National Institute for Health and Care Excellence

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Subarachnoid haemorrhage

[B] Evidence review for diagnostic accuracy of investigations

NICE guideline <number>

Evidence reviews underpinning

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Contents

1 Diagnostic investigations for SAH 6
1.1 Review question: What is the diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage? 6
1.2 Introduction 6
1.3 PICO table 6
1.4 Clinical evidence 7
1.4.1 Included studies 7
1.4.2 Excluded studies 8
1.4.3 Summary of clinical studies included in the evidence review 9
1.4.4 Quality assessment of clinical studies included in the evidence review 18
1.5 Economic evidence 21
1.6 Evidence statements 22
1.6.1 Health economic evidence statements 22
2 Diagnostic strategies in detecting subarachnoid haemorrhage 23
2.1 Review question: What is the diagnostic accuracy of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including (a) the timing, (b) location and (c) sequencing of investigations? 23
2.2 Introduction 23
2.3 PICO table 23
2.4 Clinical evidence 25
2.4.1 Included studies 25
2.4.2 Excluded studies 25
2.4.3 Summary of clinical studies included in the evidence review 26
2.4.4 Quality assessment of clinical studies included in the evidence review 29
2.5 Economic evidence 32
2.5.1 Included studies 32
2.5.2 Excluded studies 32
2.5.3 Health economic analysis 32
2.5.4 Unit costs 36
2.6 Evidence statements 36
2.6.1 Health economic evidence statements 36
2.7 The committee's discussion of the evidence 36
Diagnostic accuracy of investigations 36
2.7.1 Interpreting the evidence 36
Diagnostic strategies 38
2.7.2 Interpreting the evidence 38
2.7.3 Cost effectiveness and resource use 41
2.7.4 Other factors the committee took into account 43

Appendices 61

Appendix A: Review protocols 61
A.1 Diagnostic accuracy 61
A.2 Diagnostic strategies 70
A.3 Health economic review protocol 90
Appendix B: Literature search strategies 91
B.1 Diagnostic accuracy 91
B.1.1 Clinical search literature search strategy 92
B.1.2 Health Economics literature search strategy 97
B.2 Diagnostic strategies 100
B.2.1 Clinical search literature search strategy 100
B.2.2 Health Economics literature search strategy 105
Appendix C: Clinical evidence selection 106
Appendix D: Clinical evidence tables 108
D.1 Diagnostic accuracy 108
D.2 Diagnostic strategies 146
Appendix E: Coupled sensitivity and specificity forest plots and sROC curves 158
E.1 Diagnostic accuracy 158
E.1.1 Coupled sensitivity and specificity forest plots 158
E.1.2 sROC curves 159
E.2 Diagnostic strategies 160
E.2.1 Coupled sensitivity and specificity forest plots 160
Appendix F: Health economic evidence selection 162
Appendix G: Health economic evidence tables 164
Appendix H: Health economic model – utility scores 165
Appendix I: Excluded studies 167
I.1 Diagnostic accuracy 167
I.1.1 Excluded clinical studies 167
I.2 Diagnostic strategies 171
I.3 Excluded health economic studies 172
Appendix J: Research recommendations 173

1 Diagnostic investigations for SAH

Evidence review underpinning recommendations 1.1.6 to 1.1.12 and research recommendations in the NICE guideline.

1.1 Review question: What is the diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage?

1.2 Introduction

Investigations to confirm a diagnosis of subarachnoid haemorrhage range from low-risk non-invasive tests such as non-contrast CT or magnetic resonance head scan, to invasive tests associated with procedural risk such as lumbar puncture or cerebral angiography. In current practice most people with suspected subarachnoid haemorrhage are investigated with a non-contrast CT head scan.

The objective of this review was to assess the diagnostic accuracy of investigations for suspected SAH.

The GC discussion of the evidence and recommendations related to diagnosis accuracy of investigations is discussed in section 2.7.

1.3 PICO table

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

Table 1: PICO characteristics of review question- diagnostic accuracy

Population	Adults (16 and older) with a suspected subarachnoid haemorrhage caused by a suspected ruptured aneurysm.
Target condition	Suspected subarachnoid haemorrhage
Index tests	• Non-contrast CT head scan • Lumbar puncture • MRI head scan
Reference standards	• Final clinical diagnosis. • As no widely accepted criterion standard for SAH yet exists, the committee accepted the reference standard of a final clinical diagnosis, based on either subarachnoid blood on CT, or CSF xanthochromia, or CSF RBCs > 5 × 10^6/L in the final sample of CSF, supported by the presence of aneurysm(s) on subsequent cerebral angiography as agreed by a neurointerventionalist
Statistical measures/ Outcomes	Statistical measure to detecting SAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
Study design	• Cross-sectional studies • Cohort studies

Table 2: PICO characteristics of review question – diagnostic RCT

Population	Adults (16 and older) with a suspected subarachnoid haemorrhage caused by a suspected ruptured aneurysm.
Intervention	• Non-contrast CT • Lumbar puncture • MRI
Comparator	• Each other
Outcomes	CRITICAL: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) IMPORTANT • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Length of hospital stay • Complications (any) Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

Nineteen studies were included in the review,[12, 21, 24, 27, 44-46, 69, 71, 85, 115, 133, 152, 163, 164, 166, 170, 190, 213] these are summarised in Table 3 below. The majority of included studies were of cross-sectional study design. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

Studies reporting the diagnostic accuracy of non-contrast CT, lumbar puncture or MRI against a reference standard of a combination CT or LP and confirmatory cerebral angiography were included. Studies with a reference standard of just CT, LP or angiographic imaging were included and downgraded in quality. Only studies with a common reference standard were pooled for meta-analysis. Where studies provided insufficient information to conduct a meta-analysis (true positives, true negatives, false positives, false negatives), or too few common studies were included (≤2 studies for the same diagnostic outcome) diagnostic accuracy results were reported individually on a per-study basis. Where studies report multiple techniques of the same diagnostic test (LP with visual inspection of xanthochromia and LP with traditional inspection of xanthochromia), only the most clinically standard method was included for meta-analysis to avoid double-counting results. The comparison between techniques is reported separately.

Eleven studies provided information on the diagnostic accuracy of CT, 7 studies provided information on the diagnostic accuracy of LP, and 2 studies provided information on the diagnostic accuracy of MRI in diagnosing SAH. One study provided information on the diagnostic accuracy of both CT and MRI.

No evidence was found on the clinical effectiveness of diagnostic investigations.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D: and coupled sensitivity/specificity forest plots and sROC curves in Appendix E:.

1.4.2 Excluded studies

See the excluded studies list in Appendix H:.

1.4.3 1 Summary of clinical studies included in the evidence review

2 **Table 3: Summary of studies included in the evidence review**

Study	Population	Target condition	Index test	Reference standard	Comments
Index test: CT					
Blok 2015[21]	Patients presenting with spontaneous acute headache suspected of SAH, who had a head CT scan within 6 hours after headache onset that was reported negative for the presence of subarachnoid blood by a staff radiologist, and subsequent CSF spectrophotometry. N=760	Subarachnoid haemorrhage	**CT** Investigation with third generation CT scanner within 6 hours	**LP** Two experienced neuroradiologists and one experienced stroke neurologist. Diagnosis of aneurysmal SAH was based on the presence of red blood cells in CSF but without xanthochromia. Cases positive for bilirubin underwent subsequent angiographic investigation.	Cross-sectional study design Only patients with a negative CT reading were included for analysis
Boesiger 2005[24]	Patients presenting to ED with complaint of headache who went on to have a CT scan and LP to evaluate for SAH. N=177	Subarachnoid haemorrhage	**CT** All patients in the study had a CT scan of the head done by a GE light speed 2.x scanner, which is fifth generation CT scanner. The standard protocol 5-mm cuts through the cerebrum and 5 mm cuts through the posterior fossa.	**LP** Patients were considered positive for SAH on LP if they had at least 400 red blood cells in tube 1 and CSF that did not clear by 10-fold. Some of these patients had a CTA the same day to evaluate aneurysm (CTA performed on 2 patients). Other patients who had elevated RBC's but did not have sufficient clearing were followed up by a telephone and hospital records from 3 months to a year after the initial ED visit and were questioned about any other	Cross-sectional study design

Study	Population	Target condition	Index test	Reference standard	Comments
				events or complications. Patients were also considered positive for SAH if there was evidence for xanthochromia.	
Byyny 2008[27]	All ED patients who had non-contrast cranial CT, including the radiology diagnostic coding; all patients who had cerebrospinal fluid sent to the laboratory from the ED, including the cell count results of these cerebrospinal fluid studies (tube number, colour of cerebrospinal fluid supernatant, and RBC and WBC counts); and all patient with discharge diagnosis ICD-9 codes for spontaneous SAH or cerebral aneurysm. N=149	Subarachnoid haemorrhage	**Head CT** Sensitivity of cranial CT scan was determined as a function of presenting complaints: headache and normal mental status, headache and altered mental status, and altered mental status without history of headache. The authors used Stata 9.0 (StataCorp, College Station, TX) for data management and to perform these calculations.	**LP** Patients who had a negative CT scan result and were diagnosed by lumbar puncture.	Cross-sectional study design Study addressed whether new multidetector CT scanners perform better than older models in detecting spontaneous SAH in ED
Cooper 2016[44]	Adult (> 15 years), acute sudden headache suggestive of SAH, Glasgow coma score of 15 (alert and fully orientated), normal neurological examination subjective sensory symptoms and	Subarachnoid haemorrhage	**CT** Initial and verified non-contrast-CT reports (performed on third generation scanners)	**CT/LP + angiography** Evidence of SAH on non-contrast-CT of brain, as verified by a consultant radiologist. CSF positive for bilirubin on spectrophotometry or uniformly blood stained sample across four	Cross-sectional study design Specific reference standard used for each index test unclear.

Study	Population	Target condition	Index test	Reference standard	Comments
	stable clinical observations. N=517			bottles and positive cerebral angiographic imaging. A surrogate gold standard of No SAH including: Both non-contrast CT and LP negative or if CT LP strategy not completed, no sudden death or evidence of subsequent SAH in the following 12 months from discharge (from analysis of attendance and investigations across site at both institutions	
Cortnum 2010[45]	All patients referred to neurosurgical unit on suspicion of SAH or verified SAH N=499	Subarachnoid haemorrhage	**CT** CT scan of the head	**LP + angiography** If the CT scan was positive for SAH the patients subsequently had angiography studies performed and were allocated to appropriate treatment Patients with a negative CT had a lumbar puncture done. Cerebral spinal fluid was sent to a laboratory for cell counts and all samples were analysed for xanthochromia by spectrophotometry	Cross-sectional study design
Gee 2012[71]	All patients admitted to the hospital with a diagnosis of SAH N=134	Subarachnoid haemorrhage	**CT** CT scanner type from outside hospitals was not known, the CT scanner was upgraded from a 16-slice CT scanner to a 64-slice scanner in early 2005.	**LP** CT negative cases were followed up with subsequent LP and angiographic investigation.	Cross-sectional study design Only cases with a diagnosis of SAH were included for analysis

Study	Population	Target condition	Index test	Reference standard	Comments
Mark 2015[133]	Patients with a diagnosis of SAH and non-contrast cranial CT imaging within six hours of headache onset. N=155	Subarachnoid haemorrhage	**CT** CT scan within 6 hours	CT/ LP +/- angiography, evidence of SAH on CT or >5 RBC per microliter on CSF, and angiographic evidence of cerebral aneurysm if applicable.	Cross-sectional study design Study population included positive cases of aSAH only
Mushtaq 2014[152]	Patients presenting in emergency department with thunderclap headache. N=137	Subarachnoid haemorrhage	**CT** CT protocol included CT brain scan without contrast with axial slices. The hard copies of CT scan were interpreted by a radiologist for assessment of subarachnoid haemorrhage.	**LP** Presence of subarachnoid haemorrhage was confirmed by cerebrospinal fluid analysis after lumbar puncture (as per operational definition).	Cross-sectional study design
Perry 2011[166]	Consecutive neurologically intact adults with non-traumatic headache undergoing lumbar puncture (LP) to rule out SAH. N=3123	Subarachnoid haemorrhage	**CT** Computed tomography was ordered at the discretion of the treating physician, who was aware of the clinical decision rule study but was advised not to alter usual care because of the study. All computed tomography scanners were third generation, multi-slice scanners (from 4 to 320 slices/rotation). The protocols at the beginning of the study (2000-2) used 5 mm slices for the posterior fossa and 10 mm for the remainder of the brain. Since 2002, all sites adopted 5-7.5 mm cuts for	**LP + angiography** Any one of the following: subarachnoid blood on CT, visual xanthochromia, >5×106/L RBC in the final tube of CSF with an aneurysm or AVM on cerebral angiography.	Cross-sectional study design Subarachnoid haemorrhage was defined by any of subarachnoid blood on computed tomography, xanthochromia in cerebrospinal fluid, or any red blood cells in final tube of cerebrospinal fluid collected with positive results on cerebral angiography.

Study	Population	Target condition	Index test	Reference standard	Comments
			the brain with 2.5-5 mm for the posterior fossa		
Pouryahya 2020[170]	Patients presenting to an emergency department with a headache. N=388	Subarachnoid haemorrhage	**CT** CT was performed for patients presenting with headache.	**LP + angiography** SAH on subsequent CT or an abnormal CSF result, plus positive results on cerebral angiography or surgical confirmation.	Cross-sectional study design Only patients with a negative/normal CT head were included in the analysis.
Stewart 2014[190]	Patients with Radiological coding of SAH (i.e., patients with CT head reported as being positive for SAH/subarachnoid blood); LPs performed to exclude SAH (all LP samples processed for xanthochromia performed during the study period were examined); Medical discharge coding of SAH N=244	Subarachnoid haemorrhage	**CT** Evidence of SAH / subarachnoid blood on CT scan. One of two modern CT scanners using slip-ring technology, and either four or six slices per second, were used; a GE Light Speed 64-slice, or a Siemens Somaton 16-slice with 2.5 mm slices as standard protocol. All final reports were issued by a consultant radiologist (although initial reporting was often by a radiology registrar) and were reported as positive, negative or inconclusive (equivocal) for subarachnoid blood.	**LP** All LP samples processed for xanthochromia. CSF was analysed by spectrophotometry in accordance with national guidelines to be reported as one of four results: (1) consistent with SAH (positive), (2) no evidence to support SAH (negative), (3) inconclusive, (4) unable to interpret.	Cross-sectional study design
Index test: LP					
Cooper 2016[44]	Adult (> 15 years), acute sudden headache suggestive of SAH, Glasgow coma score of 15 (alert and fully orientated),	Subarachnoid haemorrhage	**LP** LP CSF results – all taken >12 h from the index headache.	**CT/LP + angiography** Evidence of SAH on non-contrast-CT of brain, as verified by a consultant radiologist.	Cross-sectional study design Specific reference standard used for each index test unclear.

Study	Population	Target condition	Index test	Reference standard	Comments
	normal neurological examination subjective sensory symptoms only were considered normal) and stable clinical observations. N=517			CSF positive for bilirubin on spectrophotometry or uniformly blood stained sample across four bottles and positive cerebral angiographic imaging. A surrogate gold standard of No SAH including: Both non-contrast-CT and LP negative or if CT LP strategy not completed, no sudden death or evidence of subsequent SAH in the following 12 months from discharge (from analysis of attendance and investigations across site at both institutions	
Czuczman 2013[46]	Adults with headaches billed for LPs, ≥5 RBC in final CSF tube, and either CT angiogram or magnetic resonance angiogram within 2-weeks N=280	Subarachnoid haemorrhage	**LP** CSF RBC iLRs	**LP + angiography** Either 1) presence of SAH on imaging; 2) xanthochromia with aneurysm or AVM>2mm; 3) xanthochromia and culture- or PCR negative meningitis.	Cross-sectional study design
Gangloff 2015[69]	Age>14 with acute headache Suspicious for SAH, GCS 15, and initial head CT negative for SAH with subsequent LP. N=706	Subarachnoid haemorrhage	**LP** Visual xanthochromia, iterative SPT, or UK NEQUA SPT	**Angiography** Clinical outcome of confirmed angiographic aSAH in negative head computed tomography patients was used as a reference standard.	Cross-sectional study design
Hann 2015[85]	All patients who received a headache-related diagnosis on	Ruptured intracranial aneurysms	**LP** Spectrometry and visual inspection were reviewed for	**Angiography** Presence of vascular aneurysm on	Cohort study design

Study	Population	Target condition	Index test	Reference standard	Comments
	discharge from the ED and CSF xanthochromia investigation following a negative head CT scan. N=409		each subject. Visual inspection was performed prior to spectrometry and the appearance of both pre centrifuged and post centrifuged sample was reviewed. Visual inspection was performed prior to spectrophotometry and the appearance of both pre centrifuged and post-centrifuged (supernatant sample was reviewed.	angiogram within 30-days of headache or no repeat ED visit or SAH death in 30-days.	
Perry 2006[164]	Alert patients with a chief complaint of nontraumatic acute headache or syncope associated with a headache. N=220	Subarachnoid haemorrhage	**LP** Spectrophotometry Four different definitions of positive spectrophotometry were selected a priori: (1) Traditional: an optical density >0.023 at a wavelength of 415 nm[9]; (2) Chalmers and Kiley: net bilirubin absorption >0.015 positive, 0.010 to 0.015 borderline using absorbances at 415 nm and 440 nm relative to a baseline joining absorbances at 530 nm and 360 nm[12]; (3) Chalmers revised: an optical density _0.014 at 476 nm[13]; (4) United Kingdom National External Quality Assurance Service (UK NEQAS) based on net	**CT/LP + angiography** SAH was defined by (1) subarachnoid blood on CT, (2) >5x10^6 red blood cells/L in the final CSF tube and positive angiography, or (3) visible xanthochromia in CSF and positive angiography.	Cross-sectional study design CT interpretations were verified by a radiologist or neuroradiologist with access to routine clinical information as part of usual care and blinded to the conduct of the study.

Study	Population	Target condition	Index test	Reference standard	Comments
			bilirubin and oxyhaemoglobin absorbances at 476 nm and 415 nm, respectively, relative to a baseline joining the 530 nm and 360 nm absorbances.		
Perry 2015[163]	Alert patients aged over 15 with an acute non-traumatic headache who underwent lumbar puncture to rule out subarachnoid haemorrhage. N=641	Subarachnoid haemorrhage	**LP** Cerebrospinal fluid analysis of the final tube of cerebrospinal fluid and/or xanthochromia in one or more tubes. Negative subarachnoid haemorrhage as red blood cells < 2000 × 106 /L in cerebrospinal fluid and no xanthochromia Positive as ≥ 2000 × 106 red blood cells/L or xanthochromia.	**CT/LP + angiography** Aneurysmal SAH if: subarachnoid blood on CT, visual xanthochromia, or any RBC in the final tube of CSF with an aneurysm on cerebral angiography.	Cross-sectional study design
Wood 2005[213]	Patients undergoing lumbar puncture after normal cranial CT scan with a possible diagnosis of spontaneous SAH patients were identified from a hospital laboratory database of all spectrophotometry tests for CSF xanthochromia this test is performed routinely on all CSF samples from patients with	Subarachnoid haemorrhage	**LP** CSF spectrophotometry. The erythrocyte counts in the submitted specimens where recorded for each patient, together with the laboratory report of the macroscopic appearance of the original and centrifuged samples.	**LP + angiography** Uniform CSF bloodstaining across serial samples with visual xanthochromia and positive angiography	Cross-sectional study design

Study	Population	Target condition	Index test	Reference standard	Comments
	possible diagnosis of SAH. N=253				
Index test: MRI					
Ashraf 2019[12]	Patients presenting in ED with acute severe headache (pain on VAS >6) with nausea, vomiting, neck pain, photophobia, loss of consciousness or Glasgow coma scale <13 were included in the study. N=245	Subarachnoid haemorrhage	**MRI Flair** MRI was performed by Philips Intera Achieva 1.5 T super conducting MR unit (Philips media systems, The Netherlands) with the use of head coil. FLAIR examination was performed at 6700/150 (TR/TE) with an inversion time (TI) of 2200ms, a field of view 230mm, matrix 189x256, scan time of 3min 50s and section thickness 5mm in axial plane.	**LP** Following MRI, patients underwent lumbar puncture for cerebrospinal fluid (CSF) examination after 8-12h from the onset of event	Cross-sectional study design
Khedr 2013[115]	Patients with intracranial haemorrhage who underwent MRI (including DWI, ADC, and GRE) and CT. N=61	Subarachnoid haemorrhage	**MRI DWI**, Single shot, spin-echo, echo planar DWI sequences were obtained by applying diffusion gradients in three orthogonal directions at each slice with two diffusion weightings (b value = 0 and 900 or 1000 s/mm2)	**MRI and CT** Results were compared with conventional MRI sequences and CT, interpreted by experienced neuroradiologist.	Cross-sectional study design Reported SE, SP PPV and NPV separately for small intraparenchymal haemorrhage, late subacute hematoma, haemorrhagic bran lesions, and SAH

1 See Appendix D:for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Diagnostic test accuracy for CT, lumbar puncture and MRI.

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
CT							
CT (reference standard: LP + angiography)	4308 (4)	Serious[b]	Not serious	Not serious	Not serious	Sensitivity=98.3% [a] (90.2 to 99.7 %)	MODERATE
		Serious[b]	Not serious	Not serious	Not serious	Specificity=99.9% [a] (99.5 to 100 %)	MODERATE
	155 (1)	Serious[b]	Not serious	Not serious	Not serious	Sensitivity= 95.5% (90.9 to 98.2%)	MODERATE
CT (reference standard: LP)	122 (1)	Serious[b]	Not serious	Serious[d]	Serious[e]	Sensitivity= 86%[c] (78 to 92%)	VERY LOW
		Serious[b]	Not serious	Serious[d]	Serious[e]	Specificity= 88% [c] (70 to 98%)	VERY LOW
	226 (1)	Serious[b]	Not serious	Serious[d]	Serious[e]	Sensitivity= 94% [c] (85 to 98%)	LOW
		Serious[b]	Not serious	Serious[d]	Not serious	Specificity= 98% [c] (95 to 100%)	LOW
	149 (1)	Serious[b]	Not serious	Serious[d]	Cannot be assessed	Sensitivity= 93%	LOW
	134 (1)	Serious[b]	Not serious	Serious[d]	Cannot be assessed	Sensitivity= 97%	LOW
	790 (1)	Serious[b]	Not serious	Serious[d]	Not serious	NPV= 99.9% (99.3 to 100%)	LOW
	388 (1)	Serious[b]	Not serious	Serious[d]	Cannot be assessed	NPV= 99.7%	LOW

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
LP							
LP (reference standard: CT and angiogram)	1390 (4)	Serious[b]	Not serious	Not serious	Serious[e]	Sensitivity= 92.9%[a] (64.9 to 99.6%)	LOW
		Serious[b]	Not serious	Not serious	Serious[e]	Specificity=88.9% [a] (67.5 to 96.9%)	LOW
	280 (1)	Serious[b]	Not serious	Not serious	Not serious	AUC= 0.84 (0.78 to 0.90)	MODERATE
LP (reference standard: angiography)	409 (1)	Serious[b]	Not serious	Serious[d]	Very serious[e]	Sensitivity =100%[c] (54% to 100%)	VERY LOW
		Serious[b]	Not serious	Serious[d]	Not serious	Specificity=87%[c] (75% to 83%)	LOW
	706 (1)	Serious[b]	Not serious	Serious[d]	Very serious[e]	Sensitivity =100%[c] (47.8% to 100%)	VERY LOW
		Serious[b]	Not serious	Serious[d]	Not serious	Specificity=98.1% [c] (96.7% to 99%)	LOW
LP (reference standard: CT)	220 (1)	Serious[b]	Not serious	Serious[d]	Cannot be assessed	Sensitivity =100%	LOW
		Serious[b]	Not serious	Serious[d]	Cannot be assessed	Specificity=83%	LOW
MRI							
MRI (Reference standard: CT)	61 (1)	Serious[b]	Not serious	Serious[d]	Cannot be assessed	Sensitivity =33%	LOW

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
		Serious[b]	Not serious	Serious[d]	Cannot be assessed	Specificity= 100%	LOW
MRI (Reference standard: LP)	245 (1)	Serious[b]	Not serious	Serious[d]	Cannot be assessed	Sensitivity =79%	LOW
		Serious[b]	Not serious	Serious[d]	Cannot be assessed	Specificity=97%	LOW

(a) Pooled sensitivity/specificity from diagnostic meta-analysis, all "0" values were replaced with "0.2" to allow for meta-analysis using Winbugs
(b) 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.
(c) Meta-analysis not performed due to <3 studies contributing data to outcome. Value are reported per study.
(d) Study downgraded for indirectness if the majority of the evidence involved an indirect reference standard.
(e) 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%).These thresholds were applied for outcomes of sensitivity, specificity, PPV, NPV and AUC. 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. Where imprecision cannot be assessed, the outcome was not downgraded.

1.5 Economic evidence

Please refer to section 2.5 to see the information relating to the economic evidence for this review question.

1.6 Evidence statements

1.6.1 Health economic evidence statements

Please refer to section 2.6.1 to see the health economic evidence statement for this evidence review.

2 Diagnostic strategies in detecting subarachnoid haemorrhage

Evidence review underpinning recommendations 1.1.6 to 1.1.12 and research recommendations in the NICE guideline.

2.1 Review question: What is the diagnostic accuracy of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including (a) the timing, (b) location and (c) sequencing of investigations?

2.2 Introduction

In England, the timing and sequencing of investigations to confirm a diagnosis of SAH varies between centres. At some centres people with suspected subarachnoid haemorrhage are offered a non-contrast CT head scan as the first line investigation and lumbar puncture is recommended if the CT scan is negative. Other centres advise against lumbar puncture if the CT head scan was done early after symptom onset and regardless of whether the CT scan confirms the presence on subarachnoid blood.

This review was carried out to determine the impact of the timing, location of diagnosis, and sequencing of investigations on diagnostic accuracy and clinical and cost-effectiveness of strategies for diagnosing subarachnoid haemorrhage.

2.3 PICO table

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

Table 5: PICO characteristics of review question – diagnostic accuracy

Population	Adults (16 and older) with a suspected subarachnoid haemorrhage caused by a suspected ruptured aneurysm.
Target condition	Suspected subarachnoid haemorrhage

Index tests	Timing of diagnosis (from ictus)
	• CT:
	  ○ 6-24 hours
	  ○ >24 hours
	• LP:
	  ○ <6 hours
	  ○ 12-24 hours
	  ○ >24 hours
	• MRI:
	  ○ 12-24 hours
	  ○ >24 hours
	
	Location of diagnosis
	• General hospital setting
	• Neurosurgical/neuroradiological centre
	
	Sequence of investigation
	• Any sequence and combination of CT; LP; MRI

Reference standard	• Final clinical diagnosis. • As no widely accepted criterion standard for SAH yet exists, the committee accepted the reference standard of a final clinical diagnosis, based on either subarachnoid blood on CT, or CSF xanthochromia, or CSF RBCs > 5 × 10^6/L in the final sample of CSF, supported by the presence of aneurysm(s) on subsequent cerebral angiography as agreed by a neurointerventionalist
Statistical measures/ Outcomes	• Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
Study design	• Cross-sectional studies • Cohort studies

1 **Table 6: PICO characteristics of review question – diagnostic RCT**

Population	Adults (16 and older) with a suspected subarachnoid haemorrhage caused by a suspected ruptured aneurysm.
Interventions	• Timing of diagnosis (from ictus) ○ CT: - 6-24 hours - >24 hours ○ LP: - <6 hours - 12-24 hours - >24 hours ○ MRI: - 12-24 hours - >24 hours • Location of diagnosis ○ Neurosurgical/ neuroradiological centre ○ General hospital setting • Sequence of investigations ○ Any sequence and combination of CT; LP; MRI
Comparators	• Timing of diagnosis ○ CT<6 hours ○ LP 6-12 hours ○ MRI <12 hours
Outcomes	CRITICAL: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) IMPORTANT • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Length of hospital stay • Complications (any)

	Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

2.4 Clinical evidence

2.4.1 Included studies

Seven studies were included in the review.[15, 21, 45, 132, 133, 166, 190] All included studies were of cross-sectional study design. One study employed a case-control inclusion criteria. Evidence from these studies is summarised in the clinical evidence summary below (Table 7).

Studies reporting the diagnostic accuracy of non-contrast CT, lumbar puncture, or MRI at set time points against a reference standard of a final confirmatory diagnosis were included. Where studies provided insufficient information to conduct a meta-analysis (true positives, true negatives, false positives, false negatives), or too few common studies were included (≤2 studies for the same diagnostic outcome) diagnostic accuracy results were reported individually on a per-study basis.

Five studies provided information on the diagnostic accuracy of CT within 6 hours of ictus, 2 of these studies provided information on the diagnostic accuracy of CT after 6 hours from ictus. One study provided information on the diagnostic accuracy of CT within 12 hours of ictus, and 1 study provided information on the diagnostic accuracy of CT at <1 day, 2 days, 3 days, 4-7 days and >1 week from ictus in diagnosing SAH.

No evidence was found for the comparison of MRI scans or LP or for the clinical and cost effectiveness of different diagnostic strategies in adults with suspected subarachnoid haemorrhage regarding the location and sequencing of investigations.

2.4.2 Excluded studies

See the excluded studies list in Appendix H:

2.4.3 Summary of clinical studies included in the evidence review

Table 7: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Backes 2012[15]	All patients presenting to our emergency department with a clinical suspicion of non-traumatic SAH and a normal level of consciousness. The first database included consecutive patients with confirmed SAH and the second included all patients receiving lumbar puncture with CSF spectrophotometry. N=250	Subarachnoid haemorrhage	Patients were stratified into head CT ≤ 6 hours after ictus (n=137), head CT ≥ 6 after ictus (n=113). Data regarding time of ictus and time of head CT were extracted from electronic patient files.	Lumbar puncture performed for CSF analysis at least 12 hours after ictus in cases where CT did not show a diagnosis of SAH.	Cross-sectional study design
Blok 2015[21]	Patients presenting with spontaneous acute headache suspected of SAH, who had a head CT scan within 6 hours after headache onset that was reported negative for the presence of subarachnoid blood by a staff radiologist, and subsequent CSF spectrophotometry. Patients were also included with a CT initially being reported negative for the presence of SAH, but subsequently judged	Subarachnoid haemorrhage	CT scan within 6 hours	Lumbar Puncture, CSF analysed by spectrophotometry.	Cross-sectional study design Diagnosis of aneurysmal SAH was based on the presence of red blood cells in CSF but without xanthochromia

Study	Population	Target condition	Index test	Reference standard	Comments
	positive after positive CSF spectrophotometry became available. N=760				
Cortnum 2010[45]	All patients referred to neurosurgical unit of Aalborg University Hospital from January 2000 to December 2005 on suspicion of SAH or with verified SAH. N=499	Subarachnoid haemorrhage	CT (different time points)	Lumbar puncture, samples were analysed for xanthochromia by spectrophotometry.	Cross-sectional study design.
Mark 2013[132]	Patients without evidence of subarachnoid blood by final documented radiologist interpretation, normal documented neurologic examination result, greater than 5 RBCs per microliter of cerebrospinal fluid, and at least 1 of the following criteria as evidence of subarachnoid haemorrhage: presence of xanthochromia on visual inspection of cerebrospinal fluid, angiographic evidence of cerebral aneurysm or arteriovenous malformation, or subsequent cranial imaging demonstrating	Subarachnoid haemorrhage	CT scan within 6 hours	Lumbar puncture, CSF analysis with greater than 5 red blood cells per microliter were sought within the LP results.	Matched case – control study (patients with a diagnosis of SAH as determined by lumbar puncture after a negative cranial CT result were included, a matched control cohort was selected among patients with a diagnosis of headache after negative cranial CT and lumbar puncture results). Results reported incompletely

Study	Population	Target condition	Index test	Reference standard	Comments
	subarachnoid haemorrhage performed within 48 hours after the index lumbar puncture. N=55				
Mark 2015[133]	Patients with a diagnosis of SAH and non-contrast cranial CT imaging within six hours of headache onset. N=155	Subarachnoid haemorrhage	CT scan within 6 hours	CT/ LP +/- angiography, evidence of SAH on CT or >5 RBC per microliter on CSF, and angiographic evidence of cerebral aneurysm if applicable.	Cross-sectional study design. Analysis included positive cases of aSAH only
Perry 2011[166]	Alert patients who presented with non-traumatic acute headache or with syncope associated with headache and underwent emergency head computed tomography as part of their diagnostic investigation. N=3132	Subarachnoid haemorrhage	All computed tomography scanners were third generation, multi-slice scanners. Patients were stratified into CT head ≤6 hours (n=953) or CT head >6 hours (n=2179)	Lumbar puncture was performed at the discretion of the treating physician, with consent from the patient. Local laboratory technicians assessed the cerebrospinal fluid for xanthochromia by visual comparison against white paper. Not all patients with normal results on computed tomography underwent lumbar puncture.	Cross-sectional study design. Patients deemed to be positive for SAH if they had any of subarachnoid blood identified on unenhanced head CT; visible xanthochromia in the cerebrospinal fluid; or red blood cells (>5×106/L) in the final tube of cerebrospinal fluid collected and an aneurysm identified on cerebral angiography.
Stewart 2014[190]	Patients with radiological coding of SAH (i.e. patients with CT head reported as being positive for SAH/subarachnoid blood);	Subarachnoid haemorrhage	CT scan (within 12 hours reported)	Lumbar puncture, CSF was analysed by spectrophotometry.	Cross-sectional study design.

Study	Population	Target condition	Index test	Reference standard	Comments
	LPs performed to exclude SAH (all LP samples processed for xanthochromia performed during the study period were examined); Medical discharge coding of SAH. N=244				

1 See Appendix D: for full evidence tables.

2

2.4.4 3 Quality assessment of clinical studies included in the evidence review

4 **Table 8: Clinical evidence summary: CT Scan (reference standard LP)**

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Index Test: CT scan ≤ 6 hours							
CT ≤6 hours	137 (1)	Serious[b]	Not serious	Not serious	Not serious	Sensitivity=98.5% (92.1–100%) [a]	MODERATE
		Serious[b]	Not serious	Not serious	Not serious	Specificity=100% (94.8–100%) [a]	MODERATE
	935 (1)	Serious[b]	Not serious	Not serious	Not serious	Sensitivity= 100% (97.0 - 100.0%) [a]	MODERATE
		Serious[b]	Not serious	Not serious	Not serious	Specificity= 100% (99.5 – 100%) [a]	MODERATE

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
	155 (1)	Serious[b]	Not serious	Not serious	Not serious	Sensitivity= 95.5% (90.9 – 98.2%)	MODERATE
	55 (1)	Serious[b]	Not serious	Not serious	Cannot be assessed	Sensitivity= <100%	MODERATE
	760 (1)	Very serious[b]	Not serious	Not serious	Not serious	NPV = 99.9% (99.3 – 100.0%)	LOW
Index Test: CT scan ≥ 6 hours							
CT > 6 hours	113 (1)	Serious[b]	Not serious	Not serious	Serious[c]	Sensitivity= 90.0% (76.3–97.2%) [a]	LOW
		Serious[b]	Not serious	Not serious	Not serious	Specificity=100% (95.1–100%) [a]	MODERATE
	2179 (1)	Serious[b]	Not serious	Not serious	Serious[c]	Sensitivity=85.7% (78.3 - 90.9%) [a]	LOW
		Serious[b]	Not serious	Not serious	Not serious	Specificity=100 (99.8 – 100%) [a]	MODERATE
Index Test: CT scan ≤ 12 hours							
CT ≤ 12 hours	40 (1)	Very serious[b]	Not serious	Not serious	Serious[c]	Sensitivity=95% (82 – 99%)	VERY LOW
Index Test: CT scan < 1 day to 1 week							
< 1 day	364 (1)	Serious[b]	Not serious	Serious	Cannot be assessed	Sensitivity= 100%	LOW
		Serious[b]	Not serious	Serious	Cannot be assessed	Specificity= 100%	LOW
2 days	28 (1)	Serious[b]	Not serious	Serious	Cannot be assessed	Sensitivity= 100%	LOW
		Serious[b]	Not serious	Serious	Cannot be assessed	Specificity= 100%	LOW

Index Test	Number of patients (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
3 days	22 (1)	Serious[b]	Not serious	Serious	Cannot be assessed	Sensitivity= 100%	LOW
		Serious[b]	Not serious	Serious	Cannot be assessed	Specificity= 100%	LOW
4 – 7 days	55 (1)	Serious[b]	Not serious	Serious	Cannot be assessed	Sensitivity= 96%	LOW
		Serious[b]	Not serious	Serious	Cannot be assessed	Specificity= 100%	LOW

The assessment of the evidence quality was conducted with emphasis on specificity and sensitivity as these were identified by the committee as the primary measures in guiding decision-making.

(a) Meta-analysis not performed due to <3 studies contributing data to outcome and insufficient data to populate 2x2 tables. Value represents individual study values.

(b) 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.

(c) 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%). These thresholds were applied for outcomes of sensitivity, specificity, PPV, NPV and AUC. 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. Where no confidence region is reported, outcomes are downgraded for potential risk. Where imprecision cannot be assessed, the outcome was not downgraded.

(d) Study downgraded for indirectness if the majority of the evidence involved an indirect reference standard.

2.5 Economic evidence

2.5.1 Included studies

No health economic studies were included.

2.5.2 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:.

2.5.3 Health economic analysis

The committee were concerned about the use of lumbar puncture as a second line test after a negative CT head scan in people with suspected subarachnoid haemorrhage due to the invasiveness and the cost to the NHS. This topic was prioritised for original economic analysis, but it became clear that there was insufficient data available to determine the full economic consequences of a missed diagnosis of subarachnoid haemorrhage. Therefore, a threshold analysis was undertaken to aid the committee in their consideration of the cost effectiveness of lumbar puncture. This analysis determined the QALY gain that would be required for lumbar puncture to be cost effective.

Comparators

This analysis compared two diagnostic strategies:

1. CT of the head followed by lumbar puncture if the CT scan is negative for subarachnoid haemorrhage.
2. CT of the head only - those who have a negative CT scan are discharged as an alternative diagnosis is most likely benign.

Population

From the clinical evidence presented, the committee considered that the diagnostic accuracy data reported in Perry 2011[166] was the most appropriate for the analysis as clinical practice in Canada is fairly similar to the UK NHS and was therefore likely to be most reflective of current NHS practice, it used the most appropriate reference standard and had the largest sample size. The population reported in Perry 2011 used to populate the model was a cohort of people aged over 15 with non-traumatic acute headache or with syncope associated with headache and a score on the Glasgow Coma Scale (GCS) at presentation of 15, meaning they were fully alert.

Perry reported the accuracy of CT before and after 6 hours from symptom onset. We therefore assessed the cost effectiveness of lumbar puncture in these two population groups: those that present and receive a CT scan within 6 hours of symptom onset, and those that present 6 hours post-symptom onset.

Data inputs

Diagnostic accuracy of CT

The diagnostic accuracy of CT used in the analysis is shown in Table 9 below.

Table 9: Diagnostic accuracy of CT from Perry 2011

	Sensitivity (95% CI)	Specificity (95% CI)
CT within 6 hours of symptom onset	100% (97% - 100%)	100% (99.5% - 100%)

	Sensitivity (95% CI)	Specificity (95% CI)
CT post 6 hours of symptom onset	85.7% (78.3% - 90.9%)	100% (99.8% - 100%)

Prevalence of subarachnoid haemorrhage

The prevalence of subarachnoid haemorrhage in people who presented and received CT within 6 hours and those post 6 hours from symptom onset was found to be 12.7% and 5.5% [166], respectively.

Cost of lumbar puncture

The cost of lumbar puncture was identified from NHS Reference Costs 2018/19[155]. The committee noted that for lumbar puncture to be most effective in detecting subarachnoid haemorrhage it should be undertaken at least 12 hours from the onset of symptoms. The committee considered that most people would be admitted for a lumbar puncture to be performed and would also be monitored for a short time afterwards. Therefore, the committee considered that the most appropriate cost of a lumbar puncture in this scenario is that related to a non-elective short stay, which was found to be £610 – see 2.5.4. The committee also noted the need for repeat lumbar puncture in some patients however, the number of people requiring a repeat lumbar puncture was uncertain and the cost of repeat punctures was not explicitly included in the analysis.

Threshold analysis calculations

A cohort size of 1,000 was used in each scenario (<6 hours, > 6 hours). First, the prevalence data was used to determine how many of those 1,000 people truly have subarachnoid haemorrhage. Then, the diagnostic accuracy of CT was used to determine the number of people that would be correctly diagnosed (true positives and true negatives) with the CT scan, and the proportion that would be incorrectly diagnosed on CT scan (false positives, false negatives). In this analysis we are particularly interested in people with a negative CT result as lumbar puncture in these people could confirm a diagnosis that was missed on CT scan.

When interpreting a CT scan, it is unknown whether a negative CT result is a true negative or false negative result. Hence, lumbar punctures are often done in people with high clinical suspicion of subarachnoid haemorrhage, to ensure that a negative CT scan is in fact a true result. In this analysis, the total cost of lumbar puncture in all people with a negative CT scan was calculated to enable an assessment of the cost per additional diagnosis of subarachnoid haemorrhage (assuming lumbar puncture is 100% accurate).

The total QALY gain required for lumbar puncture to be considered cost effective at a threshold of £20,000 per QALY gained was calculated by dividing the total cost of lumbar puncture by 20,000. The QALY gain required per patient was then calculated by dividing the total QALY gain by the number of false negative test results (these are the only people where the QALY gain can be achieved, as the data in table 10 indicate that CT has a 100% specificity i.e. there are no false positives).

Cost and threshold analysis - results

The results of the analysis described above are shown in Table 10 below. The results presented in brackets were calculated using the 95% confidence intervals of the diagnostic accuracy of CT.

Table 10: Analysis results for 1000 patients undergoing CT to detect subarachnoid haemorrhage

	<6 hours	>6 hours
True negative	873 (869, 873)	945 (943, 945)

	<6 hours	>6 hours
False negative	0 (0, 4)	8 (5, 12)
Total cost of lumbar puncture	£532,530 *(£532,191 - £532,530)*	£581,248 *(£579,503 - £582,577)*
Cost per additional diagnosis made	Infinite [(a)] *(£139,683 – Infinite)*	£73,903 *(£48,813 – £115,785)*
Total QALY gain required for lumbar puncture to be cost effective at £20,000 threshold	26.63 *(26.61 – 26.63)*	29.06 *(28.98 – 29.13)*
QALY gain required per person with missed diagnosis of subarachnoid haemorrhage on CT	Infinite [(a)] *(6.98 – infinite)*	3.70 *(2.44 – 5.79)*

(a) no missed diagnoses on CT (100% sensitivity)

Quality-adjusted life-years (QALYs)

A systematic search was conducted to identify studies that measure the utility of people after a SAH. The committee discussed the identified studies.[142, 175, 203] The mean utility in people post SAH ranged from 0.58 to 0.82. The most recent study[203] reported a mean utility of 0.75 at 2 years. Of the 3 studies identified, one study was German[142] and the other 2 were Swedish.[175, 203] All 3 studies used the EQ-5D. The 2 Swedish studies used the United Kingdom value set and the German study was based on the values of a European population reported by Greiner et al. 2005.[78] The countries included in the study by Greiner[78] were; Finland, Germany, The Netherlands, Spain, Sweden and the UK. Further details of the studies can be found in Appendix H:.

The mean ages of patients experiencing a SAH reported in the studies were; 55[142], 56[175], and 53.[203] The committee agreed, that on average, people who experience a SAH are typically middle aged.

Meyer 2010[142] was considered to be the most useful for the following reasons:

- Ronne-Engström 2013[175] only reported a utility value for the whole SAH population and did not stratify utility scores by outcome measure.
- The Vogelsang 2017[203] study excluded people who had a Glasgow Outcome Scale (GOS) score of < 3 at hospital discharge. Therefore, by omitting people with a GOS score of 1 and 2, it was not possible to accurately estimate the proportion of people who had died or were in a persistent vegetative state as a result of a SAH. Excluding patients with GOS scores of 1 and 2 meant the patient population included in Vogelsang 2017[203] was not representative of the whole SAH population in England.
- A disutility score in Vogelsang 2017[203] was only provided for severe disability (GOS 3). It was assumed people with moderate disability (GOS 4) would have the same utility as people with good outcomes (GOS 5). The associated utility decrement score reported for GOS 3 was 0.272.
- Meyer 2010[142] had a slightly larger sample size than Vogelsang 2017[203] – 113 vs. 88 people.

An analysis was undertaken to explore the potential number of QALYs lost from a missed SAH. The outcomes of patients diagnosed with a SAH were compared with the outcomes of patients when an acute SAH diagnosis is missed. Patients whose SAH was missed were assumed to have higher mortality and more disability, as measured on the modified Rankin Scale (mRS). The following assumptions were made.

- A utility value of 0.7 (the mid-point of the published estimates) was applied to patients with an mRS score of 0-2 and an additional utility decrement of 0.22 from Meyer 2010[142] was applied to patients with an mRS score of 3-5.

- The proportion of patients residing in each state (dead, mRS 3-5, and mRS 2-0) for patients achieving an appropriate diagnosis of SAH were taken from Meyer 2010.[142] At 12-months follow-up, 64 patients had an mRS score of 0-2, and 30 patients had a mRS score of 3-5: where the corresponding mRS scores represent no to mild disability and moderate to severe disability. Nineteen patients died within the 12-month follow-up period.
- No data were available to inform the corresponding proportions for patients in the event of an acute SAH going undiagnosed, so these values were based on committee opinion.
- It was assumed patients were 55 years old with a life expectancy of 80. A discount rate of 3.5% was applied to the utility over a time horizon of 25 years.

Table 11: Tentative calculation of QALYs gained per additional SAH diagnosed

			LYs[g]	LYs (Discounted)	EQ-5D	QALYs (Discounted) [h]
Example 1 – Assuming patients with mRS 3-5 and mRS 2-0 have the *same* life expectancy						
Diagnosed SAH[a]	Die	17%[c]	0	0	0	0
	mRS 3-5	27%[c]	25	17.1	0.48[e]	8.2
	mRS 0-2	57%[c]	25	17.1	0.7[f]	11.9
	Total					*8.9*
Undiagnosed SAH[b]	Die	30%[d]	0	0	0	0
	mRS 3-5	70%[d]	25	17.1	0.48[e]	8.2
	mRS 0-2	0%[d]	25	17.1	0.7[f]	11.9
	Total					*5.7*
QALYs gained						**3.2**
Example 2 – Assuming patients with mRS 3-5 have *reduced* life expectancy						
Diagnosed SAH[a]	Die	17%[c]	0	0	0	0
	mRS 3-5	27%[c]	*15*	*11.9*	*0.48[e]*	*5.7*
	mRS 0-2	57%[c]	25	17.1	0.7[df]	11.9
	Total					*8.3*
Undiagnosed SAH[b]	Die	30%[d]	0	0	0	0
	mRS 3-5	70%[d]	*15*	*11.9*	*0.48[e]*	*5.7*
	mRS 0-2	0%[d]	25	17.1	0.7[f]	11.9
	Total					*4.0*
QALYs gained						**4.3**

(a) Patients who present with symptoms of a SAH and are corresponding correctly diagnosed with a SAH.
(b) Patients whose SAH is misdiagnosed.
(c) Meyer 2010[142].
(d) Committee opinion.
(e) Utility decrement of 0.22[142] applied to utility value 0.7.
(f) Midpoint of estimates from published studies and committee opinion.
(g) Assumed
(h) Discounted life-years x EQ-5D

Table 11 shows the results of the analysis. The analysis was conducted assuming that the people left with disability had the same survival as those with only mild or no disability. It was then repeated assuming that the mean survival was 10 years lower for those with disability.

For the former the gain per extra case diagnosed was 3.2 QALYs and in the latter it was 4.3 QALYs.

The threshold analysis (above) determined that a QALY gain of 3.7 per person was required for lumbar puncture to be cost effective for patients who had a negative CT head scan after 6 hours ictus. The QALY analysis shows that this might be the case, but it is sensitive to the assumptions made about survival.

2.5.4 Unit costs

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

Table 12: UK costs of diagnostic tests for aneurysmal subarachnoid haemorrhage

Diagnostic test description	Cost
Computerised Tomography Scan of One Area, without contrast, 19 years and over [NHS Reference cost code: RD20A]	£78
Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over [NHS Reference cost code: RD01A]	£121
Diagnostic spinal puncture, 19 years and over (Non-elective short stay) [NHS Reference cost code: HC72A]	£610

Source: NHS Reference Costs 2018/19[155]

2.6 Evidence statements

2.6.1 Health economic evidence statements

A de novo threshold analysis comparing, a CT head scan with lumbar puncture if the CT scan result was negative and a CT head scan alone, was conducted for patients presenting with a suspected SAH for those with a negative CT scan. The analysis found that a CT head scan alone was dominant (less costly and more effective) if the CT scan was conducted within 6 hours of symptom onset as all patients presenting with a suspected SAH would be accurately diagnosed. If a patient receives a CT scan after 6 hours of symptom onset, patients are at risk of receiving a false negative result. Therefore, the cost per additional diagnosis made and the QALY gain required per person with a missed diagnosis of SAH on CT for this group of patients was £73,903 and 3.70, respectively.

Further explanatory analyses indicated that a QALY gain of 3.7 may be plausible for people receiving a false negative test result from a CT head scan >6 hours from symptom onset, however these calculations were based on a number of tenuous assumptions and therefore are highly uncertain.

2.7 The committee's discussion of the evidence

Diagnostic accuracy of investigations

2.7.1 Interpreting the evidence

2.7.1.1 Diagnostic measures that matter most

Sensitivity and specificity of tests (for example CT, lumbar puncture, MRI) to diagnose SAH were the outcomes for this review.

The committee agreed sensitivity of investigations for SAH was the most important outcome as a diagnostic indicator. The consequences of missing SAH can be catastrophic leading to neurological impairment and death and high sensitivity is essential to avoid missing people with SAH. The committee noted that because headache is a common symptom for many conditions, specificity was important to consider in order to avoid misdiagnosing SAH. Further investigations can include invasive tests such as lumber puncture and it is important to prevent people without SAH undergoing further tests.

2.7.1.2 Clinical measures that matter most

The value of correct diagnosis is appropriate treatment and the consequences of a missed diagnosis or misdiagnosis is measured by the following critical outcomes; degree of disability, health and social-related quality of life, and mortality. Return to daily activity, subsequent rebleed, length of hospital stay, and rate of major complications were considered to be important outcomes.

No diagnostic RCT evidence was found for clinical impact of diagnostic investigations, however the committee agreed that there was sufficient evidence on diagnostic test accuracy to support a recommendation.

2.7.1.3 The quality of the evidence

For the diagnostic accuracy evidence the quality of evidence varied from moderate to very low. Where evidence was downgraded, this was mostly for risk of bias, imprecision and indirectness. The majority of evidence was considered to be at high risk of bias with concerns around indirectness as per QUADAS-2 assessment regarding the use and reporting of the reference standard used to confirm diagnosis. The majority of included studies were of cross-sectional study design and so considered appropriate for review.

The committee agreed a reference standard for a final clinical diagnosis of SAH, which included:

- subarachnoid blood on CT, or
- CSF xanthochromia, or
- CSF RBCs > 5×10^6/L in the final sample of CSF, and
- supported by presence of arterial aneurysm on cerebral angiography.

The committee agreed that a diagnosis made by CT or investigation of the CSF with LP that is supported by subsequent cerebral angiography investigation would serve as an appropriate reference standard to the diagnostic accuracy of CT alone, LP alone, or MRI alone.

Few studies used a reference standard meeting these criteria, and studies that partially met the criteria were therefore included but downgraded for indirectness.

The majority of the evidence that was rated at the highest quality in this review (moderate) described the diagnostic test accuracy of non-contrast CT. The moderate quality of this evidence allowed the committee to make a strong recommendation to offer non-contrast CT as a first line of investigation. Due to the lower quality of evidence on LP and MRI, the committee made a weaker recommendation to consider LP if a CT head scan done more than 6 hours after symptom onset shows no evidence of a subarachnoid haemorrhage.

2.7.1.4 Benefits and harms

The committee highlighted that an accurate test would provide clinical benefit in correctly identifying those with the condition, allowing them to receive timely intervention to manage the bleed. The committee added that the potential harms of a poor diagnostic investigation could be severe, with missed or delayed diagnosis potentially leading to neurological

deterioration for the person with SAH. The committee noted the difficulties in comparing the tests and interpreting the evidence with the different reference standards used.

The committee discussed the evidence taking into account the limitations of the reference standards. They noted that non-contrast CT had higher reported sensitivity (pooled sensitivity of 98.3% (90.2 to 99.7%)) than LP (pooled sensitivity 92.9% (64.9 to 99.6%)) or MRI (median sensitivity 56.2%). They noted that LP and MRI had lower reported sensitivity and acknowledged much of the evidence was of low to very low quality compared to the moderate quality evidence for the non-contrast CT pooled studies. This reflected the committee's experience and the committee were confident to recommend a non-contrast CT head scan as the first-line diagnostic investigation for a suspected subarachnoid haemorrhage.

The committee discussed the specificity of the tests noting that non-contrast CT had a pooled specificity of 99.9% (99.5 to 100%) and this was better or comparable to LP and MRI and this supported their recommendation for non-contrast CT as the first line diagnostic test. Overall, the committee agreed non-contrast CT was an appropriate diagnostic test to identify people with SAH but also to avoid misdiagnosing people with SAH.

The committee also highlighted that there are potential harms associated with the diagnostic investigations. CT exposes the person under investigation to low levels of ionizing radiation, however the committee agreed that this risk will be considered by the healthcare professional before performing imaging. The committee agreed the risk of this level of radiation when someone has a suspected SAH is a reasonable risk when considering the potentially catastrophic outcomes of missing a diagnosis of SAH. The committee also noted the potential harms of LP, highlighting that as an invasive procedure, the placement of the needle in the spine may cause back discomfort or pain, particularly if repeat LPs are required. The committee also noted that the procedure can be associated with post-lumbar puncture headache, with around 25% of people undergoing a lumbar puncture developing a subsequent headache. This further supported their recommendation to offer a non-contrast CT. The committee noted that LP may sometimes need to be repeated, which will increase length of stay, morbidity and costs of investigation. These risks were considered alongside review of diagnostic test accuracy when considering the utility of LP in practice and are reflected in the weaker recommendation to consider LP following a negative CT (performed beyond 6 hours). The committee added that in some cases LP may be helpful in diagnosing other causes for headache.

The committee agreed that they could not recommend that MRI should be routinely offered, given that MRI offers no significant diagnostic advantage over CT. The committee highlighted the practical difficulties of performing an MRI on an unconscious or high-risk patient. The committee also added that some patients might have relative contraindications for MRI due to implantable electronic devices or other implanted ferromagnetic material.

Diagnostic strategies

2.7.2 Interpreting the evidence

2.7.2.1 Diagnostic measures that matter most

Sensitivity and specificity of tests (for example CT, lumbar puncture, MRI) to diagnose SAH were the outcomes for this review.

The committee agreed sensitivity of investigations for SAH was the most important outcome as a diagnostic indicator. The consequences of missing SAH can be catastrophic leading to neurological impairment and death and high sensitivity is essential to avoid missing people with SAH. The committee noted that because headache is a common symptom for many conditions, specificity was important to consider to avoid misdiagnosing SAH. Further

investigations can include invasive tests such as lumber puncture and it is important to prevent people without SAH undergoing further tests.

The committee agreed that it was important to consider the sensitivity and specificity of tests at different time points as the timing and sequencing of investigations to confirm a diagnosis of SAH varies between centres. The committee agreed that 6 hours from symptom onset is considered to be the time point between and early and late diagnosis.

No evidence was found for the effect of timing of investigation on diagnostic test accuracy of MRI scans or LP. No evidence was found for the effect of location of investigation or combination/sequence of investigations for any of CT, LP or MRI.

The committee agreed that there was sufficient evidence to demonstrate a high diagnostic test accuracy of CT within six hours, but noted the lack of evidence for other time-points. As such, the committee made a recommendation for further research reviewing the relative accuracy of CT head scans at different time intervals, for example 12 hours or 24 hours after symptom onset.

The committee agreed that with evidence demonstrating CT as an appropriate first line of investigation for diagnosing SAH, further research on the effect of timing of investigation on the diagnostic test accuracy of LP or MRI was not considered to be a priority.

2.7.2.2 Clinical measures that matter most

The value of correct diagnosis is appropriate treatment and the consequences of a missed diagnosis or misdiagnosis is measured by the following critical outcomes; degree of disability, health and social-related quality of life, and mortality. Return to daily activity, subsequent rebleed, length of hospital stay, and rate of major complications were considered to be important outcomes.

No evidence was found for the clinical effectiveness of diagnostic strategies, including timing, location and sequencing of investigations. The committee used their consensus around the clinical outcomes of diagnostic strategies and the evidence available on the effect of timing of investigation on the accuracy of non-contrast CT to form a recommendation, and further recommended research be carried out to better inform the influence timing of investigation has on diagnostic test accuracy.

2.7.2.3 The quality of the evidence

The quality of the evidence ranged from moderate to low. Most of the evidence was of low quality due to the risk of bias. All of the included studies were of cross-sectional study design and so considered appropriate for review. The evidence for CT within 6 hours of ictus was of moderate quality and gave the committee confidence to make a strong recommendation for this time period. The committee agreed that they could not make as strong a recommendation for the use of CT head beyond 6 hours given the lower quality of evidence for imaging at this time interval. The committee noted the very low and low quality of evidence presented for CT performed at <12 hours from symptom onset and <1 week from symptom onset, respectively. Given the lower quality and the small study sizes, the committee were unable to make any recommendation for CT at these time-points and made a research recommendation.

The committee agreed by consensus that healthcare professionals should allow at least 12 hours after symptom onset before doing a lumbar puncture to diagnose a subarachnoid haemorrhage.

2.7.2.4 Benefits and harms

When discussing the accuracy of the diagnostic tests the committee highlighted that an accurate test would provide clinical benefit in correctly identifying those with the condition, allowing them to receive timely intervention to manage the bleed. The potential harms of an investigation with poor diagnostic accuracy could be severe, with missed or delayed diagnosis potentially leading to neurological deterioration for the person with SAH. The aim of treatment is to prevent re-bleeding and associated morbidity and mortality. As re-bleed can occur within 24-48 hours earlier treatment is critical. The committee discussed that delaying treatment for aSAH is generally associated with an increased risk of rebleeding, which is then associated with poorer outcomes (see also evidence review M).

It is important for clinicians to be confident in the diagnostic accuracy of the test taking account of the timing of the test from the time of symptom onset. The committee noted the only evidence identified regarding timing of investigations was for CT.

The committee noted that a CT scan within 6 hours of symptom onset showed high sensitivity (over 95%) and specificity (100%) across the evidence. The committee noted that a CT scan within 6 hours of ictus has high sensitivity and specificity. The committee agreed that if a CT head scan done within 6 hours of symptom onset shows no evidence of a subarachnoid haemorrhage, subsequent LP should not routinely be offered and an alternative diagnosis should be considered.

It is plausible that very early investigation of people with suspected SAH might be beneficial but the committee were not aware of any evidence on the diagnostic accuracy or clinical impact of CT head scan earlier than 6 hours after symptom onset. Earlier identification and investigation of people with suspected SAH might also incur substantial additional costs and might not be cost-effective. The committee noted that non-contrast CT head scan is available in emergency departments across England and in current practice a CT head scan in a person with suspected SAH would be carried out without delay. A recommendation to support earlier investigation would therefore be unlikely to have a significant impact on current practice. The committee could therefore not make a recommendation for CT head scan earlier than 6 hours after symptom onset. Nevertheless, the committee emphasized that earlier diagnosis of SAH would be expected to lead to earlier treatment and better outcome, reinforcing the recommendation for immediate referral for investigation of people with suspected subarachnoid haemorrhage.

After 6 hours the sensitivity of CT is reduced across the evidence (85.7-90%). The committee noted the reduced sensitivity of CT scan beyond 6 hours in these studies. The committee acknowledged that the presence of blood in the subarachnoid space can be detected by CT scanning for many hours after the onset of symptoms, but decreased sensitivity of CT beyond 6 hours with a higher false negative rate prevented the committee from recommending CT scan as the sole diagnostic investigation beyond 6 hours after ictus. The committee made a recommendation to consider a lumbar puncture in people when there is no evidence of SAH on a CT scan done more than 6 hours after symptom onset.

While the evidence demonstrated a high level of diagnostic accuracy with CT at <6 hours compared to >6 hours, evidence at time intervals beyond this time-point was lacking. One study including 40 participants reported a sensitivity of 95% of CT within 12 hours of ictus. A second study reported the diagnostic accuracy of CT at varying time points up to seven days after ictus. Sensitivity of CT imaging was 100% at <1 day, 2 days and at 3 days, and reduced to 96% at 4-7 days. Specificity remained at 100% at every time-point. However, the committee agreed that the evidence was of too low quantity and quality to justify any recommendation. The committee agreed that further research reviewing the accuracy of investigations at different time-points would better inform future practice. As such, the committee made a recommendation for research to review the diagnostic accuracy of CT head scans at alternative time intervals (for example, 12 or 24 hours) from ictus in adults with

suspected subarachnoid haemorrhage. This area was also identified as a priority area for further research (see Appendix J:).

The committee recognised that sensitivity of CT and LP depends on the timing of the test. A CT scan has a very high sensitivity within 6 hours of the onset of symptoms, but sensitivity declines thereafter. It may not always be possible to perform a CT scan within 6 hours of the onset of symptoms, and in these cases, a negative CT scan should be interpreted in clinical context and other investigations considered if SAH is still suspected. The committee agreed that lumbar puncture should typically be done at least 12 hours from onset of acute headache to allow the release of bilirubin into the CSF, and the development of xanthochromia detectable by visual inspection and by spectrophotometry. The committee noted that LP may be performed before 12 hours from symptom onset if deemed clinically necessary to ascertain an earlier diagnosis, but highlighted that detection of xanthochromia would be unreliable at this time-point. LP performed within 12 hours of symptom onset, however, can allow analysis of red blood cell count in the CSF, although this may also be unreliable as blood from a ruptured aneurysm can take several hours to appear in the lumbar thecal sac and a traumatic LP may cause blood to leak into the CSF. As such, the committee agreed to make a consensus recommendation to allow at least 12 hours after symptom onset before doing a lumbar puncture to diagnose a subarachnoid haemorrhage. The committee also agreed that LP may remain accurate up until 2 weeks post-ictus.

2.7.3 Cost effectiveness and resource use

No economic evaluations were identified for this review. Unit costs were presented to the committee for consideration of cost effectiveness alongside the diagnostic data. As CT is both the most accurate and least costly imaging modality, the committee considered this to be a highly cost effective use of resources and made a strong recommendation that CT should be the first line imaging modality for diagnosing subarachnoid haemorrhage. The committee noted that this is current practice.

The committee were also concerned about the current use of lumbar puncture as a second line test in those who have a negative CT scan, particularly given the high accuracy of CT and the high cost of lumbar puncture (largely due to the need for admission and often an overnight stay). Consequently, assessing the cost effectiveness of lumbar puncture in those with a negative CT scan was prioritised for original economic analysis.

Insufficient data were available to assess the consequences of a missed diagnosis of subarachnoid haemorrhage. A simple threshold analysis was therefore undertaken to calculate the QALY gain required for lumbar puncture to be cost effective, and to assess whether such QALY gain would be likely in clinical practice. The analysis was undertaken for diagnostic accuracy of CT within 6 hours of onset of symptoms and CT after 6 hours of onset of symptoms.

Upon review of the clinical evidence the committee considered that the diagnostic accuracy data from Perry 2011 was the most reflective of current NHS practice and therefore most appropriate to use for these calculations. The study by Perry 2011 was considered most appropriate for the analysis as clinical practice in Canada is generally similar to the UK NHS. In addition, the study had the most appropriate reference standard and had the largest sample size of all included studies from the clinical review. Perry 2011 suggests that CT within 6 hours of symptom onset is 100% accurate (100% sensitivity and specificity), but the sensitivity of CT falls to 86% beyond 6 hours.

For both time windows, the cost analyses undertaken were based on a cohort of 1,000 people presenting to A&E with non-traumatic acute headache who were investigated with a CT head scan. For people receiving a CT scan within 6 hours of symptom onset, all those with SAH will be identified on CT. Due to the low prevalence of people in the population with SAH (12.7%) £532,530 is consequently spent on undertaking lumbar puncture with no

additional SAH diagnoses made. Using the lower 95% confidence interval for the sensitivity of CT within 6 hours of ictus, 4/127 people with subarachnoid haemorrhage would be missed on CT alone. Assuming lumbar puncture is 100% accurate and is performed in all those with a negative CT scan, the cost per additional diagnosis of SAH is £139,683. At the £20,000 threshold, this requires a QALY gain per additional SAH diagnosis of 6.98 over a person's lifetime for lumbar puncture to be cost effective.

In those that have a CT scan after 6 hours from symptom onset, 8/55 diagnoses of SAH would be missed on CT alone. If a lumbar puncture is performed in all those with a negative CT scan, the cost per additional diagnosis of SAH is £73,903, requiring a QALY gain per additional SAH diagnosis of 3.70 over a person's lifetime for lumbar puncture to be cost effective at the £20,000 threshold. Using the lower and upper 95% confidence intervals for the sensitivity of CT post 6 hours from ictus, the cost per additional diagnosis of SAH is between £48,813 and £115,785. This would require a QALY gain per additional SAH diagnosis of between 2.44 and 5.79 over a person's lifetime for lumbar puncture to be cost effective at the £20,000 threshold.

The committee discussed that there is also a possibility that if a subarachnoid haemorrhage diagnosis is missed that the person could have a re-bleed resulting in poorer outcomes both in terms of mortality and disability.

Some very tentative calculations of the QALYs gained from detecting a SAH were conducted, assuming a mortality reduction and a reduction in disability. This analysis showed that a gain of 3.2 to 4.3 QALYs might be attained, but this result was particularly sensitive to the assumptions made about long-term survival.

The data used to inform the QALY calculations were based on data obtained from a systematic search conducted to identify studies that measure the utility of people after a SAH, and committee opinion. The systematic search identified 3 studies; details of these studies can be found in Appendix H:. Each respective study included from the systematic search; Ronne-Engström 2013, Von Vogelsang 2017, and Meyer 2010, reported a utility value for people post SAH. An average utility score of 0.7 was subsequently derived from these studies and used to inform the average utility score of patients post SAH reported in Table 11.

After a utility value for the general SAH population was determined, each study was respectively reassessed to establish its applicability to inform the percentages of patients residing in a given health state (as defined by any appropriate outcome measure, for example modified Rankin Scale [mRS] or Glasgow Outcome Scale [GOS]) and a utility decrement associated with poorer outcomes. Ronne-Engström 2013 was excluded because the study only reported a utility value for the whole SAH and did not stratify outcomes by outcome measure.

Von Vogelsang 2017 was also excluded because the study only included patients with a GOS of ≥ 3 at hospital discharge and therefore was not representative of the whole SAH population. This study presented a 'flow diagram of included aSAH participants and data collection' which reported the total number of patients assessed for enrolment and the number of patients not meeting the inclusion criteria; stratified by reason for exclusion (dead, poor health, language, and emigrated). Based on the number of patients who were excluded due to death (n=30), it was possible to estimate the number of people residing in GOS score 1, but the study did not explicitly state the number of patients residing in GOS score 2. Therefore, accurately estimating the proportion of people who have died, have disability and or recovered, as required in the QALY calculations, was not possible using this study unless a number of assumptions are made regarding the excluded study participants. Furthermore, Von Vogelsang only reported a utility decrement for patients with a GOS score of 3 thus assuming patients with a score of 4 and 5 had the same quality of life, further limiting its use in the QALY calculations.

Subsequently the committee decided that Meyer 2010 was the most appropriate study to inform the percentages of patients residing in each health state and the utility decrement applied to patients with disability. A 0.22 decrement was applied for those with a mRS score of 3 – 5. The committee did discuss a potential limitation with the Meyer 2010 study noting the number of people residing in the health state mRS 3 – 5 may be higher than what is typically observed in clinical practice.

Overall, given the high accuracy of CT head scan within 6 hours, the committee agreed that it was highly unlikely that lumbar puncture would be cost effective for patients who receive a CT head scan within 6 hours. This is due the high cost of doing a large number of lumbar punctures and limited additional diagnostic benefit for subarachnoid haemorrhage in the overall population.

The committee considered the cost effectiveness of performing lumbar puncture to be more uncertain in those who have a negative CT head after 6 hours from ictus. The committee considered that there was a high probability that a small number of patients with a missed diagnosis would have significantly worse outcomes compared to patients acutely diagnosed and although a small proportion of the overall population presenting after 6 hours are likely to die as a result of misdiagnosis of SAH, the QALY gain from these groups of people could be great enough that once averaged out across all patients, lumbar puncture could be a cost effective use of resources for patients receiving a CT head scan 6 hours from ictus.

Subsequently a recommendation was made to not routinely offer lumbar puncture for people receiving a CT head scan within 6 hours of symptom onset; and to consider lumbar puncture for people where a CT head scan is done more than 6 hours after symptom onset when a CT head scan shows no evidence of a SAH.

2.7.42 Other factors the committee took into account

The committee noted that the majority of evidence on the diagnostic accuracy of investigations came from studies including individuals with a GCS of 15 who were less severely unwell than unselected people admitted to hospital with suspected SAH. The committee considered that patients presenting with suspected SAH and a GCS of less than 15 are more likely to have had a severe bleed, which is less likely to be missed on a CT head scan. The committee highlighted that, if anything, the accuracy of CT would be higher in clinical practice because of the inclusion of people with more severe bleeding. The committee also agreed that in people with a GCS less than 15 and a normal CT within 6 hours, further investigations (including lumbar puncture) to explore the possibility of alternative diagnoses should not be ruled out. The committee agreed that in each case, clinical judgement should be made for subsequent investigation beyond the initial CT scan.

The committee highlighted that CT is considered to be the preferred method of diagnosis in clinical practice given that it is quick, non-invasive, associated with a low risk of harm, and more readily available compared to alternative investigations such as LP and MRI. As such, the recommendation to offer CT as a first line of investigation was considered to be in line with current clinical practice.

The committee also noted that in most of the studies a neuroradiologist reported the CT scans and acknowledged that this is not current practice within the UK, where many cases will initially be reviewed by a general radiologist. Despite this, the committee agreed that the observed accuracy of CT reported by the included studies demonstrated a sufficient level of sensitivity and specificity relative to alternative methods of diagnosis to justify the recommendations made.

The committee added that there have been technological advancements in recent years, such as the development of multi-slice 3rd generation CT scanners which have improved the diagnostic accuracy of imaging. The committee noted that modern imaging may provide

1 better sensitivity and specificity to diagnosing SAH than that reported in the included studies,
2 further supporting the recommendations made.

3

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1 Appendices

2 Appendix A: Review protocols

A.1 3 Diagnostic accuracy

4 **Table 13: Review protocol: Diagnostic investigations for SAH (diagnostic accuracy)**

ID	Field	Content
0.	PROSPERO registration number	CRD42019132509
1.	Review title	What is the diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage?
2.	Review question	What is the diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage?
3.	Objective	To determine the accuracy of investigations in diagnosing SAH in adults.
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 final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database 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.	Intervention/Exposure/Test	• Non-contrast CT • Lumbar puncture • MRI

8.	Comparator/Reference standard/Confounding factors	Reference standard: • Final clinical diagnosis. • As no widely accepted criterion standard for SAH yet exists, the committee accepted the reference standard of a final clinical diagnosis, which must have included either subarachnoid blood on CT, or CSF xanthochromia, or CSF RBCs > 5 × 106/L in the final sample of CSF, and aneurysm on subsequent cerebral angiography as agreed by a neurointerventionalist.
9.	Types of study to be included	• Cross-sectional studies • Cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	
12.	Primary outcomes (critical outcomes)	Statistical measure to detecting SAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
13.	Secondary outcomes (important outcomes)	None
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. Diagnostic test accuracy studies risk of bias was assessed using QUADAS-2. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

<table>
<tr><td></td><td></td><td colspan="3">• 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.</td></tr>
<tr><td>16.</td><td>Strategy for data synthesis</td><td colspan="3">• Aggregate data on diagnostic accuracy of investigations will be collected and synthesized in a quantitative data analysis.
• Endnote will be used for bibliography, citations, sifting and reference management.
• WinBUGS will be used for meta-analysis of diagnostic accuracy studies if included studies are sufficiently homogeneous.
Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Not applicable</td></tr>
<tr><td rowspan="7">18.</td><td rowspan="7">Type and method of review</td><td>☐</td><td colspan="2">Intervention</td></tr>
<tr><td>☒</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td>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="5">23.</td><td rowspan="5">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>
</table>

		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SAH@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.		

29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage; diagnosis; suspected	
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	

1

2 **Table 14: Review protocol: Diagnostic investigations for SAH (test and treat)**

ID	Field	Content
0.	PROSPERO registration number	CRD42019149510
1.	Review title	What is the clinical and cost effectiveness of diagnostic investigations in adults with suspected subarachnoid haemorrhage, for example a non-contrast CT scan or a lumbar puncture?
2.	Review question	What is the clinical and cost effectiveness of diagnostic investigations in adults with suspected subarachnoid haemorrhage, for example a non-contrast CT scan or a lumbar puncture?
3.	Objective	To determine which diagnostic investigation for subarachnoid haemorrhage is the most clinically and cost-effective.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL)

		• Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language only The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database 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 or confirmed ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
7.	Intervention/Exposure/Test	• Non-contrast CT • Lumbar puncture • MRI Negative test results must receive no SAH treatment and positive test results should receive some form of SAH treatment (including neurosurgical or endovascular intervention, or conservative management – directness to be assessed against results of intervention reviews elsewhere in the guideline).
8.	Comparator/Reference standard/Confounding factors	Comparator: • To each other
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, search for non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.

11.	Context	
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Length of hospital stay • Complications (any) Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
14.	Data extraction (selection and coding)	• EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. • EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be

<table>
<tr><td></td><td></td><td colspan="3">resolved by discussion, with involvement of a third review author where necessary.</td></tr>
<tr><td>16.</td><td>Strategy for data synthesis</td><td colspan="3">• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).
• GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome.
• The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/
• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
• Subgroups will be investigated separately if meta-analysed results show heterogeneity.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Not applicable</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">Other (please specify)</td></tr>
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<tr><td rowspan="4">23.</td><td rowspan="4">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</td><td>☑</td><td>☑</td></tr>
</table>

		against eligibility criteria		
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SAH@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with		

		section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage; diagnosis; suspected	
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	

A.21 Diagnostic strategies

Table 15: Review protocol: What is the diagnostic accuracy of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including (a) the timing, (b) location and (c) sequencing of investigations?

(a) Timing of diagnosis

ID	Field	Content
0.	PROSPERO registration number	CRD42019132510
1.	Review title	What is the diagnostic accuracy of different diagnostic timing strategies in adults with suspected subarachnoid haemorrhage?
2.	Review question	What is the diagnostic accuracy of different diagnostic timing strategies in adults with suspected subarachnoid haemorrhage?

3.	Objective	To determine how the timing of investigations affects the accuracy of investigation in diagnosing subarachnoid haemorrhage.
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 final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database 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.	Intervention/Exposure/Test	Timing of diagnosis (from ictus)
		• CT:
		  ○ 6-24 hours
		  ○ >24 hours
		• LP:
		  ○ <6 hours
		  ○ 12-24 hours
		  ○ >24 hours
		• MRI:
		  ○ 12-24 hours
		  ○ >24 hours

8.	Comparator/Reference standard/Confounding factors	Reference standard: • Final clinical diagnosis. • As no widely accepted criterion standard for SAH yet exists, the committee accepted the reference standard of a final clinical diagnosis, which must have included either subarachnoid blood on CT, or CSF xanthochromia, or CSF RBCs > 5 × 106/L in the final sample of CSF, and aneurysm on subsequent cerebral angiography as agreed by a neurointerventionalist.
9.	Types of study to be included	• Cross-sectional studies • Cohort studies.

10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	
12.	Primary outcomes (critical outcomes)	Statistical measure to detecting SAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
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. Diagnostic test accuracy studies risk of bias was assessed using QUADAS-2. 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 accuracy of investigations will be collected and synthesized in a quantitative data analysis. • Endnote will be used for bibliography, citations, sifting and reference management.

<table>
<tr><td></td><td></td><td colspan="3">• WinBUGS will be used for meta-analysis of diagnostic accuracy studies if included studies are sufficiently homogeneous.

Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Strata:
• CT
• LP
• MRI</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☐</td><td colspan="2">Intervention</td></tr>
<tr><td>☒</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td colspan="2"></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3"></td></tr>
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<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 colspan="3"></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</td></tr>
</table>

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the

		NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage; diagnosis; suspected	
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	

1

2 **(b) Location of diagnosis**

ID	Field	Content
0.	PROSPERO registration number	CRD42019132520
1.	Review title	What is the diagnostic accuracy of different diagnostic location strategies in adults with suspected subarachnoid haemorrhage?
2.	Review question	What is the diagnostic accuracy of different diagnostic location strategies in adults with suspected subarachnoid haemorrhage?
3.	Objective	To determine if the location of diagnosing subarachnoid haemorrhage affects the accuracy of investigations.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language only The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database 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.	Intervention/Exposure/Test	Location of diagnosis • General hospital setting
8.	Comparator/Reference standard/Confounding factors	Reference standard: • Location of diagnosis: ○ Neurosurgical/neuroradiological centre
9.	Types of study to be included	• Cross-sectional studies • Cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	
12.	Primary outcomes (critical outcomes)	Statistical measure to detecting SAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
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.

		Diagnostic test accuracy studies risk of bias was assessed using QUADAS-2. 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 accuracy of investigations will be collected and synthesized in a quantitative data analysis. • Endnote will be used for bibliography, citations, sifting and reference management. • WinBUGS will be used for meta-analysis of diagnostic accuracy studies if included studies are sufficiently homogeneous. • Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer.		
17.	Analysis of sub-groups	Strata: Diagnostic tool • CT • LP • MRI		
18.	Type and method of review	☐	Intervention	
		☒	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date	3 February 2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑

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

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2 **(c) Sequence of diagnosis**

ID	Field	Content
0.	PROSPERO registration number	CRD42019132523
1.	Review title	What is the diagnostic accuracy of different diagnostic sequencing strategies in adults with suspected subarachnoid haemorrhage?
2.	Review question	What is the diagnostic accuracy of different diagnostic sequencing strategies in adults with suspected subarachnoid haemorrhage?

3.	Objective	To determine which sequence of investigations for diagnosing subarachnoid haemorrhage is the most accurate.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language only The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database 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.	Intervention/Exposure/Test	• Second line of investigations following CT:
		  ○ LP
		  ○ MRI
		• Second line of investigations following LP:
		  ○ CT
		  ○ MRI
		• Second line of investigations following MRI:
		  ○ CT
		  ○ LP

8.	Comparator/Reference standard/Confounding factors	Reference standard: • Final clinical diagnosis. ○ As no widely accepted criterion standard for SAH yet exists, the committee accepted the reference standard of a final clinical diagnosis, which must have included either subarachnoid blood on CT, or CSF xanthochromia, or CSF RBCs > 5 × 106/L in the final sample of CSF, and aneurysm on subsequent cerebral angiography as agreed by a neurointerventionalist.

9.	Types of study to be included	• Cross-sectional studies • Cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	
12.	Primary outcomes (critical outcomes)	Statistical measure to detecting SAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
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. Diagnostic test accuracy studies risk of bias was assessed using QUADAS-2. 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 accuracy of investigations will be collected and synthesized in a quantitative data analysis.

<table>
<tr><td></td><td></td><td colspan="3">• Endnote will be used for bibliography, citations, sifting and reference management.
• WinBUGS will be used for meta-analysis of diagnostic accuracy studies if included studies are sufficiently homogeneous.
• Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Strata:
First line investigation
• CT
• LP
• MRI</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td>☐</td><td colspan="2">Intervention</td></tr>
<tr><td></td><td></td><td>☒</td><td colspan="2">Diagnostic</td></tr>
<tr><td></td><td></td><td>☐</td><td colspan="2">Prognostic</td></tr>
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<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail</td></tr>
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		SAH@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth
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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	
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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; diagnosis; suspected	
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	

1

2 **Table 16: What is the clinical and cost effectiveness of different diagnostic strategies**
3 **in adults with suspected subarachnoid haemorrhage, including the timing,**
4 **location and sequencing of investigations?**

ID	Field	Content
0.	PROSPERO registration number	CRD42019132513
1.	Review title	What is the clinical and cost effectiveness of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including the timing, location and sequencing of investigations?
2.	Review question	What is the clinical and cost effectiveness of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including the timing, location and sequencing of investigations?
3.	Objective	To determine which strategy for diagnosing subarachnoid haemorrhage is the most clinically and cost-effective.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		Searches will be restricted by: • English language only The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database 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.	Intervention/Exposure/Test	• Timing of diagnosis (from ictus) ○ CT: - <6 hours - 6-24 hours - >24 hours ○ LP: - <12 hours - 12-24 hours - >24 hours ○ MRI: - <12 hours - 12-24 hours - >24 hours • Location of diagnosis ○ Neurosurgical/ neuroradiological centre ○ General hospital setting • Sequence of investigations ○ Any sequence and combination of CT; LP; MRI
8.	Comparator/Reference standard/Confounding factors	Comparators: • Within class comparison • To each other Negative test results must receive no SAH treatment and positive test results should receive some form of SAH treatment (including neurosurgical or endovascular intervention, or conservative management - directness to be assessed against results of intervention reviews elsewhere in the guideline).
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs.

		• If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Length of hospital stay • Complications (any) Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
14.	Data extraction (selection and coding)	• EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. • EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

		• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • Subgroups will be investigated separately if meta-analysed results show heterogeneity.

17.	Analysis of sub-groups	Strata:
		(for timing and location strategies)
		• CT
		• LP
		• MRI
		
		Subgroups if heterogeneity:
		• Subsequent treatment:
		  ○ Neurosurgical
		  ○ Endovascular
		  ○ Conservative management
		• Grade
		  ○ Good grade
		  ○ Poor grade
		• Location of aneurysm (as reported by study)
		• Characteristic of aneurysm (as reported by study)
		  ○ Size e.g. large, small
		• Neck width e.g. normal, wide
		• Timing of investigation

<table>
<tr><td></td><td></td><td colspan="3">• Location of investigation</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>
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<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>
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<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
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="3">From the National Guideline Centre:
• Ms Gill Ritchie
• Mr Ben Mayer
• Mr Audrius Stonkus
• Mr Vimal Bedia</td></tr>
</table>

		• Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
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29.	Other registration details		
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32.	Keywords	Subarachnoid haemorrhage; diagnosis; suspected	
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	

A.3 Health economic review protocol

Table 17: 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.[154] 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

B.1 Diagnostic accuracy

This literature search strategy was used for the following reviews;

- What is the diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage?

- What is the clinical and cost effectiveness of diagnostic investigations in adults with suspected subarachnoid haemorrhage, for example a non-contrast CT scan or a lumbar puncture?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[154]

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

B.1.11 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 18: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
Embase (OVID)	1974 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or 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.	Magnetic Resonance Imaging/
30.	Tomography, X-Ray Computed/ or Tomography, Emission-Computed/
31.	magnetic resonance.ti,ab.
32.	(MR* or MRI* or NMR*).ti,ab.
33.	(diffusion weighted imag* or DWI).ti,ab.
34.	(compute* adj3 tomography).ti,ab.
35.	(CT* or CAT or MDCT*).ti,ab.
36.	exp Spinal Puncture/
37.	((spinal or lumbar) adj1 (puncture* or tap*)).ti,ab.
38.	or/29-37
39.	Meta-Analysis/
40.	exp Meta-Analysis as Topic/
41.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
42.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
43.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45.	(search* adj4 literature).ab.
46.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47.	cochrane.jw.
48.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
49.	or/39-48
50.	randomized controlled trial.pt.
51.	controlled clinical trial.pt.
52.	randomi#ed.ti,ab.
53.	placebo.ab.
54.	randomly.ti,ab.
55.	Clinical Trials as topic.sh.
56.	trial.ti.
57.	or/50-56
58.	exp "Sensitivity and Specificity"/
59.	(sensitivity or specificity).ti,ab.
60.	((pre test or pretest or post test) adj probability).ti,ab.
61.	(predictive value* or PPV or NPV).ti,ab.
62.	likelihood ratio*.ti,ab.

63.	likelihood function/
64.	((area under adj4 curve) or AUC).ti,ab.
65.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
66.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
67.	gold standard.ab.
68.	or/58-67
69.	Epidemiologic studies/
70.	Observational study/
71.	exp Cohort studies/
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
74.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
75.	Controlled Before-After Studies/
76.	Historically Controlled Study/
77.	Interrupted Time Series Analysis/
78.	(before adj2 after adj2 (study or studies or data)).ti,ab.
79.	exp case control study/
80.	case control*.ti,ab.
81.	Cross-sectional studies/
82.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
83.	or/69-82
84.	28 and 38 and (49 or 57 or 68 or 83)

1 **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.	nuclear magnetic resonance imaging/
28.	computer assisted tomography/ or computer assisted emission tomography/
29.	magnetic resonance.ti,ab.
30.	(MR* or MRI* or NMR*).ti,ab.
31.	(diffusion weighted imag* or DWI).ti,ab.
32.	(compute* adj3 tomography).ti,ab.
33.	(CT* or CAT or MDCT*).ti,ab.
34.	lumbar puncture/
35.	((spinal or lumbar) adj1 (puncture* or tap*)).ti,ab.
36.	or/27-35
37.	exp "sensitivity and specificity"/
38.	(sensitivity or specificity).ti,ab.
39.	((pre test or pretest or post test) adj probability).ti,ab.
40.	(predictive value* or PPV or NPV).ti,ab.
41.	likelihood ratio*.ti,ab.
42.	((area under adj4 curve) or AUC).ti,ab.
43.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
44.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
45.	diagnostic accuracy/
46.	diagnostic test accuracy study/
47.	gold standard.ab.
48.	or/37-47
49.	Clinical study/
50.	Observational study/
51.	family study/
52.	longitudinal study/
53.	retrospective study/
54.	prospective study/
55.	cohort analysis/
56.	follow-up/
57.	cohort*.ti,ab.
58.	56 and 57
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	(before adj2 after adj2 (study or studies or data)).ti,ab.
63.	exp case control study/
64.	case control*.ti,ab.
65.	cross-sectional study/
66.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
67.	or/49-55,58-66
68.	random*.ti,ab.
69.	factorial*.ti,ab.
70.	(crossover* or cross over*).ti,ab.
71.	((doubl* or singl*) adj blind*).ti,ab.
72.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
73.	crossover procedure/
74.	single blind procedure/
75.	randomized controlled trial/
76.	double blind procedure/
77.	or/68-76
78.	systematic review/
79.	meta-analysis/
80.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
81.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
82.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
83.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
84.	(search* adj4 literature).ab.
85.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
86.	cochrane.jw.
87.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
88.	or/78-87
89.	26 and 36 and (48 or 67 or 77 or 88)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#3.	(SAH or aSAH):ti,ab
#4.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#6.	(OR #1-#5)
#7.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#8.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#9.	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#10.	magnetic resonance:ti,ab

#11.	(MR* or MRI* or NMR*):ti,ab
#12.	(diffusion weighted imag* or DWI):ti,ab
#13.	(compute* near/3 tomography):ti,ab
#14.	(CT* or CAT or MDCT*):ti,ab
#15.	MeSH descriptor: [Spinal Puncture] explode all trees
#16.	((spinal or lumbar) near/1 (puncture* or tap*)):ti,ab
#17.	(or #7-#16)
#18.	#6 and #17

B.1.21 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 19: 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

1 **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

1 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)

B.2 Diagnostic strategies

This literature search strategy was used for the following reviews;

- What is the diagnostic accuracy of different diagnostic timing strategies in adults with suspected subarachnoid haemorrhage?
- What is the diagnostic accuracy of different diagnostic location strategies in adults with suspected subarachnoid haemorrhage?
- What is the diagnostic accuracy of different diagnostic sequencing strategies in adults with suspected subarachnoid haemorrhage?
- What is the clinical and cost effectiveness of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including the timing, location and sequencing of investigations?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[154]

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

B.2.1 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 20: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
Embase (OVID)	1974 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None

Medline (Ovid) search terms

85.	exp Subarachnoid Hemorrhage/
86.	((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.
87.	(SAH or aSAH).ti,ab.

88.	Intracranial Aneurysm/
89.	((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.
90.	or/1-5
91.	letter/
92.	editorial/
93.	news/
94.	exp historical article/
95.	Anecdotes as Topic/
96.	comment/
97.	case report/
98.	(letter or comment*).ti.
99.	or/7-14
100.	randomized controlled trial/ or random*.ti,ab.
101.	15 not 16
102.	animals/ not humans/
103.	exp Animals, Laboratory/
104.	exp Animal Experimentation/
105.	exp Models, Animal/
106.	exp Rodentia/
107.	(rat or rats or mouse or mice).ti.
108.	or/17-23
109.	6 not 24
110.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
111.	25 not 26
112.	limit 27 to English language
113.	Magnetic Resonance Imaging/
114.	Tomography, X-Ray Computed/ or Tomography, Emission-Computed/
115.	magnetic resonance.ti,ab.
116.	(MR* or MRI* or NMR*).ti,ab.
117.	(diffusion weighted imag* or DWI).ti,ab.
118.	(compute* adj3 tomography).ti,ab.
119.	(CT* or CAT or MDCT*).ti,ab.
120.	exp Spinal Puncture/
121.	((spinal or lumbar) adj1 (puncture* or tap*)).ti,ab.
122.	or/29-37
123.	Meta-Analysis/
124.	exp Meta-Analysis as Topic/
125.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
126.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
127.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
128.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

129.	(search* adj4 literature).ab.
130.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
131.	cochrane.jw.
132.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
133.	or/39-48
134.	randomized controlled trial.pt.
135.	controlled clinical trial.pt.
136.	randomi#ed.ti,ab.
137.	placebo.ab.
138.	randomly.ti,ab.
139.	Clinical Trials as topic.sh.
140.	trial.ti.
141.	or/50-56
142.	exp "Sensitivity and Specificity"/
143.	(sensitivity or specificity).ti,ab.
144.	((pre test or pretest or post test) adj probability).ti,ab.
145.	(predictive value* or PPV or NPV).ti,ab.
146.	likelihood ratio*.ti,ab.
147.	likelihood function/
148.	((area under adj4 curve) or AUC).ti,ab.
149.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
150.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
151.	gold standard.ab.
152.	or/58-67
153.	Epidemiologic studies/
154.	Observational study/
155.	exp Cohort studies/
156.	(cohort adj (study or studies or analys* or data)).ti,ab.
157.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
158.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
159.	Controlled Before-After Studies/
160.	Historically Controlled Study/
161.	Interrupted Time Series Analysis/
162.	(before adj2 after adj2 (study or studies or data)).ti,ab.
163.	exp case control study/
164.	case control*.ti,ab.
165.	Cross-sectional studies/
166.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
167.	or/69-82
168.	28 and 38 and (49 or 57 or 68 or 83)

1 **Embase (Ovid) search terms**

90.	*subarachnoid hemorrhage/

91.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
92.	(SAH or aSAH).ti,ab.
93.	exp intracranial aneurysm/
94.	((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.
95.	or/1-5
96.	letter.pt. or letter/
97.	note.pt.
98.	editorial.pt.
99.	Case report/ or Case study/
100.	(letter or comment*).ti.
101.	or/7-11
102.	randomized controlled trial/ or random*.ti,ab.
103.	12 not 13
104.	animal/ not human/
105.	Nonhuman/
106.	exp Animal Experiment/
107.	exp Experimental animal/
108.	Animal model/
109.	exp Rodent/
110.	(rat or rats or mouse or mice).ti.
111.	or/14-21
112.	6 not 22
113.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
114.	23 not 24
115.	limit 25 to English language
116.	nuclear magnetic resonance imaging/
117.	computer assisted tomography/ or computer assisted emission tomography/
118.	magnetic resonance.ti,ab.
119.	(MR* or MRI* or NMR*).ti,ab.
120.	(diffusion weighted imag* or DWI).ti,ab.
121.	(compute* adj3 tomography).ti,ab.
122.	(CT* or CAT or MDCT*).ti,ab.
123.	lumbar puncture/
124.	((spinal or lumbar) adj1 (puncture* or tap*)).ti,ab.
125.	or/27-35
126.	exp "sensitivity and specificity"/
127.	(sensitivity or specificity).ti,ab.
128.	((pre test or pretest or post test) adj probability).ti,ab.
129.	(predictive value* or PPV or NPV).ti,ab.
130.	likelihood ratio*.ti,ab.
131.	((area under adj4 curve) or AUC).ti,ab.
132.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.

133.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
134.	diagnostic accuracy/
135.	diagnostic test accuracy study/
136.	gold standard.ab.
137.	or/37-47
138.	Clinical study/
139.	Observational study/
140.	family study/
141.	longitudinal study/
142.	retrospective study/
143.	prospective study/
144.	cohort analysis/
145.	follow-up/
146.	cohort*.ti,ab.
147.	56 and 57
148.	(cohort adj (study or studies or analys* or data)).ti,ab.
149.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
150.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
151.	(before adj2 after adj2 (study or studies or data)).ti,ab.
152.	exp case control study/
153.	case control*.ti,ab.
154.	cross-sectional study/
155.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
156.	or/49-55,58-66
157.	random*.ti,ab.
158.	factorial*.ti,ab.
159.	(crossover* or cross over*).ti,ab.
160.	((doubl* or singl*) adj blind*).ti,ab.
161.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
162.	crossover procedure/
163.	single blind procedure/
164.	randomized controlled trial/
165.	double blind procedure/
166.	or/68-76
167.	systematic review/
168.	meta-analysis/
169.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
170.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
171.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
172.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
173.	(search* adj4 literature).ab.

174.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
175.	cochrane.jw.
176.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
177.	or/78-87
178.	26 and 36 and (48 or 67 or 77 or 88)

1 **Cochrane Library (Wiley) search terms**

#19.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#20.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#21.	(SAH or aSAH):ti,ab
#22.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#23.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#24.	(OR #1-#5)
#25.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#26.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#27.	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#28.	magnetic resonance:ti,ab
#29.	(MR* or MRI* or NMR*):ti,ab
#30.	(diffusion weighted imag* or DWI):ti,ab
#31.	(compute* near/3 tomography):ti,ab
#32.	(CT* or CAT or MDCT*):ti,ab
#33.	MeSH descriptor: [Spinal Puncture] explode all trees
#34.	((spinal or lumbar) near/1 (puncture* or tap*)):ti,ab
#35.	(or #7-#16)
#36.	#6 and #17

B.2.2 Health Economics literature search strategy

Please see section B.1.2 for the health economics literature search strategy.

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of Evidence review for diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage.

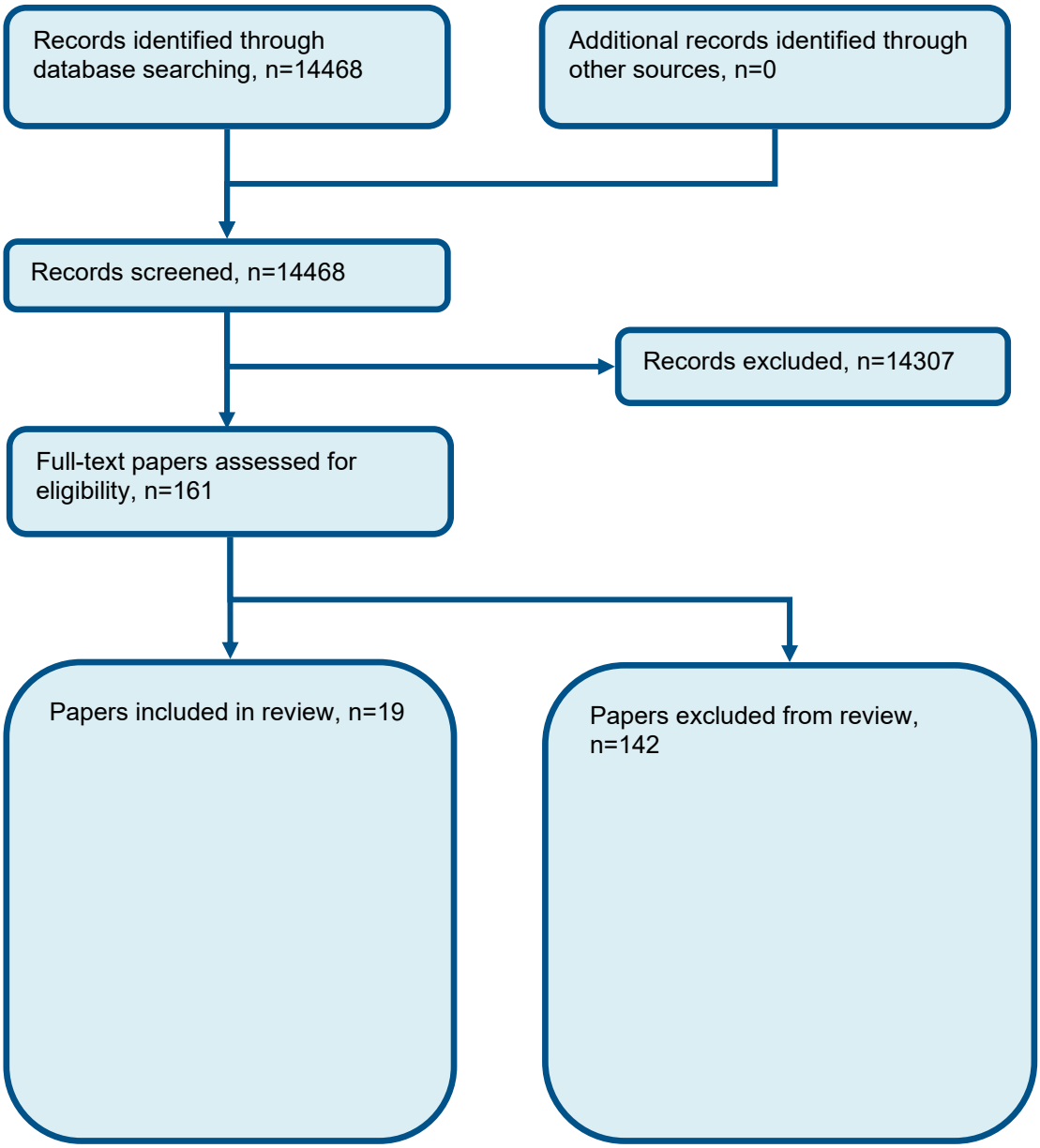
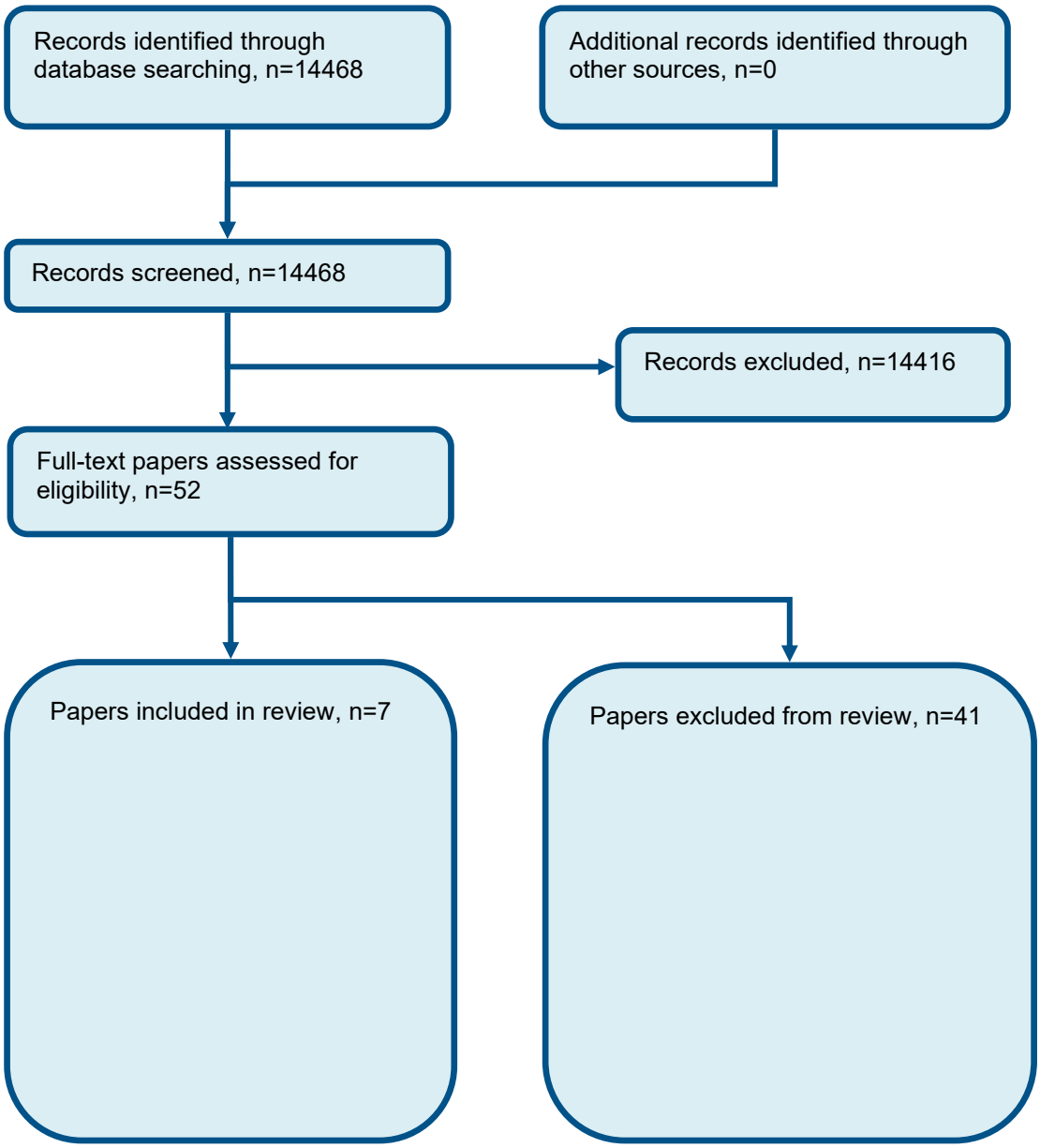


Figure 2: Flow chart of clinical study selection for the review of Evidence review for diagnostic strategies in adults with suspected subarachnoid haemorrhage including (a) the timing, (b) location and (c) sequencing of investigations



1

Appendix D: Clinical evidence tables

D.1 Diagnostic accuracy

Reference	Ashraf 2019[12]
Study type	Cross-sectional study
Study methodology	Data source: not reported Recruitment: consecutive patients
Number of patients	n = 245
Patient characteristics	Age, mean (SD): 52.13 (10.45) Gender (male to female ratio): 132/113 Ethnicity: not reported Setting: Radiology department of Combined military hospital, Lahore, Pakistan Country: Pakistan Inclusion criteria: patients of age 20-70 years of either gender presenting in ED with acute severe head ache (pain on VAS >6) with nausea, vomiting, neck pain, photophobia, loss of consciousness or Glasgow coma scale <13 were included in the study. Exclusion criteria: patients with history of trauma and intracranial tumors, patients who had history of intracranial haemorrhage (medical record), uncooperative and non-willing patients were excluded from the study.
Target condition(s)	Detection of acute subarachnoid haemorrhage in patients presenting with severe headache
Index test(s) and reference standard	Index test – MRI (FLAIR) MRI was performed by Philips Intera Achieva 1.5 T super conducting MR unit (Philips media systems, The Netherlands) with the use of head coil. FLAIR examination was performed at 6700/150 (TR/TE) with an inversion time (TI) of 2200ms, a field of view 230mm, matrix 189x256, scan time of 3min 50s and section thickness 5mm in axial plane.

Reference	**Ashraf 2019[12]**
	Reference standard –Lumbar puncture Following MRI, patients underwent lumbar puncture for cerebrospinal fluid (CSF) examination after 8-12h from the onset of event. Time between measurement of index test and reference standard:8 – 12 hours after the onset of the event

2×2 table Acute subarachnoid haemorrhage

	Reference standard +	Reference standard −	Total
Index test +	11	8	11
Index test −	3	223	226
Total	14	231	245

Statistical measures	Index text MRI Sensitivity – 79% Specificity – 97% PPV – 57.89% NPV – 99%
Source of funding	Not stated
Limitations	Risk of bias: Serious Indirectness: None

1

Reference	**Blok 2015[21]**
Study type	Cross-sectional study
Study methodology	Data source: consecutive series of patients in 11 non-academic hospitals in the Netherlands
Number of patients	N = 760
Patient characteristics	Median age (range): 45 years (17-87) Female: 466 Male: 294

Reference	Blok 2015[21]
	Setting: non-academic hospitals in the Netherlands Country: Netherlands Inclusion criteria: patients presenting between January 2007 and January 2013 with spontaneous acute headache suspected of SAH, who had a head CT scan within 6 hours after headache onset that was reported negative for the presence of subarachnoid blood by a staff radiologist, and subsequent CSF spectrophotometry. Patients were also included with a CT initially being reported negative for the presence of SAH, but subsequently judged positive after positive CSF spectrophotometry became available. Exclusion criteria: (1) Glasgow Coma Scale score ≤14 at presentation, (2) unknown time of ictus, (3) age 16 years or younger, and (4) lumbar puncture performed earlier than 12 hours after headache onset.
Target condition(s)	Suspected subarachnoid haemorrhage
Index test(s) and reference standard	Index test: CT scan within 6 hours (n=760). Two experienced neuroradiologists and one experienced stroke neurologist from 2 academic tertiary care hospitals independently reviewed all admission CT scans of patients with a positive finding of bilirubin according to the local CSF analysis protocol. The reviewers of the head CTs were blinded for any clinical or radiologic follow-up information. Reference standard: Lumbar puncture CSF was analysed by spectrophotometry and interpreted according to local criteria. Time points of lumbar puncture not specified. The CSF results of 52 patients were initially considered positive for SAH by local spectrophotometric criteria.
Statistical measures	Index test CT scan: Negative predictive value: 99.9% (95% CI 99.3 – 100.0%)
Source of funding	No targeted funding reported
Limitations	1) Paper reports 11 false negatives from CT scan which were not re-evaluated 2) Diagnosis of aneurysmal SAH was based on the presence of red blood cells in CSF but without xanthochromia
Comments	For patients with CSF results that were initially interpreted as positive for SAH by local criteria and a negative head CT on independent review, the results of additional cerebrovascular imaging were obtained, and the patients' hospital records were reviewed for readmissions for SAH. For patients in whom an aneurysm was found on vascular imaging, the aneurysm was considered an incidental, unruptured aneurysm if the initial CSF results were considered falsely positive based on one of the following criteria: (1) the sample contained ,100 3 106/L red blood cells in CSF,8 (2) an alternative explanation for the positive CSF result was found, or (3) a second method of CSF spectrophotometric analysis showed negative results; for example, bilirubin-excess value 0.24 (>0.20 is abnormal), but absorption units at 450 to 460 nm <0.05.

Reference	**Boesiger 2005[24]**
Study type	Retrospective cross-sectional
Study methodology	Data source: not reported Recruitment: not reported
Number of patients	n = 177
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not stated Setting: Academic Level1 trauma centre in a mostly rural region of Eastern North Carolina. Country: USA Inclusion criteria: A search of the Emergency department (ED) and Laboratory medical records for a year period was done to identify adult patients presenting to ED with complaint of headache. If the patient went on to have a CT scan and LP to evaluate for SAH. Exclusion criteria: patients who had history of trauma in the past 3 months, were aged 17 years or less, did not have rule-out SAH as the indication for LP documented in the physician records or LP consent form, Had a history of recent neurosurgery.
Target condition(s)	Detection of intracranial aneurysms in those suffering from subarachnoid haemorrhage
Index test(s) and reference standard	Index test - CT All patients in the study had a CT scan of the head done by a GE light speed 2.x scanner, which is fifth generation CT scanner. The standard protocol 5-mm cuts through the cerebrum and 5 mm cuts through the posterior fossa. Reference standard – Lumbar puncture (CTA was performed on 2 patients) Patients were considered positive for SAH on LP if they had at least 400 red blood cells in tube 1 and CSF that did not clear by 10-fold. Some of these patients had a CTA the same day to evaluate aneurysm. Other patients who had elevated RBC's but did not have sufficient clearing were followed up by a telephone and hospital records from 3 months to a year after the initial ED visit and were questioned about any other events or complications. Patients were also considered positive for SAH if there was evidence for Xanthochromia.

Reference	**Boesiger 2005[24]**
	Time between measurement of index test and reference standard: not specified
2×2 table SAH	

	Reference standard +	Reference standard −	Total
Index test +	6	1	7
Index test −	0	170	170
Total	6	171	177

Statistical measures	Index text CT Sensitivity – 100% Specificity – 99.4% PPV – 85.71 NPV – 170%
Source of funding	Not reported
Limitations	Risk of bias: Serious Indirectness: None
Comments	All “0” values were replaced with “0.2” to allow for meta-analysis using Winbugs

1

Reference	**Byyny 2008[27]**
Study type	Cross-sectional study
Study methodology	Data source: Not reported Recruitment: All ED patients diagnosed with SAH using non-contrast cranial CT, and discharge International Classification diseases, Ninth revision(ICD-9)
Number of patients	n = 149
Patient characteristics	Age, mean (SD): Not reported Gender (male to female ratio): Not reported Ethnicity: Not reported

<table>
<tr><td>Reference</td><td colspan="4">Byyny 2008[27]</td></tr>
<tr><td></td><td colspan="4">Setting: Department of emergency medicine. Tertiary academic ED.

Country: USA

Inclusion criteria: All ED patients who had non-contrast cranial CT, including the radiology diagnostic coding; all patients who had cerebrospinal fluid sent to the laboratory from the ED, including the cell count results of these cerebrospinal fluid studies (tube number, colour of cerebrospinal fluid supernatant, and RBC and WBC counts); and all patient with discharge diagnosis ICD-9 codes for spontaneous SAH or cerebral aneurysm.</td></tr>
<tr><td>Target condition(s)</td><td colspan="4">Detection of all spontaneous subarachnoid haemorrhages and those caused by aneurysm or arteriovenous malformation</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="4"><u>Index test – CT</u>
A 4-slice 4-detector GE Light Speed Scanner (GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK) was used at the time of the study.

<u>Reference standard LP</u>
Patients who had a negative CT scan result and were diagnosed by lumbar puncture.

Time between measurement of index test and reference standard: Not reported</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>139</td><td>n/a</td><td>n/a</td></tr>
<tr><td></td><td>Index test −</td><td>10</td><td>n/a</td><td>n/a</td></tr>
<tr><td></td><td>Total</td><td>149</td><td>n/a</td><td>n/a</td></tr>
<tr><td>Statistical measures</td><td colspan="4"><u>Index text head CT</u>
Sensitivity-93%
Specificity – not reported
PPV – not reported
NPV – not reported</td></tr>
</table>

Reference	**Byyny 2008[27]**
Source of funding	Not stated
Limitations	Risk of bias: Serious Indirectness: None

1

Reference	**Claveau 2014[41]**
Study type	Prospective cross-sectional study
Study methodology	Data source: Adult patients from university-affiliated tertiary care hospitals in Canada Recruitment: Consecutive patients recruited
Number of patients	n = 3123
Patient characteristics	Age, mean (SD): patients over 15 years Gender (male to female ratio): Not reported Ethnicity: Not reported Setting: university-affiliated tertiary care hospitals in Canada. Country: Canada Inclusion criteria: Alert patients over 15 years of age were eligible if they presented with nontraumatic acute headache or syncope associated with headache. Exclusion criteria: Patients were excluded if headache onset was more than 14 days prior to emergency presentation or if they had a history of recurrent headaches or were transferred with a confirmed diagnosis.
Target condition(s)	Detection of intracranial aneurysms in those suffering from subarachnoid haemorrhage
Index test(s) and reference standard	Index test CT Patients were considered positive for subarachnoid haemorrhage if subarachnoid blood was identified on a CT scan;

<table>
<tr><td>Reference</td><td colspan="5">Claveau 2014[41]</td></tr>
<tr><td></td><td colspan="5">Reference standard – Lumbar puncture – Xanthochromia

If they had visible xanthochromia in the cerebrospinal fluid (CSF); or if they had red blood cells (. 5 3 106) in the final tube of CSF and an aneurysm identified on a cerebral angiogram. Patients with red blood cells in the CSF without an aneurysm on a cerebral angiogram were deemed negative for subarachnoid haemorrhage. Those with arteriovenous malformation were considered as having a definite alternative cause of headache.

Time between measurement of index test and reference standard: not specified</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td colspan="2" rowspan="4"></td></tr>
<tr><td></td><td>Index test +</td><td>n/a</td><td>n/a</td><td></td></tr>
<tr><td></td><td>Index test −</td><td>n/a</td><td>n/a</td><td></td></tr>
<tr><td></td><td>Total</td><td></td><td></td><td></td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text - CT All patients
Sensitivity - 92.9 %
LR(-) – 0.07 (0.05-0.11)

Index text - CT <6 hours
Sensitivity - 100 %
LR(-) – 0.00 (0.00 – 0.02)

Index text - CT >6 hours
Sensitivity - 85.7 %
LR(-) – 0.14 (0.14 – 0.17)</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not stated</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Serious
Indirectness: None</td></tr>
</table>

1

2

Reference	**Cooper 2016[44]**
Study type	Retrospective cross-sectional study
Study methodology	Data source: Patients who entered into the CDU pathway by emergency medicine consultant or specialist trainee Recruitment: retrospective case review, identified through written and computer records.
Number of patients	n = 517
Patient characteristics	Age, mean (SD): 39.5 years (14.1) Gender (male to female ratio): Not reported Ethnicity: Not reported Setting: ED CDU's of two large UK tertiary hospitals, Leeds General Infirmary and St James' University hospital. Country: UK Inclusion criteria: Adult (> 15 years), acute sudden headache suggestive of SAH, Glasgow coma score of 15 (alert and fully orientated), normal neurological examination subjective sensory symptoms only were considered normal) and stable clinical observations. Exclusion criteria: likely recurrent headache syndrome (e.g. migraine, tension). Seizures, suspicion of meningitis, trauma and features or raised intracranial pressure.
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test 1 –LP/CSF Index test 2 - CT Gold standard for presence of SAH were as follows: 1. Evidence of SAH on Nc-CT of brain, as verified by a consultant radiologist. 2. CSF positive for bilirubin on spectrophotometry or uniformly blood stained sample across four bottles and positive cerebral angiographic imaging.

Reference	**Cooper 2016[44]**				
	A surrogate gold standard of No SAH Both non-contrast CT and LP negative or if CT LP strategy not completed, no sudden death or evidence of subsequent SAH in the following 12 months from discharge (from analysis of attendance and investigations across site at both institutions Reference standard 1 – CT/angiogram Reference standard 2 -LP Time between measurement of index test and reference standard: LP results were taken >12 h from the index headache.				
2×2 table Index test 1 LP CSF (reference angiogram)		Reference standard +	Reference standard −	Total	
	Index test +	1	10	11	
	Index test −	0	298	298	
	Total	1	308	309	
2×2 table Index test 2 CT (reference LP)		Reference standard +	Reference standard −	Total	
	Index test +	13	0	13	
	Index test −	1	496	497	
	Total	14	496	510	
Statistical measures	Index text LP/CSF (Reference standard Angiogram) Sensitivity – 100% Specificity – 96.8% PPV – 9.1% NPV – 100% Index text CT (LP) Sensitivity – 92.9% Specificity – 100% PPV – 100% NPV – 99.8%				
Source of funding	Not specified				
Limitations	Risk of bias: Serious				

Reference	**Cooper 2016[44]**
	Indirectness: None
Comments	All “0” values were replaced with “0.2” to allow for meta-analysis using Winbugs

1

Reference	**Cortnum 2010[45]**
Study type	Retrospective cross-sectional study
Study methodology	Data source: n/a Recruitment: n/a
Number of patients	n = 499
Patient characteristics	Age, mean (SD): no details Gender (male to female ratio): no details Ethnicity: no details Setting: Neurosurgical unit at Aalborg hospital. Country: Denmark Inclusion criteria: All patients referred to neurosurgical unit on suspicion of SAH or verified SAH Exclusion criteria: not specified
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test CT If the CT scan was positive for SAH the patients subsequently had angiography studies performed and were allocated to appropriate treatment Reference standard – LP Patients with a negative CT had a lumbar puncture done. Cerebral spinal fluid was sent to a laboratory for cell counts and all samples were analysed for xanthochromia by spectrophotometry

Reference	**Cortnum 2010[45]**
	Time between measurement of index test and reference standard: Lumbar puncture was done 12 hours after the onset of symptoms
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	295	0	295
Index test −	1	203	204
Total	296	203	499

Statistical measures	Index text CT Sensitivity – 99.7% Specificity – 100% PPV – 100% NPV – 99.5%
Source of funding	Not stated
Limitations	Risk of bias: Serious Indirectness: Serious – indirect reference standard used; positive CT not reviewed further – only LP in CT negative cases, no angiography or further investigation

1

Reference	**Czuczman 2016[46]**
Study type	Cross-sectional study
Study methodology	Data source: Records of 4,496 consecutive adult patients billed for LPs between 2001 and 2009 were reviewed. Recruitment: Consecutive
Number of patients	n = 280
Patient characteristics	Age, mean (SD): TP – 50.2(12.6); TN -42.7(15.2) Gender (male to female ratio): TP – 5/21; TN – 82/112 Ethnicity: no details

Reference	Czuczman 2016[46]
	Setting: Tertiary emergency department Country: USA Inclusion criteria: Presence of headache (HA), _ 5 RBCs in the final LP tube collected, and CT angiography (CTA) or magnetic resonance angiography (MRA) performed within 2 weeks of the ED visit. Exclusion criteria: consisted of presence of ventriculoperitoneal shunt, neurosurgery within 4 weeks preceding the ED visit, CSF sent primarily for cytology, unequivocal history of trauma within 2 weeks preceding the ED visit, failed LP, or no LP performed at our hospital (i.e., no CSF sent).
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test LP CSF RBC iLRs Reference standard – Either 1) presence of SAH on imaging; 2) xanthochromia with aneurysm or AVM>2mm; 3) xanthochromia and culture- or PCR- negative meningitis. **A true-positive (TP) SAH was defined**, **prior to any analysis, as:** 1)presence of SAH on imaging or 2) xanthochromia and an aneurysm or AVM > 2 mm on imaging or 3) xanthochromia and culture- or PCR-positive meningitis. **A true-negative (TN) case was defined as:** 1) no SAH on imaging and 2) no aneurysm or AVM of any size on imaging and

<table>
<tr><td>Reference</td><td colspan="4">Czuczman 2016[46]</td></tr>
<tr><td></td><td colspan="4">3) no culture- or PCR-positive meningitis and

4) no xanthochromia after at least 12 hours of HA (to account for the amount of time it can take for xanthochromia to develop after an SAH).

These definitions for TP and TN were selected to be conservative and to ensure that patients included either had definitive SAH or definitely did not have SAH.

Time between measurement of index test and reference standard: Lumbar puncture was done 12 hours after the onset of symptoms</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>26</td><td>n/a</td><td>n/a</td></tr>
<tr><td></td><td>Index test −</td><td>n/a</td><td>196</td><td>n/a</td></tr>
<tr><td></td><td>Total</td><td>n/a</td><td>n/a</td><td>280</td></tr>
<tr><td>Statistical measures</td><td colspan="4">Index text LP
Neither TP or TN (Gray zone) - 58
Sensitivity – N/A
Specificity – N/A
PPV – N/A
NPV – N/A
LR for RBC <100: 0 (0-0.3) 0 (0-0.2)
LR for RBC <100 <RBC<10,000: 1.6 (1.1–2.3) 1.6 (1.1–2.2)
LR for RBC >10,000: 6.3 (3.0–13.1) 6.3 (2.8–13.8)*
LR for percent change in RBC count >63%: 0.1 (0.03–0.4) 0.1 (0–0.3)
LR for percent change in RBC count <63%: 3.6 (2.7–4.7) 3.6 (2.8–4.8)
AUC (final tube RBC count) – 0.84 (95% CI 078 – 0.90)</td></tr>
<tr><td>Source of funding</td><td colspan="4">Not stated</td></tr>
<tr><td>Limitations</td><td colspan="4">Risk of bias: Serious
Indirectness: None</td></tr>
</table>

Reference	**Gangloff 2015[69]**
Study type	Retrospective cross-sectional study
Study methodology	Data source: The population consisted of all patients who had cerebrospinal fluid tested for spectrophotometric xanthochromia between 2003 and 2009 identified through the clinical-laboratory database Recruitment: n/a
Number of patients	n = 706
Patient characteristics	Age, mean (SD): 41(14) Gender (female %): 52% Ethnicity: n/a Setting: ED Country: Canada Inclusion criteria: >14 years old, had an initial Glasgow Coma Score of 15, a non-traumatic acute headache with a suspected subarachnoid haemorrhage recorded in the initial ED differential diagnosis and an initial negative head CT scan. Exclusion criteria: Not reported
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test - Sen/Spec visual xanthochromia, iterative SPT, or UK NEQUA SPT Reference standard - Presence of any aneurysm and presence of either visual xanthochromia or >5 × 10^6 RBC/L in last CSF tube. Limitations – Absence of a reference standard applied to all patients, angiograms to establish presence or absence of aneurysm were not performed on all subjects. Red blood cells and visual xanthochromia being elements of the definition of aSAH, the present study does not permit to compare between visual versus spectrophotometric xanthochromia; neither does it permit a reliable diagnostic accuracy assessment of spectrophotometric xanthochromia. In order to assess reliably the diagnostic accuracy of spectrophotometric xanthochromia, a standardized spectrophotometric method should be used and studied in a prospective, multi-centre and blinded fashion against a gold-standard method for aSAH, usually angiography. Time between measurement of index test and reference standard: Time between headache onset and lumbar puncture was estimated greater than 12 h in 466 patients (67.5%),with a median of 13 h.

Reference	Gangloff 2015[69]				
2×2 table (visual)		Reference standard +	Reference standard −	Total	
	Index test +	4	9	13	
	Index test −	1	692	693	
	Total	5	701	706	
2×2 table (spectrophotometric iterative method)		Reference standard +	Reference standard −	Total	
	Index test +	5	57	62	
	Index test −	0	644	644	
	Total	5	701	706	
2×2 table (spectrophotometric UK national external Quality assessment service 2008)		Reference standard +	Reference standard −	Total	
	Index test +	5	13	18	
	Index test −	0	688	688	
	Total	5	701	706	
Statistical measures	**Visual:** Sensitivity – 80% [28.4–99.5] Specificity – 98.7% [97.5–99.4]; AUC – 89.4 [69.8–100] **Spectrophotometric iterative method:** Sensitivity – 100% [47.8–100] Specificity – 91.9% [89.6–93.9] AUC – 95.9 [94.9– 96.9] **Spectrophotometric UK national external Quality assessment service 2008:** Sensitivity – 100% [47.8–100] Specificity – 98.1% [96.7–99.0] AUC – 99.1 [98.5–99.5] <u>Presence of aneurysmal SAH</u>				

Reference	**Gangloff 2015[69]**
	Visual xantho: positive – 4; negative=1; Spectroiteraative Xanto: Positive – 5; Negative – 0 Spectro UK NEQAS 2008 xanto: Positive – 5; negative – 0 Absence of aneurysmal SAH Visual xantho: positive – 9; negative=692; Spectroiteraative Xanto: Positive – 56; Negative – 645 Spectro UK NEQAS 2008 xanto: Positive – 13; negative – 688
Source of funding	Not stated
Limitations	Risk of bias: Serious Indirectness: None
Comments	Spectrophotometric UK national external Quality assessment service 2008 data used for pooled comparison.

1

Reference	**Gee 2012[71]**
Study type	Cross-sectional study
Study methodology	Data source: patients admitted through the ED Recruitment: Accessed ED electronic medical records and the Department of Neurosurgery research database to identify all patients admitted from the ED with a diagnosis of SAH from January 1, 2005 to December 31, 2008.
Number of patients	n = 134
Patient characteristics	Age, mean (SD): Not reported Gender (male to female ratio): not reported Ethnicity: not specified Setting: ED Country: USA Inclusion criteria: All patients admitted to the hospital with a diagnosis of SAH

<table>
<tr><td>Reference</td><td>Gee 2012[71]</td></tr>
<tr><td></td><td>Exclusion criteria: not specified</td></tr>
<tr><td>Target condition(s)</td><td>SAH</td></tr>
<tr><td>Index test(s) and reference standard</td><td><u>Index test CT</u>
CT scanner type from outside hospitals was not known, the CT scanner was upgraded from a 16-slice CT scanner to a 64-slice scanner in early 2005.

Reference standard – LP
CT negative cases were followed up with subsequent LP and angiographic investigation.

Time between measurement of index test and reference standard: not specified</td></tr>
<tr><td>2×2 table</td><td>
<table>
<tr><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td>Index test +</td><td>131</td><td></td><td></td></tr>
<tr><td>Index test −</td><td>3</td><td></td><td></td></tr>
<tr><td>Total</td><td>134</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Statistical measures</td><td><u>Index text Spectrophotometry and visual inspection when inconclusive results were considered positive</u>
Sensitivity – 97%
Specificity – n/a
PPV – n/a
NPV – n/a</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Limitations</td><td>Risk of bias: Very serious
Indirectness: None</td></tr>
</table>

Reference	**Hann 2015[85]**
Study type	Cohort study
Study methodology	Data source: Not reported Recruitment: Not reported
Number of patients	n = 409
Patient characteristics	Age, mean (SD): 37.8(no SD) Gender (male to female ratio): 56.2 % female Ethnicity: not specified Setting: ED at the Royal Brisbane and Women's hospital Country: Australia Inclusion criteria: All patients who received a headache related diagnosis on discharge from the ED and CSF xanthochromia investigation following a negative head CT scan. Exclusion criteria: not specified
Target condition(s)	Detection of ruptured aneurysms
Index test(s) and reference standard	Index test LP (Spectrophotometry and visual inspection) Spectrometry and visual inspection was reviewed for each subject. Visual inspection was performed prior to spectrometry and the appearance of both pre centrifuged and post centrifuged sample was reviewed. Visual inspection was performed prior to spectrophotometry and the appearance of both pre centrifuged and post-centrifuged (supernatant sample was reviewed. The appearance of pre-centrifuged specimen was classified as bloodstained or non-bloodstained. Visual inspection for supernatant was considered positive for xanthochromia if the appearance was described as yellow. If the pre-centrifuged specimen was bloodstained but, supernatant appearance not reported, visual inspection was considered inconclusive. A negative xanthocroic result for visual inspection was defined as colourless supernatant. Reference standard – DSA, CTA or MRA Aneurysmal SAH was defined as an angiogram evidence of vascular aneurysm within 30 days of headache presentation.

Reference	Hann 2015[85]				
	Time between measurement of index test and reference standard: <30 days				
2×2 table CSF Spectrophotometry and visual inspection when inconclusive results considered positive		Reference standard +	Reference standard −	Total	
	Index test +	6	88	94	
	Index test −	0	315	315	
	Total	6	403	409	
2×2 table CSF Spectrophotometry and visual inspection when inconclusive results considered negative		Reference standard +	Reference standard −	Total	
	Index test +	6	82	88	
	Index test −	0	321	321	
	Total	6	403	409	
2×2 table CSF visual inspection when inconclusive results considered positive		Reference standard +	Reference standard −	Total	
	Index test +	5	20	25	
	Index test −	1	383	384	
	Total	6	403	409	
CSF 2×2 table visual inspection when inconclusive results considered negative		Reference standard +	Reference standard −	Total	
	Index test +	3	4	7	
	Index test −	3	399	402	
	Total	6	403	409	

Reference	**Hann 2015[85]**
Statistical measures	Index text Spectrophotometry and visual inspection when inconclusive results were considered positive Sensitivity – 100% Specificity – 78.2% PPV – 6.4% NPV – 100% Index text Spectrophotometry and visual inspection when inconclusive results were considered positive Sensitivity - 100% Specificity – 79.7% PPV – 6.8% NPV – 100% Index text visual inspection when inconclusive results were considered positive Sensitivity – 83.3% Specificity – 95.0% PPV – 99.7% NPV – 20% Index text visual inspection when inconclusive results were considered negative Sensitivity – 50.0% Specificity – 99.0% PPV – 99.2% NPV – 42.9%
Source of funding	One of the authors is supported by a grant from the Queensland Emergency Medicine Research Foundation.
Limitations	Risk of bias: Serious Indirectness: None

Reference	**Khedr 2013[115]**
Study type	Cross-sectional study
Study methodology	Data source: n/a Recruitment: Consecutive patients
Number of patients	n = 61
Patient characteristics	Age, mean (range): 56 (19-83) Gender (male to female ratio): 51/10 Ethnicity: n/a Setting: Country: Egypt Inclusion criteria: Intracranial hematoma unrelated to neoplasm; patients performed MRI (including DWI and GRE) and CT with time interval between the CT and MRI examinations 2-4 h.
Target condition(s)	Subarachnoid haemorrhage
Index test(s) and reference standard	Index test MRI DWI Single shot, spin-echo, echo planar DWI sequences were obtained by applying diffusion gradients in three orthogonal directions at each slice with two diffusion weightings (b value = 0 and 900 or 1000 s/mm^2) Reference standard – MRI and CT Results were compared with conventional MRI sequences and CT, interpreted by experienced neuroradiologist. Time between measurement of index test and reference standard: time interval between CT and MRI 2-4 hours.

2×2 table

	Reference standard +	Reference standard −	Total
Index test +	1	0	1
Index test −	2	58	60
Total	3	58	61

Reference	**Khedr 2013[115]**
Statistical measures	Index text – MRI(DWI) Sensitivity – 33.3% Specificity – 100% PPV – 100 % NPV – 96.6%
Source of funding	Not specified
Limitations	Risk of bias: Serious Indirectness: None

1

Reference	**Mark 2015[133]**
Study type	Retrospective chart review - multicentre cross-sectional study. Only those with a final diagnosis of SAH were included in the study analysis
Study methodology	Data source: Patients were evaluated in the 21 EDs of an integrated health delivery system between January 2007 and June 2013. The authors identified by chart review a retrospective cohort of patients diagnosed with aSAH in the setting of a normal mental status and performance of early cranial CT.
Number of patients	N = 155
Patient characteristics	Median age: 55 years Female: 122 Male: 33 Setting: multicentre; emergency department records of participating hospitals Country: USA Inclusion criteria: Patients who had an ED or hospital encounter with a diagnosis code of SAH, Hunt-Hess clinical grade 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 visualised on imaging, if applicable.

Reference	**Mark 2015[133]**
	Exclusion criteria: 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 July2010.
Target condition(s)	Subarachnoid Haemorrhage
Index test(s) and reference standard	Index test: CT <6 hours Non-contrast cranial CT imaging within six hours of headache onset. 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. Reference standard for presence of SAH: Final diagnosis determined by combination of subsequent investigation including Lumbar Puncture CSF + Xanthochromia investigation and angiographical imaging.
2x2 table <6 hours	

	Reference standard +	Reference standard -	
Index test +	148		
Index test -	7		
	155		

Statistical measures	Imaging rule: cranial CT performed within 6 hours of headache onset. Sensitivity – 95.5% (95% CI [90.9-98.2]) Specificity – n/a +LR – n/a -LR – n/a
Source of funding	Funded by a Kaiser Permanente Northern California Community Benefits Grant
Limitations	Risk of bias: serious Indirectness: none

1

2

Reference	**Mushtaq 2014[152]**
Study type	Cross-sectional study

Reference	**Mushtaq 2014[152]**				
Study methodology	Data source: n/a Recruitment: n/a				
Number of patients	n = 137				
Patient characteristics	Age, mean (SD): 45.93 (9.57) Gender (male to female ratio): 96/41 Ethnicity: not specified Setting: ED of Radiology department, Nishtar hospital Multan Country: Pakistan Inclusion criteria: Patients presenting in ED with thunderclap headache				
Target condition(s)	Detection of subarachnoid haemorrhage				
Index test(s) and reference standard	<u>Index test – CT</u> CT protocol included CT brain scan without contrast with axial slices. The hard copies of CT scan were interpreted by a radiologist for assessment of subarachnoid haemorrhage. <u>Reference standard – Lumbar puncture</u> Presence of subarachnoid haemorrhage was confirmed by cerebrospinal fluid analysis after lumbar puncture (as per operational definition). Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Mushtaq 2014[152]**				
	Index test +	95	3	98	
	Index test −	16	23	39	
	Total	111	26	137	
Statistical measures	Index text CT Sensitivity – 86% Specificity – 88% PPV – 97% NPV – 59%				
Source of funding	Not stated				
Limitations	Risk of bias: Serious Indirectness: None				

1

Reference	**Pouryahya 2020[170]**
Study type	Retrospective cross-sectional study.
Study methodology	Data source: Two resources were utilised for the data collection 1. Patients aged 18 years and over, presenting for the first time with a headache were identified by searching the ED electronic medical records (EMRs; Symphony, EMIS Health, Leads, UK). Recruitment: Data from the pathology database was retrieved for patients who underwent LP during their ED stay.
Number of patients	n = 137
Patient characteristics	Age, mean (SD): Not reported Gender (male to female ratio): Not reported Ethnicity: not specified Setting: ED of participating hospitals Country: Australia

Reference	**Pouryahya 2020[170]**
	Inclusion criteria: Patients presenting in ED with thunderclap headache Exclusion criteria: Patients under 18 years and patients who had presented with headaches before the index case.
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test – CT Non-contrast CT performed at admission. Reference standard – Lumbar puncture A diagnosis of SAH was defined by an abnormal cerebrospinal fluid result. Positive LPs were further investigated by repeat LP, angiography, surgical intervention or follow up. Time between measurement of index test and reference standard: not specified
2×2 table	

	Reference standard +	Reference standard −	Total
Index test +	n/a	n/a	
Index test −	1	387	388
Total	1	387	388

Statistical measures	Index text CT Sensitivity – n/a Specificity – n/a PPV – n/a NPV – 99.7%
Source of funding	Not stated
Limitations	Risk of bias: Serious – only those with a negative CT were included in the study analysis. Indirectness: None

Reference	Perry 2006[164]
Study type	Prospective cross-sectional study
Study methodology	Data source: n/a Recruitment: CSF samples from consecutive patients undergoing LP to rule out SAH from July 2002 to January 2004
Number of patients	n = 220
Patient characteristics	Age, mean (SD): 42 (16) Gender (male to female ratio): 100/120 Ethnicity: not stated Setting: This study was a planned sub-study of an ongoing multi-centre study at 6 Canadian tertiary care EDs of alert, neurologically intact acute headache patients. Three of the 6 sites with a combined annual census of 160 000 visits, participated in this sub-study. The study was set in 3 university affiliated tertiary care emergency departments. Country: Canada Inclusion criteria: Alert patients at least 15 years of age with a chief complaint of nontraumatic acute headache or syncope associated with a headache. Alert was defined as a Glasgow Coma Scale score of 15. Nontraumatic was defined as the absence of falls or direct trauma to the head in the previous 7 days. Acute was defined as an interval of _1 hour from headache onset to peak intensity, and an interval of 14 days from headache onset to presentation. Exclusion criteria: (1) history of 3 or more recurrent headaches of the same character and intensity as the presenting headache over a period of _6 months, (2) referred from other centres with a confirmed SAH by either CT or LP, (3) returned for reassessment of the same headache if already investigated with both CT and LP, (4) papilledema, (5) new focal neurological deficits, (6) previous diagnosis of cerebral aneurysm or SAH, (7) previous diagnosis of a brain neoplasm, or (8) known hydrocephalus.

Reference	**Perry 2006[164]**				
Target condition(s)	Detection of subarachnoid haemorrhage				
Index test(s) and reference standard	Index test LP spectrophotometry Four different definitions of positive spectrophotometry were selected a priori: (1) Traditional: an optical density _0.023 at a wavelength of 415 nm9; (2) Chalmers and Kiley: net bilirubin absorption _0.015 positive, 0.010 to 0.015 borderline using absorbances at 415 nm and 440 nm relative to a baseline joining absorbances at 530 nm and 360 nm12; (3) Chalmers revised: an optical density _0.014 at 476 nm13; (4) United Kingdom National External Quality Assurance Service (UK NEQAS) based on net bilirubin and oxyhaemoglobin absorbances at 476 nm and 415 nm, respectively, relative to a baseline joining the 530 nm and 360 nm absorbances Reference standard – CT/LP + angiography ; >5*106 red blood cells/L in the final CSF tube; positive angiography CT interpretations were verified by a radiologist or neuroradiologist with access to routine clinical information as part of usual care, and were blinded to the conduct of the study. The time of onset was compared with the time of LP to calculate the time interval from headache onset to LP. SAH was defined by (1) subarachnoid blood on CT, (2) >5*10^6 red blood cells/L in the final CSF tube and positive angiography, or (3) visible xanthochromia in CSF and positive angiography. All subjects lacking a normal CT and LP were telephoned at 30 days. Time between measurement of index test and reference standard: unclear				
2×2 table (visual inspection)		Reference standard +	Reference standard −	Total	
	Index test +	2	6	8	
	Index test −	2	210	212	
	Total	4	216	220	
2×2 table (traditional)		Reference standard +	Reference standard −	Total	
	Index test +	4	153	157	
	Index test −	0	63	63	
	Total	4	216	220	
2×2 table (Chalmers and Kiley)		Reference standard +	Reference standard −	Total	
	Index test +	0	24	24	
	Index test −	4	192	196	
	Total	4	216	220	

Reference	Perry 2006[164]				
2×2 table (Chalmers revisited)		Reference standard +	Reference standard −	Total	
	Index test +	4	153	n/a	
	Index test −	0	63	n/a	
	Total	4	216	220	
2×2 table (UK NEQAS)		Reference standard +	Reference standard −	Total	
	Index test +	4	37	41	
	Index test −	0	179	179	
	Total	4	216	220	
Statistical measures	Index text Xanthochromia detection – Visual inspection Sensitivity - 50% Specificity – 97% Index text Xanthochromia detection – Traditional Sensitivity – 100% Specificity – 29% Index text Xanthochromia detection –Chalmers and Kiley Sensitivity – 0% Specificity – 89% Index text Xanthochromia detection – Chalmers revisited Sensitivity – 100% Specificity – 29% Index text Xanthochromia detection – UK NEQAS Sensitivity – 100% Specificity – 83%				
Source of funding	This study was supported by the following sources: The Ontario Ministry of Health and Long Term Care, the physicians of Ontario through the Physician's Services Foundation, the Canadian Institutes for Health Research. Dr Perry is a Career Scientist funded by the Ontario Ministry of Health and Dr Stiell holds a distinguished Scientist award from the Canadian Institutes for Health Research.				
Limitations	Risk of bias: Serious				

Reference	**Perry 2006[164]**
	Indirectness: None

1

Reference	**Perry 2011[166]**
Study type	Prospective cross-sectional study
Study methodology	Data source: n/a Recruitment: Consecutive patients
Number of patients	n = 3123
Patient characteristics	Age, mean (SD): 45.1 (no SD) Gender (male to female ratio): Ethnicity: N/A Setting: 11 tertiary care emergency departments across Canada, 2000-9. Country: Canada Inclusion criteria: Neurologically intact adults with a new acute headache peaking in intensity within one hour of onset in whom a computed tomography was ordered by the treating physician to rule out subarachnoid haemorrhage. Exclusion criteria: patients with onset of headache more than 14 days previously; recurrent headaches (three or more headaches of similar character and intensity as presenting headache); transfer from another hospital with confirmed subarachnoid haemorrhage; focal neurological deficits; papilledema; or history of subarachnoid haemorrhage, aneurysm, ventricular shunt, or brain neoplasm
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test - CT Computed tomography was ordered at the discretion of the treating physician, who was aware of the clinical decision rule study but was advised not to alter usual care because of the study. All computed tomography scanners were third generation, multi-slice scanners (from 4 to 320 slices/rotation). The protocols at the beginning of the study (2000-2) used 5 mm slices for the posterior fossa and 10 mm for the remainder of the brain. Since 2002, all sites adopted 5-7.5 mm cuts for the brain with 2.5-5 mm for the posterior fossa

<table>
<tr><td>Reference</td><td colspan="4">Perry 2011[166]</td></tr>
<tr><td></td><td colspan="4">Reference standard
Lumbar puncture was performed at the discretion of the treating physician, with consent from the patient, according to usual practice. Local laboratory technicians unaware of the study assessed the cerebrospinal fluid for xanthochromia by visual comparison against white paper

Time between measurement of index test and reference standard: not reported</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>223</td><td>0</td><td>223</td></tr>
<tr><td></td><td>Index test −</td><td>7</td><td>2892</td><td>2899</td></tr>
<tr><td></td><td>Total</td><td>240</td><td>2892</td><td>3132</td></tr>
<tr><td>Statistical measures</td><td colspan="4">Patients that SAH was detected rather than total SAH detected
All patients
Index text CT
Sensitivity - 92.9%
Specificity – 100%
PPV – 100%
NPV – 99.4 %
LR(+) – infinity
LR(-) – 0.07 (0.05 to 0.11)

Scan ≤6 hours from headache onset
Index text CT
Sensitivity – 100%
Specificity – 100%
PPV – 100%
NPV – 100%
LR(+) – infinity
LR(-) – 0.00 (0.00 to 0.02)

Scan ≥6 hours from headache onset
Index text CT
Sensitivity – 85.7%
Specificity – 100%
PPV – 100%
NPV – 92.2</td></tr>
</table>

Reference	**Perry 2011[166]**
	LR(+) – infinity LR(-) – 0.14 (0.14 to 0.17)
Source of funding	Not specified
Limitations	Risk of bias: Serious Indirectness: None

1

2

Reference	**Perry 2015[163]**
Study type	Cross-sectional study. Sub-study of multicentre cohort study
Study methodology	Data source: n/a Recruitment: n/a
Number of patients	n = 641
Patient characteristics	Age, mean (SD): normal LP result- 41.6(15.5); abnormal LP result 45.1 (16.2) Gender (male to female ratio): 745/994 Ethnicity: not specified Setting: 12 Canadian academic emergency departments, from November 2000 to December 2009. Country: Canada Inclusion criteria: Alert patients aged over 15 with an acute non-traumatic headache who underwent lumbar puncture to rule out subarachnoid haemorrhage.

<table>
<tr><td>Reference</td><td colspan="4">Perry 2015[163]</td></tr>
<tr><td></td><td colspan="4">Exclusion criteria: if presented more than 14 days after the onset of headache; had recurrent headaches; were transferred from another hospital with a confirmed sub-arachnoid haemorrhage; and had focal neurological deficits, papilledema, or a history of subarachnoid haemorrhage, aneurysm, ventricular shunt, or brain neoplasm.</td></tr>
<tr><td>Target condition(s)</td><td colspan="4">Detection of subarachnoid haemorrhage</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="4">Index test LP (risk threshold low risk of xanthochromia and low risk of xanthochromia)
Cerebrospinal fluid analysis of the final tube of cerebrospinal fluid and/or xanthochromia in one or more tubes. Negative subarachnoid haemorrhage as red blood cells < 2000 × 106 /L in cerebrospinal fluid and no xanthochromia Positive as ≥ 2000 × 106 red blood cells/L or xanthochromia.
The decision of whether a lumbar puncture was warranted and when it was performed was at the discretion of the treating physician.

Reference standard – CT
Computed tomography was performed at the discretion of the treating physician.

Time between measurement of index test and reference standard: N/A</td></tr>
<tr><td>2×2 table Patients with abnormal LP results</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>15</td><td>55</td><td>70</td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>571</td><td>571</td></tr>
<tr><td></td><td>Total</td><td>15</td><td>626</td><td>641</td></tr>
<tr><td>Statistical measures</td><td colspan="4">Index text LP
Sensitivity (of risk threshold) – 100% (CI 74.7-100.0%)
Specificity (of risk threshold) – 91.2% (CI 88.6-93.3%)
PPV – 21.4% (CI 12.9-33.2%)
NPV – 100% (CI 99.2-100.0%)
LR(+) – 11.4% (8.8-14.6%)
LR(-) – 0 (NA)
AUC – 0.948</td></tr>
</table>

Reference	**Perry 2015[163]**
Source of funding	This research was funded by the Canadian Institutes of Health Research (grants: 67107, 153742), the Ontario Ministry of Health and Long Term Care, and the physicians of Ontario through the Physician's Services Incorporated Foundation (01–39). JPP is supported by a Canadian Institutes of Health Research New Investigator Award and was previously supported as a career scientist by the Ontario Ministry of Health. IGS is a distinguished professor and university health research chair, University of Ottawa. CH is supported by a Canadian Institutes of Health Research New Investigator Award and was previously supported by a Mentored Clinician Scientist Award from the Vancouver Coastal Health Research Institute.
Limitations	Risk of bias: Serious Indirectness: None
Comments	All "0" values were replaced with "0.2" to allow for meta-analysis using Winbugs

1

Reference	**Stewart 2014[190]**
Study type	Retrospective cross-sectional study
Study methodology	Data source: patient records from a large city teaching hospital
Number of patients	N = 244
Patient characteristics	Mean age (range) : 48.5 years (18-87) Female: 144 Male: 100 Setting: Two hospitals (Torbay Hospital & Royal Devon and Exeter Hospital) Country: United Kingdom Inclusion criteria: Radiological coding of SAH (i.e., patients with CT head reported as being positive for SAH/subarachnoid blood); LPs performed to exclude SAH (all LP samples processed for xanthochromia performed during the study period were examined); Medical discharge coding of SAH Exclusion criteria: patients aged less than 18 years and those who had sustained traumatic haemorrhages; hospital notes were reviewed to exclude those cases in which a diagnosis of SAH was not suspected in the differential diagnosis
Target condition(s)	Subarachnoid haemorrhage

Reference	**Stewart 2014[190]**
Index test(s) and reference standard	Index test: Patients with CT head reported as being positive for SAH/subarachnoid blood. One of two modern CT scanners using slip-ring technology, and either four or six slices per second, were used; a GE Light Speed 64-slice, or a Siemens Somaton 16-slice with 2.5 mm slices as standard protocol. All final reports were issued by a consultant radiologist (although initial reporting was often by a radiology registrar) and were reported as positive, negative or inconclusive (equivocal) for subarachnoid blood. (65 patients had a SAH; 57 patients had CT scan within 12 hours, 31 were scanned within 6 hours but prognostic data for this group not clear) Reference test: All LP samples processed for xanthochromia performed during the study period were examined. CSF was analysed by spectrophotometry in accordance with national guidelines to be reported as one of four results: (1) consistent with SAH (positive), (2) no evidence to support SAH (negative), (3) inconclusive, (4) unable to interpret. Those patients in the latter two categories (equivocal LPs) were followed-up to identify the result of any further relevant investigation performed to date within the region (notably CT angiography or MR angiography). Timing of LP not stated within paper.
2×2 table	

	SAH diagnosed	SAH not diagnosed	Total	The performance of CT alone versus gold standard of CT plus LP (with angiography if LP equivocal)
CT positive	61	3	64	
CT negative	4	158	162	
Total	65	161	226	

Statistical measures	Sensitivity – 93.8% (CI 84-98%) Specificity – 98% (CI 93-99%) Positive predictive value – 95.3% (calculated by Review Manager) Negative predictive value – 97.5% (calculated by Review Manager)
Source of funding	Funding not stated
Limitations	One patients CT was equivocal and was excluded from analysis. In the CT negative group: • further LP failed in 10 patients (due to technical difficulty, insufficient sample or patient refusal) and excluded from analysis • 9 had equivocal LP; of which 5 were negative after subsequent CT or MR angiography, but excluded from the analysis as not 'true negatives' as tested by the gold standard of negative CT and LP). • 2 of the equivocal LP were not tested further and could not be included in the analysis. Risk of Bias - serious Indirectness - none
Comments	Also reported diagnostic accuracy of CT when performed within 12 h of ictus

1

Reference	**Wood 2005[213]**
Study type	Retrospective cross-sectional study
Study methodology	Data source: not reported Recruitment: consecutive
Number of patients	n = 253
Patient characteristics	Age, mean (SD): Not specified Gender (male to female ratio): Not specified Ethnicity: Not specified Setting: princess Alexandra Hospital Brisbane Australia Country: Australia Inclusion criteria: patients undergoing lumbar puncture after normal cranial CT scan with a possible diagnosis of spontaneous SAH patients were identified from a hospital laboratory database of all spectrophotometry tests for CSF xanthochromia this test is performed routinely on all CSF samples from patients with possible diagnosis of SAH Exclusion criteria: Al patients not undergoing both CT scan and lumbar puncture comma or patients with evidence of SAH on CT were excluded.
Target condition(s)	Detection of subarachnoid haemorrhage
Index test(s) and reference standard	Index test LP Lumbar puncture CSF - the erythrocyte counts in the submitted specimens where recorded for each patient, together with the laboratory report of the macroscopic appearance of the original and centrifuged samples. The degree of xanthochromia on spectrophotometry is expressed as xanthochromic index. And this result was recorded in every case. Only patients with CSF taken at

<table>
<tr><td>Reference</td><td colspan="4">Wood 2005[213]</td></tr>
<tr><td></td><td colspan="4">lumbar puncture during their initial presentation were included in the analysis. Patients with post-treatment specimens from CSF drains or shunts were excluded

<u>Reference standard – CT, angiography</u>
Patient case records were reviewed retrospectively, together with CT scan, angiography, CSF results. The clinical history and examination findings were recorded comma together with the treating Physician’s differential diagnosis. Patients were assessed as having potential diagnosis of SSAH if there was a history of sudden onset or unusually severe headache, abrupt loss of consciousness, Meningism or if it was otherwise documented by the treating doctor as a suspect diagnosis. Patients in whom SAH did not enter the differential diagnosis where excluded. The CT scan images were available, where reviewed by the principle investigator, together with the official radiologist’s report of the scan in all cases. Similarly, the results of subsequence angiographic studies were recorded. The timing of the CT scan in relation to the onset of symptoms was recorded for each patient. CT scans performed within 24-hour of ictus were classified as early. Scans performed beyond this time were classified as delayed.

Diagnosis – Patients were assessed as having a potential diagnosis if there was a history sudden onset or unusually severe headache, abrupt loss of consciousness, meningism, or if it was otherwise documented by the treating doctor as a suspect diagnosis.

Time between measurement of index test and reference standard: not specified</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>2</td><td>59</td><td>61</td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>179</td><td>179</td></tr>
<tr><td></td><td>Total</td><td>2</td><td>238</td><td>240</td></tr>
<tr><td>Statistical measures</td><td colspan="4"><u>Index text LP spectrophotometry (XI)</u>
Sensitivity – 100%
Specificity -75%
PPV -3.3%
NPV – 100%</td></tr>
</table>

Reference	**Wood 2005[213]**
Source of funding	Not stated
Limitations	Risk of bias: Serious Indirectness: None
Comments	All “0” values were replaced with “0.2” to allow for meta-analysis using Winbugs

1

D.2 Diagnostic strategies

Reference	**Backes 2012[15]**
Study type	Cross-sectional study
Study methodology	Data source: Patients were retrieved from 2 prospective databases
Number of patients	n = 250
Patient characteristics	Age: 48 (17-88) Gender (male to female ratio): 83/167 Setting: University Medical Centre Utrecht, the Netherlands Country: Netherlands Inclusion criteria: all patients presenting to our emergency department between January 1, 2005, and January 1, 2012, with a clinical suspicion of non-traumatic SAH and a normal level of consciousness (defined as Glasgow Coma scale score of 15). The first database included consecutive patients with confirmed SAH and the second included all patients receiving lumbar puncture with CSF spectrophotometry Exclusion criteria: (1) Glasgow Coma scale score ≤14; (2) referral from another hospital with a confirmed diagnosis of SAH; (3) unknown time of ictus; (4) focal deficits at presentation; (5) >14 days between ictus and diagnostic work-up; (6) age younger than 16 years; and (7) lumbar puncture in the month before presentation.
Target condition(s)	Suspected subarachnoid haemorrhage

Reference: **Backes 2012**[15]

Index test(s) and reference standard

Index test: All patients were scanned with a modern 16 to 256 slices per rotation multi-detector row third-generation scanner with a slice thickness of 5 mm. All scans were interpreted by experienced neuro-radiologists. Patients were stratified into head CT ≤ 6 hours after ictus (n=137), head CT ≥ 6 after ictus (n=113). Data regarding time of ictus and time of head CT were extracted from electronic patient files.

Reference standard:
If the CT scan does not reveal a diagnosis, then a lumbar puncture is performed for CSF analysis at least 12 hours after ictus. The CSF was protected from (day) light in aluminium foil and centrifuged at 1500 rotations per minute during 10 minutes. The supernatant was stored at 4°C until analysis. The CSF was analysed using visual inspection and absorption spectrophotometry for the presence of bilirubin. Spectrophotometry was performed with a Beckman DU 650 spectrophotometer (Beckman Coulter). The diagnosis of SAH was made if plain head CT scan showed blood in the subarachnoid space or if CSF spectrophotometry was positive for bilirubin, which was defined as an absorption level 0.05 at wavelength 458 nm.

2 x 2 table

CT scan ≤ 6 hours

	SAH positive	SAH negative	Total
CT positive	68	0	68
CT negative	1	68	69
Total	69	69	137

CT scan ≥ 6 hours

	SAH positive	SAH negative	Total
CT positive	37	0	37
CT negative	5	71	76
Total	42	71	113

Statistical measures

Index test CT scan:
% Sensitivity (95%CI): ≤ 6 hours: 98.5 (92.1–100); >6 hours: 90.0 (76.3–97.2)
% Specificity(95%CI): ≤ 6 hours: 100 (94.8–100); >6 hours: 100 (95.1–100)
PPV(95%CI): ≤ 6 hours: 100 (94.6–100); >6 hours: 100 (90.3–100)
NPV(95%CI): ≤ 6 hours: 98.6 (92.3–100); >6 hours: 94.8 (87.2–98.6)

Source of funding: Not stated

Limitations: Risk of bias: Serious
Indirectness: none

Reference	**Backes 2012[15]**
Comments	The authors have considered other conditions aside from SAH within their calculations within their analysis (perimesencephalic haemorrhage, arterio-venous malformation, idiopathic headache, viral meningitis, migraine, sinusitis, postcoital headache, bacterial meningitis, viral encephalitis, retinal haemorrhage, medication induced headache)

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Reference	**Blok 2015[21]**
Study type	Cross-sectional study
Study methodology	Data source: consecutive series of patients in 11 non-academic hospitals in the Netherlands
Number of patients	N = 760
Patient characteristics	Median age (range): 45 years (17-87) Female: 466 Male: 294 Setting: non-academic hospitals in the Netherlands Country: Netherlands Inclusion criteria: patients presenting between January 2007 and January 2013 with spontaneous acute headache suspected of SAH, who had a head CT scan within 6 hours after headache onset that was reported negative for the presence of subarachnoid blood by a staff radiologist, and subsequent CSF spectrophotometry. Patients were also included with a CT initially being reported negative for the presence of SAH, but subsequently judged positive after positive CSF spectrophotometry became available. Exclusion criteria: (1) Glasgow Coma Scale score ≤14 at presentation, (2) unknown time of ictus, (3) age 16 years or younger, and (4) lumbar puncture performed earlier than 12 hours after headache onset.
Target condition(s)	Suspected subarachnoid haemorrhage
Index test(s) and reference standard	Index test: CT scan within 6 hours (n=760). Two experienced neuroradiologists and one experienced stroke neurologist from 2 academic tertiary care hospitals independently reviewed all admission CT scans of patients with a positive finding of bilirubin according to the local CSF analysis protocol. The reviewers of the head CTs were blinded for any clinical or radiologic follow-up information. Reference standard: Lumbar puncture CSF was analysed by spectrophotometry and interpreted according to local criteria. Time points of lumbar puncture not specified. The CSF results of 52 patients were initially considered positive for SAH by local spectrophotometric criteria.

Reference	Blok 2015[21]
Statistical measures	Index test CT scan: Negative predictive value: 99.9% (95% CI 99.3 – 100.0%)
Source of funding	No targeted funding reported
Limitations	Risk of bias: serious Indirectness: none
Comments	3) Paper reports 11 false negatives from CT scan which were not re-evaluated 4) Diagnosis of aneurysmal SAH was based on the presence of red blood cells in CSF but without xanthochromia For patients with CSF results that were initially interpreted as positive for SAH by local criteria and a negative head CT on independent review, the results of additional cerebrovascular imaging were obtained, and the patients' hospital records were reviewed for readmissions for SAH. For patients in whom an aneurysm was found on vascular imaging, the aneurysm was considered an incidental, unruptured aneurysm if the initial CSF results were considered falsely positive based on one of the following criteria: (1) the sample contained ,100 3 106/L red blood cells in CSF,8 (2) an alternative explanation for the positive CSF result was found, or (3) a second method of CSF spectrophotometric analysis showed negative results; for example, bilirubin-excess value 0.24 (>0.20 is abnormal), but absorption units at 450 to 460 nm <0.05.

1

Reference	Cortnum 2010[45]
Study type	Cross-sectional study
Study methodology	Data source: database from major Danish university hospital
Number of patients	N = 499
Patient characteristics	Patient demographic details not specified within the article Setting: Neurosurgical unit Country: Denmark Inclusion criteria: All patients referred to neurosurgical unit of Aalborg University Hospital from January 2000 to December 2005 on suspicion of SAH or with verified SAH.
Target condition(s)	Subarachnoid haemorrhage

Reference	**Cortnum 2010[45]**					
Index test(s) and reference standard	Index test: CT scan All patients had a CT scan of the head performed. If the CT scan was positive for SAH, the patients subsequently had angiography studies performed and were allocated to appropriate treatment. Throughout the study period a range of different CT scanners were used at our institution and referring hospitals. All scanners used were considered contemporary standard equipment at the time. CT scan < 1 day n = 364 CT scan 2 days n = 28 CT scan 3 days n = 22 CT scan 4 – 7 days n = 55 CT scan > 1 week n = 30 Reference test: Lumbar puncture Patients with a negative CT scan had a lumbar puncture done. Cerebral spinal fluid was sent to the laboratory for cell counts and all samples were analysed for xanthochromia by spectrophotometry. Lumbar punctures were done no earlier than 12 hours after onset of symptoms.					
Statistical measures	Time	Diagnosis by CT scan	Diagnosis by LP	Negative CT Negative LP	Sensitivity %	Specificity %
	< 1 day	243	0	121	100	100
	2 days	14	0	14	100	100
	3 days	5	0	17	100	100
	4 – 7 days	25	1	29	96	100
	>1 week	8	0	22	-	-
Source of funding	Source of funding not stated					
Limitations	Risk of bias: serious Indirectness: Serious – indirect reference standard used; positive CT not reviewed further – only LP in CT negative cases, no angiography or further investigation					

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Reference	**Mark 2013[132]**
Study type	Matched case – control study (Patients with a diagnosis of subarachnoid haemorrhage as determined by lumbar puncture after a negative cranial CT result were screened for inclusion. A matched control cohort was selected among patients with a diagnosis of headache after negative cranial CT and lumbar puncture results)
Study methodology	Data source: databases from 21 emergency departments from 2000 to 2011

Reference	Mark 2013[132]
Number of patients	N = 55 (case) N = 168 (control)
Patient characteristics	Mean age (SD, range): Case:52 (15, 22-92); Control: 48 (17, 18-87) Female: 159 Male: 64 Setting: 21 emergency departments at Northern California Kaiser Permanente Hospitals Country: USA Inclusion criteria: Patients were aged >18 years, CT without evidence of subarachnoid blood by final documented radiologist interpretation, normal documented neurologic examination result (aside from isolated single cranial nerve deficits), greater than 5 RBCs per microliter of cerebrospinal fluid, and at least 1 of the following criteria as evidence of subarachnoid haemorrhage: presence of xanthochromia on visual inspection of cerebrospinal fluid, angiographic evidence of cerebral aneurysm or arteriovenous malformation, or subsequent cranial imaging (such as magnetic resonance imaging [MRI]) demonstrating subarachnoid haemorrhage performed within 48 hours after the index lumbar puncture. Controls were matched to cases by year and presenting ED in a ratio of 3 controls for every case, in an attempt to control for variations in ED practice and CT technology over time. The primary inclusion criterion was a documented concern for subarachnoid haemorrhage in the emergency physician chart according to the presenting complaints. Exclusion criteria: Cases were excluded from the study if patients had a known untreated cerebral aneurysm or arteriovenous malformation, underwent lumbar puncture before CT, or had documentation of head trauma occurring within the 4 weeks before the index presentation. Exclusion criteria for controls were identical to those of cases, with the addition of the following: microbiologic evidence of infection in cerebrospinal fluid samples (by culture, antigen testing, or polymerase chain reaction testing), presumed immunocompromised status (known infection with HIV, solid organ transplant recipient, active hematologic cancer, active chemotherapy, or steroid use of 10 mg prednisone equivalents per day for 4 weeks or more), more than 5 RBCs or WBCs per microliter of cerebrospinal fluid, or the presence of visible cerebrospinal fluid xanthochromia.

Reference	**Mark 2013[132]**
Target condition(s)	Subarachnoid Haemorrhage
Index test(s) and reference standard	CT scan: (n=55) patients had a CT scan completed on admission to the emergency department for suspected subarachnoid haemorrhage. CT examinations were performed with either single-slice helical scanning technology or, in the majority of cases, multi-slice cine technology (i.e., fifth- and sixth-generation CT). Written reports and physical or digital copies of radiology studies (when available) were examined to determine the computed tomogram manufacturer and model and protocol used. Protocols varied between medical centres and over time, with supratentorial imaging slice thickness ranging from 5 to 10 mm and posterior fossa slice thickness ranging from 2.5 to 7 mm. Lumbar puncture: All of the patients with negative CT scan for SAH went on to have a lumbar puncture (timing of procedure unclear). Cerebrospinal fluid analysis with greater than 5 red blood cells per microliter were sought within the LP results.
Statistical measures	Imaging rule: cranial CT performed within 6 hours of headache onset. External validation of the imaging rule revealed less than 100% sensitivity; 11 patients with subarachnoid haemorrhage had a negative cranial CT result within 6 hours of headache onset.
Source of funding	Not reported
Limitations	Risk of bias: serious Indirectness: none

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Reference	**Mark 2015[133]**
Study type	Retrospective chart review - multicentre cross-sectional study. Only those with a final diagnosis of SAH were included in the study analysis
Study methodology	Data source: Patients were evaluated in the 21 EDs of an integrated health delivery system between January 2007 and June 2013. The authors identified by chart review a retrospective cohort of patients diagnosed with aSAH in the setting of a normal mental status and performance of early cranial CT.
Number of patients	N = 155
Patient characteristics	Median age: 55 years Female: 122 Male: 33 Setting: multicentre; emergency department records of participating hospitals

Reference	**Mark 2015[133]**
	Country: USA Inclusion criteria: Patients who had an ED or hospital encounter with a diagnosis code of SAH, Hunt-Hess clinical grade 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 visualised on imaging, if applicable. Exclusion criteria: 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 July2010.
Target condition(s)	Subarachnoid Haemorrhage
Index test(s) and reference standard	Index test: CT <6 hours Non-contrast cranial CT imaging within six hours of headache onset. 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. Reference standard for presence of SAH: Final diagnosis determined by combination of subsequent investigation including Lumbar Puncture CSF + Xanthochromia investigation and angiographical imaging.
2x2 table <6 hours	

	Reference standard +	Reference standard -	
Index test +	148		
Index test -	7		
	155		

Statistical measures	Imaging rule: cranial CT performed within 6 hours of headache onset. Sensitivity – 95.5% (95% CI [90.9-98.2]) Specificity – n/a +LR – n/a -LR – n/a
Source of funding	Funded by a Kaiser Permanente Northern California Community Benefits Grant

Reference	**Mark 2015[133]**
Limitations	Risk of bias: serious Indirectness: none

Reference	**Perry 2011[166]**
Study type	Prospective cross-sectional
Study methodology	Data source: prospective cohort of patients
Number of patients	n = 3132
Patient characteristics	Mean (SD) Age: 45.1 (17.1) Gender (male to female ratio): 1243/1889 Setting: 11 university affiliated tertiary care teaching hospitals Country: Canada Inclusion criteria: Alert patients aged over 15 who presented with non-traumatic acute headache or with syncope associated with headache and underwent emergency head computed tomography as part of their diagnostic investigation. We defined “alert” as a Glasgow coma score of 15 (scale ranges from 3 to15, with 15 being normal), “non-traumatic” as no falls or direct trauma to the head in the previous seven days, and “acute” as headache reaching maximum intensity in less than one hour after onset. Exclusion criteria: onset of headache more than 14 days previously; recurrent headaches (three or more headaches of similar character and intensity as presenting headache); transfer from another hospital with confirmed subarachnoid haemorrhage; focal neurological deficits; papilloedema; or history of subarachnoid haemorrhage, aneurysm, ventricular shunt, or brain neoplasm.
Target condition(s)	Subarachnoid haemorrhage
Index test(s) and reference standard	Index test: All computed tomography scanners were third generation, multi-slice scanners (from 4 to 320 slices/rotation). The protocols at the beginning of the study (2000-2) used 5 mm slices for the posterior fossa and 10 mm for the remainder of the brain. Since 2002, all sites

Reference	**Perry 2011[166]**				
	adopted 5-7.5 mm cuts for the brain with 2.5-5 mm for the posterior fossa. Patients were stratified into CT head ≤6 hours (n=953) or CT head >6 hours (n=2179) <u>Reference standard:</u> Lumbar puncture was performed at the discretion of the treating physician, with consent from the patient, according to usual practice. Local laboratory technicians unaware of the study assessed the cerebrospinal fluid for xanthochromia by visual comparison against white paper. Not all patients with normal results on computed tomography underwent lumbar puncture. Overall, the group of patients undergoing lumbar puncture was a slightly higher risk group than those without. (Timing of LP not specified) Patients were deemed to be positive for subarachnoid haemorrhage if they had any of subarachnoid blood identified on unenhanced head computed tomography; visible xanthochromia in the cerebrospinal fluid; or red blood cells (>5×106/L) in the final tube of cerebrospinal fluid collected and an aneurysm identified on cerebral angiography (digital subtraction, computed tomography, or magnetic resonance angiography).				
2x2 table <6 hours		Reference standard +	Reference standard -		
	Index test +	121	0	121	
	Index test -	0	832	832	
		121	832	953	
2x2 table >6 hours		Reference standard +	Reference standard -		
	Index test +	102	76	178	
	Index test -	17	1984	2001	
		119	2060	2179	
Statistical measures	<u>Index test CT scan:</u> % Sensitivity (95%CI): ≤ 6 hours: 100 (97.0 to 100.0); >6 hours: 85.7 (78.3 to 90.9) % Specificity (95%CI): ≤ 6 hours: 100 (99.5 to 100); >6 hours: 100 (99.8 to 100) PPV (95%CI): ≤ 6 hours: 100 (96.9 to 100); >6 hours: 100 (96.3 to 100) NPV (95%CI): ≤ 6 hours: 100 (99.5 to 100); >6 hours: 99.2 (98.7 to 99.5)				
Source of funding	Not stated				
Limitations	Risk of bias: serious Indirectness: none				

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Reference	**Stewart 2014[190]**
Study type	Cross-sectional study
Study methodology	Data source: patient records from a large city teaching hospital.
Number of patients	N = 244
Patient characteristics	Mean age (range) : 48.5 years (18-87) Female: 144 Male: 100 Setting: Two hospitals (Torbay Hospital & Royal Devon and Exeter Hospital) Country: United Kingdom Inclusion criteria: Radiological coding of SAH (i.e. patients with CT head reported as being positive for SAH/subarachnoid blood); LPs performed to exclude SAH (all LP samples processed for xanthochromia performed during the study period were examined); Medical discharge coding of SAH Exclusion criteria: patients aged less than 18 years and those who had sustained traumatic haemorrhages; hospital notes were reviewed to exclude those cases in which a diagnosis of SAH was not suspected in the differential diagnosis
Target condition(s)	Subarachnoid haemorrhage
Index test(s) and reference standard	Index test: Patients with CT head reported as being positive for SAH/subarachnoid blood. One of two modern CT scanners using slip-ring technology, and either four or six slices per second, were used; a GE Light Speed 64-slice, or a Siemens Somaton 16-slice with 2.5 mm slices as standard protocol. All final reports were issued by a consultant radiologist (although initial reporting was often by a radiology registrar) and were reported as positive, negative or inconclusive (equivocal) for subarachnoid blood. (65 patients had a SAH; 57 patients had CT scan within 12 hours, 31 were scanned within 6 hours but prognostic data for this group not clear not clear) Reference test: All LP samples processed for xanthochromia performed during the study period were examined.

Reference	Stewart 2014[190]
	CSF was analysed by spectrophotometry in accordance with national guidelines to be reported as one of four results: (1) consistent with SAH (positive), (2) no evidence to support SAH (negative), (3) inconclusive, (4) unable to interpret. Those patients in the latter two categories (equivocal LPs) were followed-up to identify the result of any further relevant investigation performed to date within the region (notably CT angiography or MR angiography). Timing of LP not stated within paper.
Statistical measures	Diagnostic strategy of CT ≤ 12 hours: Sensitivity: 95% (95% CI 82 – 99%)
Source of funding	Funding not stated
Limitations	Risk of bias: serious Indirectness: none
Comments	Paper states that 31/65 patients found to have SAH were scanned within 6 h and there were no false negative scans in this group. 77% of patient population presented out of hours

1

Appendix E: Coupled sensitivity and specificity forest plots and sROC curves

E.1 Diagnostic accuracy

E.1.1 Coupled sensitivity and specificity forest plots

Figure 3: CT (reference standard: LP + angiography)

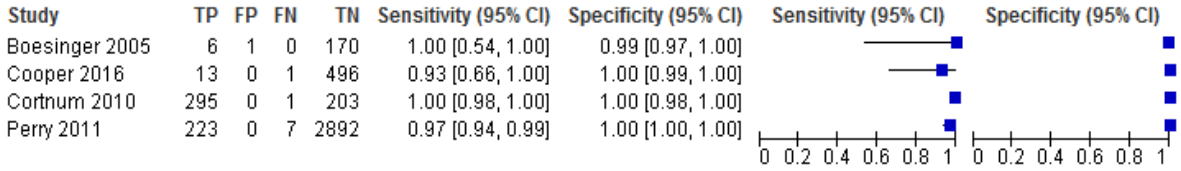


Figure 4: CT (reference standard: LP)

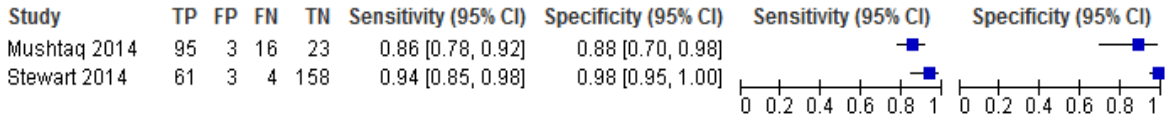


Figure 5: Lumbar Puncture (reference standard: CT + angiogram)

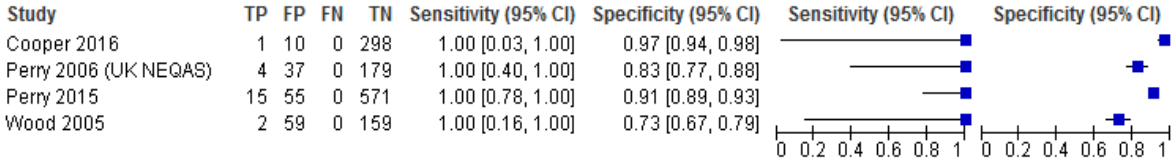


Figure 6: Lumbar Puncture (reference standard: angiography)

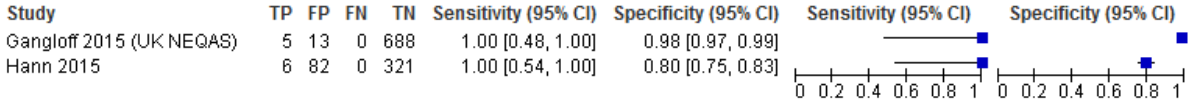


Figure 7: MRI (reference standard: CT)

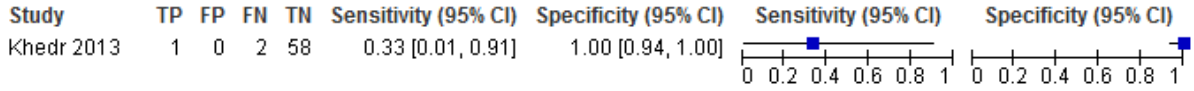
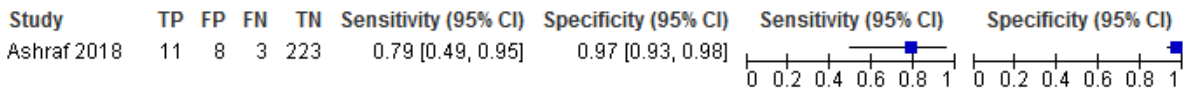


Figure 8: MRI (reference standard: LP)



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E.1.23 sROC curves

Key:

- Solid line represents the ROC summary curve
- Dotted line represents the 95% confidence region of the ROC
- Solid circle represents pooled ROC
- Clear circles represent ROC of individual studies

Figure 9: CT (Reference standard: LP + angiography)

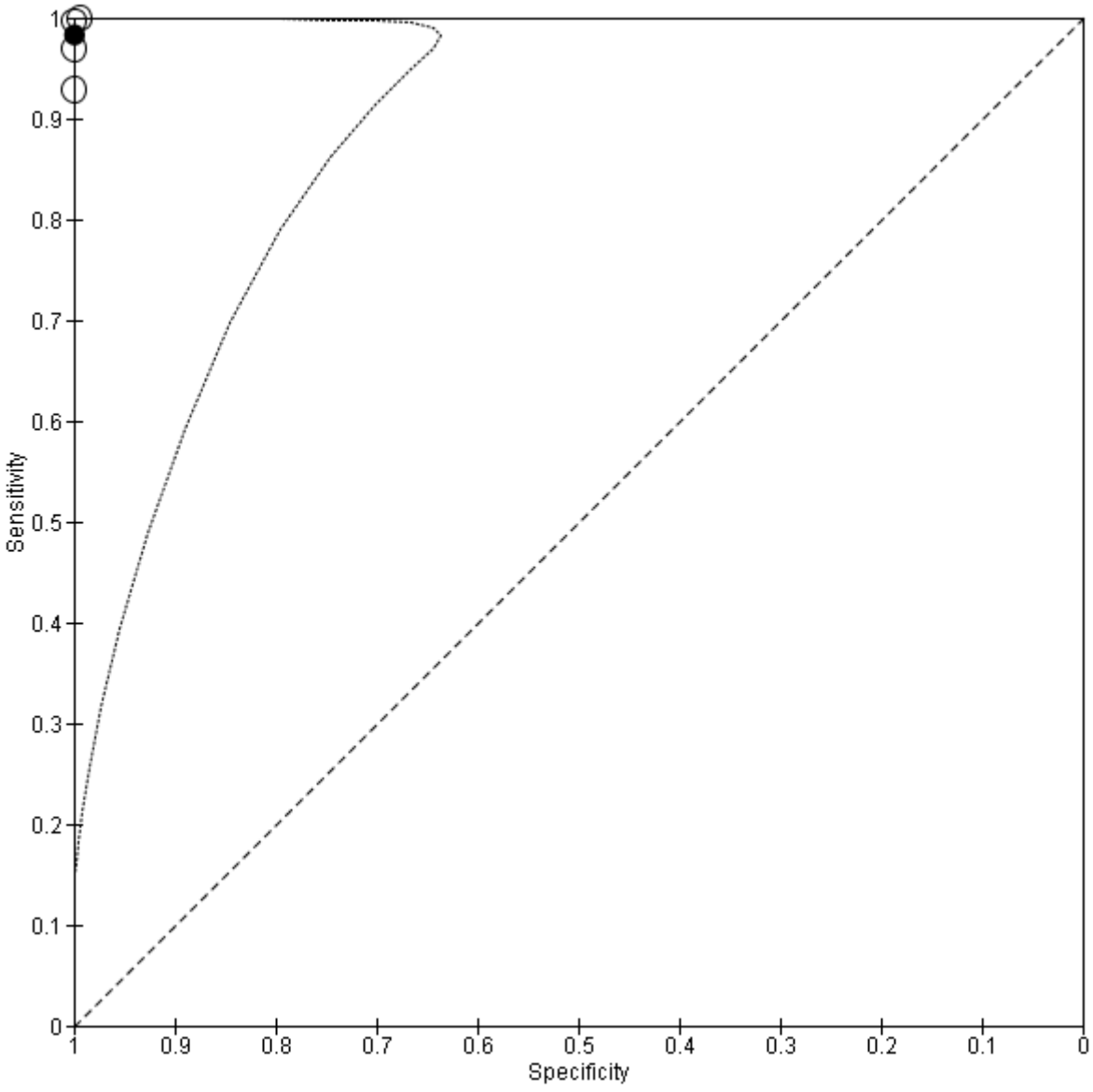

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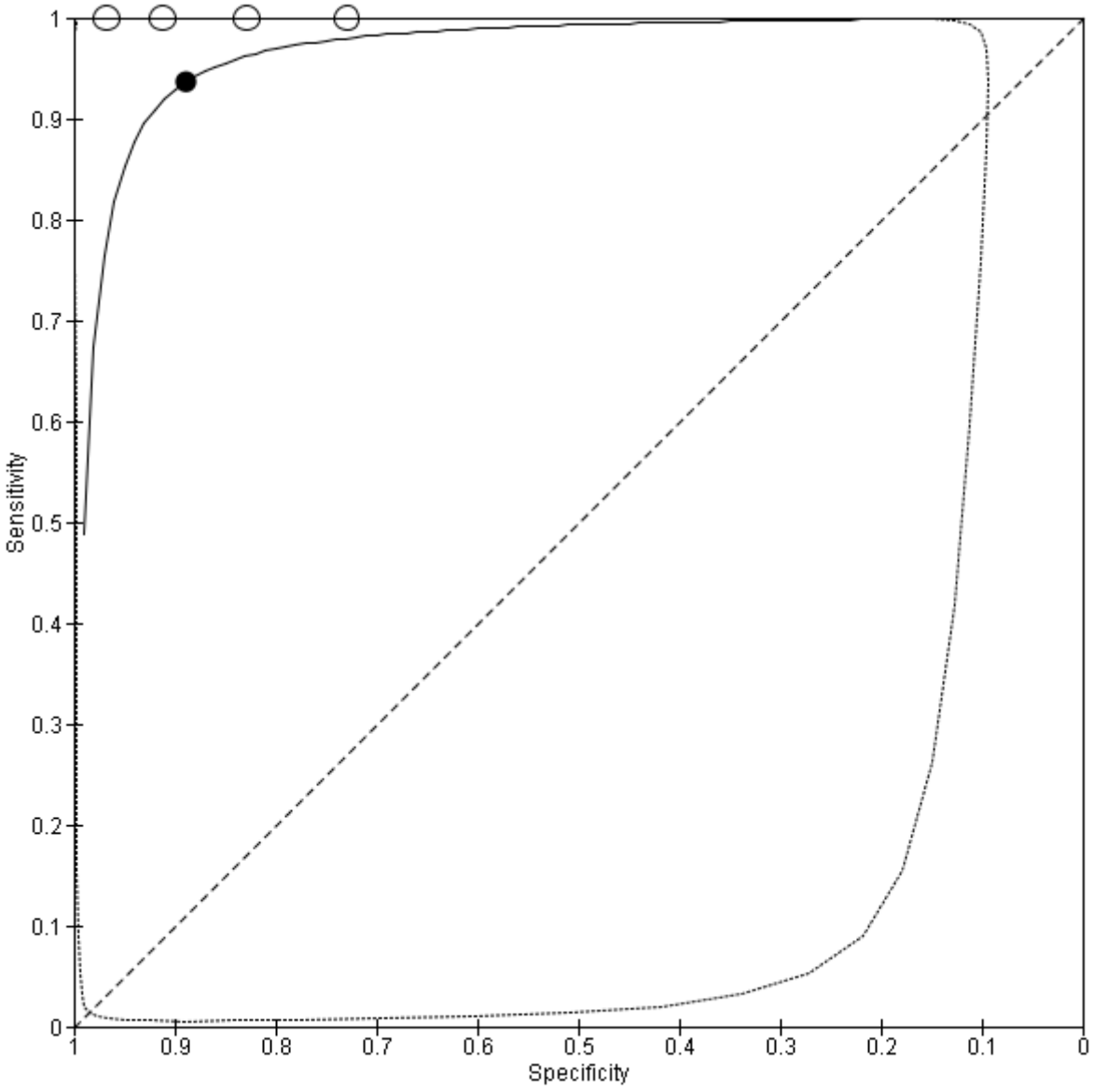
Figure 10: Lumbar puncture (reference standard: CT + angiogram)



E.2 Diagnostic strategies

E.2.1 Coupled sensitivity and specificity forest plots

Figure 11: CT scan ≤ 6 hours (reference standard: LP)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Backes 2012	68	0	1	68	0.99 [0.92, 1.00]	1.00 [0.95, 1.00]
Perry 2011	121	0	0	832	1.00 [0.97, 1.00]	1.00 [1.00, 1.00]

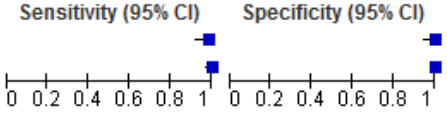
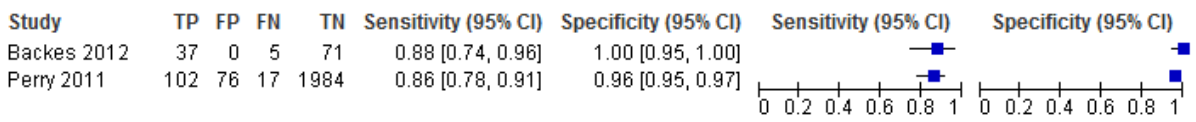


Figure 12: CT scan ≥ 6 hours (reference standard: LP)



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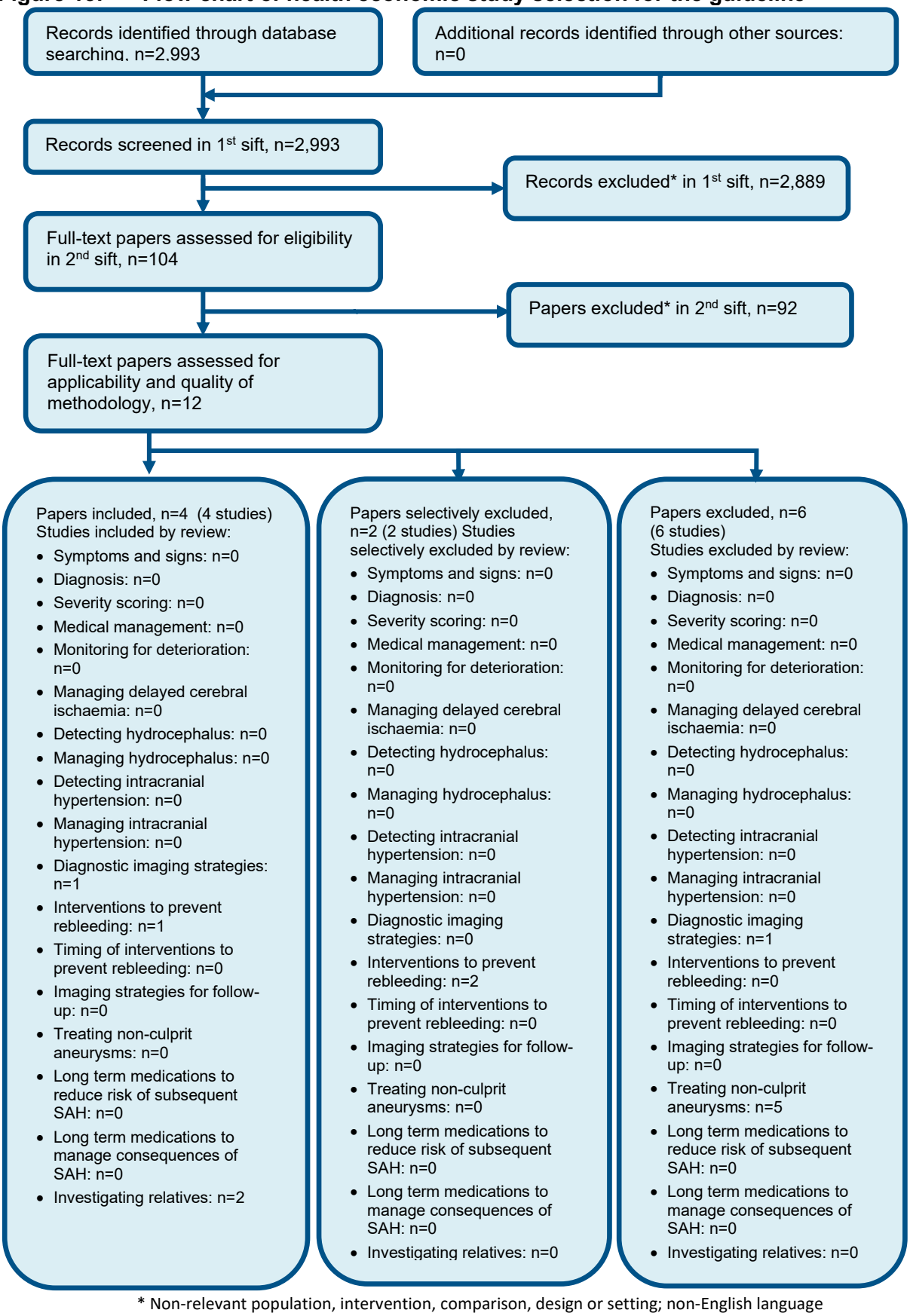
Appendix F: Health economic evidence selection

Figure 13: Flow chart of health economic study selection for the guideline



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

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Appendix G: Health economic evidence tables

No economic studies identified.

Appendix H: Health economic model – utility scores

Table 21, Table 22, and Table 23 provide summaries of the key study characteristics used to inform the utility value used for interpreting the results of the threshold analysis outlined in section 2.5.3.

Table 21: Key study characteristics from von Vogelsang 2017[203]

	Description
Population	Patients who have had an aSAH
Mean age (SD)	53.1 (14.2)
Sample size	88
Male %	34.09%
Study design	Prospective cohort study
Study details	The purpose of this study was to evaluate the health-related quality of life dynamics of patients over time, 2 years following an aSAH and compare the results with the general population. Data was collected at time periods; 6 months, 1 year, and 2 years. Patients were identified from the database for hospital statistics at Karolinska University Hospital in Stockholm. All consecutive patients admitted for a aSAH between march 2006 and September 2007 that met the following inclusion criteria were included in the analysis; (i) Swedish citizenship (to enable follow-up), (ii) Glasgow Outcome Scale (GOS) ≥ 3 at hospital discharge, and (iii) able to communicate in Swedish.
Country	Sweden
Patient characteristics	Treatment modality %: • Open surgery – 38.6% • Endovascular procedure – 61.4% Aneurysm location %: • Anterior circulation – 87.5% • Posterior circulation – 12.5% Glasgow Outcome Scale at hospital discharge % (n): • 3: severe disability – 15.9% (14) • 4: moderate disability – 27.3% (24) • 5: good recovery – 56.8% (50) Number of comorbidities at follow-up: • 0 – 61.4% (54) • 1 – 27.3% (24) • 2 – 8.0% (7) • 3 – 3.4% (3)
Methods for obtaining utility scores	Patients were followed up with EQ-5D postal questionnaires. The United Kingdom value set was used to calculate the $EQ\text{-}5D_{index}$.
Mean utility	$EQ\text{-}5D_{index}$ mean(±SD) • 6 months after aSAH – 0.74 (0.24) • 1 year after aSAH – 0.76 (0.24) • 2 years after aSAH – 0.75 (0.25)

Table 22: Key study characteristics from Ronne-Engström 2013[175]

	Description
Population	Patients who have had a spontaneous aSAH

	Description
Mean age (SD)	56 (12)
Sample size	755
Male %	28%
Study design	Prospective cohort study
Study details	The purpose of this study was to evaluate health related quality of life following a spontaneous aSAH and compare the results with the general population. In addition, the extent to which the five dimensions of the EQ-5D could be predicted based on; demographic parameters, localisation of aneurysms, and treatment methods was assessed. The median follow-up was 12 months (8 months and 18 months, 25th and 75th percentile respectively). Patients were identified from the neurovascular database at Uppsala University Hospital. All consecutive patients admitted for a spontaneous aSAH between 1996 and 2010, admitted in the acute phase with a complete dataset regarding demographic and clinical parameters, as well as measurement of HRQoL were included in the study.
Country	Sweden
Patient characteristics	Treatment modality: • Coiling – 66% • Clipping – 30% • Both techniques – 3% • No treatment – 1% Aneurysm location %: • Anterior circulation – 86% • Posterior circulation – 14% Glasgow Outcome Scale at follow-up % • 2: vegetative – 0.5% • 3: severe disability – 35.8% • 4: moderate disability – 37.2% • 5: good recovery – 26.5%
Methods for obtaining utility scores	Research nurses assessed outcomes either by having patients fill out and return the EQ-5D form or via structure telephone interview. The United Kingdom value set was used to calculate the EQ-5D$_{index.}$
Mean utility	EQ-5D$_{index}$ mean($\pm$SD) • 0.583 (0.422)

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2 **Table 23: Key study characteristics from Meyer 2010[142]**

	Description
Population	Patients who have had an aSAH
Mean age (SD)	54.39 (14.10)
Sample size	113
Male %	32.7%
Study design	Prospective cohort study
Study details	The purpose of this study was to evaluate the outcomes and HRQoL of patients 12-months after discharge following a SAH and compare these results with the general population and differences in intervention. Data was collected at discharge and 12-months follow-up. Patients with ruptured and unruptured cerebral aneurysms treated at the Department of Neurology and Neuroradiology at the University of Bonn between January 2004 and December 2005 were screened for participation in the study. Patients were included in the study if they met the following inclusion criteria; (i) they had a definite SAH proven by cCT, cMRI, or

	Description
	lumbar puncture, (ii) they had an intracranial aneurysm as demonstrated by intra-arterial or by cCT angiography that was considered to be the cause of SAH, and (iii) they were in a clinical sate that justified treatment with either coiling or clipping.
Country	Germany
Patient characteristics	Treatment modality %: • Neurosurgery – 50.4% • Endovascular treatment – 49.6% Hunt and Hess scale at admission % (n): • Grade 1 – 5.3% (6) • Grade 2 – 21.2% (24) • Grade 3 – 34.5% (39) • Grade 4 – 29.2% (33) • Grade 5 – 9.7% (11) WFNS at admission % (n): • Grade 1 – 24.8% (28) • Grade 2 – 23.0% (26) • Grade 3 – 16.8% (19) • Grade 4 – 18.6% (21) • Grade 5 – 16.8% (19)
Methods for obtaining utility scores	Patients were followed up with EQ-5D questionnaires. The $EQ\text{-}5D_{index}$ score was based on the European study by Greiner et al. 2005. The countries included in the study were; Finland, Germany, The Netherlands, Spain, Sweden and the UK.
Mean utility	$EQ\text{-}5D_{index}$ mean(±SD) • At discharge – 0.69 (0.26) • At 12-month follow-up – 0.82 (0.22)

Appendix I: Excluded studies

I.1 Diagnostic accuracy

I.1.1 Excluded clinical studies

Table 24: Studies excluded from the clinical review

Reference	Reason for exclusion
Abu Bakar 2005[1]	Inappropriate comparison – no reference standard; no relevant outcomes
Acker 2018[2]	Inappropriate comparison – angiography
Agid 2006[5]	Inappropriate comparison – angiography
Amagasaki 2004[7]	Inappropriate comparison - angiography
Anzalone 1995[11]	Inappropriate comparison – angiography
Aulbach 2016[13]	Inappropriate comparison – angiography
Avrahami 1998[14]	Inappropriate comparison – enhanced CT scan compared to non-enhanced scan
Backes 2012[15]	Inappropriate comparison – no reference standard
Bakshi 1999[18]	Inappropriate comparison – comparison of flair images
Bechan 2015[19]	Inappropriate comparison – angiography
Berlit 1988[20]	Inappropriate comparison – angiography

Reference	Reason for exclusion
Bo 2008[22]	No relevant outcomes
Bodelle 2014[23]	No relevant outcomes
Bonatti 2017[25]	Inappropriate comparison – contrast images compared to non-contrast images
Brunell 2013[26]	No relevant outcomes
Carstairs 2006[29]	No relevant outcomes
Chalouhi 2020[30]	Not review population – people with ICH confirmed by CT
Chan 2007[31]	No relevant outcomes
Chang 2018[32]	Incorrect intervention/incorrect comparison – computer network optimization
Chen 2001[35]	Inappropriate comparison – angiography
Chen 2012[36]	Inappropriate comparison – angiography
Cho 2019[37]	Inappropriate comparison – learning models
Chrysikopoulos 1996[38]	Inappropriate comparison – incorrect reference standard
Chute 2002[40]	Inappropriate comparison – incorrect reference standard
Claveau 2014[41]	Inappropriate study design – commentary
Colen 2007[42]	Inappropriate comparison – angiography
Compagnone 2006[43]	Inappropriate population – cerebral ischemia
Dammert 2004[47]	Inappropriate comparison – angiography
Delgado Almandoz 2009[50]	Inappropriate comparison – angiography
Dincer 2012[51]	Inappropriate population – craniotomy
Donmez 2011[53]	Inappropriate comparison – angiography
Dooms 1986[54]	Inappropriate comparison – incorrect reference standard
Dupont 2008[58]	Inappropriate comparison – incorrect reference standard
Dupont 2010[57]	No relevant outcomes
El Khaldi 2007[59]	Inappropriate comparison – angiography
Elsamman 2010[60]	No relevant outcomes
Ergun 2011[61]	Inappropriate comparison – angiography
Escobar-de la Garma 2018[62]	No relevant outcomes
Fainardi 2008[63]	No relevant outcomes
Farahmand 2013[64]	Inappropriate comparison – angiography
Ferda 2009[65]	No relevant outcomes
Frolich 2016[67]	Inappropriate comparison –reference standard not reported
Gaughen 2010[70]	Inappropriate comparison – angiography
Gerardin 2009[72]	Inappropriate comparison – angiography
Ghoshhajra 1979[73]	No relevant outcomes
Goergen 1993[75]	No relevant outcomes
Gouliamos 1992[76]	Inappropriate comparison – angiography
Grandin 1998[77]	Inappropriate comparison – angiography
Grossi 1995[79]	No relevant outcomes
Gunawardena 2004[80]	Inappropriate comparison – incorrect reference standard
Guo 2008[82]	Inappropriate comparison – angiography
HaiFeng 2017[83]	Systematic review - references checked
Han 2011[84]	Inappropriate comparison – angiography
Hayashi 2018[88]	Inappropriate comparison – MRI scout positive group compared to MRI scout negative group

Reference	Reason for exclusion
Hillman 1993[91]	No relevant outcomes
Houkin 1994[94]	Inappropriate comparison – angiography
Hsiang 1996[95]	No relevant outcomes
Hsu 2019[96]	Inappropriate comparison - MRI within 7 days of hospital admission vs MRI within 8-15 days
Hui 2007[97]	Inappropriate comparison – angiography
Ichiba 2017[98]	No relevant outcomes
Ida 1997[99]	No relevant outcomes
Indrajit 2007[100]	Inappropriate comparison – angiography
Jabbarli 2014[101]	Inappropriate comparison – CTA compared to no CTA
Jenkins 1988[104]	Inappropriate comparison – incorrect reference standard
Jiang 2015[105]	Inappropriate comparison – contrast CT compared to non-contrast CT
Jung 2006[106]	Inappropriate comparison – angiography
Karamessini 2004[109]	Inappropriate comparison – angiography
Karttunen 2003[110]	No relevant outcomes
Kayhan 2014[111]	Inappropriate comparison – bone subtraction CTA in SAH
Kendall 1976[112]	No relevant outcomes
Kershenovich 2006[113]	Incorrect study design – literature review
Khan 2013[114]	Inappropriate comparison – angiography
Kidwell 2004[116]	Inappropriate population – focal stroke symptoms
Kumar 2014[119]	No relevant outcomes
Lagares 2012[120]	No relevant outcomes
Landtblom 2002[122]	No relevant outcomes
Lee 2019[123]	Incorrect study intervention – SAH patients tested for neurological outcomes
Li 2017[125]	Inappropriate comparison – angiography
Liang 1999[126]	Inappropriate population – brain tumours, AVM, cavernous angioma, chronic haemorrhagic infarction
Lim 2014[127]	Inappropriate comparison – incorrect reference standard
Lum 2016[128]	Inappropriate population – comparison of patients with and without DCI
Lummel 2011[129]	Inappropriate comparison – comparison of flair techniques
MacKinnon 2013[130]	Inappropriate comparison – angiography
Mark 2016[134]	Inappropriate comparison –reference standard not reported
Marshall 2010[135]	Inappropriate study design – literature review
Marshman 2014[136]	Incorrect study design – mock sampling
Martin 2015[137]	Inappropriate comparison – utility of LP in CT negative patients
Maslehaty 2012[138]	No relevant outcomes
Maslehaty 2011[140]	No relevant outcomes
Maslehaty 2011[139]	No relevant outcomes
Migdal 2015[143]	No relevant outcomes
Miley 2008[144]	Inappropriate study design – CTA reviewed by specialists
Millon 2012[145]	Inappropriate comparison – assessment of technical quality
Milosevic Medenica 2010[146]	Inappropriate comparison – angiography
Mitchell 2001[147]	Inappropriate comparison – different sequences of MRI scan

Reference	Reason for exclusion
Modesti 1978[148]	No relevant outcomes
Mohan 2019[149]	Systematic review - references checked
Morgenstern 1998[150]	Inappropriate comparison – incorrect reference standard
Mortimer 2016[151]	Inappropriate comparison – angiography
Nagy 2013[153]	Incorrect study design – literature review
Ni 2016[156]	No relevant outcomes
Nijjar 2007[157]	No relevant outcomes
Noguchi 2000[158]	Incorrect study design – simulated model
Ohkawa 1998[160]	No relevant outcomes
O'Neill 2005[159]	Inappropriate comparison – incorrect reference standard
Park 2019[161]	Inappropriate comparison - people with intracerebral haemorrhage compared to healthy controls
Pechlivanis 2009[162]	Inappropriate comparison – angiography
Perry 2008[165]	No relevant outcomes
Petersmann 2014[167]	Inappropriate comparison – comparison of chemiluminescent assays
Petzold 2011[168]	No relevant outcomes
Pierot 2013[169]	Inappropriate comparison – angiography
Prestigiacomo 2010[171]	Inappropriate comparison – angiography
Rana 2013[172]	No relevant outcomes
Saboori 2011[176]	Inappropriate comparison – angiography
Saeedi 2018[178]	Inappropriate comparison – incorrect reference standard
Sames 1996[179]	Inappropriate comparison – incorrect reference standard
Sandoval 2004[180]	Paper not in English
Sanelli 2011[181]	Inappropriate population – suspected vasospasm
Sankhla 1996[182]	inappropriate comparison – incorrect reference standard
Sato 2011[183]	Incorrect study design – in vitro experimental haematoma
Satoh 1988[184]	Inappropriate comparison – incorrect reference standard
Shimoda 2010[187]	No relevant outcomes
Suazo 2018[191]	Systematic review - references checked
Suzuki 2020[192]	Inappropriate comparison – frequency of contrast extravasation
Takahashi 2017[193]	Inappropriate population – DCI patients
Topcuoglu 2003[195]	Inappropriate comparison – angiography
Tsementzis 1985[196]	No relevant outcomes
Valle Alonso 2018[198]	Paper not in English
van Gelder 2003[199]	Systematic review - references checked
Vatter 2011[200]	Inappropriate population – suspected vasospasm post-surgery
Velthuis 1998[201]	Inappropriate comparison – angiography
Vieco 1995[202]	Inappropriate comparison – comparison of findings between specialists
Walkoff 2016[204]	Inappropriate population – oncotic and myotic aneurysms
Wallmann 2001[206]	Incorrect study design – literature review
Wang 2010[207]	Inappropriate comparison – angiography
Westerlaan 2011[210]	Systematic review - references checked
Wiesmann 2002[211]	Inappropriate comparison - different sequences of MRI scan
Wilcock 1996[212]	inappropriate comparison – angiography

Reference	Reason for exclusion
Wu 2016[215]	No relevant outcome - health economic study
Yuan 2005[216]	Inappropriate comparison – reference standard not reported
Zhang 2013[217]	incorrect population – patients with vasospasm
Zhao 2016[218]	Inappropriate comparison - angiography

I.21 Diagnostic strategies

2 **Table 25: Studies excluded from the clinical review**

Reference	Reason for exclusion
Adams Jr 1983[3]	Inappropriate comparison – no relevant outcomes
Agid 2010[4]	Inappropriate comparison – no relevant outcomes
Alfaro 1995[6]	Inappropriate population – CT for emergency medicine
Andaluz 2008[8]	Inappropriate comparison – no relevant outcomes
Anderson 1997[9]	Inappropriate comparison – no relevant outcomes
Anzalone 2015[10]	Inappropriate comparison – no relevant outcomes
Bakker 2014[16]	Inappropriate comparison – no relevant outcomes
Bakr 2017[17]	Inappropriate comparison – no relevant outcomes
Carpenter 2016[28]	Systematic review – references checked
Chappell 2003[33]	Inappropriate study design – unclear methodology
Chaudhary 2008[34]	Inappropriate comparison – no relevant outcomes
Chu 2014[39]	Systematic review – references checked
de Falco 2004[48]	Inappropriate comparison – importance of early detection of headache
Delgado Almandoz 2012[49]	Inappropriate comparison – no relevant outcomes
Ditta 2013[52]	Inappropriate comparison – no relevant outcomes
Dsouza 2018[55]	Inappropriate comparison – no relevant outcomes
Dubosh 2016[56]	Systematic review – references checked
Fiebach 2004[66]	Inappropriate comparison – no relevant outcomes
Gamal 2015[68]	Inappropriate study design – unclear methodology
Gill 2018[74]	Inappropriate comparison – no relevant outcomes
Guo 2014[81]	Systematic review – references checked
Hashimoto 2000[86]	Inappropriate comparison – no relevant outcomes
Hattingen 2008[87]	Inappropriate comparison – DSA compared to MRI
Heasley 2005[89]	Inappropriate comparison – no relevant outcomes
Heit 2016[90]	Inappropriate comparison – DSA compared to CTA
Hochberg 2011[92]	Inappropriate comparison - assessing accuracy of reviewer
Hon 2009[93]	Inappropriate comparison - developmental venous abnormalities
Jager 2000[102]	Inappropriate comparison – no relevant outcomes
Jayaraman 2004[103]	Inappropriate comparison – incorrect reference standard
Kalra 2015[107]	Systematic review – references checked
Kangasniemi 2004[108]	Inappropriate comparison – no relevant outcomes
Kokkinis 2008[117]	Inappropriate comparison – no relevant outcomes
Kucukay 2012[118]	Inappropriate comparison – comparison between two DSA types
Lai 1999[121]	Inappropriate comparison – no relevant outcomes
Li 2014[124]	Inappropriate comparison – no relevant outcomes
Malabarey 2013[131]	Inappropriate study design – review article

Reference	Reason for exclusion
McCormack 2012[141]	Inappropriate study design – commentary article
Rinkel 1991[173]	Inappropriate comparison – no relevant outcomes
Romner 1989[174]	Incorrect comparison – MRI for neurobehavioral functioning
Sadigh 2018[177]	Inappropriate comparison – no relevant outcomes
Savitz 2008[185]	Inappropriate study design – review / editorial
Sayer 2015[186]	Inappropriate comparison – no relevant outcomes
Sidman 1996[188]	Unclear reference standard
Steffens 2018[189]	Inappropriate study design – review article
Taylor 2016[194]	Inappropriate study design – case report / economic paper
Tulla 2018[197]	Inappropriate comparison – no relevant outcomes
Wallace 2013[205]	Inappropriate comparison – no relevant outcomes
Watson 2008[208]	Inappropriate comparison – assessment of fluid ferritin levels
Westafer 2016[209]	Incorrect study design – review article
Woodfield 2014[214]	Inappropriate study design – unclear methodology

I.3 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 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 26: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.1 Diagnostic accuracy

Research question: What is the relative accuracy of CT head scans at different time intervals, for example 12 hours or 24 hours after symptom onset, to diagnose subarachnoid haemorrhage?

Why this is important:

In current practice, people with suspected aSAH are investigated with non-contrast CT head scan, followed by lumbar puncture (LP) and analysis of cerebrospinal fluid if the diagnosis remains uncertain. LP is an invasive procedure and exposes the person to associated risks.

Evidence suggests that the sensitivity of CT head scan decreases over time, but a CT head scan within 6 hours of symptom onset can safely rule out SAH and obviate the need for LP. The diagnostic accuracy of non-contrast CT head scan and need for LP at later time points (within 12 or 24 hours) is uncertain.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults (16 and older) with suspected SAH. Index test: Non-contrast CT head scan within 12 hours and within 24 hours of ictus. Reference standard: A final clinical diagnosis of SAH (based on subarachnoid blood on CT head scan, indication of SAH on analysis of cerebrospinal fluid, or presence of aneurysm on cerebral angiography). Outcome: Sensitivity, specificity, negative predictive value, positive predictive value.
Importance to patients or the population	If the diagnostic accuracy of non-contrast CT head scan within specified time intervals of ictus is high, lumbar puncture would not be required to confirm the diagnosis. This could reduce the number of patients exposed to the risks of lumbar puncture and would facilitate earlier appropriate management.
Relevance to NICE guidance	Evidence about the diagnostic accuracy of non-contrast CT head scan at additional time points may influence future NICE guidance and further reduce the need for lumbar puncture in people with suspected SAH.
Relevance to the NHS	If the diagnostic accuracy of non-contrast CT head scan within specified time intervals of ictus is high, lumbar puncture would not be required to confirm the diagnosis. This could reduce morbidity associated with lumbar puncture, lead to earlier confirmation of the diagnosis, reduce length of hospital stay. It would also therefore likely reduce costs, thus resulting in a positive resource impact.
National priorities	None
Current evidence base	The current evidence base suggests that the diagnostic accuracy of non-contrast CT head scan in people with suspected SAH is high within 6 hours of ictus, but there is uncertainty about diagnostic accuracy at later time points.
Equality	None
Study design	Cross-sectional or cohort study
Timeframe	2 years
Feasibility	The study is feasible and could be carried out within a reasonable timescale.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

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