 1994[64]	Systematic review - references checked
Kwee 2007[65]	Systematic review - references checked
Lindgren 2018[66]	Systematic review - references checked
Lindvall 2012[67]	Inappropriate study design – non comparative study
Liu 2018[68]	Inappropriate study design - no relevant outcomes
Lizza 2014[69]	Inappropriate comparison – stroke or delayed cerebral infarction
Lublinsky 2019[70]	Inappropriate study design - no relevant outcomes
Ma 2015[71]	Inappropriate intervention – flow cytometry
Maimaitili 2013[72]	Inappropriate study design - no relevant outcomes
Marquardt 2000[73]	Inappropriate study design - no relevant outcomes
Mooney 2018[74]	Inappropriate study design/inappropriate comparison – no angiographic follow up

Study	Exclusion reason
Morais 2017[75]	Inappropriate comparison – single cohort studied at multiple time points
Moritz 2012[76]	Inappropriate study design - no relevant outcomes
Mortimer 2015[77]	Inappropriate study design - no relevant outcomes
Murakami 2019[78]	Not review population - patients with unruptured aneurysms
Murias Quintana 2015[79]	Inappropriate study design – non comparative study
Nagano 2016[80]	inappropriate comparison – no angiographic follow up
Nakagawa 2017[81]	Inappropriate comparison – DSA up to 10 days post SAH
Niiro 2000[84]	Inappropriate population – all types of aneurysm
Nossek 2015[85]	Inappropriate study design - no relevant outcomes
Ocal 2019[86]	Inappropriate comparison - surpass flow diverter only versus stent + flow diverter
Okada 2016[87]	Inappropriate study design no relevant outcomes
Peschillo 2017[88]	Inappropriate study design – case series
Petridis 2017[89]	Inappropriate study design - no relevant outcomes
Piano 2020[90]	Inappropriate study design – non comparative study
Pierot 2015[91]	Systematic review - references checked
Piske 2009[92]	Inappropriate comparison – outcomes compared by aneurysm size
Poon 2006[93]	Systematic review - references checked
Potter 2016[94]	Systematic review - references checked
Proust 2010[95]	Inappropriate comparison – outcomes 6 months post-surgery
Qin 2017[96]	Inappropriate study design – non comparative study
Raffi 2003[97]	Inappropriate study design - No relevant outcomes
Raschi 2012[98]	Inappropriate study design – modelling
Rautio 2019[99]	Inappropriate study design – non-comparative study
Ruppert 2007[100]	Inappropriate study design - no relevant outcomes
Saatci 2003[101]	Inappropriate study design - non-comparative study
Serafin 2011[102]	Systematic review - references checked
Slater 2015[103]	Inappropriate study design - no relevant outcomes
Slosberg 1997[104]	Inappropriate comparison – overall results
Sprengers 2009[105]	Inappropriate study design – non comparative study
Sun 2013[106]	Systematic review - references checked
Tailor, 2010[107]	Inappropriate study design - non-comparative,
Tao 2016[108]	Inappropriate study design – study protocol
Thaker 2012[109]	Inappropriate study design – no comparison group
Tsutsumi 2001[110]	Inappropriate study design – non comparative study
Tsutsumi 1998[111]	Inappropriate study design – non comparative study
van Amerongen 2014[112]	Systematic review - references checked
van Eijck 2015[113]	Inappropriate study design - no relevant outcomes
Vendrell 2009[114]	Inappropriate comparison – single cohort studied at multiple time points
Wang 2011[116]	Inappropriate study design – no angiographic follow up
Wang 2016[115]	Systematic review - references checked
Waqas 2020[117]	No relevant outcomes
Wardlaw 2000[118]	Inappropriate population – unruptured aneurysms
Weidauer 2007[119]	Inappropriate study design - no relevant outcomes

Study	Exclusion reason
Weng 2008[120]	Systematic review - references checked
Wenz 2015[121]	Inappropriate study design – non comparative study
Wermer 2005[123]	Inappropriate study design – non comparative study
Wermer 2006[124]	Inappropriate study design – non comparative study
Wermer 2004 [122]	Inappropriate study design- Markov economical model
Wisniewski 2019[125]	No relevant outcomes
Woo 2015[126]	Inappropriate comparison – no angiographic follow up
Xia 2014[127]	Inappropriate population - Pargonimiasis
Yan 2018[128]	Systematic review - references checked
Yu 2004[129]	Inappropriate comparison – patients with SAH and mass effect / all patients followed up
Yu 2007[130]	Inappropriate study design - no relevant outcomes
Zenteno 2008[131]	Inappropriate study design – case series
Zijlstra 2016[132]	Systematic review - references checked

I.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 8: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	