National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[A] Evidence review for symptoms and signs

NICE guideline NG228

Methods, evidence and recommendations

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Final

National Institute for Health and Care Excellence

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Evidence review underpinning recommendations 1.1.1 to 1.1.6 in the NICE guideline.

1.1 Review question: What symptoms and signs indicate subarachnoid haemorrhage?

1.2 Introduction

Acute, sudden and severe headache is a common presenting symptom and places a significant burden on emergency medical services. Most people with acute headache will have a benign cause but people with suspected subarachnoid haemorrhage are potentially at risk of re-bleeding, disability and death. A missed diagnosis of SAH can therefore have severe consequences; however investigation of all people with headache, or other symptoms suggestive of subarachnoid haemorrhage, will expose some people to unnecessary risk and may not be a cost-effective strategy.

In current practice, the clinical history and physical examination are used to identify people with suspected subarachnoid haemorrhage who require further investigation. Patients with subarachnoid haemorrhage can present with a wide range of signs and symptoms and in people with a neurological deficit the decision to proceed with further investigation may be straightforward, but management decisions for people who are neurologically intact are more difficult.

This review was carried out to assess the diagnostic value of symptoms and signs of subarachnoid haemorrhage.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (16 and older) with a suspected subarachnoid haemorrhage caused by a suspected 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.
Diagnostic variable(s) under consideration	• History of headache (herald/sentinel/prodromal headache) • Sudden severe headache • Painful/stiff neck • Nausea and vomiting • Photophobia • Blurred/double vision • Loss of consciousness • Confusional state • Focal neurology (hemiparesis) • Seizure • High blood pressure (>140/90)
Reference standard/	Reference standard: • confirmed diagnosis of SAH (by CT, LP +/- angiography or post-mortem)

Confounding factors	Confounding factors: • Age

Outcome(s)	Diagnostic association of signs and symptoms with a confirmed diagnosis of aSAH.
	Measured by:
	• Diagnostic accuracy data
	  ○ Sensitivity, specificity, PPV, NPV
	• Association data
	  ○ Adjusted RR or OR

Study design	• Prospective and retrospective cohort studies with multivariate analysis will be included preferentially. • Cross-sectional studies Studies will only be included if all the key confounders have been accounted for in a multivariate analysis. In the absence of multivariate analysis, studies that account for key confounders with univariate analysis or matched groups will be considered.

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted to identify studies reviewing the signs and symptoms indicating a SAH.

Five papers from 4 cohort studies were included in the review,[55, 97, 130, 132, 133] these are summarised in **Table 2** below. The trials included in this evidence review used signs and symptoms for a SAH to develop diagnostic decision tools. The diagnostic accuracy of these clinical decision tools and the individual signs and symptoms in diagnosing SAH were reported by these studies. The accuracy of the tools or signs and symptoms was measured against a final diagnosis of SAH, confirmed by non-contrast CT or LP (with or without supporting angiographic imaging). Where studies provided insufficient information to conduct a meta-analysis (true positives, true negatives, false positives, false negatives), or too few studies were included (≤2 studies for the same diagnostic outcome) diagnostic accuracy results were reported individually on a per-study basis.

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

1.4.2 Excluded studies

See the excluded studies list in Appendix H:.

1.4.3 Summary of studies included in the evidence review

Table 2: Summary of studies

Study	Population	Analysis	Signs/symptoms	Outcomes	Comments
Kelly 2014[55]	Alert and neurologically intact adult patients with confirmed SAH N=59	Retrospective analysis of patients with diagnosis of SAH. Study design: Retrospective cohort review	**Rule 1** 1. Age ≥ 40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion **Rule 2** 1. Age ≥ 45 y 2. Arrival by ambulance 3. Vomiting (≥1 episodes) 4. Diastolic blood pressure ≥100mmHg **Rule 3** 1. Age 45-55 y 2. Neck pain or stiffness 3. Arrival by ambulance 4. Systolic blood pressure ≥ 160mmHg	SAH Reference standard: Diagnosis of SAH by CT head scan, CT angiography, conventional angiography, MRI or LP supported by specialist neurosurgical opinion.	Unclear how rule was applied, i.e. if all criteria had to be present or only one. Assumed patients applied if one or more of the variables were present.
Mark 2015[97]	Patients who had an ED or hospital encounter with a diagnosis code of SAH. N=155	Retrospective analysis of patients with diagnosis of SAH. Study design:	A negative result being defined as absence of all four clinical criteria. 1. Age ≥40 y	SAH Reference standard: Evidence of SAH on non-contrast cranial CT	Analysis only included patients with confirmed diagnosis of SAH. Not possible to assess rule specificity.

Study	Population	Analysis	Signs/symptoms	Outcomes	Comments
		Retrospective cohort review	2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion	or >5 RBC per microliter on CSF analysis, and angiographic evidence of cerebral aneurysm.	
Pathan 2018[130]	Age older than 15 years, new atraumatic headache, and headaches that reached maximal intensity in 1 hour. N=145	Retrospective review of computerized medical records of all patients registered with a headache. Study design: Retrospective cohort review	**Ottawa Rule** For alert patients older than 15y with new severe non traumatic headache reaching maximum intensity within 1 h. Investigate if ≥1 high-risk variables present: 1. Age ≥ 40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion 5. Thunderclap headache (instantly peaking pain) 6. Limited neck flexion on examination	SAH Reference standard: subarachnoid blood visible on a plain CT film or xanthochromia in the cerebrospinal fluid.	
Perry 2013[132]; Perry 2010[133a]	Consecutive adult patients whose chief reason for visiting the emergency department was a non-traumatic headache that reached maximal intensity within 1 hour were considered for enrolment.	Potential refinement of the rules was assessed using multivariate recursive partitioning analysis. The estimated sensitivity, specificity, and C statistic for subarachnoid haemorrhage, including	For patients presenting with severe headache: **Rule 1** Investigate if ≥1 high-risk finding present: 1. Age ≥ 40 y 2. Neck pain or stiffness	SAH Reference standard: Subarachnoid blood on unenhanced CT of the head; xanthochromia in the cerebrospinal fluid; or RBC (>1 × 106/L) in the final tube of CSF	Unclear of variables used for multivariate analysis to determine symptoms/signs included in clinical rules.

[a] derivation study, data not reported.

Study	Population	Analysis	Signs/symptoms	Outcomes	Comments
	N=2131	95%CIs, were calculated for the refined rule. Study design: Prospective cohort review	3. Witnessed loss of consciousness 4. Onset during exertion **Rule 2** Investigate if ≥1 high-risk findings present: 1. Age ≥ 45 y 2. Arrival by ambulance 3. Vomiting (≥1 episodes) 4. Diastolic blood pressure ≥100mmHg **Rule 3** Investigate if ≥1 high-risk findings present: 1. Age 45-55 y 2. Neck pain or stiffness 3. Arrival by ambulance 4. Systolic blood pressure ≥ 160mmHg **Ottawa Rule** For alert patients older than 15y with new severe non traumatic headache reaching maximum intensity within 1 h. Investigate if ≥1 high-risk variables present: 1. Age ≥ 40 y	fluid, with an aneurysm or arteriovenous malformation on cerebral angiography.	

Study	Population	Analysis	Signs/symptoms	Outcomes	Comments
			2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion 5. Thunderclap headache (instantly peaking pain) 6. Limited neck flexion on examination		

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: Clinical decision rules for detecting SAH

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Decision rules							
Rule 1: 1. Age ≥40 y 2. Neck pain or stiffness 3. Loss of consciousness 4. Onset during exertion	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity=98.5% (94.6 – 99.6%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity=27.6% (25.7 – 29.6%)	MODERATE
	155 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity =95.5% (90.9-98.2%)	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Serious[d]	Sensitivity =96.6% (88.5-99.1%)	VERY LOW
Rule 2: 1. Age ≥ 45 y	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity= 95.5% (90.4 – 97.9%)	MODERATE

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
2. Arrival by ambulance 3. Vomiting (≥1 episodes) 4. Diastolic blood pressure ≥100mmHg		Serious[a]	Not serious	Not serious	Not serious	Specificity= 30.6% (28.6 – 32.6%) [e]	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity =100% (93.9-100%)	LOW
Rule 3: 1. Age 45-55 y 2. Neck pain or stiffness 3. Arrival by ambulance 4. Systolic blood pressure ≥ 160mmHg	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity= 97.0% (92.5 – 98.8%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity=35.6% (33.6 – 37.7%) [e]	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Serious[d]	Sensitivity =89.8% (79.5-95.3%)	VERY LOW
Ottawa rule: 1. Age ≥ 40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion 5. Thunderclap headache (instantly peaking pain) 6. Limited neck flexion on examination	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity=100% (97.2 – 100%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity=15.3% (13.8 – 16.9%)	MODERATE
	145 (1)	Serious[a]	Not serious	Not serious	Very serious[d]	Sensitivity=100% (46.3 – 100%)	VERY LOW
		Serious[a]	Not serious	Not serious	Not serious	Specificity=44.2% (36 – 53%)	MODERATE

Reference standard: confirmed diagnosis of SAH by non-contrast CT or LP +/- angiography. For Kelly 2014 and Mark 2015, the timing of the reference standard relative to symptom onset was <14 days and <6 hours, respectively. The timing of reference standard diagnosis relative to symptom onset was unclear for Pathan 2018 and Perry 2010/2013.

a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

b) Where possible, inconsistency was assessed by inspection of the sensitivity and specificity plots. The evidence was

- *downgraded by 1 increment if the individual study values varied across 2 areas: where values of individual studies are both above and below 50%, or both above and below 90%*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where values of individual studies are above and below 50%, and also above and below 90%*

c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

d) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. Two clinical decision thresholds were determined at the value above which a test would be recommended (90%), and a second below which a test would be considered of no clinical use (60%).The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold, and downgraded by 2 increments when the range covered two thresholds

e) Results within the paper differ from analysis from forest plots. The results given in the table are taken from the paper directly.

Table 4: Clinical evidence summary: Individual signs & symptoms for detecting SAH

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95% CI)	Quality
Signs & Symptoms							
Arrived by ambulance	2131 (1)	Serious[a]	Not serious	Not serious	Serious[d]	Sensitivity = 61.4% (52-70%)	LOW
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 76.1% (74-78%)	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Serious[d]	Sensitivity = 69.5% (56-81%)	VERY LOW
Onset during exertion	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 19.2% (13-27%)	MODERATE
		Serious[a]	Not serious	Not serious	Serious[d]	Specificity = 89.7% (88-91%)	LOW
	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 20.3% (20-43%)	LOW
Onset during sexual activity	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 9.8% (5-16%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 93.8% (93-95%)	MODERATE
Headache awoke patient from sleep	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 12.1% (7-19%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 82.6% (81-84%)	MODERATE
Thunderclap headache	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 82.4% (75-89%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 45.3% (43-48%)	MODERATE
Worst headache of life	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 99.2% (96-100%)	MODERATE

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95% CI)	Quality
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 24.4% (23-26%)	MODERATE
Loss of consciousness	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 10.6% (6-17%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 94.7% (94-96%)	MODERATE
Loss of consciousness (witnessed)	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 5.3% (2-11%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 96.4% (95-97%)	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 18.6% (10-31%)	LOW
Neck pain or stiffness	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 76.5% (68-83%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 68.4% (66-70%)	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 42.4% (30-56%)	LOW
Vomiting	2131 (1)	Serious[a]	Not serious	Not serious	Serious[d]	Sensitivity = 65.9% (57-74%)	LOW
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 73.6% (72-76%)	MODERATE
	59 (1)	Very serious[a]	Not serious	Not serious	Serious[d]	Sensitivity = 66.1% (53-78%)	VERY LOW
Able to walk since headache	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 76.6% (68-83%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 9.9% (9-11%)	MODERATE

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95% CI)	Quality
Emergency department transfer	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 16.7% (11-24%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 91.9% (91-93%)	MODERATE
Limited flexion	2131 (1)	Serious[a]	Not serious	Not serious	Not serious	Sensitivity = 28.3% (21-37%)	MODERATE
		Serious[a]	Not serious	Not serious	Not serious	Specificity = 96.8% (96-98%)	MODERATE
Diastolic blood pressure >100 mmHg	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 10.2% (4-21%)	LOW
Systolic BP >160 mmHg	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 30.5% (19-44%)	LOW
Age >40 years	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 79.6% (67-89%)	LOW
Age >45 years	59 (1)	Very serious[a]	Not serious	Not serious	Serious[d]	Sensitivity = 69.5% (56-81%)	VERY LOW
Age 45-55 years	59 (1)	Very serious[a]	Not serious	Not serious	Not serious	Sensitivity = 27.1% (16-40%)	LOW

a) *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.*

b) *Where possible, inconsistency was assessed by inspection of the sensitivity and specificity plots. The evidence was*
   - *downgraded by 1 increment if the individual study values varied across 2 areas: where values of individual studies are both above and below 50%, or both above and below 90%*
   - *downgraded by 2 increments if the individual study values varied across 3 areas, where values of individual studies are above and below 50%, and also above and below 90%*

c) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect*

d) *Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. Two clinical decision thresholds were determined at the value above which a test would be recommended (90%), and a second below which a test would be considered of no clinical use (60%).The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold, and downgraded by 2 increments when the range covered two thresholds.*

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 F:.

1.6 Evidence statements

1.6.1 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The Committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee noted the primary objective of the evidence review was to assess the diagnostic accuracy and diagnostic association of signs and symptoms with a confirmed diagnosis of subarachnoid haemorrhage. Sensitivity, specificity and adjusted odds ratios or risk ratios for diagnosing subarachnoid haemorrhage were the outcomes for this review. The committee agreed that sensitivity of signs and symptoms for SAH was the most important outcome as a diagnostic indicator to correctly identify a high proportion of people with SAH and rule out the disease in those without. A highly sensitive symptom or sign would identify with accuracy those with SAH who require further neurological imaging and possible subsequent intervention. This would likely minimise the risk of neurological morbidity or subsequent rebleed that could be caused by delay to treatment. The committee agreed that a diagnostic accuracy with sensitivity of ≥90% would provide value in clinical practice. The committee also considered specificity important to correctly rule in SAH, identifying a large proportion of those without SAH with few false positive results. This would mean that few people with suspected SAH without the condition would undergo potentially unnecessary neurological imaging. The committee agreed that a specificity of ≥90% would reflect a highly accurate test.

Evidence was identified for the diagnostic accuracy of 4 clinical decision rules. These included:

- Rule 1: age ≥40 y; neck pain or stiffness; loss of consciousness; onset during exertion.
- Rule 2: age ≥ 45 y; arrival by ambulance; vomiting (≥1 episodes); diastolic blood pressure ≥100mmHg.
- Rule 3: age 45-55 y; neck pain or stiffness; arrival by ambulance; systolic blood pressure ≥ 160mmHg.

- Ottawa rule: age ≥ 40 y; neck pain or stiffness; witnessed loss of consciousness; onset during exertion; thunderclap headache (instantly peaking pain); limited neck flexion on examination.

The diagnostic accuracy of each of 18 individual signs and symptoms for SAH was also included for review.

No evidence was found for the diagnostic association (as reported by adjusted RR or OR) of signs and symptoms or clinical decision tools for a final diagnosis of SAH.

1.7.1.2 The quality of the evidence

From the studies included in this evidence review, 3 were retrospective cohort reviews and 1 was a large prospective cohort study. The committee noted the smaller size of the retrospective cohort studies and agreed that the larger size and prospective nature of the Perry study provided a more valuable source of information to inform discussions. Most of the evidence presented in the review was of moderate quality. This was generally due to a high risk of bias as not all patients within the studies underwent the reference standard investigation of a CT scan and/or lumbar puncture. In cases where eligible participants did not undergo CT imaging or investigation with LP, efforts were made to follow up by telephone and review of medical records to screen for possible subsequent SAH. There was also potential bias as it was unclear from the included studies why specific variables were selected for use within the clinical decision rules. The committee noted possible selection bias as some of the studies only included patients with confirmed SAH. Despite these limitations, the moderate quality of the evidence, particularly supported by the statistical precision demonstrated by relatively narrow confidence intervals, provided the committee with the necessary confidence to inform the recommendations. The committee used the evidence available and their experience of clinical practice to make a firm recommendation to be aware of a set of signs and symptoms which indicate SAH as a possible diagnosis and would justify immediate referral for further assessment.

1.7.1.3 Benefits and harms

Some centres have a low threshold for carrying out CT scan in people presenting at an Emergency Department with acute headache because of concern that a missed diagnosis of SAH can have severe consequences. However, there is potential harm if every patient presenting at ED with acute severe headache is referred for CT, as many patients would be exposed unnecessarily to ionising radiation and such a policy is unlikely to be cost-effective. Other conditions or common causes of ‘thunderclap’ headache not due to SAH include migraine, cough, coitus and exertion.

Identifying the symptoms and signs that accurately indicate a SAH would highlight the people in whom further diagnostic investigation is clinically justified. The committee noted that a set of symptoms and signs correctly identifying those with the condition, would enable timely investigation and subsequent intervention to manage the bleed. The committee acknowledged the potential harms of symptoms and signs with low diagnostic accuracy in identifying people with SAH could be severe, with missed or delayed diagnosis leading to neurological deterioration for the person with SAH.

The committee discussed the evidence from five papers reporting 4 cohort studies of signs and symptoms used in clinical assessment to indicate SAH.

One study used multivariate analysis and recursive partitioning to create clinical decision rules with high sensitivity so that a negative result would rule out subarachnoid haemorrhage. Accuracy of these decision rules with a diagnosis of SAH were reported in a further 3 studies.

No decision rules or individual signs or symptoms had levels of sensitivity and specificity of more than 90%.

All of the decision rules showed relatively high levels of sensitivity (ranging from 89.8% to 100%) and low levels of specificity (ranging from 15.3% to 44.2%). The evidence showed that Rule 1 (age ≥40 y; neck pain or stiffness; loss of consciousness; onset during exertion) had a median sensitivity of 96.6% and a specificity of 27.6%. Rule 2 (age ≥ 45 y; arrival by ambulance; vomiting (≥1 episodes); diastolic blood pressure ≥100mmHg) had a median sensitivity of 97.8% and a specificity of 30.6%. Rule 3 (age 45-55 y; neck pain or stiffness; arrival by ambulance; systolic blood pressure ≥ 160mmHg) had a median sensitivity of 93.4% and a specificity of 35.6%. The Ottawa rule (age ≥ 40 y; neck pain or stiffness; witnessed loss of consciousness; onset during exertion; thunderclap headache; limited neck flexion) demonstrated the highest level of sensitivity at 100%, with a median specificity of 29.8%. All tests reached a point of clinically important sensitivity, but none passed the threshold for clinically important specificity agreed by the committee.

The committee agreed that the high sensitivity of decision rules shows that as diagnostic tools, they would identify most people with SAH who may need further investigation and intervention. However, the committee noted that the rules are based on symptoms and signs that are not specific to SAH (for example age ≥ 45years, arrival by ambulance, vomiting, raised diastolic BP), resulting in a low specificity. Hence, the rules incorrectly indicated a significant number of patients as having a SAH.

The committee acknowledged that the low specificity of the decision rules would lead to potentially unnecessary investigation with CT head scan or lumbar puncture in a large proportion of patients who did not have SAH, which reduces the value of the tools. The committee agreed that they could not make a recommendation to use these tools.

The diagnostic accuracy of the individual parameters used within these clinical decision rules were also reviewed by the committee, including arrival by ambulance, onset during exertion or sexual activity, thunderclap headache, loss of consciousness, neck pain or stiffness, limited neck flexion, vomiting, and high blood pressure. The evidence showed that thunderclap headache, neck pain or stiffness, and vomiting had highest diagnostic accuracy of individual symptoms and signs with regards to combined sensitivity and specificity. Taking the evidence from the largest and prospective study, thunderclap headache had a sensitivity of 82.4% and specificity of 45.3%, neck pain or stiffness a sensitivity of 76.5% and specificity of 68.4%, and vomiting a sensitivity of 65.9% and specificity of 73.6%. While these did not meet the threshold of 90% sensitivity and specificity the committee considered these were useful in distinguishing people who might benefit from further investigation. The committee also noted that, from their clinical experience, signs and symptoms of photophobia and altered neurology (such as reduced consciousness, a seizure or a focal neurological deficit) also raise the clinical suspicion of SAH and considered these important to consider during a clinical assessment.

The committee agreed that on balance, and based on their clinical experience and the available evidence, most people who have SAH present with an unexplained sudden severe headache, usually described as a ‘thunderclap’ headache. The mean time to peak intensity of headache reported in people with subarachnoid haemorrhage ranged from 10s to over 3 minutes. The committee therefore defined ‘thunderclap’ headache as sudden onset severe headache, typically peaking in intensity within 1-5 minutes and recommended that a careful history should be be taken to establish the rate of onset and time to peak intensity of headache in people with suspected SAH. The committee agreed that headache meeting the definition for thunderclap headache should alert clinicians to the possibility of SAH, whilst acknowledging that thunderclap headache is associated with other conditions and causes such as migraine, cough, coitus or exertion.

Based on their clinical experience and on the evidence presented, the committee also agreed that people with suspected SAH require a holistic clinical assessment. The committee

made a recommendation that clinicians should be aware that other symptoms and signs (such as neck pain or stiffness, photophobia, vomiting) are potentially also important parts of the clinical presentation, and these non-specific symptoms are more likely to be associated with a missed diagnosis of SAH.

1.7.2 Cost effectiveness and resource use

No published economic evaluations were identified for this review.

The committee noted that in current practice the symptoms and signs used to select people for investigation for subarachnoid haemorrhage vary substantially. Due to the concerns about a missed diagnosis, however, investigations such as a CT head scan are frequently performed to help rule out subarachnoid haemorrhage.

The committee considered that the recommendations are unlikely to have a substantial impact on current practice and will therefore not have a substantial resource impact.

1.7.3 Other factors the committee took into account

The committee agreed that to reduce the incidence of missed cases, clinicians should have a high index of suspicion for SAH in people with acute severe headache or other sudden unexplained neck pain or stiffness, vomiting, photophobia or new symptoms or signs of altered brain function. The committee also acknowledged that urgent investigation to confirm a diagnosis of SAH facilitates early treatment to prevent rebleeding from a ruptured aneurysm and reduces disability and death The committee discussed the necessity for immediate referral to an emergency department of a person with suspected SAH for urgent review by a senior clinician. The committee agreed that if the senior clinical decision maker confirms unexplained thunderclap headache or other symptoms or signs that suggest SAH, the person should be referred for urgent non-contrast CT head scan.

The committee discussed that some people with a SAH are retrospectively found to have had a ‘sentinel’ headache up to 2 weeks before the index event. A sentinel headache can be a sudden onset and severe headache, which could indicate a ‘warning leak’ of blood from an intracranial aneurysm. Nevertheless, the committee did not consider that ‘sentinel’ headache could be diagnosed prospectively to identify patients at risk of clinically overt SAH.

The committee recognised that the Ottawa rule is a clinical decision tool that has shown capacity to accurately rule out SAH with a high level of sensitivity. However, the committee highlighted the low specificity of the Ottawa rule and other clinical decision rules, and that only components of the score, rather than the overall rules are used widely in clinical practice. These factors supported the committee’s decision to recommend a set of symptoms and signs as clinical indicators of SAH. The committee agreed that the recommendations made reflect current practice.

The difficulty of diagnosis in people with learning disabilities or with impaired consciousness was discussed by the committee. In such circumstances the health professional should seek information on symptoms and signs observed by the patient’s relatives, carers or witnesses where possible. A recommendation was made to reflect this point.

References

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Symptoms and signs for SAH

ID	Field	Content
0.	PROSPERO registration number	CRD42019160031
1.	Review title	What symptoms and signs indicate subarachnoid haemorrhage?
2.	Review question	What symptoms and signs indicate subarachnoid haemorrhage?
3.	Objective	To determine which symptoms and signs indicate subarachnoid haemorrhage as a possible diagnosis. Review aims to inform diagnosis with signs and symptoms of an initial haemorrhage and subsequent haemorrhages at long-term follow-up.
4.	Searches	The following databases will be searched: • 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 suspected subarachnoid haemorrhage caused by a suspected ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
7.	Signs and symptoms	• History of headache (herald/sentinel/prodromal headache) • Sudden severe headache • Painful/stiff neck • Nausea and vomiting • Photophobia • Blurred/double vision • Loss of consciousness

		• Confusional state • Focal neurology (hemiparesis) • Seizure • High blood pressure (>140/90)
8.	Reference standard/ Confounding factors	Reference standard: • confirmed diagnosis of SAH (by CT, LP +/- angiography or post-mortem) Confounding factors: • Age
9.	Types of study to be included	• Prospective and retrospective cohort studies with multivariate analysis will be included preferentially. • Cross-sectional studies Studies will only be included if all the key confounders have been accounted for in a multivariate analysis. In the absence of multivariate analysis, studies that account for key confounders with univariate analysis or matched groups will be considered.
10.	Other exclusion criteria	Exclusions: • Studies that do not account for key confounders. • Non English studies • Conference abstracts
11.	Context	In clinical practice a number of signs and symptoms might indicate that a person has experienced an aneurysmal subarachnoid haemorrhage. An understanding of which signs and symptoms better indicate aSAH as a cause can facilitate further diagnostic investigations to confirm diagnosis and guide treatment.

12.	Primary outcomes (critical outcomes)	Diagnostic association of signs and symptoms with a confirmed diagnosis of aSAH.
		Measured by:
		• Diagnostic accuracy data
		  ○ Sensitivity, specificity, PPV, NPV
		• Association data
		  ○ Adjusted RR or OR.

13.	Secondary outcomes (important outcomes)	n/a
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.

		A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. QUADAS will be used to assess diagnostic association reviews. 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	Aggregate data on diagnostic association of signs and symptoms will be collected and synthesized in a quantitative data analysis. If more than one study covered the same combination of population, sign/symptom and outcome then meta-analysis will be used to pool results. Meta-analysis will be carried out using the generic inverse variance function on Review Manager using fixed effect model. Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer. Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables 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 sign/symptom. Publication or other bias will only be taken into consideration in the quality assessment if it is apparent. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses 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 presented using random effects. If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables.

<table>
<tr><td></td><td></td><td colspan="3">Endnote will be used for bibliography, citations, sifting and reference management.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Strata:
• n/a
Subgroups:
• History of SAH
  ○ Personal previous SAH
  ○ No history of SAH
  ○ Familial history of SAH</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>
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<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☒</td><td colspan="2">Other (diagnostic association)</td></tr>
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<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></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 Elizabeth Pearton • 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; symptoms; signs	
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 6: 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.[112] **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 symptoms and signs indicate subarachnoid haemorrhage?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[112]

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 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 June 2020	Exclusions Observational studies
Embase (OVID)	1974 – 23 June 2020	Exclusions Observational studies

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracerebral or intra-cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracerebral or intra-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.	exp "signs and symptoms"/
30.	Symptom Assessment/
31.	diagnosis/ or prognosis/
32.	(clinical adj2 (manifestation* or feature* or finding* or aspect* or marker* or present*)).ti,ab.
33.	(present* adj2 (feature* or finding* or factor*)).ti,ab.
34.	(physical adj2 (manifestation* or characteristic* or feature* or finding*)).ti,ab.
35.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
36.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
37.	or/29-36
38.	*Headache/ or *headache disorders/ or *migraine disorders/
39.	(headache* or migraine*).ti,ab.
40.	(head adj3 pain*).ti,ab.
41.	((pain* or stiff*) adj2 neck*).ti,ab.
42.	*Vomiting/
43.	(vomit* or emesis or emeses or sick or sickness or nausea).ti,ab.
44.	*Blood Pressure/
45.	(blood adj2 pressure).ti,ab.
46.	*Unconsciousness/
47.	(consciousness or unconsciousness or semiconsciousness or semi consciousness).ti,ab.
48.	*Delirium/ or *Confusion/
49.	(delirium* or deliria or confus*).ti,ab.
50.	((alter* or chang*) adj2 mental state*).ti,ab.
51.	*Seizures/
52.	(spasm* or seizure* or convuls*).ti,ab.
53.	*paresis/ or *paraparesis/
54.	(hemipares* or monopares* or paresis or pareses or parapares* or plegia* or hemiplegia* or paraplegia* or paralys* or palsy).ti,ab.
55.	(focal adj2 (neurolog* or sign* or deficit)).ti,ab.
56.	(impair* adj2 (brain or neurolog* or nerve* or nervous system* or spine or spinal)).ti,ab.
57.	(weak* adj2 (arm* or leg* or limb* or body or muscle*)).ti,ab.
58.	*Photophobia/
59.	Photophobi*.ti,ab.
60.	((sensitiv* or intoleran* or pain* or discomfort) adj2 light).ti,ab.
61.	*Diplopia/
62.	diplopia.ti,ab.
63.	((double or blur* or hazy or altered or change* or loss) adj3 vision).ti,ab.
64.	or/38-63
65.	28 and (37 or 64)
66.	Epidemiologic studies/
67.	Observational study/
68.	exp Cohort studies/
69.	(cohort adj (study or studies or analys* or data)).ti,ab.
70.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

71.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
72.	Controlled Before-After Studies/
73.	Historically Controlled Study/
74.	Interrupted Time Series Analysis/
75.	(before adj2 after adj2 (study or studies or data)).ti,ab.
76.	exp case control study/
77.	case control*.ti,ab.
78.	Cross-sectional studies/
79.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	or/66-79
81.	65 and 80

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.	symptom assessment/
28.	diagnosis/
29.	prognosis/

30.	(clinical adj2 (manifestation* or feature* or finding* or aspect* or marker* or present*)).ti,ab.
31.	(present* adj2 (feature* or finding* or factor*)).ti,ab.
32.	(physical adj2 (manifestation* or characteristic* or feature* or finding*)).ti,ab.
33.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
34.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
35.	symptomatology/
36.	or/27-35
37.	*headache/
38.	*migraine/
39.	(headache* or migraine*).ti,ab.
40.	(head adj3 pain*).ti,ab.
41.	*neck pain/
42.	((pain* or stiff*) adj2 neck*).ti,ab.
43.	*vomiting/
44.	(vomit* or emesis or emeses or sick or sickness or nausea).ti,ab.
45.	*Blood Pressure/
46.	(blood adj2 pressure).ti,ab.
47.	*consciousness/
48.	(consciousness or unconsciousness or semiconsciousness or semi consciousness).ti,ab.
49.	*delirium/
50.	*confusion/
51.	(delirium* or deliria or confus*).ti,ab.
52.	((alter* or chang*) adj2 mental state*).ti,ab.
53.	*seizure/
54.	(spasm* or seizure* or convuls*).ti,ab.
55.	*paresis/
56.	*paraplegia/
57.	(hemipares* or monopares* or paresis or pareses or parapares* or plegia* or hemiplegia* or paraplegia* or paralys* or palsy).ti,ab.
58.	(focal adj2 (neurolog* or sign* or deficit)).ti,ab.
59.	(impair* adj2 (brain or neurolog* or nerve* or nervous system* or spine or spinal)).ti,ab.
60.	(weak* adj2 (arm* or leg* or limb* or body or muscle*)).ti,ab.
61.	*paralysis/
62.	*Photophobia/
63.	Photophobi*.ti,ab.
64.	((sensitiv* or intoleran* or pain* or discomfort) adj2 light).ti,ab.
65.	*Diplopia/
66.	diplopia.ti,ab.
67.	((double or blur* or hazy or altered or change* or loss) adj3 vision).ti,ab.
68.	or/37-67
69.	26 and (36 or 68)
70.	Clinical study/
71.	Observational study/
72.	family study/

73.	longitudinal study/
74.	retrospective study/
75.	prospective study/
76.	cohort analysis/
77.	follow-up/
78.	cohort*.ti,ab.
79.	77 and 78
80.	(cohort adj (study or studies or analys* or data)).ti,ab.
81.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
82.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
83.	(before adj2 after adj2 (study or studies or data)).ti,ab.
84.	exp case control study/
85.	case control*.ti,ab.
86.	cross-sectional study/
87.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
88.	or/70-76,79-87
89.	69 and 88

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 8: 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/

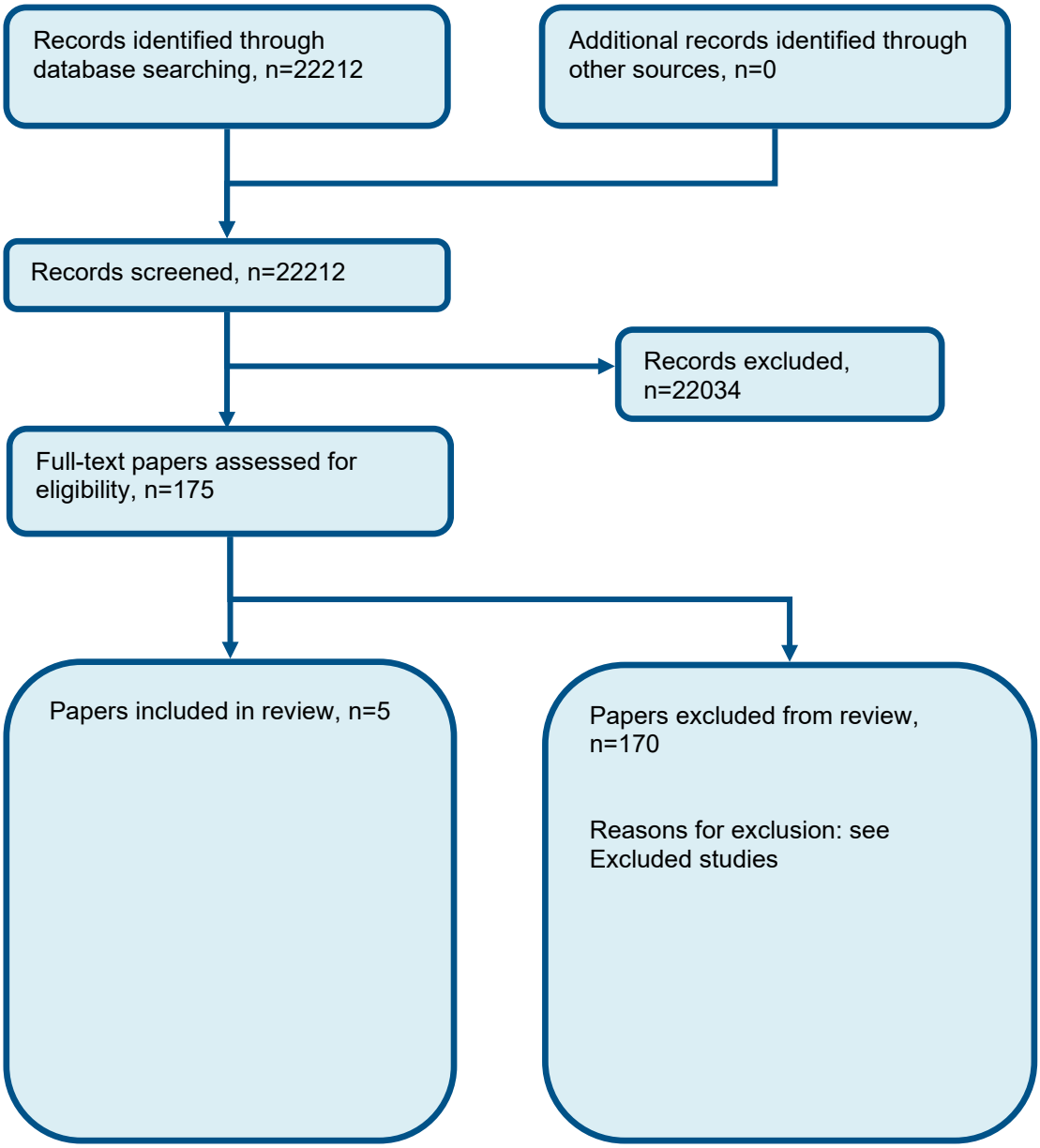
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or 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 symptoms and signs for SAH



Appendix D: Clinical evidence tables

Reference	Kelly 2014[55]
Study type and analysis	Retrospective multi-centre cohort study The estimated sensitivity for subarachnoid haemorrhage, including 95% CIs, were calculated for the clinical decision rules. Potential cases were identified from the ED data management database by final ED diagnosis of 'subarachnoid haemorrhage, non-traumatic' or 'haemorrhage, intracranial, nontraumatic'.
Number of participants and characteristics	N= 59 Inclusion: Cases were adult patients aged greater than 16 years with confirmed SAH presenting to the ED of two community teaching hospitals without specialist neurosurgical units in Melbourne, Australia, between 2000 and 2011. Exclusion: Patients were excluded if they were aged <16 years, had a history of trauma within the last 7 days (collapse associated with onset of headache leading to head injury was not an exclusion), history of previous SAH, known cerebral aneurysm or cerebral neoplasm, it was more than 14 days from symptom onset, there was absence of 'sudden' headache, there was a history of three or more headaches with similar characteristics and intensity over more than 6 months, GCS was <15, there were new focal neurological signs or there was failure to confirm the diagnosis of SAH by CT head scan, CT angiography, conventional angiography, MRI or LP supported by specialist neurosurgical opinion.
Diagnostic variable(s)	• Complaint of neck pain or stiffness • Onset with exertion • Witnessed loss of consciousness • Arrival by ambulance • Vomited at least once • Diastolic blood pressure >100 mmHg • Systolic BP >160 mmHg • Age >40 years • Age >45 years • Age 45-55 years

Reference	**Kelly 2014[55]**			
Clinical Decision Rules	Rule 1 1. Age ≥40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion Investigate if ≥1 high-risk findings present: Rule 2 1. Age ≥ 45 y 2. Arrival by ambulance 3. Vomiting (≥1 episodes) 4. Diastolic blood pressure ≥100mmHg Investigate if ≥1 high-risk findings present: Rule 3 1. Age 45-55 y 2. Neck pain or stiffness 3. Arrival by ambulance 4. Systolic blood pressure ≥160mmHg			
Reference standard	Reference standard: Diagnosis of SAH by CT head scan, CT angiography, conventional angiography, MRI or LP supported by specialist neurosurgical opinion. Follow-up: <14 days from symptom onset			
Outcomes and effect sizes: CDR		Rule 1	Rule 2	Rule 3
	True Positive	57	59	53
	False Positive	NA	NA	NA
	False Negative	2	0	6
	True Negative	NA	NA	NA
	Sensitivity	96.6% (95% CI 88.5–99.1%)	100% (95% CI 93.9–100%)	89.8% (95% CI 79.5–95.3%)
	Specificity	NA	NA	NA

Reference	Kelly 2014[55]			
	Negative predictive value	NA	NA	NA
Outcomes and effect sizes: Signs and symptoms	Sign/symptom	True positive	False Negative	Sensitivity
	Complaint of neck pain or stiffness	25	34	42.4%
	Onset with exertion	12	47	20.3%
	Witnessed loss of consciousness	11	48	18.6%
	Arrival by ambulance	41	18	69.5%
	Vomited at least once	39	20	66.1%
	Diastolic blood pressure >100 mmHg	6	53	10.2%
	Systolic BP >160 mmHg	18	41	30.5%
	Age >40 years	47	12	79.6%
	Age >45 years	41	18	69.5%
	Age 45-55 years	16	43	27.1%
Comments	Cohort only included confirmed SAH cases. Only sensitivity available.			
Risk of Bias	High risk of bias This was given due potential bias around the selection of participants and index test with (a) selective analysis of only participants with confirmed SAH (b) a lack of clarity regarding the application of the variables within the clinical decision rule. There were no concerns regarding applicability.			

Reference	Mark 2015[97]
Study type and analysis	Retrospective multicentre cohort study The estimated sensitivity, for subarachnoid haemorrhage, including 95% CIs, were calculated for the clinical decision rule.
Number of participants and characteristics	N= 155 Inclusion: Patients who had an ED or hospital encounter with an associated International Statistical Classification of Diseases and Related Health Problems, ninth edition (ICD-9) diagnosis code of SAH between January 2007 and June 2013. Hunt-Hess clinical grade

Reference	Mark 2015[97]	
	of 1 or 2 at the time of ED presentation, non-contrast cranial CT imaging within six hours of headache onset, either evidence of SAH on non-contrast cranial CT or greater than five red blood cells per microliter on cerebrospinal fluid analysis, and angiographic evidence of cerebral aneurysm thought to be consistent with the clinical presentation and pattern of haemorrhage visualized on imaging, if applicable. Exclusion: Patients were electronically excluded if they had an ICD-9 coded diagnosis of head or neck trauma within 24 hours of the index encounter, lacked continuous KFHP membership within the two weeks preceding diagnosis, were under 18 years of age or had a prior diagnosis of SAH Consecutive adult patients from the emergency departments of 10 university-affiliated urban Canadian tertiary care teaching hospitals from April 2006 to July 2010.	
Diagnostic variable(s)	1. Age ≥40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion A negative result being defined as absence of all four clinical criteria.	
Reference standard	SAH Reference standard: Evidence of SAH on non-contrast cranial CT or >5 RBC per microliter on CSF analysis, and angiographic evidence of cerebral aneurysm thought to be consistent with clinical presentation and pattern of haemorrhage visualised on imaging. All CT examinations were performed without contrast using multi-slice cine technology (16 slice or higher). Either general radiologists or neuroradiologists made the final interpretation of CT images Follow-up: CT performed <6 hours from symptom onset. Timing of alternative investigation unclear	
Outcomes and effect sizes		
	True Positive	148/155
	False Positive	NA
	False Negative	7/155
	True Negative	NA
	Sensitivity	95.5% (95% CI [90.9-98.2]
	Specificity	NA
	Negative predictive value	NA

Reference	Mark 2015[97]
Comments	Cohort only included confirmed SAH cases. Only sensitivity available.
Risk of Bias	Moderate risk of bias This was given due potential bias around the selection of participants with a selective analysis of only participants with confirmed SAH. There were no concerns regarding applicability.

Reference	Pathan 2018[130]	
Study type and analysis	Retrospective cohort study The estimated sensitivity and specificity for subarachnoid haemorrhage, including 95% CIs, were calculated for the Ottawa rule.	
Number of participants and characteristics	N= 145 Inclusion: All patients registered with a primary complaint of a headache from 1st January 2016 to 31st December 2016 were identified. Age older than 15 years, new atraumatic headache, and headaches that reached maximal intensity in 1 hour Exclusion: Any new neurological deficits, prior diagnosis of cerebral aneurysms/SAH/brain tumours, and those with recurrent headaches in last 6 months	
Stratification strategy	Ottawa Rule	
	For alert patients olderthan15 years with new severe non-traumatic headache reaching maximum intensity within 1 h Investigate if ≥1 high-risk variables present: 1. Age ≥40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion 5. Thunderclap headache (instantly peaking pain) 6. Limited neck flexion on examination	
Reference standard	Reference standard: subarachnoid blood visible on a plain CT film or xanthochromia in the cerebrospinal fluid. Follow-up: unclear	
Outcomes and effect sizes		Ottawa Rule
	True Positive	5

Reference	Pathan 2018[130]	
	False Positive	78
	False Negative	0
	True Negative	62
	Sensitivity	100% (95% CI 46.3 % - 100 %)
	Specificity	44.2 % (95% CI, 36 % - 53 %)
	Negative predictive value	100%
Risk of Bias	Moderate risk of bias This was given due potential bias around the reference standard with not all patients having the reference test. There were no concerns regarding applicability.	

Reference	Perry 2013[132] (merged with Perry 2010[133])
Study type and analysis	Prospective multi-centre cohort study Multivariate recursive partitioning analysis. The estimated sensitivity, specificity, and C statistic for subarachnoid haemorrhage, including 95% CIs, were calculated for the refined rule.
Number of participants and characteristics	N= 2131 Inclusion: Consecutive adult patients from the emergency departments of 10 university-affiliated urban Canadian tertiary care teaching hospitals from April 2006 to July 2010. Adult patients (defined as patients 16 years or older) whose chief reason for visiting the emergency department was a non-traumatic headache that reached maximal intensity within 1 hour were considered for enrolment. We enrolled patients who had a Glasgow Coma Scale score of 15 of 15 (i.e., alert and oriented), had not sustained a fall or direct head trauma in the previous 7 days, and who had presented within 14 days of headache onset Exclusion: Patients were ineligible if they had a history of 3 or more recurrent headaches of the same character and intensity as the presenting headache over a period greater than 6 months (i.e., established recurrent headache syndromes); were referred from another hospital with a confirmed subarachnoid haemorrhage; returned for reassessment of the same headache if already investigated with both CT and lumbar puncture; had papilledema on funduscopic examination (as determined by the treating physician); had new

Reference	Perry 2013[132] (merged with Perry 2010[133])
	focal neurologic deficits (e.g., isolated cranial nerve palsies, limb weakness); or had a previous diagnosis of cerebral aneurysm, subarachnoid haemorrhage, brain neoplasm, or hydrocephalus.
Diagnostic variable(s)	• Arrived by ambulance • Time from peak onset • Pain severity at peak • Onset during exertion • Onset during sexual activity • Headache awoke patient from sleep • Thunderclap headache • Reported worse headache of life • Loss of consciousness • Neck pain or stiffness • Vomiting • Able to walk since headache • Emergency department transfer • Limited flexion • Heart rate • Blood pressure • Temperature • CT obtained • Lumbar Puncture
Reference standard	SAH Reference standard: subarachnoid blood on unenhanced CT of the head; xanthochromia in the cerebrospinal fluid; or red blood cells (>1 × 106/L) in the final tube of cerebrospinal fluid, with an aneurysm or arteriovenous malformation on cerebral angiography. This outcome was established a priori by consensus of 5 emergency physicians and 1 neurosurgeon. Follow-up: Timing of CT/LP relative to symptom onset unclear. Patients discharged without both CT imaging and normal lumbar puncture findings (or without both CT imaging and lumbar puncture performed) were evaluated using a structured telephone interview

Reference	Perry 2013[132] (merged with Perry 2010[133])						
	at 1 month and 6 months after emergency department assessment as well as a medical records review to identify any patients who developed a subsequent subarachnoid haemorrhage.						
Stratification strategy	Rule 1	Rule 2	Rule 3	Ottawa Rule			
	Investigate if ≥1 high-risk findings present: 1. Age ≥40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion	Investigate if ≥1 high-risk findings present: 1. Age ≥ 45 y 2. Arrival by ambulance 3. Vomiting (≥1 episodes) 4. Diastolic blood pressure ≥100mmHg	Investigate if ≥1 high-risk findings present: 1. Age 45-55 y 2. Neck pain or stiffness 3. Arrival by ambulance 4. Systolic blood pressure ≥160mmHg	For alert patients older than15 years with new severe non-traumatic headache reaching maximum intensity within 1 h Investigate if ≥1 high-risk variables present: 1. Age ≥40 y 2. Neck pain or stiffness 3. Witnessed loss of consciousness 4. Onset during exertion 5. Thunderclap headache (instantly peaking pain) 6. Limited neck flexion on examination			
Outcomes and effect sizes		Rule 1	Rule 2	Rule 3	Ottawa Rule		
	True Positive	130	126	128	132		
	False Positive	1447	1287	1388	1694		
	False Negative	2	6	4	0		
	True Negative	552	712	611	305		
	Sensitivity	98.5% (94.6-99.6)	95.5% (90.4-97.9)*	97.0% (92.5-98.8)*	100% (97.2-100)		
	Specificity	27.6% (25.7-29.6)	30.6% (28.6-32.6)	35.6% (33.6-37.7)	15.3% (13.8-16.9)		
	Negative predictive value	99.6%	99.0%	99.4%	100%		
	Sign/symptom	True positive	False Positive	True negative	False Negative	Sensitivity	Specificity
	Arrived by ambulance	81	478	1521	51	61.40%	76.10%
	Onset during exertion	25	206	1793	107	19.20%	89.70%

Reference	Perry 2013[132] (merged with Perry 2010[133])						
	Onset during sexual activity	13	124	1875	119	9.80%	93.80%
	Headache awoke patient from sleep	16	348	1651	116	12.10%	82.60%
	Thunderclap headache	109	1093	906	23	82.40%	45.30%
	Worst headache of life	131	1511	488	1	99.20%	24.40%
	Loss of consciousness	14	106	1893	118	10.60%	94.70%
	Loss of consciousness (witnessed)	7	72	1927	125	5.30%	96.40%
	Neck pain or stiffness	101	632	1367	31	76.50%	68.40%
	Vomiting	87	528	1471	45	65.90%	73.60%
	Able to walk since headache	101	1801	198	31	76.60%	9.90%
	Emergency department transfer	22	162	1837	110	16.70%	91.90%
	Limited flexion	37	64	1935	95	28.30%	96.80%
Comments	*Analysis reported in article differ from analysis from forest plots (sensitivity for Rule 2 - 97.0% and sensitivity for Rule 3 – 95.5%)						
Risk of Bias	Moderate risk of bias This was given due potential bias around the reference standard with not all patients having the reference test. There were no concerns regarding applicability.						

Appendix E: Forest plots

E.1 Signs & Symptoms

Figure 2: Diagnostic accuracy for clinical decision rules for detecting SAH

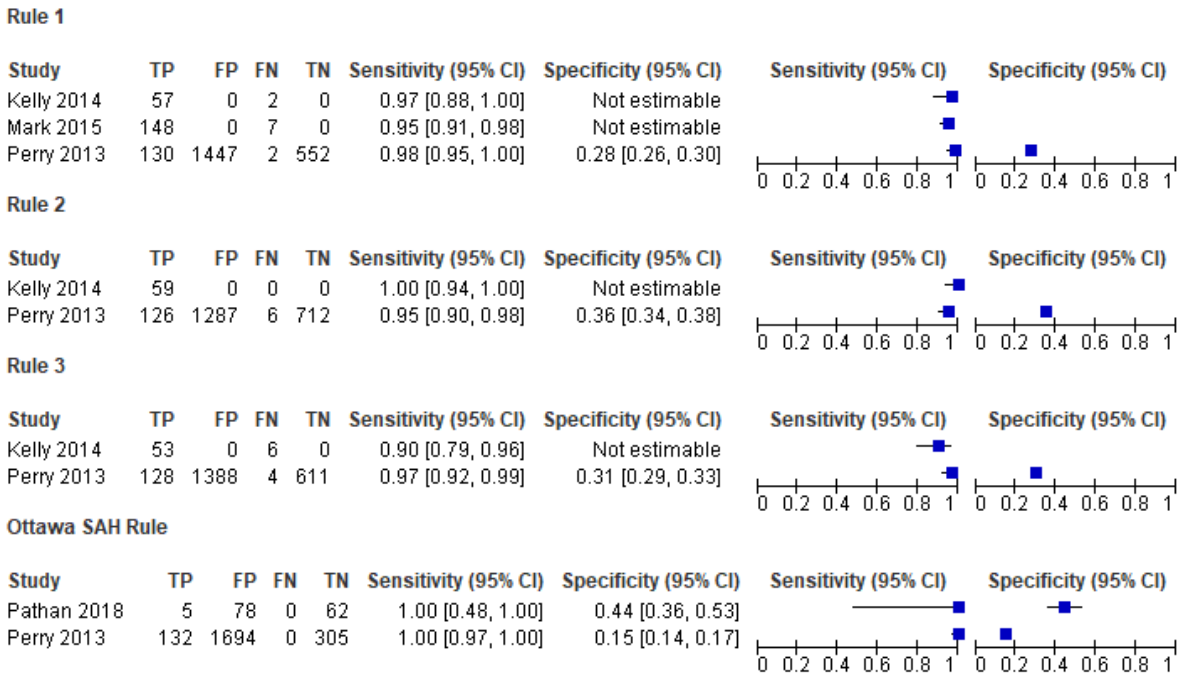
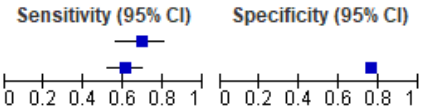


Figure 3: Diagnostic accuracy for individual signs and symptoms for detecting SAH

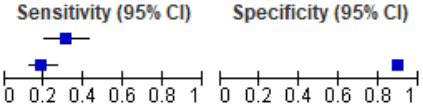
Arrived by ambulance

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	41	0	18	0	0.69 [0.56, 0.81]	Not estimable
Perry 2013	81	478	51	1521	0.61 [0.52, 0.70]	0.76 [0.74, 0.78]



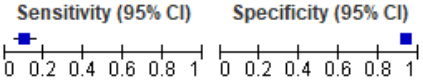
Onset during exertion

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	21	0	47	0	0.31 [0.20, 0.43]	Not estimable
Perry 2013	25	206	107	1793	0.19 [0.13, 0.27]	0.90 [0.88, 0.91]



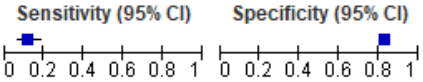
Onset during sexual activity

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	13	124	119	1875	0.10 [0.05, 0.16]	0.94 [0.93, 0.95]



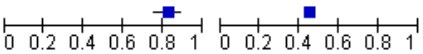
Headache awoke patient from sleep

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	16	348	116	1651	0.12 [0.07, 0.19]	0.83 [0.81, 0.84]



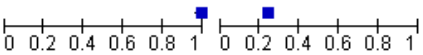
Thunderclap headache

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	109	1093	23	906	0.83 [0.75, 0.89]	0.45 [0.43, 0.48]



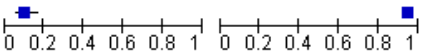
Worst headache of life

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	131	1511	1	488	0.99 [0.96, 1.00]	0.24 [0.23, 0.26]



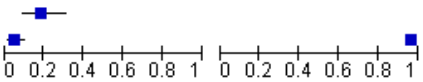
Loss of consciousness

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	14	106	118	1893	0.11 [0.06, 0.17]	0.95 [0.94, 0.96]



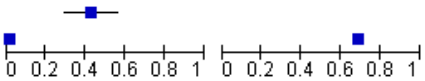
Loss of consciousness (witnessed)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	11	0	48	0	0.19 [0.10, 0.31]	Not estimable
Perry 2013	7	72	125	1927	0.05 [0.02, 0.11]	0.96 [0.95, 0.97]



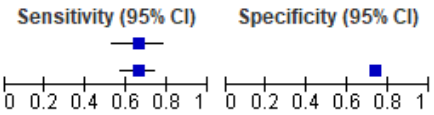
Neck pain or stiffness

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	25	0	34	0	0.42 [0.30, 0.56]	Not estimable
Perry 2013	101	632	6670	1367	0.01 [0.01, 0.02]	0.68 [0.66, 0.70]



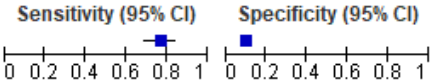
Vomiting

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	39	0	20	0	0.66 [0.53, 0.78]	Not estimable
Perry 2013	87	528	45	1471	0.66 [0.57, 0.74]	0.74 [0.72, 0.76]



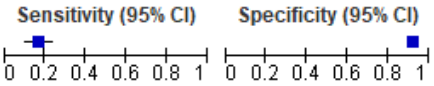
Able to walk since headache

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	101	1801	31	198	0.77 [0.68, 0.83]	0.10 [0.09, 0.11]



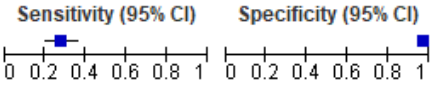
Emergency department transfer

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	22	162	110	1837	0.17 [0.11, 0.24]	0.92 [0.91, 0.93]



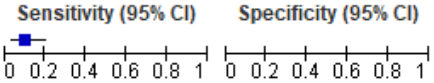
Limited flexion

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perry 2013	37	64	95	1935	0.28 [0.21, 0.37]	0.97 [0.96, 0.98]



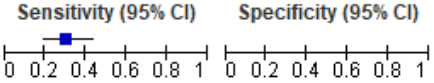
Diastolic BP >100mmHg

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	6	0	53	0	0.10 [0.04, 0.21]	Not estimable



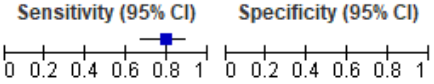
Systolic BP >160 mmHg

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	18	0	41	0	0.31 [0.19, 0.44]	Not estimable



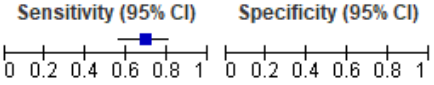
Age >40 years

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	47	0	12	0	0.80 [0.67, 0.89]	Not estimable



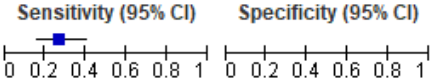
Age >45 years

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	41	0	18	0	0.69 [0.56, 0.81]	Not estimable



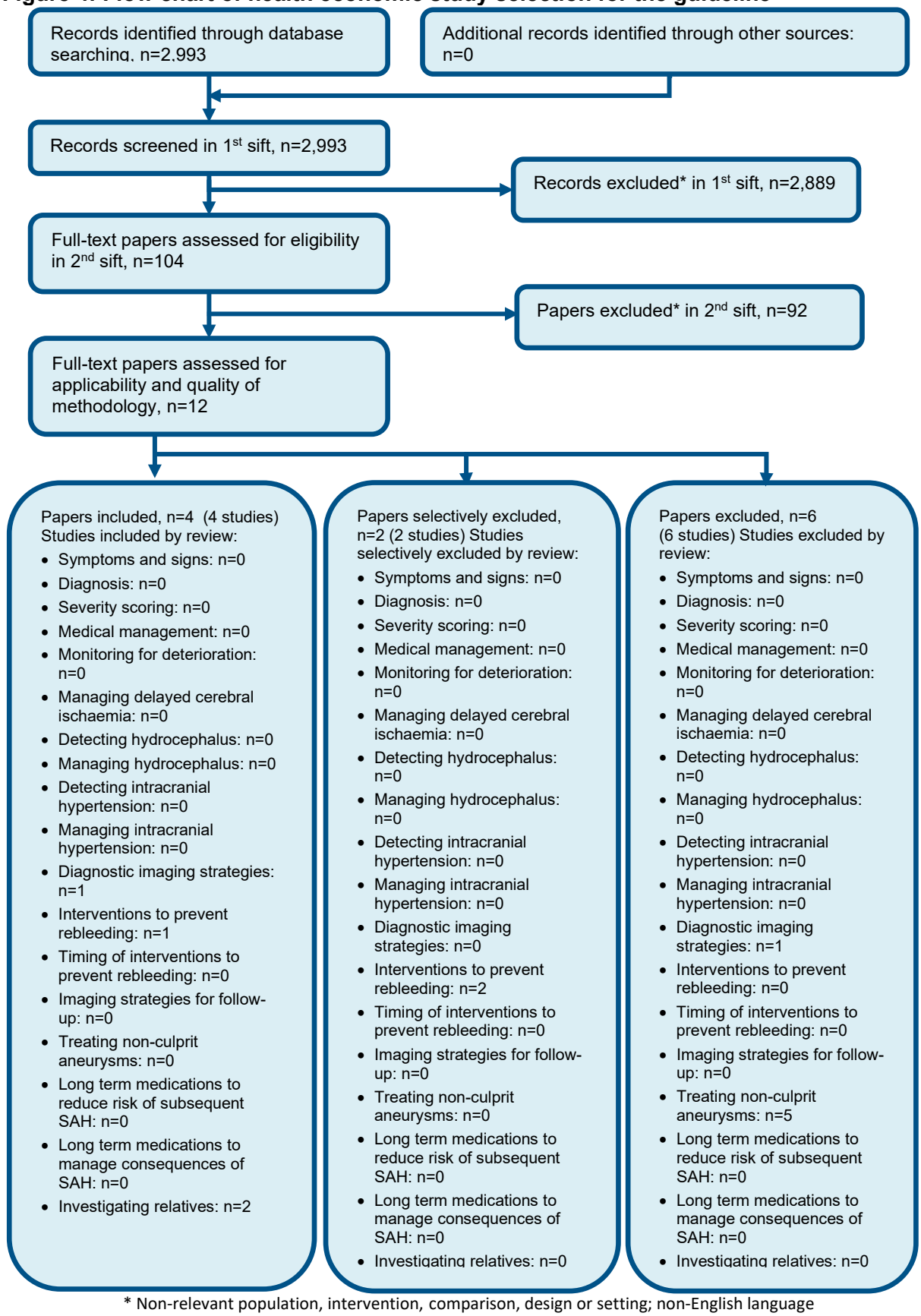
Age 45-55 years

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kelly 2014	16	0	43	0	0.27 [0.16, 0.40]	Not estimable



Appendix F:Health economic evidence selection

Figure 4: Flow chart of health economic study selection for the guideline



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

Appendix G: Health economic evidence tables

None.

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 9: Studies excluded from the clinical review

Reference	Reason for exclusion
Acuna 2011[1]	Inappropriate analysis – incidence of symptoms
Alimohamadi 2016[2]	Inappropriate review focus– effect of electrolyte imbalance in SAH
Ariesen 2003[3]	Systematic review – references checked
Arima 2012[4]	Inappropriate study design – interventional study
Arima 2012[5]	No relevant outcomes
Asari 1993[6]	Inappropriate study design – prognostic risk factors for SAH
Backes 2015[8]	No relevant outcomes
Backes 2016[7]	Inappropriate population – patients with unruptured aneurysms
Bassi 1991[9]	Inappropriate comparison – symptoms in diagnosed and misdiagnosed SAH
Bhat 2011[10]	Inappropriate study design – No relevant outcomes
Bijlenga 2017[11]	Inappropriate study design – screening tool assessment
Bolouki 2019[12]	Inappropriate review focus– predictors of hospital mortality in SAH patients
Bonilha 2001[13]	Inappropriate study design – No relevant outcomes
Breen 2008[14]	Inappropriate analysis/no usable outcome data – proportion of patients with SAH and headache
Canhao 1999[15]	Inappropriate study design/review focus – prognostic risk factors for SAH
Chertcoff 2017[16]	No usable outcome – aetiology of confirmed cases of convexity subarachnoid haemorrhage
Cho 2016[17]	Inappropriate population – majority of included patients children
Donnan 1994[18]	Inappropriate study design – literature review
Duan 2018[19]	Inappropriate study design – risk factors for DCI
Ellamushi 2001[20]	Inappropriate study design – risk factors for multiple aneurysms
Feigin 2005[21]	Systematic review – references checked
Fogelholm 1993[22]	Inappropriate study design/review focus – smoking as a prognostic risk factor
Fogelholm 1987[23]	Inappropriate study design/review focus – smoking as a prognostic risk factor
Foreman 2018[24]	Inappropriate study design – No relevant outcomes
Fridriksson 2001[25]	Inappropriate review focus – long term prognostic risk factors
Garbe 2013[26]	Inappropriate review focus – long term prognostic risk factors
Giordan 2018[27]	Inappropriate population – unruptured intracranial aneurysms
Giroud 1995[28]	Inappropriate review focus – long term prognostic risk factors
Greving 2014[29]	Systematic review – references checked
Gu 2006[30]	Inappropriate review focus – long term prognostic risk factors
Guo 2011[31]	Inappropriate review focus – long term prognostic risk factors for early re-bleeding
Ha 2011[32]	Inappropriate review focus – factors affecting surgical outcomes of proximal middle

Reference	Reason for exclusion
	cerebral artery aneurysms
Haffaf 2019[33]	Inappropriate review population – majority of patients with unruptured aneurysms
Hamann 1995[34]	Inappropriate review population – raised urine catecholamine
Hamdan 2014[35]	Inappropriate review focus – long term prognostic risk factors
Han 2017[36]	Inappropriate population – traumatic brain injury
Hanefeld 2018[37]	Inappropriate study design – No relevant outcomes
Harmsen 1990[38]	Inappropriate review focus – long term prognostic risk factors
Hatcher 2017[39]	Inappropriate study design – No relevant outcomes
Hauerberg 1991[40]	No relevant outcome – patients with warning leak prior to SAH
Hillen 2003[41]	Inappropriate study design – No relevant outcomes
Honig 2015[42]	Inappropriate review population – fever
Hylleraas 2010[43]	Inappropriate population – headache in people without SAH
Inamasu 2015[44]	No usable outcome – BP on admission
Inamasu 2015[45]	Inappropriate review comparison – chronic hypertension compared to admission BP in SAH
Ivan 2019[46]	No relevant outcome – aneurysm characteristics
Jabbarli 2018[47]	Inappropriate review focus – long term prognostic risk factors
Jabbarli 2020[48]	Systematic review - references checked
Jakobsson 1996[49]	No relevant outcome – potential leaks prior to SAH
Jerntorp 1992[50]	Inappropriate study design/ No relevant outcomes
Jiang 2016[51]	No relevant outcome – aneurysm characteristics
Juvela 1995[52]	No relevant outcome – association of DCI with aspirin in SAH
Kann 1997[53]	Inappropriate review focus – carotid artery disease in ICH patients
Katz 2009[54]	Inappropriate study design/ No relevant outcomes
Khan 2017[56]	Inappropriate review focus – comparing timing of CT scan
Kim 1999[58]	Inappropriate population – stroke
Kim 2018[57]	Inappropriate population – head injury patients
Kinnecom 2007[59]	Inappropriate population – cerebral amyloid angiopathy
Kleinpeter 2003[60]	Inappropriate review focus – long term prognostic risk factors
Koivunen 2015[61]	Inappropriate population – intracerebral haemorrhage
Konczalla 2014[62]	Inappropriate study design – No relevant outcomes
Koopman 2019[63]	Inappropriate study design/ No relevant outcomes
Korja 2013[64]	Inappropriate review focus – long term prognostic risk factors
Koshy 2010[65]	Inappropriate review focus – long term prognostic risk factors
Kumral 1999[66]	Inappropriate population – caudate stroke
Lacey 2018[67]	Inappropriate study design/ No relevant outcomes
Lai 2014[68]	Inappropriate study design/ No relevant outcomes
Lansley 2016[69]	Inappropriate comparison – comparison of assessment for SAH between clinicians and neurospecialists
Le Roux 1998[70]	Inappropriate review focus – angiography after surgery
Le Roux 1996[71]	Inappropriate study design – No relevant outcomes
Leira 2005[72]	No relevant outcome – headache and cavity volume
Lepojarvi 1996[73]	Inappropriate population – carotid endarterectomy
Leppala 1999[74]	Inappropriate review focus – long term prognostic risk factors
Lewis 2002[75]	Inappropriate study design – case series

Reference	Reason for exclusion
Li 2018[76]	Inappropriate study design/ No relevant outcomes
Li 2017[77]	Inappropriate study design/No relevant outcomes
Li 2015[78]	Inappropriate population – spontaneous ICH / cerebral infarction
Li 2017[79]	Inappropriate review focus – long term prognostic risk factors
Liang 2018[80]	Inappropriate review focus – predictors of remission
Lindbohm 2016[82]	Inappropriate analysis – Hazard ratios for long-term risk factors of SAH
Lindbohm 2017[81]	Inappropriate analysis – Hazard ratios for long-term risk factors of SAH
Lindbohm 2016[83]	Systematic review – references checked
Lindekleiv 2011[84]	No relevant outcomes – incidence rates
Linn 1998[85]	Inappropriate comparison – comparison of headache symptoms between different conditions
Linn 1994[86]	Inappropriate comparison – all headache patients compared to aSAH
Liotta 2013[87]	Inappropriate study design – No relevant outcomes
Little 2007[88]	Inappropriate study design – case series
Liu 2016[89]	Inappropriate review focus – long term prognostic risk factors
Ljubisavljevic 2017[90]	No relevant outcome – predictors of headache in SAH patients
Lo 2015[91]	Systematic review – references checked
Loumiotis 2011[92]	Inappropriate population – unruptured aneurysms
Lund Haheim 2006[93]	Inappropriate review focus – long term prognostic risk factors
Ma 2019[96]	Inappropriate study design – No relevant outcomes
Ma 2019[95]	Inappropriate population – ICH
Ma 2019[94]	Citation only
Mark 2017[98]	Inappropriate study design/ No relevant outcomes
Menon 2007[99]	Inappropriate study design – descriptive analysis
Mensing 2018[101]	Systematic review – references checked
Mensing 2014[100]	Inappropriate review focus – long term prognostic risk factors
Meretoja 2012[102]	Inappropriate study design/ No relevant outcomes
Migdal 2015[103]	Inappropriate review focus – risk/benefit of LP
Misbach 2001[104]	Inappropriate population – stroke
Mitsos 2008[105]	Inappropriate study design/ No relevant outcomes
Miyagi 2015[106]	Inappropriate comparison – renal function in ICH
Moon 2019[107]	No relevant outcomes – growth of asymptomatic aneurysms
Morgenstern 2001[108]	Inappropriate study design – therapeutic efficacy study
Munoz-Rivas 2016[109]	Inappropriate review focus – diabetes in SAH
Nabaweesi-Batuka 2016[110]	Inappropriate review focus – clinical features of aneurysms
Nahed 2005[111]	Inappropriate review focus – long term prognostic risk factors
Naval 2009[113]	Inappropriate population – spontaneous ICH
Neil-Dwyer 1998[114]	Inappropriate review focus – risk factors for poor outcome
Nemer 1998[115]	Inappropriate population – headache for meningitis, ICH or tumour
Newman 2018[116]	Inappropriate review focus – review of comorbidities in SAH
Nieuwkamp 2009[117]	Systematic review – references checked
Nogueira 1992[118]	Inappropriate population – spontaneous ICH
Nogueira 2018[119]	Inappropriate population – intracranial haemorrhage survivors

Reference	Reason for exclusion
Oder 1991[120]	Inappropriate study design/ No relevant outcomes
Ogun 2002[121]	Inappropriate study design/ No relevant outcomes
Ogun 2001[122]	Inappropriate study design/ No relevant outcomes
Ogunlaja 2019[123]	Inappropriate study design – literature review
Ohkuma 2003[124]	Inappropriate review focus – long term prognostic risk factors
Ohtani 2003[125]	Inappropriate study design/ No relevant outcomes
Ois 2019[126]	Inappropriate review focus – indicators for poor outcome
Olavarria 2014[127]	Inappropriate population – ICH
Oppong 2019[128]	Inappropriate review focus – long term prognostic risk factors
Ozeren 2006[129]	Inappropriate population – ICH
Pavlovic 2018[131]	Inappropriate comparison – comparison of findings between specialists
Perry 2005[134]	No relevant outcome – physician comfort of performing LP
Pierot 2020[135]	Inappropriate population – ruptured and unruptured aneurysms
Pinto 1996[136]	No usable outcomes – comparison of SAH with seizures to without seizures
Plata Bello 2016[137]	Inappropriate comparison – idiopathic SAH compared to aSAH
Polmear 2003[138]	Systematic review – references checked
Powell 2018[139]	Inappropriate review focus – long term prognostic risk factors
Qian 2016[140]	Inappropriate review focus – long term prognostic risk factors
Refai 2008[141]	No usable outcome – chart review and aetiology of SAH patients
Rico 2014[142]	Inappropriate review focus – aetiology of SAH
Rodriguez-Luna 2018[143]	No relevant outcomes
Rosenorn 1994[144]	No relevant outcome – comparison between localization of aneurysm and size
Rush 2016[145]	No relevant outcome – seizure association with mortality in SAH
Sacco 1984[146]	Inappropriate study design/No relevant outcomes
Sahraian 2019[147]	Not review population – not SAH
Sare 2009[148]	Not review population – acute stroke
Savitz 2008[149]	Inappropriate comparison – literature review
Sayer 2015[150]	Inappropriate review focus – diagnosis by LP in CT negative cases
Shimizu 1984[151]	Inappropriate population – cerebral haemorrhage and cerebral infarction
Sim 2016[152]	No usable outcomes – characteristics of patients and aneurysm with SAH
Suthar 2016[153]	Inappropriate review population – ICH
Suwatcharangkoon 2016[154]	Inappropriate study design/ No relevant outcomes
Swope 2014[155]	Inappropriate study design/ No relevant outcomes
Teping 2018[156]	Inappropriate study design/ No relevant outcomes
Toftdahl 1995[157]	No relevant outcome – comparison between hypertension and risk of early death
Tolias 1996[158]	Inappropriate study design/No relevant outcomes
Tsermoulas 2013[159]	Inappropriate study design/ No relevant outcomes
Tsou 2019[160]	Inappropriate comparison – predictors of neurological deterioration
Valenca 2002[161]	Inappropriate study design/ No relevant outcomes
Valle Alonso 2018[162]	Not in English
Vermeulen 2007[163]	No relevant outcomes – missed diagnosis of SAH

Reference	Reason for exclusion
Verweij 1988[164]	Inappropriate study design/ No relevant outcomes
Vlak 2013[165]	Inappropriate population – unruptured aneurysms
Wan 2016[166]	Inappropriate population – ICH
Wang 2017[167]	Inappropriate comparison – relationship between GOS; DCI and LOC
Wei 1994[168]	Not review population – bedside diagnosis of neurological emergencies
Woo 2002[169]	Inappropriate population – ICH
Wu 2016[170]	Inappropriate population – stroke
Ye 2017[171]	Inappropriate study design/ No relevant outcomes
Yeh 2010[172]	Inappropriate population – headache only
Yost 2018[173]	Inappropriate population – spontaneous spinal SAH
Yuksen 2018[174]	Inappropriate population – traumatic brain injury
Zia 2007[175]	Inappropriate study design/ No relevant outcomes
Zidverc-Trajkovic 1998[176]	Inappropriate population - ICH

H.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 10: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	