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Final Report

Management of sudden onset severe headache presenting to the Emergency Department: a systematic review and qualitative study (NIHR200486)

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Scientific summary

Background

Sudden onset severe headache may be caused by a primary headache disorder or may be secondary to a more serious problem, such as subarachnoid haemorrhage (SAH). Very few patients who present to an Emergency Department (ED) with headache have suffered a SAH, but early identification is important to reduce the risk of death or severe disability. While many patients who have suffered SAH present to the ED with stroke-like symptoms, diagnosis is particularly challenging in alert, neurologically intact adults presenting with acute headache. Clinical features separating these patients from higher volume complaints with similar presentation (e.g. migraine) are often unreliable indicators of who requires further investigation. Existing guidelines recommend non-contrast computed tomography (CT) of the brain followed by lumbar puncture (LP) to exclude SAH in headache patients. However, guidelines pre-date the introduction of more sensitive CT scanners, in addition, LP can cause complications and has significant resource consequences.

Objectives

The aim of this project was to establish a clinically effective and acceptable care pathway for the management of neurologically intact adult patients who present to the ED with sudden onset severe headache with a clinical suspicion of SAH. Interventions of interest included specific diagnostic tests and clinical decision rules used for ruling out SAH in patients presenting with sudden onset severe headache.

The objectives were:

(1) To undertake a systematic review to assess the effectiveness of different care pathways for excluding SAH in neurologically intact adult patients presenting to hospital with sudden onset severe headache.

(2) To undertake a qualitative study to explore patient views and experiences of the management of headache in the ED and the acceptability of care pathways.

Methods

We undertook a systematic review of the effectiveness of different care pathways for patients presenting to hospital with sudden onset severe headache. Eighteen electronic databases were searched in February 2020 for studies of neurologically intact patients presenting to hospital with non-traumatic sudden onset severe headache (reaching maximum intensity within one hour) with a clinical suspicion of SAH. Studies had to assess a care pathway for ruling out SAH, including clinical decision rules and diagnostic tests. Studies were assessed for quality using criteria relevant to the study design. The majority of studies were assessed using the QUADAS-2 tool for diagnostic accuracy studies. Economic studies were assessed using the Drummond checklist. Other study designs were assessed using quality assessment tools specifically developed for the review. Where sufficient information was reported, diagnostic accuracy data were extracted into 2x2 tables to calculate sensitivity, specificity, false-positive and false-negative rates. Where equivalent diagnostic strategies or tools were used in three or more studies, hierarchical bivariate meta-analysis was used to synthesise results. Where results could not be pooled due to insufficient reporting, they were synthesised narratively. Systematic reviews, economic studies and clinician surveys were synthesised narratively.

The qualitative study was severely affected by the COVID-19 pandemic. Changes to the clinical pathway and local and national restrictions greatly affected patient recruitment and the number of patients presenting to hospital with sudden onset severe headache. As a result, we were unable to conduct the qualitative study.

Patient and clinician engagement

The project team included four clinicians with expertise in emergency medicine, acute medicine, neurology, stroke and headache, and a patient collaborator with experience of presenting to the ED with sudden onset severe headache. Three additional patients who presented to the ED at Leeds Teaching Hospitals NHS Trust with sudden onset severe headache and additional clinicians with expertise in emergency medicine, acute medicine, neurology, neuroradiology and an NHS commissioner were recruited to our advisory group. The patients' and clinicians' perspective were collected at various points through the project including at team meetings, during protocol development and when interpreting the results of the systematic review and drawing conclusions.

Results

A total of 15,750 records were identified, of which 316 were ordered for full paper screening; 51 studies were eligible for inclusion in the review. There were 37 cohort/before and after studies, four cost-effectiveness studies, three systematic reviews and seven clinician surveys, described below.

Cohort/before and after studies

Twelve studies had a low risk of bias for all domains, the other 25 were at risk of bias.

Thirteen studies assessed the clinical decision rules developed by Perry and his team in Canada. Perry *et al.* developed three clinical decision rules (Rules 1, 2 and 3) in a large prospective cohort study published in 2010, these rules were also assessed in four smaller retrospective cohort studies from the UK and Australia. Perry *et al.* then refined Rule 1 to develop the Ottawa SAH Rule in 2013. The Ottawa SAH Rule states that alert patients ≥15 years old with new severe atraumatic headache, reaching maximum intensity within 1 hour, require investigation if one of the following findings are present: age ≥40, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache (instantly peaking pain) or limited neck flexion on examination. Perry validated the Ottawa SAH Rule in another large prospective cohort study in 2017; it was also assessed in six smaller retrospective cohort studies from the UK, the USA, Hong Kong, Taiwan and Australia. In 2020 Perry *et al.* undertook a large prospective before and after study to assess both the Ottawa SAH Rule and the 6-hour CT rule, although there is likely to be some patient overlap between this study and Perry's 2017 validation study. Eight studies (including the cohort used to derive the Ottawa SAH Rule, Perry 2013) with a total of 8114 patients were pooled; the overall prevalence of SAH in these studies ranged from 1.6% to 10% with a population-weighted mean prevalence of 4.99%. Sensitivity estimates were 100% in all but one study (conducted in Hong Kong) but specificity estimates varied widely from 8 to 44%. The pooled sensitivity across the eight studies was 99.5% (95% CI 91 to 100) and pooled specificity was 24% (95% CI 16 to 34), the pooled false positive rate (FPR) was 76% (95% CI 66 to 84). Therefore, whilst the Ottawa SAH Rule is very sensitive for identifying SAH patients, the high FPR suggests that it's use would result in around 76% SAH-negative patients potentially undergoing further investigation with CT and/or LP unnecessarily, resulting in greater healthcare resource use and higher rates of adverse events related to LP and CT exposure. There was considerable heterogeneity in the FPR which may have been due to study population differences or inconsistent application of the Ottawa SAH Rule; retrospective application of the rule may have varied according to the quality of patient records reviewed. No studies assessed the accuracy of the Ottawa SAH Rule in patient subgroups by time to headache peak, such as the subgroup of patients

with 'thunderclap headache', which peaks within one minute and is more likely to be caused by SAH than headache that takes longer to peak. There were no studies of other clinical decision rules for SAH.

The diagnostic accuracy of CT was assessed in nine studies, although three Canadian studies had significant patient overlap so only the largest study was included in the meta-analysis. Four studies (from Canada, the Netherlands and Spain) presented diagnostic accuracy data for CT undertaken within 6 hours of headache onset, with CT images assessed by a neuroradiologist or radiologist who routinely interprets brain CT images; pooled sensitivity was 99.2% (95% CI 93 to 100) and specificity was 100% (95% CI 99.0 to 100). Around 1018 patients (95% CI 112 to 9807) may need to undergo additional testing to identify one case of SAH in patients who were classed as negative by CT undertaken within 6 hours. Three studies (from Canada, the Netherlands and the UK) assessed CT regardless of time interval; pooled sensitivity was 94% (95% CI 91 to 96) and pooled specificity was 100%. Two studies reported diagnostic accuracy data for CT undertaken beyond 6 hours of headache onset; 85.7% and 90%.

The diagnostic accuracy of LP (CSF analysis using either visual inspection or spectrophotometric assessment) was assessed in 11 studies from Canada, the UK, the USA, Sweden, Spain and the Netherlands. Most studies recruited patients who had a normal CT scan result, therefore, the prevalence of SAH was very low in most studies. Visual inspection for xanthochromia had a pooled sensitivity of 85% (95% CI 60 to 95) for detecting SAH and a pooled specificity of 98% (95% CI 95 to 99); 3 studies reported sufficient data for pooling (population weighted prevalence of SAH 2%). Spectrophotometric inspection of CSF (UK NEQAS) had a pooled sensitivity of 100% and pooled specificity of 95% (95% CI 86 to 98); 3 studies (population weighted prevalence of SAH 0.65%). Two studies reported rates of LP-related complications; in one study 9.5% patients returned to the ED with post-LP headache and one study reported that 5.3% of patients had LP-related complications resulting in a return visit to the ED or hospitalisation.

The pathway of non-contrast CT followed by LP was assessed in six studies from Canada, the UK, Spain, Italy and the Netherlands. Only one study reported sufficient information to reconstruct 2x2 tables, so it was not possible to undertake bivariate meta-analysis for the CT-LP pathway. The pathway was highly sensitive for detecting SAH, although specificity was quite low in some studies, owing to the high false-positive rate for LP. The pathway also identified other significant pathologies, such as intracerebral haemorrhage, brain tumour, and meningitis.

Two Dutch studies assessed CT angiography (CTA) after normal CT/LP; no cases of SAH were identified, although 6-19% patients had a vascular abnormality identified, including aneurysm, cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, cervical dissection and ischemia.

Three studies assessed patient assessment using history and examination. A Canadian study and a UK study investigated the adequacy of patient assessment for SAH and a Dutch study assessed neurologic examination for neck stiffness as a predictor of SAH. Using physicians' clinical suspicion (without the use of a clinical decision rule) resulted in missed cases of SAH. Neurologic examination for neck stiffness was a poor predictor of SAH (sensitivity 67%, specificity 89%). Adequacy of recording of history and complete examination in medical records was poor.

Cost-effectiveness studies

The four cost-effectiveness studies modelled different diagnostic strategies (LP, CTA, MRI/MRA or no further follow-up) for patients presenting with thunderclap headache who had a negative CT result. The results suggest that LP is likely to be the most effective and cost-effective strategy, however, all four studies had specific quality issues and were undertaken from a US Medicare perspective, limiting their reliability and relevance to UK decision makers.

Systematic reviews

Three SRs of variable quality were included. A review with a low risk of bias assessed specific headache and patient characteristics, physical examination, CSF analysis, CT and clinical decision rules for SAH; the review was published in 2016, therefore, includes fewer studies assessing diagnostic tests/decision rules than our review. The review found that a history of neck pain and neck stiffness on examination were the individual findings most strongly associated with SAH, that CT within 6 hours was highly accurate and that CSF analysis had lower diagnostic accuracy. They concluded that LP appears to benefit relatively few patients and that clinical decision rules to identify subsets of patients most likely to benefit post-CT LP await external validation.

A review with an unclear risk of bias assessed CT within 6 hours of headache onset; not all studies restricted their inclusion criteria to neurologically intact patients with sudden onset severe headache, therefore, findings may not be generalisable to our population of interest. CT within 6 hours of headache onset was found to be extremely sensitive for ruling out aneurysmal SAH.

The other review was conducted to derive American College of Emergency Physicians clinical policy and not all included studies met our review inclusion criteria; the review had a high risk of bias. The review concluded that the only risk stratification that reliably identifies the need for neuroimaging is the Ottawa SAH Rule, but that it has poor specificity, that CT performed within 6 hours of symptom onset is sufficient to preclude further diagnostic workup for SAH and that CTA appears to be a reasonable alternative to LP to safely rule out SAH.

Clinician surveys

Seven surveys explored clinicians' approach to the investigation of patients with sudden onset severe headache. One UK-based survey of unclear quality reported that ED clinicians had a higher risk tolerance for missed SAH diagnosis than neurospecialists, with neurospecialists more likely to advocate routine LPs compared with ED clinicians. Two poor quality UK-based surveys assessed knowledge of acute headache management amongst emergency and acute medicine clinicians and the need for a guideline; 95% of respondents in one of the surveys indicated that they would find a Trust acute headache guideline useful, whilst only 22% of respondents in the other survey were aware of a local protocol for the investigation of acute headache. A large, good quality survey of ED clinicians from Australia, Canada, the UK and the USA aimed to determine ED practice for investigating acute headache and whether clinicians would consider using a clinical decision rule; responses varied between countries and 96% reported that they would consider using a well-validated clinical decision rule to determine the need for investigations to rule out SAH. A good quality survey of ED clinicians in the USA and Canada assessed knowledge of headache management and adherence to clinical policy; responses varied according to site, academic setting and experience level. One Australian survey of unclear quality interviewed ED clinicians to identify factors that influenced their decisions about diagnostic testing for headache patients after a normal brain CT; patient interaction/preference was at the forefront of the identified factors. A poor quality Australian survey of ED clinicians and trainees assessed ED practice on several aspects of the investigation of acute headache.

Patient and clinician engagement

Clinical and patient members of the project team and advisory group were unsurprised by the findings relating to the diagnostic accuracy of CT, LP and the Ottawa SAH Rule. They highlighted the importance of involving the patient in the decision of whether additional testing is required after a negative CT result; communicating the level of certainty in the diagnostic test result and possible adverse effects of subsequent diagnostic tests to aid the decision-making process. Clinicians also discussed the variation in practice regarding inpatient versus ambulatory LP; two patient advisors and the patient collaborator expressed a preference for ambulatory LP, if LP was necessary. However, no studies were identified assessing the setting for LP, therefore, further primary research is required to address this question. The difficulties associated with diagnosing SAH in patients who present several days after headache onset was also discussed; there is a lack of guidance and consistency in how these patients are assessed. It was concluded that further primary research is required in order to develop guidance for the assessment of this small patient subgroup.

Conclusions

The evidence suggests that in view of its high false positive rate, the Ottawa SAH Rule does little to aid clinical decision making for sudden onset severe headache patients. Use of the tool would potentially result in around 76% of SAH-negative patients undergoing further investigation with CT and/or LP unnecessarily, resulting in greater healthcare resource use and higher rates of adverse events. There was a lack of data to assess the accuracy of the Ottawa SAH Rule in patient subgroups by time to headache peak. The Ottawa SAH Rule was developed for use in patients whose headache peaked within one hour of onset, however patients who present with 'thunderclap headache', which peaks within one minute, are more likely to have suffered a SAH. There were no studies of other clinical decision rules for SAH. Clinical advisors indicated that a variety of clinical decision rules are used in current NHS practice.

Non-contrast CT undertaken within 6 hours of headache onset, with CT images assessed by a neuroradiologist or radiologist who routinely interprets brain CT images, is highly accurate for identifying SAH. However, in centres without specialist neuroradiology expertise, the accuracy is likely to be lower; studies included in the meta-analysis benefited from neuroradiology expertise. CT undertaken beyond 6 hours from headache onset is much less sensitive for detecting SAH (sensitivity ≤90%). LP (with spectrophotometric CSF analysis using the UK NEQAS protocol) following negative CT was highly sensitive, although there was a 5% rate of false positives. Only two studies reported the rates of LP-related complications resulting in patients returning to the ED or hospitalisation; 5.3% and 9.5%. The pathway of non-contrast CT followed by LP was highly sensitive for detecting SAH, although specificity was quite low in some studies, owing to the high false-positive rate for LP. In view of the reduced sensitivity of CT beyond 6 hours from headache onset, LP may be beneficial in patients who have CT beyond 6 hours, where a clinical suspicion of SAH remains. The CT-LP pathway also identified other significant pathologies, such as intracerebral haemorrhage, brain tumour, and meningitis. Clinician and patient advisory group members emphasised the importance of shared decision making when considering whether subsequent tests should be undertaken after receiving a negative CT result.

Further research is recommended to determine the safety and acceptability of ambulatory LP in those patients who require further assessment after negative non-contrast CT. Further research may be beneficial in order to develop guidance for the assessment of the subgroup of patients who present several days after headache onset.

Study registration

This study is registered as PROSPERO CRD42020173265.

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Plain English summary

It is common for people with severe headaches to seek help at hospital emergency departments, but usually these headaches are not harmful, e.g. migraine. When severe headaches come on instantly, often described as feeling like a 'thunderclap', they can be a sign of a more serious condition.

Subarachnoid haemorrhage (SAH) occurs when a weakened blood vessel supplying the brain suddenly bursts. This can lead to disability or death if not diagnosed and treated quickly, but diagnosis can be difficult in people who don't show signs other than headache.

This project aimed to review all previous research looking at diagnostic strategies and tests for assessing patients with a sudden onset severe headache and summarise how accurate they are.

We found 51 studies on the accuracy of clinical decision rules and diagnostic tests for ruling out SAH in people with sudden severe headaches. Our results showed:

- The Ottawa SAH clinical decision rule was not very good at ruling out SAH, and using it could result in around 75% of headache patients being tested unnecessarily.
- Brain computed tomography (CT) scans done within six hours of headache onset may be accurate enough to find all cases of SAH without the need for more testing, but accuracy drops considerably over time.
- Lumbar puncture after CT finds any missed cases of SAH (as well as other serious conditions, such as stroke, cancer and meningitis), but 5% of results were false positives, and 5-10% of patients returned to hospital with side effects.

The decision to do more tests after a negative CT scan result should be shared between the doctor and the patient. Our patient advisors said they would prefer lumbar puncture to be done without admission to hospital, but more research is recommended to prove the safety of outpatient lumbar puncture.

List of abbreviations

BP	Blood pressure
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
ED	Emergency Department
FNR	False negative rate
FPR	False positive rate
GCS	Glasgow Coma Scale
LP	Lumbar puncture
LR	Likelihood ratio
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NNT	Number needed to test
QALYs	Quality adjusted life years
RBC	Red blood cell
SAH	Subarachnoid haemorrhage
UK NEQAS	UK National External Quality Assessment Service

1 Background

1.1 Description of the underlying health problem

Non-traumatic acute headache accounts for between 0.5 and 4.5% of adult Emergency Department (ED) attendances,[1-7] with around 15% of these being thunderclap headache.[3] Data from NHS England report that there were 15.4 million attendances at EDs in total in 2016,[8] suggesting that in England there are up to 690,000 ED attendances for non-traumatic headache and up to 100,000 ED attendances for thunderclap headache each year.

Sudden onset severe headache, including thunderclap headache (reaching maximum intensity within a minute), may be caused by a primary headache disorder, or may be secondary to a more serious underlying pathology, such as subarachnoid haemorrhage (SAH). Around 1-3% of patients who present to an ED with headache[1, 9, 10] and around 11% of patients who present with thunderclap headache[11] are diagnosed with SAH.

SAH refers to bleeding into the space between the pial and arachnoid membranes around the brain. It can be the result of head trauma or spontaneous haemorrhage, often caused by a rupture of a cerebral aneurysm (abnormal bulge in an artery).[12] Aneurysmal SAH is associated with a poor prognosis, early diagnosis is an important determinant of outcomes; without prompt treatment, approximately 25-30% of patients suffer re-bleeds within weeks, often resulting in death or severe disability.[12-14] Treatment options for aneurysmal SAH include neurosurgical clipping and endovascular coiling of the aneurysm, although outcomes are poor in up to a third of patients, despite treatment.[15]

While many patients who have suffered SAH present to the ED with stroke-like symptoms, or loss of consciousness, diagnosis is particularly challenging in alert, neurologically intact adults presenting with acute headache. Clinical features separating these patients from higher volume complaints with similar presentation (e.g. migraine) are often unreliable indicators of who requires further investigation.

1.2 Description of current NHS service provision

In order to exclude SAH in patients presenting with severe headache, existing guidelines recommend non-contrast computed tomography (CT) of the brain, followed by lumbar puncture (LP) if the CT result is negative for SAH.[16-20] However, existing guidelines for the management of headache are several years old and pre-date the introduction of more sensitive modern CT scanners and clinical decision rules for ruling out SAH.

A recent meta-analysis of the diagnostic accuracy of early CT (within 6 hours of symptom onset) for the diagnosis of spontaneous SAH, using a modern generation multidetector CT scanner, reported overall sensitivity of 98.7% and specificity of 99.9%.[21] This high diagnostic accuracy raises concerns about the value of LP in CT negative patients. However, the accuracy of CT is partly dependent on radiologist expertise; local hospitals are less likely to have specialist neuroradiologists available to review CT scan results. There is also variation in CT hardware and software across the UK, which will impact on image quality, sensitivity and specificity. In addition to diagnosing or excluding SAH, non-contrast brain CT may show evidence of other serious causes of headache, such as intracranial haemorrhage or cerebral oedema.[13]

Patients who undergo LP are generally admitted to hospital until LP has been performed and results are available. LP should be performed a minimum of 12 hours after onset of the headache, but remains a useful indicator of SAH for up to 2 weeks, although sensitivity declines over time.[22] Whilst

the sensitivity of LP for the investigation of SAH is very high, specificity is lower, owing to potential contamination of the cerebrospinal fluid (CSF) sample when undertaking the LP. CSF analysis may provide diagnostic information for other causes of headache, such as meningitis. However, LP can be associated with complications such as cerebral and spinal herniation, headache, low back pain and infections.[23, 24xxxx]

In addition to the risk of complications, the use of LP following negative CT has significant resource consequences. Patients are often admitted to hospital until 12 hours have elapsed since headache onset before LP can be undertaken. LP is associated with increased rates of hospital admission, prolonged length of stay and higher management costs.[10] EDs in England have been managing increased levels of demand over recent years; unnecessary and potentially harmful LP procedures may serve only to increase the system resource burden. The high sensitivity of CT means that the vast majority of patients who have a negative CT scan require no further hospital treatment, with diagnoses of primary headache disorders such as migraine or tension-type headache. This has led a number of research studies to question the therapeutic value of this diagnostic strategy.[9, 25, 26] There is also evidence of variation in current NHS practice and inconsistent application of the recommended practice of CT followed by LP, as shown in a recent survey of ED consultants and neurospecialists.[27]

In view of this, and the potentially low therapeutic value and complications associated with LP following negative CT, updated evidence-based guidance is needed. It is important to identify which patients presenting to the ED with sudden onset severe headache may benefit from LP, and in which patients SAH can be safely ruled out based on CT alone.

1.3 Aim and objectives

The aim of this research was to establish a clinically effective and acceptable care pathway for the management of neurologically intact adult patients who present to the ED with sudden onset severe headache with a clinical suspicion of SAH. Interventions of interest included specific diagnostic tests and clinical decision rules used for ruling out SAH in patients presenting with sudden onset severe headache.

The objectives were:

1) To undertake a systematic review to assess the clinical effectiveness and cost-effectiveness of different care pathways for excluding SAH in neurologically intact adult patients presenting to an ED with sudden onset severe headache with a clinical suspicion of SAH.

Specifically, we aimed to assess the following aspects of the care pathway:

The diagnostic accuracy of different clinical decision rules for determining which patients require assessment to rule out SAH.

The accuracy of specific diagnostic tests for ruling out SAH in those patients who require assessment, such as LP and CT scan, taking into consideration potential issues which may impact diagnostic accuracy, such as the age of the CT scan technology and hardware/software used, radiologist expertise and time since headache onset.

The research also aimed to assess alternative care pathways, such as LP provided on an ambulatory basis for those patients who require LP.

2) To undertake a qualitative study with patients who have presented to an ED with sudden onset severe headache to explore the acceptability of care pathways to patients, and patients' experiences of the management of headache in the ED.

2 Methods of the systematic review

A systematic review of clinical and cost-effectiveness evidence on diagnostic strategies for patients presenting to the ED with sudden onset severe headache was undertaken. The review was conducted according to the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance on undertaking reviews[28] and is reported according to the general principles of the PRISMA statement.[29] The research protocol was registered on PROSPERO, the international database of prospectively registered systematic reviews in health and social care (http://www.crd.york.ac.uk/prospero/), as CRD42020173265.

2.1 Literature searches

Systematic searches of published and unpublished literature were undertaken to identify studies relating to the management of patients with sudden onset severe headache, suspicious of SAH, presenting to the ED. An information specialist (MH) developed the search strategy in Ovid MEDLINE. The strategy consisted of terms for headache combined with terms for either SAH or ED. Free text terms and subject headings for each concept were gathered by analysing key studies identified through scoping searches, searching the thesaurus of each database for relevant subject headings, and through consultation with the review team and clinical experts. No date or language limits were applied.

The MEDLINE search strategy was adapted for use in all other databases searched. The following databases were searched on 10th February 2020: MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Wiley), Database of Abstracts of Reviews of Effects (CRD databases), Cochrane Database of Systematic Reviews (Wiley), Health Technology Assessment database (CRD databases), Science Citation Index (Web of Science), NHS EED (CRD databases) and Econlit (Ovid).

Resources containing unpublished literature were also searched. To identify any ongoing or completed but unpublished studies ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, the EU Clinical Trials Register and the Conference Proceedings Citation Index – Science (Web of Science) were searched. In addition, PROSPERO was searched to identify any unpublished or ongoing reviews. Relevant guidelines were identified through searches of the following websites: NHS Evidence, NHS Clinical Knowledge Summaries, ECRI Guidelines database and the Trip database.

Search strategies for all databases and resources are presented in Appendix 1 (Section 8).

In addition to searching electronic sources, reference lists of relevant systematic reviews, guidelines and included studies were screened and clinical advisors were consulted to identify additional studies.

Update searches were planned to be conducted in August 2020. However, owing to urgent work relating to COVID-19, the information specialist was unable to undertake update searches at that time. Therefore, all clinical members of the project team and advisory group were consulted in August 2020 regarding any relevant recent studies they were aware of. In addition, Dr Jeff Perry, Department of Emergency Medicine, University of Ottawa, who was involved in several studies included in the systematic review, was also consulted in August 2020.

2.2 Study selection

Two researchers (MW and RW) independently undertook the screening of titles and abstracts of identified studies using the pre-defined eligibility criteria outlined in Section 2.3. Records were

screened using the Rayyan QCRI web application and researchers were blinded to each other's decisions whilst undertaking screening.[30]

Full manuscripts of potentially relevant studies were obtained, where possible, and independently screened by two researchers. MW and RW undertook the majority of full paper screening, although RH (Health Economist) was involved in screening full papers of economic studies. Disagreements at each stage of the study selection process were resolved through discussion. Authors of potentially relevant conference abstracts were contacted for additional information, where contact details were available. Relevant foreign language studies were translated and included in the review.

2.3 Inclusion and exclusion criteria

The systematic review adopted broad criteria to ensure all relevant evidence was considered. Whilst thunderclap headache is defined as a severe headache that peaks within one minute, the review inclusion criteria were broader, to include patients whose headache reached maximum intensity within an hour (consistent with previous research on clinical decision rules to rule out SAH).[31, 32] Patients may be referred directly from primary care to a medical assessment unit with sudden onset severe headache suspicious of SAH, therefore, studies assessing patients who presented to other hospital departments were also considered for inclusion, rather than restricting to patients who presented to the ED.

Participants: Neurologically intact, alert adult patients presenting to hospital with sudden onset severe headache (reaching maximum intensity within one hour), with a clinical suspicion of SAH. Studies of patients who had suffered a head injury (i.e. traumatic headache) were excluded.

Interventions: Any care pathway for ruling out SAH in such patients, including clinical decision rules and specific diagnostic tests, such as CT or LP. International studies in which the intervention was relevant to UK practice were included.

Comparator: Any or no comparator.

Outcomes: Outcomes of interest included the diagnosis of SAH and other significant neurological diagnoses (including diagnostic test accuracy, where sufficient data were reported to calculate test accuracy), surgical intervention received, quality of life (including quality adjusted life years), mortality, adverse events, patient preference, admission/discharge rates, re-attendance rates (due to the original headache or adverse effects of LP or other diagnostic test) and cost-effectiveness. Of particular interest was the diagnosis of aneurysmal SAH that is potentially operable, rather than small non-aneurysmal bleeds that are not amenable to surgical intervention.

Study designs: Any primary study design (other than single case studies). We planned to restrict the selection criteria to larger case series (over 100 patients) in order to focus on the more robust studies, in the event that we identified a large number of case series. Up to date systematic reviews and economic evaluations were also included.

2.4 Data extraction

A data extraction form was developed, piloted on a sample of studies and refined. Data extraction was undertaken by one researcher and independently checked by a second researcher for accuracy, with any discrepancies resolved by discussion. MW and RW undertook the majority of data extraction and checking, although RH (Health Economist) checked all economic studies. In cases of multiple

publications of the same study, the publication with the largest sample, most complete reporting, or longest follow-up was data extracted.

Data were extracted on study methods (including study design, country and setting), patient characteristics (including dates of recruitment, description of headache, timeframe from headache onset to maximum intensity and timeframe from headache onset to presentation to hospital), intervention characteristics (including details of the intervention and whether it was applicable to NHS practice), outcome measures (primary and secondary outcomes assessed and timepoint) and results (diagnostic accuracy 2x2 tables were produced where sufficient data were reported). Where results were missing or limited (e.g. conference abstracts) authors were contacted to request additional data, where contact details were available. Data extraction was undertaken using Microsoft Word.

2.5 Quality assessment

The quality assessment of included studies was conducted as part of the data extraction process using criteria relevant to the study design. The majority of cohort/before and after studies were assessed using the QUADAS-2 tool for diagnostic accuracy studies.[33] The QUADAS-2 tool was not appropriate for some of the cohort/before and after studies where a reference standard test was not used, therefore, a quality assessment tool was developed specifically for the review. The quality of the identified economic and decision modelling studies was assessed according to an updated version of the checklist developed by Drummond *et al*.[34] Quality assessment tools for systematic reviews and clinician surveys were developed specifically for the review. Further details are presented below.

The QUADAS-2 tool was tailored specifically for the review and review-specific guidance was developed, as described below.

Domain 1: Patient selection – risk of bias. Several prospective studies intended to enrol consecutive patients but were unable to do so; reasons included lack of patient consent or the study form not being completed by the treating physician. Some retrospective studies intended to enrol consecutive patients but were unable to do so because the required data were missing from medical records. Where the characteristics of the 'missed potentially eligible' patients were reported to be similar to those of the included patients and there were no apparent inappropriate exclusions, then the risk of bias was considered to be 'low'. Where characteristics of 'missed potentially eligible' patients differed from the included patients and the study appeared to have inappropriately excluded patients then the risk of bias was considered 'high'.

Domain 1: Patient selection – concerns regarding applicability. When studies did not report specific details relating to the time to peak intensity of the headache, it was considered 'unclear' whether the included patients matched the review question (neurologically intact patients presenting with sudden onset severe headache peaking within an hour).

Domain 2: Index test – risk of bias. The option 'not applicable' was added to the question 'if a threshold was used, was it pre-specified?' as some of the tests assessed do not have a test threshold (such as the Ottawa SAH Rule).

Domain 2: Index test – concerns regarding applicability. For studies that retrospectively applied the Ottawa SAH Rule using medical records, the applicability concern was considered 'unclear' when it was not clear whether all relevant data were available in the medical records to retrospectively apply the Ottawa SAH Rule. If it was clear that much of the required data were missing, then the concern was considered 'high'.

Domain 3: Reference standard – risk of bias. The option 'not applicable' was added to the question 'were the reference standard results interpreted without knowledge of the index test results?' as often the choice of reference standard depends upon the result of the index test; for example it would be unethical to continue to perform certain diagnostic tests on a patient with a positive CT scan result.

Domain 3: Reference standard – concerns regarding applicability. When the conduct of the reference standard differed from standard NHS practice then the level of applicability concern was considered 'high'. For example, studies of lumbar puncture where xanthochromia was assessed using visual inspection, since spectrophotometry is used in NHS practice.

Domain 4: Flow and timing – risk of bias. The question 'did all patients receive the same reference standard' was not considered to be a key question, when deciding the overall risk of bias for Domain 4. As stated above, it would be unethical to perform certain diagnostic tests (e.g. LP) when they are not clinically required. For patients with a non-diagnostic CT and LP, clinical follow-up (either by telephone or medical record review) for more than a month was considered acceptable; up to 2% patient loss to follow-up was considered to be acceptable.

For studies without a reference standard test, where the QUADAS-2 tool was not appropriate, a quality assessment tool was developed and piloted, including questions relating to: the clarity of participant inclusion criteria; representativeness of the selected sample; similarity of groups at baseline (if applicable); clarity of description and consistency of delivery of the intervention; reliability and consistency of methods of outcome assessment; attrition; and duration of follow-up. Each study was given an overall risk of bias judgement; studies that had a low risk of bias for all key domains were judged to have a low overall risk of bias. Studies that had a high risk of bias for one or more key domains were judged to have a high overall risk of bias, and studies that had an unclear risk of bias (and no high risk of bias) for one or more key domains were judged to have an unclear overall risk of bias. Key domains were the representativeness of the selected sample, clarity of description and consistency of delivery of the intervention, reliability and consistency of methods of outcome assessment, attrition and duration of follow-up.

The quality of the identified economic and decision modelling studies was assessed according to an updated version of the checklist developed by Drummond *et al*.[34] This tool assesses whether the study was designed to properly address the decision problem presented. Domains encompass the appropriateness and completeness of the model's inputs (in terms of data on costs and effectiveness) and structural assumptions (e.g. relevance of chosen comparisons, model design, discounting, time horizon), whether uncertainty was properly accounted for, and whether outcomes are presented in an appropriate way that is relevant to NHS practice.

A quality assessment tool for systematic reviews was developed and piloted. It included questions relating to: clarity of the research question and inclusion criteria; adequacy of the search strategy; reporting of study selection process (PRISMA diagram); adequacy of reporting of details of included studies; appropriateness of quality assessment; appropriateness of synthesis; and consistency of conclusions with synthesis. Again, studies were given an overall risk of bias judgement. Key domains were the adequacy of the search strategy, clarity of reporting of the study selection process, appropriateness of quality assessment, synthesis and conclusions.

A quality assessment tool for assessing clinician surveys was developed using a guide for appraising survey reports developed by Burns and Kho.[35] It included questions relating to: clarity of the research question; representativeness of the sample; systematic development of the survey; testing/piloting of

the survey; administration of the survey; sample size/response rate; and reporting of results. Again, studies were given an overall risk of bias judgement, based on all criteria assessed.

2.6 Data synthesis

Characteristics of the included studies are summarised in Section 3.2 of this report and tabulated in Appendix 3 (Section 8). Quality assessment results are discussed in Section 3.3 and tabulated in Appendix 4 (Section 8). The results for the different care pathways, clinical decision rules and diagnostic tests assessed in the included studies are presented in separate sections within Section 3.4. The results were interpreted in the context of the quality of the individual studies.

Diagnostic accuracy data were extracted into 2x2 tables from studies where sufficient information was reported. Estimates of sensitivity, specificity, false-positive and false-negative rates were calculated and tabulated. Where appropriate, forest plots were presented to illustrate within- and between-study variability in the accuracy of diagnostic tests and tools.

Where equivalent diagnostic strategies or tools were used in three or more studies, the hierarchical bivariate model described by Reitsma *et al.*[36] was fitted, along with an extension described in Simmonds *et al*.[37] to meta-analyse sensitivity and specificity. Bivariate meta-analytic models account for the correlation between sensitivity and sensitivity inherent to diagnostic studies, but do not account for within-person correlation between test results, e.g. that arising when the same patients are assessed using CT and LP within the same study. The aforementioned extension includes logistic regression analysis to account for the use of multiple tests performed on the same participants. Meta-analyses used standard random-effects DerSimonian-Laird methods. A continuity correction of 0.5 was applied where necessary if no/negligible bias was introduced into the model results.

All analyses were conducted using the *lme4*[38] and *meta*[39] packages in R.[40] Figures were produced using the *ggplot2* package.[41]

Subgroups were identified and analysed separately to account for underlying differences in diagnostic strategies. Most notably, the diagnostic accuracy of CT conducted within 6 hours of headache onset was analysed separately where possible (pre-defined subgroup), as CT accuracy is known to drop rapidly outside of this time frame. The accuracy of different methods of cerebrospinal fluid (CSF) analysis was also assessed, i.e. where samples drawn from LP were assessed using spectrophotometry, or those where only visual inspection was performed. Additional pre-defined subgroups were patients whose headache took longer than five minutes to reach maximum intensity (who are less likely to have suffered SAH) and patients who present with exertional headache (who are more likely to present within 6 hours of headache onset); unfortunately there was insufficient data to undertake subgroup analyses for these subgroups of patients.

If results could not be pooled due to inconsistent or insufficient reporting for feasible meta-analysis, results were synthesised narratively.

Up to date systematic reviews assessing the diagnostic accuracy of specific tests (such as CT and LP), symptoms and clinical decision rules for spontaneous SAH are summarised in a narrative synthesis. Economic studies and clinician surveys are also summarised in a narrative synthesis.

3 Results of the systematic review

3.1 Flow of studies through the systematic review

The electronic searches identified a total of 15,750 records after deduplication between databases. Three hundred and sixteen potentially relevant studies were ordered for full paper screening; one paper was unavailable,[42] therefore 315 records were screened. Two hundred and sixty-four studies were excluded at the full paper stage. Details of these studies, along with the reason for their exclusion, are provided in Appendix 2 (Section 8).

Scanning the reference lists of systematic reviews, guidelines and included studies identified no additional relevant studies. No additional studies were identified from contact with clinical members of the project team and advisory group.

Figure 1 presents the flow of studies through the study selection process. Table 1 presents the 51 studies that were included in the systematic review.

Figure 1 Flow diagram of the study selection process

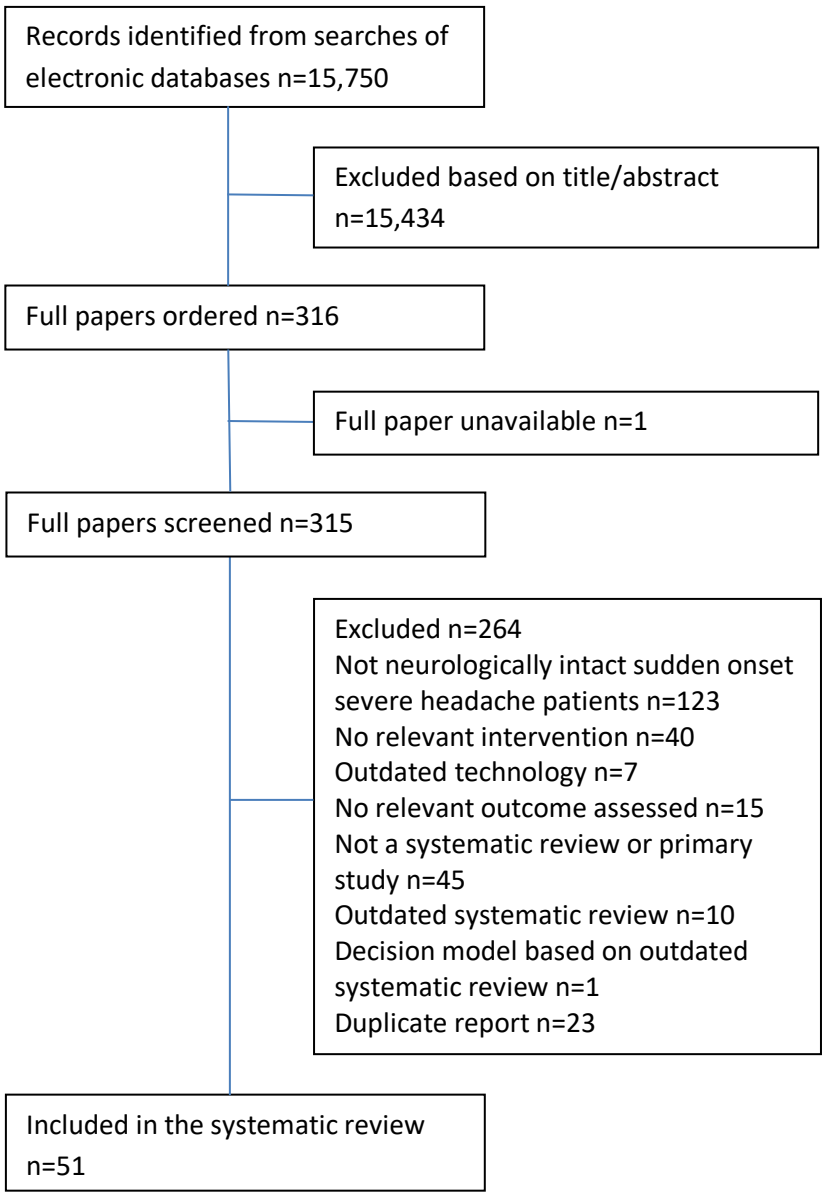


Table 1 Studies included in the systematic review

Study details	Intervention	Study design
Perry, 2010[43] Canada	CT and Canadian clinical decision rules (Rule 1, 2 and 3)	Prospective cohort study
Matloob, 2013[44] UK	Canadian clinical decision rules (Rule 1, 2 and 3) vs current practice	Retrospective cohort study
MacDonald, 2012[45] UK	Canadian clinical decision rules (Rule 1, 2 and 3)	Retrospective cohort study
Kelly, 2014[46] Australia	Canadian clinical decision rules (Rule 1, 2 and 3)	Retrospective cohort study
Perry, 2013[31] Canada	Canadian clinical decision rules (Rule 1, 2 and 3) and the Ottawa SAH Rule	Prospective cohort study
Yiangou, 2017[47] UK	Canadian clinical decision rules (Rule 1, 2 and 3) and the Ottawa SAH Rule vs current practice	Retrospective cohort study
Perry, 2017[48] Canada	Ottawa SAH Rule	Prospective cohort study
Bellolio, 2015[32] USA	Ottawa SAH Rule	Retrospective cohort study
Wu, 2019[49] Taiwan	Ottawa SAH Rule	Retrospective cohort study
Chu, 2018[50] Australia	Ottawa SAH Rule	Retrospective cohort study (sub-study of a prospective cohort study)
Pathan, 2018[51] UK	Ottawa SAH Rule vs current practice	Retrospective cohort study
Cheung, 2018[52] Hong Kong	Ottawa SAH Rule and modified Ottawa SAH Rule	Retrospective cohort study
Perry, 2020[53] Canada	Ottawa SAH Rule and 6-hour CT rule	Prospective before and after study
Perry, 2002[10] Canada	Pathway of CT followed by LP	Retrospective cohort study
Perry, 2008[54] Canada	Pathway of CT followed by LP	Prospective cohort study
Valle Alonso, 2018[55] Spain	Pathway of CT followed by LP	Retrospective cohort study
Cooper, 2016[9] UK	Pathway of CT followed by LP	Retrospective cohort study
Blok, 2015[56] Netherlands	Pathway of CT followed by LP	Retrospective cohort study
Dutto, 2009[57] Italy	Diagnostic protocol of CT followed by LP	Before and after study
Khan, 2017[58] Canada	CT scan (<6 hours, >6 hours)	Secondary analysis of two prospective cohort studies
Perry, 2011[59] Canada	CT scan (<6 hours, >6 hours)	Prospective cohort study
Backes, 2012[60] Netherlands	CT scan (<6 hours, >6 hours)	Retrospective cohort study
Austin, 2018[61] UK	Interpretation of CT scans for SAH by Emergency Physicians	Interim analysis of a retrospective cohort study

Migdal, 2015[62] USA	LP (CSF analysis) after normal CT	Retrospective cohort study
Perry, 2015[63] Canada	LP (CSF analysis) after normal CT	Sub-study of a prospective cohort study
Dupont, 2008[64] USA	LP (CSF analysis) after normal CT	Retrospective cohort study
Sansom, 2014[65] UK	LP (CSF analysis) after normal CT	Retrospective cohort study
Horstman, 2012[66] Netherlands	LP (CSF analysis) after normal CT	Retrospective cohort study
Brunell, 2013[67] Sweden	LP (CSF analysis)	Retrospective cohort study
Gangloff, 2015[68] Canada	Visual inspection of CSF vs spectrophotometry after normal CT	Retrospective cohort study
Perry, 2006[69] Canada	Visual inspection of CSF vs spectrophotometry	Sub-study of a prospective cohort study
Heiser, 2015[70] USA	Validation of a clinical prediction rule to differentiate between traumatic LP and SAH	Retrospective cohort study
Alons, 2015[71] Netherlands	CTA after normal CT/LP	Retrospective cohort study
Alons, 2018[72] Netherlands	CTA after normal CT/LP	Retrospective cohort study and meta-analysis
Locker, 2004[73] UK	Adequacy of history, examination and investigation	Retrospective cohort study
Perry, 2005[74] Canada	Patient assessment made by attending physicians	Prospective cohort study
Backes, 2015[75] Netherlands	Neurologic examination for neck stiffness as a predictor of SAH	Retrospective cohort study
Taylor, 2016[76]	LP versus no follow up	Decision analysis
Wu, 2016[77]	CTA versus LP	Cost-effectiveness analysis
Malhotra, 2016[78]	CTA, LP, no follow up	Cost-effectiveness analysis
Ward, 2012[79]	CT alone, CT followed by LP, CT followed by CTA, CT followed by MRI/MRA	Cost-effectiveness analysis
Dubosh, 2016[21]	CT	Systematic review and meta-analysis
Carpenter, 2016[25]	History, physical examination, CSF analysis, CT and clinical decision rules for spontaneous SAH	Systematic review and meta-analysis
Writing Subcommittee of the American College of Emergency Physicians, 2019[80]	4 different clinical questions relating to risk-stratification strategies, non-opioids for primary headache, non-contrast head CT performed within 6 hours of headache onset, and CTA	Systematic review
Chu, 2019[81] Australia	To identify factors that influence emergency physicians' decisions about diagnostic testing after normal CT	Semi-structured interviews with emergency medicine clinicians

Perry, 2009[82] Australia, Canada, UK and USA	To determine current ED practice for investigating acute headache	Survey of emergency physicians
Lansley, 2016[27] UK	To establish if emergency medicine and neuroscience specialists have different risk tolerances for investigation of suspected spontaneous SAH	Survey of consultants in emergency medicine and neuroscience specialties
Binks, 2017[83] UK	To assess knowledge of acute headache management and the need for a guideline	Survey of doctors of all grades
Rogers, 2014[84] Australia	To establish current ED practice for investigating acute headache	Survey of emergency medicine physicians and trainees
Dobb, 2013[85] UK	To explore the approach of emergency medicine and acute medicine clinicians to the investigation of thunderclap headache	Survey of emergency medicine and acute medicine clinicians
Kumar, 2019[86] USA and Canada	To assess physician knowledge on imaging and LP test performance and assess practice patterns using case-based scenarios	Survey of emergency medicine clinicians

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; CTA, computed tomography angiography; ED, Emergency Department, LP, lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SAH, subarachnoid haemorrhage

3.2 Characteristics of studies included in the systematic review

There were 37 cohort/before and after studies, four cost-effectiveness studies, three systematic reviews and seven clinician surveys included in the systematic review, described below. Details of all included studies are tabulated in Appendix 3 (Section 8).

3.2.1 Cohort/before and after studies

Clinical decision rules

Thirteen studies assessed the Canadian clinical decision rules. Perry *et al*. developed three clinical decision rules (Rules 1, 2 and 3) in a large (n=1999) Canadian prospective cohort study published in 2010.[43] These rules were then assessed in three smaller (n=59 to 280) retrospective cohort studies undertaken in the UK[44, 45] and Australia.[46] Perry *et al*. refined Rule 1 to develop the Ottawa SAH Rule in a large (n=2131) prospective cohort study published in 2013.[31] The four Canadian clinical decision rules are described below; patients require investigation if one or more findings are present.

Rule 1: Age ≥40 years; neck pain or stiffness; witnessed loss of consciousness; onset during exertion.

Rule 2: Age ≥45 years; arrival by ambulance; ≥1 episode of vomiting; diastolic blood pressure (BP) ≥100 mm Hg.

Rule 3: Age 45-55 years; neck pain or stiffness; arrival by ambulance; systolic BP ≥160 mm Hg.

Ottawa SAH Rule: Age ≥40 years; neck pain or stiffness; witnessed loss of consciousness; onset during exertion; thunderclap headache (instantly peaking pain); limited neck flexion on examination.

Perry *et al.* validated the Ottawa SAH Rule in another large (n=1153) prospective cohort study in 2017.[48] The Ottawa SAH Rule was also assessed in five smaller (n=137-913) retrospective cohort studies undertaken in the USA,[32] the UK,[51] Hong Kong,[52] Taiwan[49] and Australia.[50] Another smaller (n=162) UK retrospective cohort study assessed Rules 1, 2 and 3 and the Ottawa SAH Rule.[47] In 2020 Perry *et al.* undertook a large (n=3672) prospective before and after study to assess a physician education programme to encourage the use of both the Ottawa SAH Rule and the 6-hour CT rule,[53] there is likely to be some patient overlap between this study and the study published in 2017.[48]

The overall prevalence of SAH in the studies that recruited alert, neurologically intact, acute non-traumatic headache patients ranged from 1.6%[49] to 10%,[52] although not all SAH patients had aneurysmal SAH. One study only recruited patients with SAH.[46]

No studies of other clinical decision rules for SAH were identified.

Pathway of CT followed by LP

The pathway of CT followed by LP was assessed in a large (n=592) Canadian prospective cohort study,[54] four retrospective cohort studies from Canada,[10] the UK,[9] Spain[55] and the Netherlands[56] (n=85-891) and a small before and after study undertaken in Italy (n=70).[57] The overall prevalence of SAH in the studies that recruited alert, neurologically intact, acute non-traumatic headache patients ranged from 1.1%[10] to 11.8%;[55] the study with the highest prevalence only included patients who presented to the ED within 6 hours of symptom onset. One study only recruited patients with a negative CT result who went on to receive LP, therefore the prevalence of SAH in this study was much lower (0.1%).[56]

CT

The diagnostic accuracy of CT (at any time from headache onset) was assessed in three large Canadian cohort studies; two prospective studies by Perry *et al.* (n=1999 and n=3132)[43, 59] and a secondary analysis of Perry's studies (n=2412) by Khan *et al.*[58] The prevalence of SAH in these studies ranged from 6.5%[43] to 8%.[58] There was significant patient overlap between these three studies, therefore, only the largest most recent study was included in our meta-analysis.[59]

The diagnostic accuracy of CT (at any time from headache onset) was also assessed in two retrospective cohort studies from the UK (n=510)[9] and the Netherlands (n=250).[60] The prevalence of SAH was 2.7% in the UK study, which recruited neurologically pristine patients with sudden onset severe headache.[9] However the Dutch study recruited patients from databases of SAH patients and patients in whom SAH was ruled out using CT and LP; the prevalence of SAH in this study was 35.2%,[60] therefore, patients are not likely to be representative of those who present to hospital with a sudden onset severe headache in NHS practice.

All of these studies used a third generation CT scanner. The largest, most recent, Perry study (undertaken from 2000 to 2009) provided additional technical details: 4-320 slices per rotation; from 2000 to 2002, 5 mm slices for the posterior fossa and 10 mm for the remainder of the brain were used; from 2002 onwards, 2.5-5 mm slices for the posterior fossa and 5-7.5 mm for the remainder of the brain were used.[59] The Dutch study (undertaken from 2005-2012) specified that 16-256 slices per rotation with a slice thickness of 5 mm were used.[60] In all studies the CT results were interpreted by neuroradiologists or general radiologists who routinely interpret head CT images.

Another Canadian study by Perry *et al.* (2020) assessed the diagnostic accuracy of CT within 6 hours of headache onset.[53] The accuracy of CT within 6 hours of headache onset was also assessed in the 2011 study by Perry *et al.*,[59] the Dutch study by Backes *et al.*,[60] a Spanish study by Valle Alonso *et*

al.,[55] and a Dutch study by Blok *et al.*[56] The prevalence of SAH amongst patients who received CT within 6 hours of headache onset ranged from 9.2%[53] to 12.7%[59] (excluding the study by Backes *et al.* which recruited from SAH databases (41.5% SAH prevalence) and the study by Blok that only recruited CT-negative patients (0.13% SAH prevalence)).

A UK cohort study (n=250) compared the interpretation of CT scans by Emergency Physicians (images were viewed on desktop screens) with neuroradiologists (images were viewed using dedicated high definition screens).[61]

LP

Perry *et al.* assessed the diagnostic accuracy of LP (CSF analysis) in CT-negative patients in a sub-study (n=1739) of a large Canadian prospective cohort study.[63] LP (CSF analysis) in CT-negative patients was also assessed in four smaller (n=30-245) retrospective cohort studies from the USA, [62, 64] the UK[65] and the Netherlands.[66] A large (n=453) Swedish retrospective cohort study also assessed LP (CSF analysis) in patients where the majority had previously undergone CT with a negative result.[67] The prevalence of SAH in most of the studies of LP in CT-negative patients was between 0 and 1.1%.[62, 63, 65, 67] However, in one study the prevalence of SAH was 9.2%; possible reasons why SAH prevalence was much higher in this study of CT-negative patients could relate to the type of CT scanner used (the study was conducted from 1998 to 2008) and the delay in undertaking CT (mean time from headache onset to CT was 29.5 hours).[64] One small study only included patients with an initial negative CT result, but positive LP result (bilirubin detected in the CSF); the prevalence of aneurysm in this study was 43%.[66] Two of the studies that assessed the pathway of CT followed by LP also reported the diagnostic accuracy of LP after negative CT.[9, 55] The prevalence of SAH amongst patients who received LP in these two studies was 0.3%[9] and 0%.[55]

The method of assessing CSF for xanthochromia varied between studies, with Canadian and American studies predominantly using visual inspection (where stated) and UK and European studies predominantly using spectrophotometry (where stated). In some studies LP was not always undertaken at least 12 hours from symptom onset. Standard NHS practice is to take the CSF sample at least 12 hours from symptom onset to allow xanthochromia to develop, and to analyse samples using spectrophotometry.[22]

Two Canadian studies (n=220 and 706) compared visual inspection of CSF versus spectrophotometry; the prevalence of SAH in these studies was 0.5% and 0.7%.[68, 69] There is likely to be some patient overlap between these two studies and the other Perry study described above.[63]

A large (n=676) American retrospective cohort study was undertaken to validate a clinical prediction rule to differentiate between traumatic LP and SAH.[70] This study also included only patients who had an abnormal CSF result; the prevalence of SAH was 7.2%.

CT angiography

Two small (n=70 and 88) Dutch retrospective cohort studies assessed CT angiography (CTA) after normal CT/LP.[71, 72] CTA was undertaken using an Aquilion One, Aquilion 64 (Toshiba Medical Systems) or GE Lightspeed 64-slice CT scanner. There were no cases of SAH in either study.

History and examination

Perry *et al.* undertook a large (n=747) prospective cohort study of patient assessment for SAH (without the use of a clinical decision rule) made by attending emergency physicians.[74] Again, there is likely to be some patient overlap between this study and other Canadian studies by Perry and colleagues.[59] The prevalence of SAH in this study was 6.7%.

A UK retrospective cohort study (n=353) assessed the adequacy of history, examination and investigation for SAH.[73] The prevalence of SAH in this study was 2%.

A Dutch retrospective cohort study (n=247) assessed neurologic examination for neck stiffness as a predictor of SAH.[75] This study recruited patients from databases of SAH patients and patients in whom SAH was ruled out using CT and LP; the prevalence of SAH in this study was 46%, therefore, patients are not likely to be representative of those who present to hospital with a sudden onset severe headache in NHS practice. There is likely to be some patient overlap between this study and the other study by Backes *et al.* that assessed the diagnostic accuracy of CT.[60]

3.2.2 Cost-effectiveness studies

Four studies were included in the cost-effectiveness review; Malhotra *et al.*, Taylor *et al.*, Wu *et al.* and Ward *et al.*[76-79] A comparison of the assumptions and inputs used in each model, however, highlighted that the studies by Malhotra *et al.* and Wu *et al.* were essentially two publications of the work, with largely overlapping methods and results. Consequently, these two studies are treated as a single study for the purposes of the synthesis. None of the identified studies adopted a UK perspective, with all four taking a US Medicare perspective. Due to differences in costs and practice between these countries, the relevance of these studies to UK decision makers is likely to be limited.

Three of the four studies adopted a cost-utility approach, considering the costs and quality adjusted life years (QALYs) generated by alternative diagnostic strategies. The fourth study, Taylor *et al.*, presents a decision analysis considering the optimum testing threshold for LP and consequently considers only health benefits and not costs.[76] This study, while technically not a cost-effectiveness study, was included for completeness as it provides an indicator of previous approaches to decision modelling in this area.

The modelled population in Malhotra *et al.*,[78] Wu *et al.*[77] and Taylor *et al.*[76] consisted of patients presenting with thunderclap headache to an ED who went on to have a negative CT scan. Ward *et al.*[79] presents a slight variation on this population, modelling patients prior to CT scan. The inclusion of an initial CT scan in all modelled diagnostic strategies, however, means that the population is comparable to the other studies. All four studies considered LP as a potential diagnostic strategy. Comparator strategies differed across studies, with Malhotra *et al.* and Ward *et al.* considering multiple alternative diagnostic strategies.[78, Ward #23714, 79] Three studies (Malhotra *et al.*, Taylor *et al.*, and Ward *et al.*) considered CT angiography as a comparator strategy,[76, 78, 79] and three studies (Malhotra *et al.*, Taylor *et al.*, and Wu *et al.*) considered no further follow up as a comparator strategy.[76-78] Ward *et al.* was the only study to consider MRI/MRA as a potential diagnostic strategy.[79]

The approach to model design taken in each of the evaluations was broadly similar, with all studies utilising a decision tree approach that sought to account for both the mortality and morbidity consequences associated with misdiagnosis of SAH. There were, however, some structural differences across the included studies, particularly relating to how false positives and the range of complications were accounted for. With regards to the former, Ward *et al.*[79] does not appear to account for the possibility of over-diagnosis, or does so in only a limited fashion, while Malhotra *et al.*[78] excludes this possibility in patients receiving LP.

There was significant overlap in the sources used to populate each model, particularly relating to the sensitivity and specificity of modelled diagnostic strategies. There were, however, important differences in assumed prevalence of SAH in presenting patients and the diagnostic accuracy of initial CT. Specifically, modelled prevalence of SAH was assumed to be considerably lower in Malhotra/Wu

et al. (8.41%)[77, 78] compared with Ward *et al.*[79](12%; Taylor did not report this). Modelled sensitivity of initial CT scan in Malhotra/Wu *et al.* was also higher than assumed in Ward *et al.* (98% vs 95.8%), though both assumed 100% specificity. In comparison, Taylor *et al.* assumed 98% sensitivity of CT and 67.8% specificity.[76]

3.2.3 Systematic reviews

A systematic review published in 2016 assessed the diagnostic accuracy of non-contrast brain CT using a modern generation multidetector scanner (16-slice technology or greater) within 6 hours of headache onset to exclude SAH.[21] Five studies were included in the review, although two of the studies did not meet the inclusion criteria for our review as they did not restrict their inclusion criteria to neurologically intact sudden onset severe headache patients. Therefore, the findings of this review may not be entirely applicable to neurologically intact acute headache patients presenting in practice.

Another systematic review published in 2016 assessed the diagnostic accuracy of history, physical examination, imaging and lumbar puncture for spontaneous SAH.[25] This review included 20 studies, although 11 of the studies did not meet our inclusion criteria as they did not restrict their inclusion criteria to neurologically intact sudden onset severe headache patients, did not include a relevant intervention or assessed outdated CT technology (over 25 years old). Again, the findings of this review may not be entirely applicable to neurologically intact acute headache patients presenting in current NHS practice.

A systematic review conducted to derive American College of Emergency Physicians clinical policy was published in 2019.[80] The review addressed four clinical questions, three of which were relevant to our review. Eleven studies were included within these three clinical questions, four of the studies did not meet the inclusion criteria for our review as they did not restrict their inclusion criteria to neurologically intact sudden onset severe headache patients or did not include a relevant intervention. Again, the generalisability of the review findings may be limited.

3.2.4 Clinician surveys

There were three surveys of clinicians conducted in the UK. One study surveyed 62 doctors of all grades to assess knowledge of acute headache management and the perceived need for a guideline.[83] One study surveyed 160 emergency medicine and acute medicine clinicians in Scotland to explore their approach to the investigation of a patient with thunderclap headache.[85] The final UK study surveyed 23 consultants in emergency medicine and 35 consultants in neuroscience specialties to establish whether they had different risk tolerances for investigation of suspected spontaneous SAH, and to establish if their risk-benefit appraisals concur with current guidelines.[27]

There were two surveys of clinicians conducted in Australia. One study surveyed 878 emergency medicine physicians and trainees to establish current clinical practice on several aspects of the investigation of 'acute headache'.[84] The other Australian study used semi-structured interviews with 15 emergency medicine clinicians to identify factors that influence their decisions about diagnostic testing after a normal CT brain scan for ED patients with a headache suspicious of a SAH.[81]

One study surveyed 168 emergency physicians at 2 academic hospitals and 4 community hospitals in the USA and Canada to assess physician knowledge on imaging and LP test performance and to assess practice patterns, variation and adherence to clinical policy using case-based scenarios.[86]

The final study surveyed 1149 emergency physicians from Australia, Canada, the UK and the USA to determine ED practice for investigating acute headache patients, whether emergency physicians

would consider using a clinical decision rule for acute headache and what the required sensitivity of such a rule would be for SAH.[82]

3.3 Quality of studies included in the systematic review

Results of the quality assessment of the included studies are tabulated in Appendix 4 (Section 8).

3.3.1 Cohort/before and after studies

Twenty eight cohort/before and after studies were assessed using the QUADAS-2 tool for diagnostic accuracy studies.[33] The QUADAS-2 tool was not appropriate for nine of the cohort/before and after studies where no reference standard test was used. Therefore, these studies were assessed using a quality assessment tool developed specifically for the review (described in Section 2.5).

QUADAS-2 results

The QUADAS-2 tool developers emphasise that QUADAS-2 should not be used to generate a summary quality score. However, if a study is judged as 'low' on all domains relating to bias or applicability, then it is appropriate to have an overall judgement of 'low risk of bias' or 'low concern regarding applicability'. If a study is judged 'high' or 'unclear' on one or more domains, then it may be judged 'at risk of bias' or as having 'concerns regarding applicability'.

Ten studies had a low risk of bias for all domains.[31, 48, 53, 54, 58-60, 64, 69, 74] The other 18 studies should be considered to be at risk of bias.

For the patient selection domain 21 studies had a low risk of bias, seven were unclear and none of the studies had a high risk of bias. For the index test domain 15 studies had a low risk of bias, ten studies were unclear and three studies had a high risk of bias. For the reference standard domain 21 studies had a low risk of bias, five studies were unclear and two had a high risk of bias. For the flow and timing domain 17 studies had a low risk of bias, seven were unclear and four had a high risk of bias.

Only four studies had a low concern regarding applicability for all domains.[9, 31, 48, 55] The other 24 studies should be considered as having concerns regarding applicability to current NHS practice.

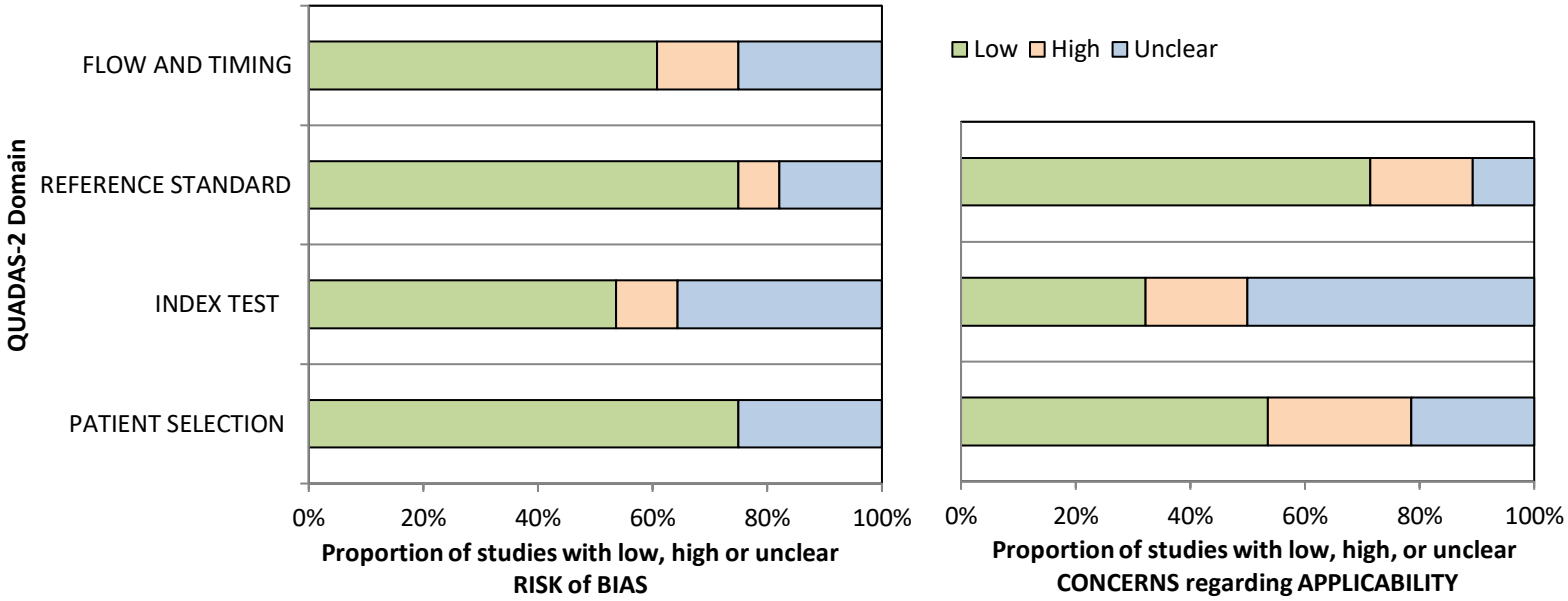
There were low applicability concerns relating to patient selection for 15 studies, the level of concern was unclear for six studies and there were high concerns for seven studies. There were low applicability concerns relating to the index test for only nine studies, the level of concern was unclear for 14 studies and there were high concerns for five studies. There were low applicability concerns relating to the reference standard test for 20 studies, the level of concern was unclear for three studies and there were high concerns for five studies.

Figure 2 presents a graphical summary of the QUADAS-2 results.

Studies not eligible for QUADAS-2

Two of the cohort/before and after studies assessed using the quality assessment tool developed specifically for the review were considered to have a low overall risk of bias.[66, 67] Six studies were considered to have an unclear overall risk of bias.[10, 57, 62, 71-73] One study was considered to have a high overall risk of bias owing to incomplete reporting of outcome data, although the study was only reported as a conference abstract and poster.[65]

Figure 2 QUADAS-2 results



3.3.2 Cost-effectiveness studies

The results of the quality checklist show that the included studies meet many of the outlined quality standards. However, there are some specific issues highlighted by the checklist that may significantly impact on the conclusions that can be drawn from these studies.

Of particular importance with regards to Malhotra/Wu *et al.* is the uncertainty around the time horizon applied and whether the indicated one-year time horizon is long enough given the potential for long-term morbidity associated with SAH.[77, 78] In this regard it is notable that the total costs and QALYs differ substantially from the other studies because of this assumption.

All included studies also suffer from a lack of appropriate RCT data to populate important model inputs. Specifically, the data used to model test sensitivity and specificity were not based upon randomised comparisons, but instead drawn from a range of single armed observational studies. While this approach may be considered reasonable in the absence of alternatives, it represents a significant potential source of bias. Differences in patient characteristics and diagnostic protocols may contribute significantly to variation in estimates of test sensitivity and specificity, and consequently any such differences in diagnostic accuracy may not be accurately reflected by the models.

More generally, we also note the observation highlighted by Wu *et al.* regarding the specificity of LP and the possibility of test failure due to the incidence of traumatic taps where accurate results cannot be obtained.[77] In this regard it is notable that neither Ward *et al.*[79] nor Taylor *et al.*[76] account for the possibility of test failure and consequently both studies potentially misrepresent the costs and benefits associated with this strategy.

3.3.3 Systematic reviews

The systematic review by Carpenter *et al.* was well reported and had a low overall risk of bias.[25] The systematic review by Dubosh *et al.* had an unclear overall risk of bias; the research question was not clearly reported and it was unclear whether the synthesis methods were appropriate (two of the included studies only included patients with negative CT results, therefore the authors of the review estimated the true positives and true negatives).[21] The systematic review published by the Writing Subcommittee of the American College of Emergency Physicians had a high overall risk of bias; the research question was not clearly reported (lack of clear, detailed inclusion and exclusion criteria) and the study selection process was unclear with no reasons for the exclusion of full papers reported.[80]

3.3.4 Clinician surveys

Two of the clinician surveys were judged to be good quality.[82, Kumar, 2019 #19749, 86] Two of the clinician surveys were of unclear quality; in both studies it was unclear whether the sample was representative and whether there was a systematic approach to survey development.[27, 81] Three of the clinician surveys were judged to be poor quality; all three studies did not report a systematic approach to survey development, along with other flaws such as a lack of piloting of the survey instrument or poor reporting of results.[83-85]

3.4 Results of studies included in the systematic review

The results extracted from each of the included studies are presented in further detail in Appendix 3 (Section 8).

3.4.1 Cohort/before and after studies

Clinical decision rules

It is conventional in analysis of diagnostic accuracy to report results in terms of sensitivity - patients correctly identified as having SAH, and specificity, where patients without SAH are identified as being SAH negative. The Canadian decision rules were retrospectively constructed to have 100% sensitivity for SAH, and as such are distinguishable only by their specificity and false positive rate – the inverse of specificity. A key issue with the implementation of high-sensitivity decision rules is the often high investigation rate, which if followed up will result in more frequent exposure of patients to unnecessary follow-up procedures. Under current recommendations, patients with sudden onset severe headache suspicious of SAH would undergo CT, followed by lumbar puncture if the CT scan result was negative. Diagnostic accuracy is presented in terms of both sensitivity/specificity and false negative rate (FNR)/false positive rate (FPR) for ease of interpretation.

Note that the confidence intervals presented alongside the diagnostic accuracy statistics for each study were calculated by CRD from 2x2 tables reconstructed from the original studies. As such, these figures may not match those reported in the original studies (presented in Appendix 3, Section 8), due to different methods for accounting for no events, differences in rounding, or incomplete data reporting. In particular, this is the case where there were no false negatives/positives observed, and thus we had no information with which to calculate the standard error. In such instances the confidence interval presented would be 100 – 100%, while the confidence interval in the original study may be 85 – 100%, for example.

The Canadian clinical decision rules

Three of the studies identified were designed to derive and validate the decision rules developed by Perry *et al.* in 2010 (Rule 1, 2 and 3),[43] and presented sufficient information to reconstruct 2x2 tables. The Perry studies were conducted prospectively in Canada,[31, 43] while the study by Matloob *et al.* was a retrospective cohort study based in the UK.[44] All included patients had a Glasgow Coma Scale (GCS) score of 15, and had acute headache peaking within one hour.

The Canadian decision rules were constructed to allow clinicians to screen patients according to the presence of clinical characteristics associated with a high risk of SAH in neurologically intact (GCS 15) adult (defined as ≥16 years) patients with non-traumatic, sudden headache (peaking within one hour of onset). Each rule comprises four variables, if one or more is present in a patient, further investigation (i.e. CT) should be performed. A summary of the diagnostic performance of each rule across the three studies is presented in

Table ***2***.

Table 2 Summary of diagnostic performance of the Canadian clinical decision rules in identified studies

Study	N	Sens (%)	95% CI	Spec (%)	95% CI	FNR (%)	95% CI	FPR (%)	95% CI
Canadian decision rule 1									
Perry 2010	1999	100	100 - 100	28.4	26.3 – 30.4	0.0	0.0 - 0.0	71.6	69.6 – 73.7
Matloob 2013	112	100	100 - 100	42.6	33.3 – 51.9	0.0	0.0 - 0.0	57.4	48.1 – 66.7
Perry 2013	2131	98.5	96.4 - 100	27.6	25.7 – 29.6	1.5	0.0 – 3.6	72.4	70.4 – 74.3
Canadian decision rule 2									
Perry 2010	1999	100	100 - 100	36.5	34.4 – 38.7	0.0	0.0 – 0.0	63.5	61.3 – 65.6
Matloob 2013	112	100	100 - 100	26.9	18.5 – 35.2	0.0	0.0 – 0.0	73.1	64.8 – 81.5
Perry 2013	2131	95.5	91.9 – 99.0	35.6	33.5 – 37.7	4.6	1.0 – 8.1	64.4	62.3 – 66.5
Canadian decision rule 3									
Perry 2010	1999	100	100 - 100	38.8	36.6 – 41.1	0.0	0.0 – 0.0	64.1	58.9 – 63.3
Matloob 2013	112	100	100 - 100	37.0	27.9 – 46.1	0.0	0.0 – 0.0	63.0	53.9 – 72.1
Perry 2013	2131	97.0	94.0 – 99.9	30.6	28.5 – 32.6	3.0	0.1 – 6.0	69.4	67.4 – 71.5

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

Prevalence of SAH was 6.5% and 6.2% in Perry *et al.* 2010 and 2013 respectively,[31, 43] while this was 3.6% in Matloob *et al.*, 2013.[44] Pooled diagnostic accuracy estimates for these three studies are presented in Table 3. There was a high concern of bias around patient flow in the study by Matloob *et al.*; however, the results appear largely in line with those observed in other studies, and thus it is unlikely that any potential bias in results influenced the validity of the pooled analyses.

In some instances, the confidence intervals (CIs) of pooled estimates are wider than those in the included studies. In random-effects models, precision decreases with increasing heterogeneity and thus confidence intervals widen, this is particularly the case where there are few events (i.e. low numbers of false negatives/positives).

Table 3 Bivariate meta-analysis of diagnostic performance of Canadian decision rules 1 to 3

Pooled	Sens (%) (95% CI)	Spec (%) (95% CI)	FNR (%) (95% CI)	FPR (%) (95% CI)
Canadian Rule 1 (n=3)	99.3 (97.1 – 99.8)	28.4 (27.0 – 29.8)	0.75 (0.19 – 2.94)	71.6 (70.2 – 73.0)
Canadian Rule 2 (n=3)	98.7 (90.9 – 99.8)	35.8 (34.3 – 37.3)	1.34 (0.19 – 9.10)	64.2 (62.7 – 65.7)
Canadian Rule 3 (n=3)	99.4 (91.6 – 100.0)	35.0 (30.4 – 40.0)	0.57 (0.0 – 8.45)	65.0 (60.1 – 70.0)

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; Sens, sensitivity; Spec, specificity.

The bivariate meta-analyses show that the Canadian clinical decision rules each have near perfect sensitivity for identifying patients at high risk of SAH, and are distinguishable only by the width of the associated confidence intervals. The false positive rates associated with these decision rules are high, with Rule 2 having the lowest false positive rate at 64.2% (95% CI 62.7 to 65.7), but also the highest rate of false negatives at 1.34% (95% CI 0.19 to 9.10).

A further three studies investigating the diagnostic performance of the Canadian decision rules were included in the systematic review, but reported insufficient information to be included in the formal synthesis above.[45-47]

MacDonald *et al*. (2012) is a retrospective cohort study which included 280 neurologically intact patients presenting with acute headache. Diagnostic accuracy was not reported in full. The authors found that none of the 8 patients with SAH would have been missed using any of the three clinical decision rules; however, there were nine other cases of significant pathologies that would have been missed by employing the rules.[45]

Kelly *et al*. (2014) is a retrospective cohort study including 59 neurologically intact patients with confirmed SAH, who presented with sudden onset headache. Applied retrospectively, Rule 1 was found to have a sensitivity of 96.6% (95% CI 88.5 to 99.1), Rule 2 had a sensitivity of 100% (95% CI 93.9 to 100), and the sensitivity of Rule 3 was 89.8% (95% CI 79.5 to 95.3). Specificity was not reported. The authors found that the addition of vomiting at presentation to Rules 1 and 3 increased their sensitivity to 100% in this population.[46] Kelly *et al*. was judged to be at a high risk of bias for its application of the decision rules.

Yiangou *et al*. (2017) is a retrospective cohort study including 162 neurologically intact patients presenting with acute headache. The authors compared the diagnostic accuracy of Rules 1, 2 and 3 and the Ottawa SAH Rule with current practice at one hospital in North-West England. Based on 'current practice', no patients with SAH were missed, and 42.6% of the population were investigated with CT. Retrospective application of the Canadian SAH decision rules would have increased the CT investigation rate to 54.3%, 64.8%, and 50.0% for Rules 1, 2, and 3 respectively. One patient with SAH would have been missed using Rule 3.[47]

The Ottawa subarachnoid haemorrhage rule

The Canadian decision rules were further refined by Perry *et al.* in 2013, with the addition of two further clinical factors to 'Rule 1': 'Thunderclap headache (instantly peaking pain)', and 'Limited neck flexion on examination', forming the Ottawa SAH Rule.[31] Eight studies (including the derivation cohort, Perry 2013) assessing the diagnostic performance of the Ottawa SAH Rule were identified in the systematic review, including a total of 8114 patients.[31, 32, 47, 49-53] There was a mixture of retrospective and prospective study designs, conducted across centres in Canada, the USA, the UK, Hong Kong, Taiwan, and Australia. A summary of the diagnostic performance of the Ottawa SAH Rule in each cohort is presented in Table 4. One study (Perry 2017)[48] was excluded from this analysis due to a significant overlap in the included patient population with the larger Perry 2020 study.[53]

Table 4 Summary of diagnostic performance of the Ottawa SAH Rule across identified studies

Study	N	Sens (%)	95% CI	Spec (%)	95% CI	FNR (%)	95% CI	FPR (%)	95% CI
Perry 2013	2131	100	100 - 100	15.3	13.7 – 16.8	0.0	0.0 – 0.0	84.7	83.2 – 86.3
Bellolio 2015	454	100	100 - 100	7.6	5.17 – 10.1	0.0	0.0 – 0.0	92.4	89.9 – 94.8
Yiangou 2017	162	100	100 - 100	38.7	31.4 – 46.6	0.0	0.0 – 0.0	61.0	53.4 – 68.6
Cheung 2018	500	94.0	87.4 - 100	32.9	28.5 – 37.2	6.0	0.0 – 12.6	67.1	62.8 – 71.5
Chu 2018	137	100	100 - 100	22.4	15.3 – 29.4	0.0	0.0 – 0.0	77.6	70.6 – 84.7
Pathan 2018	145	100	100 - 100	44.3	36.1 – 52.5	0.0	0.0 – 0.0	55.7	47.5 – 63.9
Wu 2019	913	100	100 - 100	37.0	33.8 – 40.1	0.0	0.0 – 0.0	63.0	59.9 – 66.2
Perry 2020	3672	100	100 - 100	12.7	11.6 – 13.9	0.0	0.0 – 0.0	87.3	86.1 – 88.4

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

The overall prevalence of SAH in these studies ranged from 1.6% (Wu *et al.*, 2019)[49] to 10% (Cheung *et al.*, 2018),[52] with a population-weighted mean prevalence of 4.99%. The sensitivity estimates were 100% across all but one of the studies, but specificity varied widely from 8 to 44%. The results of the bivariate meta-analysis of the key measures of diagnostic performance are presented in Table 5.

Table 5 Bivariate meta-analysis of Ottawa SAH Rule diagnostic performance

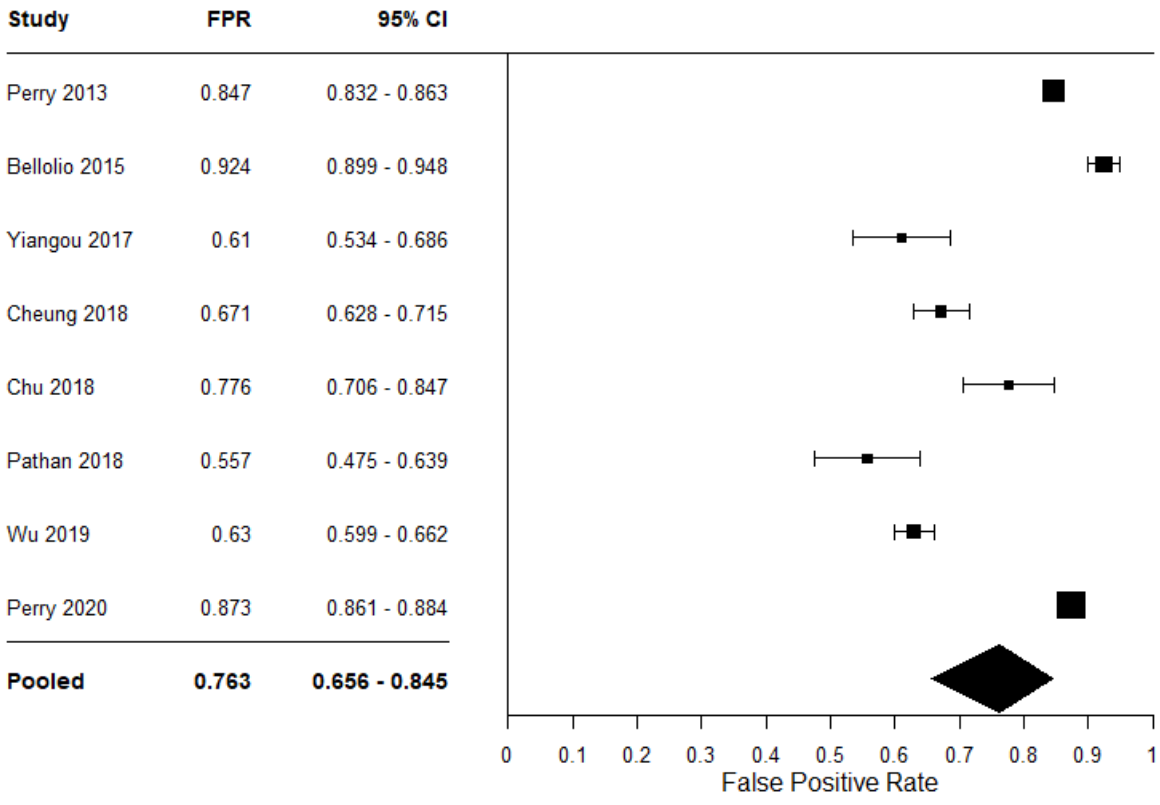
	Sens (%) (95% CI)	**Spec (%) (95% CI)**	**FNR (%) (95% CI)**	**FPR (%) (95% CI)**
Pooled (n=8)	99.5 (90.8 – 100)	23.7 (15.5 – 34.4)	0.49 (0.00 – 9.2)	76.3 (65.6 – 84.5)

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; Sens, sensitivity; Spec, specificity.

The results of the meta-analysis show that the Ottawa SAH Rule is very sensitive, with a pooled sensitivity of 99.5% (95% CI 90.8 to 100), and indeed would have produced 100% sensitivity across the included studies if the study in Asian Chinese patients by Cheung *et al.*[52] were excluded from the analysis (See Figure 4 below). There was no basis in terms of study quality or risk of bias for the exclusion of Cheung *et al.*, so this result is only illustrative of the impact of this study.

It can be seen that strict application of the Ottawa SAH Rule would result in 76.3% of SAH-negative patients undergoing further investigation with CT and/or LP unnecessarily (FPR 76.3%, 95% CI 65.6 to 84.5). This would result in greater healthcare resource use, and higher rates of adverse events related to LP and CT radiation exposure. Figure 3 is a forest plot of the false positive rates generated in each study, and in the bivariate meta-analysis.

Figure 3 Forest plot of false positive rates across 8 studies assessing the Ottawa SAH Rule

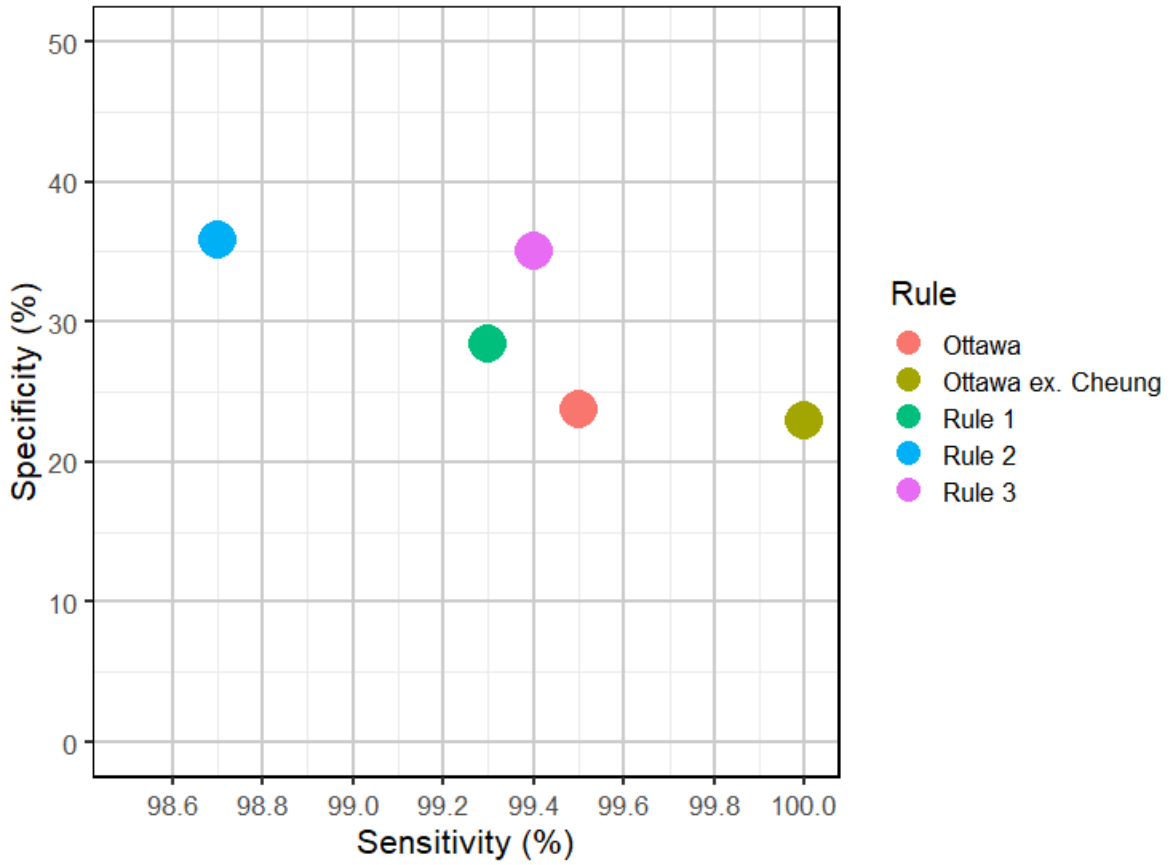


The forest plot illustrates the heterogeneity in the false positive rates observed across the included studies. This heterogeneity may have been driven by differences in population characteristics and study methodology. Prospective studies would have been likely to have more complete records of patient characteristics, but clinicians' adherence to and application of the Ottawa SAH Rule varied across studies. The retrospective application of the Ottawa SAH Rule may also have varied according to the quality of patient records reviewed in studies of this type. There may also have been inconsistencies in the application of rules by different authors and clinicians, affecting estimates of diagnostic accuracy.

Assuming the prevalence of SAH in the population of neurologically intact patients presenting to the ED with sudden onset severe headache in practice is equal to that observed in the included studies, the pre-test probability of SAH is 4.99%. The post-test probability is used to illustrate the diagnostic value of a test, and is defined as the probability of a patient having SAH given a positive result of a diagnostic test, in this case, being designated as 'high-risk' using the Ottawa SAH Rule. The post-test probability of a patient having SAH increases to 6.4% in 'high risk' individuals. In this sense, the Ottawa SAH Rule is not a useful indicator of whether a patient has suffered a SAH, and does little to aid clinical decision-making.

As illustrated in Figure 4 below, each of the decision rules trades off sensitivity against specificity. Rule 2 has the highest specificity and thus the lowest number of false positive results, and Rule 3 had only marginally lower specificity but improved sensitivity. The Ottawa SAH Rule had the highest sensitivity but lowest specificity.

Figure 4 Comparison of pooled diagnostic accuracy of decision rules



In summary, whilst the Ottawa SAH Rule is very sensitive for identifying SAH patients, the low specificity suggests that around 75% of SAH-negative patients would undergo further investigation with CT and/or LP and possibly CTA unnecessarily. In practice this would result in greater healthcare resource use and increased rates of adverse events linked to exposure to these potentially harmful diagnostics.

Pathway of CT followed by LP

Six studies assessed the diagnostic accuracy of non-contrast CT followed by LP in a neurologically intact, sudden onset severe headache population.[9, 10, 54-57] A total of 2915 patients were included across centres in Canada and Europe, with a mixture of prospective and retrospective study designs. Only one study reported sufficient information to reconstruct 2x2 tables,[54] so it was not possible to undertake bivariate meta-analysis for the CT-LP pathway.

Perry *et al.* (2002) included 891 neurologically intact patients with non-traumatic acute headache, peaking within one hour.[10] The study presented a retrospective summary of the CT-LP pathway at one university centre in Canada. CT was performed on 35.1% patients, 9 of whom were positive for SAH, and 8 were positive for other acute processes. LP was performed on 9.5% of patients, with SAH diagnosed in one patient who had not previously undergone CT. The pathway identified potentially dangerous conditions in 3.6% of patients, including 6 brain tumours, 4 cases of bacterial meningitis, and 3 cases of temporal arteritis.

Perry *et al.* (2008) included 592 patients, 61 of whom had SAH (prevalence 10.3%).[54] Fifty-five cases were diagnosed by CT, and six by presence of CSF xanthochromia. The CT-LP pathway was found to have a sensitivity of 100% (95% CI 94 to 100), and a specificity of 67% (95% CI 63 to 71).

Valle Alonso *et al.* (2018) included 74 patients who underwent LP following a negative CT scan (the full study population also included 11 patients with SAH on CT).[55] No cases of SAH were identified by LP, but there was one false-positive and two inconclusive results in which bleeding was later ruled out by CTA. Seven patients experienced post-puncture headache, two of whom were admitted for pain management. Significant pathologies (other than SAH) were identified in 9.4% of patients, comprising 4.7% with meningitis, and reversible cerebral vasoconstriction syndrome in 4.7%.

Cooper *et al.* (2016) included 517 patients managed on a clinical decision unit pathway for exclusion of SAH in a UK teaching hospital.[9] A total of 98.6% of patients had a CT scan, and 309 underwent LP, out of 490 patients initially negative on CT plus one who received LP without first undergoing CT. 182 eligible patients did not have LP due to procedure failure (n=18), patient refusal or contraindication (n=65), or at the decision of the attending doctor (n=99). CT was positive for SAH in 13 patients, six had a lesion identified on angiography, and seven were perimesencephalic SAH. LP was positive for SAH in 11 patients, but 10 of these cases were subsequently ruled out on angiography. There were other significant aetiologies diagnosed in 14 patients by CT (e.g. cerebral infarction, venous sinus thrombosis), and in a further 17 patients by LP (16 cases of viral meningitis, one of nonocclusive sagital sinus thrombosis).

Blok *et al.* (2015) included 760 acute headache patients with suspected SAH who underwent CT within 6 hours of headache onset with a negative result, with a subsequent LP.[56] CSF samples were considered SAH positive in 52 (7%) patients, but only one was later confirmed to have a non-aneurysmal perimesencephalic haemorrhage, no subarachnoid blood was identified in the other 51 patients. Angiography was undertaken in 28 of the patients with positive CSF findings, incidental

aneurysms were identified in 8 patients (3 were previously coiled). Four of the incidental aneurysms were treated.

Dutto *et al.* (2009) was a before-after study, which included 25 alert patients with suspected SAH and thunderclap headache or symptoms in keeping with non-traumatic SAH prior to implementation of a diagnostic protocol and 45 patients after implementation.[57] 95.5% of patients underwent CT after implementation versus 96% before, 2 patients received LP. There were no cases of SAH identified in either population.

In summary, the pathway of LP followed by CT appears to be highly sensitive for detecting cases of SAH, although specificity was relatively low in some of the above studies, owing to the high rate of false positives yielded by LP. Because of the ambiguity of LP results, this pathway was often followed up with angiography to confirm the presence of aneurysm and to rule out traumatic tap. This pathway also identified other significant pathologies such as intracerebral haemorrhage, brain tumour, and bacterial/viral meningitis.

Computed tomography (CT)

CT within 6 hours of symptom onset

Four studies presented sufficient diagnostic accuracy data to be included in bivariate meta-analysis for non-contrast CT within 6 hours of headache onset.[53, 55, 59, 60] One further study (Khan *et al.* 2017)[58] also reported diagnostic accuracy data for CT within 6 hours but was likely to have substantial patient overlap with the population covered in Perry *et al.* 2011.[59] There were a total of 2377 patients included in this analysis, originating from studies in Canada, the Netherlands and Spain.

The analyses are presented in two iterations due to the inconsistencies in reporting of SAH cases between studies. Perry *et al.* 2020 classed two incidental aneurysms with traumatic tap on LP as SAH, and thus as false negatives. This is not in line with the other studies included in this analysis, nor with our interpretation of what constitutes a false negative, as incidental aneurysms that have not bled are not SAH, and are not something non-contrast CT can detect. Therefore, additional analyses in which these two patients were reclassified as true negatives are also presented. The diagnostic performance in each study (as calculated by CRD) is summarised in Table 6.

Table 6 Summary of diagnostic performance of non-contrast CT (<6 hours from onset) across identified studies

Study	N	Sens (%)	95% CI	Spec (%)	95% CI	FNR (%)	95% CI	FPR (%)	95% CI
Perry 2011	953	100	100 – 100	100	100 – 100	0.0	0.0 – 0.0	0.0	0.0 – 0.0
Backes 2012	135	100	100 – 100	100	100 – 100	0.0	0.0 – 0.0	0.0	0.0 – 0.0
Valle Alonso 2018	85	100	100 – 100	98.7	96.1 – 100	0.0	0.0 – 0.0	1.3	0.0 – 3.9
Perry 2020	1204	95.5	91.6 – 99.4	100	100 – 100	4.5	0.7 – 8.4	0.0	0.0 – 0.0
Perry 2020 (adjusted)	*1204*	*97.2*	*94.2 – 100*	*100*	*100 – 100*	*2.8*	*0.0 – 5.8*	*0.0*	*0.0 – 0.0*

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

The prevalence of SAH in patients who underwent CT within 6 hours of symptom onset appeared to be higher than in the general sudden onset severe headache population. SAH prevalence in these studies ranged from 9.2% to 41.5%. The methods used to identify patients in the study by Backes *et al.* meant SAH patients were overrepresented in this population, when this study is excluded, the three remaining studies had a population-weighted average prevalence (i.e. the prevalence across the included populations) of 10.8%. Two studies (excluding Backes) reported on the wider CT population

(CT undertaken at any time point since headache onset), in which the population-weighted average prevalence was 7.0%. One reason for this trend may be that patients presenting to hospital with headache soon after symptom onset are more likely to have severe underlying pathology than those who present later. It is also possible that patients with more severe symptoms are triaged to receive CT more quickly, thus reducing delay from symptom onset to receipt of a scan. This may have implications for consideration of the pre- and post-test probability of disease in the population presenting to hospital more quickly.

Table 7 presents the results of the two bivariate meta-analyses undertaken on these studies.

Table 7 Bivariate meta-analysis of CT (<6 hours from onset) diagnostic performance

	Sens (%) (95% CI)	**Spec (%) (95% CI)**	**FNR (%) (95% CI)**	**FPR (%) (95% CI)**
Pooled (n=4)	99.2 (92.6 – 99.9)	100 (99.0 – 100)	0.81 (0.00 – 7.36)	0.04 (0.00 – 1.0)
Reclassified Perry 2020 (n=4)	98.7 (96.5 – 100)	100 (99.7 – 100)	1.34 (0.50 – 3.52)	0.00 (0.00 – 0.34)

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; Sens, sensitivity; Spec, specificity.

While the point estimate of sensitivity in the meta-analysis in which two patients in the study by Perry *et al.* (2020) were reclassified is marginally lower, it should be noted that the uncertainty around this estimate is improved. This result therefore represents a more precise estimate of the sensitivity of CT within 6 hours, given the available evidence. Random effects meta-analysis models such as those used for diagnostic accuracy will down-weight an input drawn from a trial if between-study heterogeneity is high. As the three studies Perry (2011),[59] Backes,[60] and Valle Alonso[55] form a cluster at 100% sensitivity, Perry (2020)[53] is an outlier at 95.5%. Therefore, by reducing this heterogeneity in the reclassified analysis, the weight of the lower result (Perry 2020) is increased, thereby reducing the estimate for sensitivity from that in the original analysis. While this may appear counter-intuitive, the information provided by this analysis is increased by reducing the uncertainty associated with the result.

One further study (Blok *et al.*, 2015) assessed the diagnostic accuracy of CT performed within 6 hours of symptom onset.[56] The authors retrospectively reviewed the records of 760 neurologically intact acute headache patients who had a CT conducted within 6 hours of symptom onset that was initially judged to be negative for SAH (by a staff radiologist), and subsequently underwent LP. Seven percent of CSF samples were initially considered positive for SAH, but blood was identified in the basal cisterns of only one patient (on review by two neuroradiologists and a neurologist). No subarachnoid blood was identified in the remaining patients. Eight incidental aneurysms were identified using CT angiography, four of which were treated. The negative predictive value for detection of blood on CT by staff radiologists in a non-academic centre was 99.9% (95% CI 99.3 to 100).

If we are to assume the prevalence of SAH in patients who receive CT within 6 hours of symptom onset in Perry *et al.*, 2011 (12.7%),[59] Valle Alonso *et al.*, 2018 (11.8%),[55] and Perry *et al.*, 2020 (9.2%)[53] is representative of this population in practice, the pre-test probability of SAH in neurologically intact sudden onset severe headache patients presenting to the ED who have CT within 6 hours of symptom onset is 10.8%. Using the pooled estimates of diagnostic accuracy from the original analysis, the post-test probability of having SAH after a negative CT result within 6 hours of symptom onset is 0.098%. Assuming a hypothetical follow-up test has 100% accuracy, this means that 1018 (95% CI 112 to 9,806) patients would have to undergo further investigation to identify a single case of SAH. Using the reclassified analysis, the number needed to test (NNT) would be 658 (95% CI 250 to 1749) to identify one SAH patient. As described above, whilst this lower NNT figure

appears counter-intuitive, the precision of the estimate is increased, as shown by the smaller confidence interval range.

CT regardless of time interval

Three studies reported sufficient information on the diagnostic accuracy of CT (at any time interval from headache onset) to be included in bivariate meta-analysis.[9, 59, 60] These studies are summarised in Table 8 below, comprising 3889 patients from centres in Canada, the Netherlands, and the UK. Two studies were of a retrospective design, and one was a prospective cohort study.

Table 8 Summary of diagnostic performance of non-contrast CT (any time) across identified studies

Study	N	Sens (%)	95% CI	Spec (%)	95% CI	FNR (%)	95% CI	FPR (%)	95% CI
Perry 2011	3132	92.9	89.7 – 96.2	100	100 – 100	7.08	3.8 – 10.3	0.00	0.0 – 0.0
Backes 2012	247	97.6	94.4 - 100	100	100 – 100	2.38	0.0 – 5.6	0.00	0.0 – 0.0
Cooper 2016	510	92.9	79.4 - 100	100	100 – 100	7.14	0.0 – 20.6	0.00	0.0 – 0.0

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

The specificity of CT for SAH appears high, with false positive results being extremely rare (there were none reported in the included studies). The sensitivity of unenhanced CT scans taken at any time in this population ranged from 92.9% to 97.6%, however, it should be noted that there may have been differences in the composition of the populations between these studies. The prevalence of SAH in Perry *et al.* (2011) and Cooper *et al.* (2016) was 6.2% and 2.7% respectively,[9, 59, Cooper #2535] while 35.2% of patients included in Backes *et al.* (2012) had SAH.[60] It is possible that the methods used to retrospectively select patients by Backes *et al*. increased the apparent diagnostic performance of CT.

Bivariate meta-analysis was performed to generate a pooled estimate of the diagnostic performance of CT undertaken at any point after symptom onset, the results of which are presented in Table 9. These estimates should not be taken at face value, as the diagnostic performance of CT is highly dependent upon the time since symptom onset.

Table 9 Bivariate meta-analysis of CT (any time) diagnostic performance

	Sens (%) (95% CI)	Spec (%) (95% CI)	FNR (%) (95% CI)	FPR (%) (95% CI)
Pooled (n=3)	94.1 (91.0 – 96.2)	100 (100 – 100)	5.92 (3.85 – 8.99)	0.00 (0.00 – 0.00)

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; Sens, sensitivity; Spec, specificity.

Three further studies, Perry *et al.* (2010), Khan *et al*. (2017), and Austin *et al*. (2018) assessed the diagnostic accuracy of CT performed at any time after symptom onset.[43, 58, 61] There appeared to be significant overlap in the patient populations recruited to Perry (2010)[43] and Khan (2017)[58] with Perry (2011),[59] which had the largest sample size and the most complete reporting, thus, these studies with significant patient overlap were excluded from the synthesis.

The study by Austin *et al.* (2018) was only reported as a conference abstract, reporting an interim analysis of a retrospective cohort study, including 250 patients with suspected SAH who underwent CT.[61] This study assessed the ability of emergency physicians to interpret CT scans on standard resolution screens, compared to a reference standard of interpretation by a neuroradiologist using a high-definition display. The sensitivity of CT interpreted by an emergency physician was 84% (95% CI 63.9 to 95.5), and the reported specificity was 95% (95% CI 90.9 to 97.2). One case of venous sinus thrombosis was also interpreted as negative by emergency physicians. This study was

considered to have a high risk of bias due to the difference in hardware used between the two specialty types for examining CT images.

In summary, CT is highly accurate for the detection and ruling out of SAH if undertaken within 6 hours of headache onset, with scans interpreted by a neuroradiologist or radiologist who routinely interprets brain CT images. However, this level of accuracy may not hold in smaller local centres without specialist neurology input, and there is currently insufficient data from such centres to make recommendations on best practice. This is not to say that LP follow-up should be used routinely in these settings, but that the balance of risks remains unknown until relevant data are collected.

It is well understood that CT performed within 6 hours of symptom onset is more sensitive to the presence of blood in the subarachnoid space than CT performed beyond 6 hours. The present meta-analyses support this conclusion; CT conducted within 6 hours of symptom onset had a sensitivity of 99.2% (95% CI 92.6 to 100), whereas the sensitivity of CT at any time was 94.1% (95% CI 91.0 to 96.2). Results from Perry (2011)[59] and Backes (2012)[60] suggest CT scans performed >6 hours after symptom onset have significantly poorer performance, reporting sensitivities of 85.7% (95% CI 78.3 to 90.9) and 90.0% (95% CI 76.3 to 97.2) respectively. The bimodal nature of the diagnostic performance of CT means that the 'at any time' statistics are misleading, and the timing of CT has a significant impact upon the pre- and post-test probabilities of SAH.

Lumbar puncture (LP)

Eleven studies examined the diagnostic accuracy of CSF xanthochromia/bilirubin in neurologically intact sudden onset severe headache patients judged to be SAH-negative using non-contrast CT.[9, 55, 62-70] CSF analysis was undertaken using a number of methods, including visual inspection and a variety of spectrophotometric assays and assessment protocols. Two studies also sought to validate novel CSF analysis methods to rule out SAH, and to distinguish between traumatic tap and SAH.[63, 70]

Visual CSF inspection

Five studies examined the diagnostic accuracy of visible xanthochromia in CT-negative patients.[62-64, 68, 69] Three of these studies included sufficient information to calculate the diagnostic accuracy of visible xanthochromia (see results in Table 10). There were relatively few cases of SAH across these studies (2% prevalence), resulting in wide confidence intervals around estimates of sensitivity and the FNR.

Table 10 Summary of diagnostic performance of visual CSF inspection across identified studies

Study	N	Sens (%)	95% CI	Spec (%)	95% CI	FNR (%)	95% CI	FPR (%)	95% CI
Perry 2006	220	50.0	0.0 – 100	96.8	94.4 – 99.1	50.0	0.0 - 100	3.21	0.9 – 5.6
Dupont 2008	117	92.9	79.4 – 100	95.1	91.0 – 99.3	7.1	0.0 – 20.6	4.85	0.7 – 9.0
Gangloff 2015	706	80.0	44.9 – 100	98.7	97.9 – 99.5	20.0	0.0 – 55.1	1.28	0.5 – 2.1

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

Estimates of sensitivity varied widely across the three included studies, ranging from 50% to 93%. This was due to the very low numbers of SAH cases in these populations, for example, Perry (2006) included only two cases, one of which was not identified using visible xanthochromia.[69] As is suggested by the results of the bivariate meta-analysis presented in Table 11, presence of visible xanthochromia appeared to be a strong indicator of SAH when identified, with consistently low rates of false positives.

Table 11 Bivariate meta-analysis of visual CSF inspection diagnostic performance

	Sens (%) (95% CI)	**Spec (%) (95% CI)**	**FNR (%) (95% CI)**	**FPR (%) (95% CI)**
Pooled (n=3)	84.9 (60.0 – 95.5)	97.6 (95.3 – 98.8)	15.1 (4.5 – 40.1)	2.43 (1.23 – 4.75)

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

The results of the meta-analysis show visual CSF inspection for xanthochromia to be highly specific, but with high levels of uncertainty around estimates of sensitivity, due to the marked differences reported in the underlying studies. The pooled FNR of 0.15 shows that CSF analysis using visual inspection should not be used in isolation following a negative CT. A significant number of SAH cases could be missed unless all xanthochromia negative patients undergo further investigation using CTA. However, CTA exposes patients to additional radiation and risks associated with contrast materials, such as contrast-induced nephropathy. Furthermore, the opportunity costs associated with increasing CTA coverage for LP-negative patients could be significant.

The diagnostic accuracy of visual CSF inspection for xanthochromia was also assessed in Migdal *et al*. (2015).[62] A subgroup analysis included 245 patients with 'low risk clinical features', which aligned with the population included in this review. There were no cases of SAH identified in the subgroup relevant to the review. 13/245 (5.3%) patients had LP-related complications that resulted in a return visit to the ED or hospitalisation.

Perry *et al*. (2015) examined the diagnostic accuracy of visible xanthochromia in 'abnormal' CSF samples drawn from 1739 (mostly) CT-negative patients, i.e. with $>1x10^6$/L red blood cells in the final tube of CSF, and/or visible xanthochromia in one or more tubes. There were 15 (0.9%) patients classed as having aneurysmal SAH, 7 of whom had visible xanthochromia in their CSF. The sensitivity of visible xanthochromia was 46.7% (95% CI 22.3 to 72.6), and its specificity was 97.3% (95% CI 95.6 to 98.4).

Spectrophotometric CSF analysis

Three studies reported the diagnostic accuracy of spectrophotometric CSF analysis following negative CT.[9, 68, 69] Samples were analysed for presence of bilirubin using the UK National External Quality Assessment Service (UK NEQAS) protocol/assay.[22] The results reported in these studies are summarised in Table 12. A total of 1235 patients were included in these studies based in Canada and the UK, Perry *et al.* (2006) was a sub-study of a prospective cohort, while Gangloff *et al.* and Cooper *et al.* were of a retrospective cohort design.

Table 12 Summary of diagnostic performance of spectrophotometric CSF inspection (UK NEQAS)

Study	**N**	**Sens (%)**	**95% CI**	**Spec (%)**	**95% CI**	**FNR (%)**	**95% CI**	**FPR (%)**	**95% CI**
Perry 2006	220	100	100 - 100	83.0	78.0 – 88.0	0.0	0.0 – 0.0	17.0	12.0 – 22.0
Gangloff 2015	706	100	100 - 100	98.1	96.8 – 99.1	0.0	0.0 – 0.0	1.9	0.9 – 2.9
Cooper 2016	309	100	100 - 100	96.8	94.8 – 98.7	0.0	0.0 – 0.0	3.3	0.1 – 5.2

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

The prevalence of SAH in these studies was low, as patients had already been classed as SAH-negative based on CT scan results. The population-weighted prevalence of SAH was 0.65%. The rate of false positives (and subsequent rate of angiographic follow-up) was particularly high in Perry (2006), this may be because of reported limitations in the spectrophotometric equipment used by the

authors, or a lack of standardisation for the timing of LP; a substantial proportion of patients (45%) underwent LP <12 hours after ictus.

The rate of false positives generated by CSF spectrophotometry in the more recent studies was substantially lower, and is likely to better represent the diagnostic accuracy of CSF spectrophotometry in current UK practice. The three studies were synthesised using bivariate meta-analysis, the results of which are presented in Table 13.

Table 13 Bivariate meta-analysis of spectrophotometric CSF inspection (UK NEQAS)

	Sens (%) (95% CI)	**Spec (%) (95% CI)**	**FNR (%) (95% CI)**	**FPR (%) (95% CI)**
Pooled (n=3)	100 (100 – 100)	95.2 (86.0 – 98.5)	0.00 (0.00 – 0.00)	4.78 (1.52 – 14.0)

Abbreviations: CI, confidence interval; FNR, false negative rate; FPR, false positive rate; N, number; Sens, sensitivity; Spec, specificity.

The pooled analysis of CSF spectrophotometry show this method of analysis to have greater sensitivity (i.e. 100%) than visual inspection based on point estimates, with a marginally worse rate of false positives. The high FPR appears to be driven primarily by Perry (2006), which, as previously mentioned, may have differed from the UK NEQAS analysis guidelines, in both the recommended time since symptom onset, and wavelengths used to analyse the sample.[69]

Three further studies assessed CSF spectrophotometry: Horstman *et al*. (2012), Brunell *et al*. (2013), and Sansom *et al*. (2014).[65-67] These were retrospective cohort studies based in the Netherlands, Sweden, and the UK, respectively. A total of 543 patients who underwent LP after a negative CT scan result were included in these studies.

Horstman *et al*. included 30 patients with sudden severe headache and a negative CT result but bilirubin detected in the CSF.[66] Aneurysms were identified in 13 of these patients, all of whom presented between four and 14 days after symptom onset. Coiling was performed in nine patients, and clipping in two; two patients were not treated due to poor clinical condition or refusal of further tests. Two patients died within three months.

Brunell *et al*. included 453 patients who underwent LP to exclude SAH, 400 of whom (88%) presented with thunderclap headache.[67] Patients who were not alert and neurologically intact were included in this population. Fourteen (3%) patients had a pathological diagnosis based on LP, most commonly aseptic meningitis, and five (1.1%) had SAH. Four SAH patients presented with thunderclap headache and had non-aneurysmal SAH which did not require surgical intervention. The other SAH patient had reduced consciousness and prior history of SAH, and therefore did not strictly meet the inclusion criteria for this systematic review, or the other studies included in this review.

In Sansom *et al*. CSF samples were analysed using spectrophotometry according to UK national guidelines, all samples were negative for xanthochromia in the 60 thunderclap headache patients.[65] However, 8/60 CSF examinations were abnormal for other CSF parameters (protein, glucose, cells, microscopy); cerebral infarction was confirmed in two of the eight patients with subsequent scans.

RBC-based CSF analysis thresholds

Two studies explored methods to distinguish true subarachnoid haemorrhage from the effects of traumatic tap, where blood enters the CSF samples drawn from a patient due to the lumbar puncture procedure itself.

A prospective study by Perry *et al.* published in 2015 enrolled 1739 patients who had undergone LP following a negative CT scan.[63] 641 of these patients had an abnormal CSF analysis result, defined as $>1x10^6$/L red blood cells (RBCs) in the final tube of CSF, or the presence of xanthochromia. The authors found that the presence of fewer than $2000x10^6$/L RBCs in addition to no xanthochromia excluded a diagnosis of aneurysmal SAH, with a sensitivity of 100% (95% CI 74.7 to 100), and specificity of 91.2% (95% CI 88.6 to 93.3).

Heiser *et al*. (2015) sought to validate a clinical prediction rule to differentiate between traumatic LP and SAH, based on the results of a retrospective cohort study in which 676 patients underwent LP (without previous CT).[70] SAH was confirmed in 49 (7.2%) patients using diagnostic imaging. The incidence of traumatic LP was 24.4%, and the clinical prediction rule of $>2000x10^6$/L RBCs and/or presence of xanthochromia (as in Perry 2015) had a sensitivity of 81.6% (95% CI 68.0 to 91.2) and a specificity of 97.3% (95% CI 95.7 to 98.4). The authors identified no clinical factors that would improve the sensitivity of this decision rule without decreasing specificity. These results are not directly comparable to those reported in Perry *et al.* (2015),[63] as this population was not pre-screened with CT.

Finally, Valle Alonso *et al.* included 74 patients who underwent LP (method of analysis not specified) following negative CT within six hours of symptom onset (the full study population also included 11 patients with SAH on CT).[55] LP was positive in one patient and inconclusive in two patients, however, further imaging ruled out bleeding in all three patients. No SAH cases were reported in the following six months, but seven patients experienced post-puncture headache, two of whom were admitted for pain control.

In summary, spectrophotometry-based CSF analysis appeared to have a higher sensitivity but lower specificity than visual inspection for xanthochromia. However, many studies assessing LP were of insufficient size to capture the few patients missed by CT. It appears from these studies, however, that spectrophotometric CSF analysis is 100% sensitive to SAH cases and is useful for identifying other pathologies such as meningitis.

CT Angiography

Two studies by Alons *et al.* in 2015 and 2018 evaluated the diagnostic accuracy of CTA in patients who had previously undergone non-contrast CT to rule out SAH.[71, 72] Alons (2015) was a retrospective cohort study that included 70 patients, none of whom had SAH.[71] Vascular abnormalities were identified in 13 (19%) patients, eight of which were incidental aneurysms; three were clipped and three were coiled. Other pathologies identified included cerebral venous thrombosis and reversible cerebral vasoconstriction syndrome. The second Alons study (2018) included 88 patients, and again no cases of SAH were identified.[72] Five (5.7%) patients had vascular abnormalities identified on CTA; one of which was an aneurysm, treated with clip ligation. There were also cases of cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, and a cervical dissection. One patient experienced an allergic reaction to the iodinated contrast media.

History and examination

Three studies explored the use of historical and emergent clinical factors as predictors for SAH in alert patients with non-traumatic acute severe headache. Two of these studies were retrospective cohort studies,[73, 75] while the third was a prospective cohort study.[74]

Backes *et al*. included a total of 247 patients meeting the review inclusion criteria.[75] The authors explored the use of neurological examination for neck stiffness as a predictor of SAH. SAH was

identified using CT or LP in 114 (46%) patients. Neck stiffness was identified in 82 patients, although this was mild or ambiguous for 18 of these patients. Neck stiffness appeared to be a stronger predictor of SAH in patients assessed between 6-72 hours since symptom onset than those presenting within 6 hours of onset. Sensitivity was 59.5% (95% CI 47.4 to 70.7) and specificity was 93.1% (95% CI 84.5 to 97.7) in those assessed within 6 hours, while sensitivity was 86.2% (95% CI 68.3 to 96.1) and specificity was 83.3% (95% CI 69.8 to 92.5) in those assessed between 6 and 72 hours since symptom onset. Presence of neck stiffness was more strongly predictive of SAH in patients with other high-risk clinical characteristics, such as in those aged 40 or over, those with vomiting, and those who experienced transient loss of consciousness.

Locker *et al*. included 353 patients, 36 of whom met the criteria for this review, i.e. with first or worst headache of this character and normal neurological examination.[73] Four characteristics were selected as predictors of secondary headache, these were: age >65 years, temperature >38◦C, systolic BP >160 mmHg, and presence of neck stiffness. The presence of at least one of these features in the whole study population predicted secondary headache with a sensitivity of 37.8% and specificity of 82.1%.

Perry *et al*. (2005) recruited 747 alert, neurologically intact patients with acute headache peaking within 1 hour of onset.[74] This study examined the predictive value of a physician's patient assessment for predicting SAH, without the use of a clinical decision rule. The sensitivity of 'clinical suspicion' was 93% (95% CI 81 to 97), and specificity was 49% (95% CI 45 to 53).

3.4.2 Cost-effectiveness studies

Results of both Malhotra *et al*. and Ward *et al*. suggest that no follow up to a negative CT is not a cost-effective diagnostic strategy.[78, 79] The Malhotra study found no follow up to be dominated by LP, i.e. LP was less costly but more effective. Sensitivity analysis suggested that LP remains the most cost-effective strategy unless CT sensitivity exceeds 99.2% or SAH prevalence is below 3.2%.[78] The Ward study found no follow up to be a cheaper option compared to other active diagnostic strategies including LP, and that no follow up produced greater health benefits compared with CTA and MRA (primarily due to the complication rates associated with these strategies).[79] Lower health benefits compared to LP, however, led Ward to conclude that LP was the more cost-effective strategy. Similar to the Malhotra study, sensitivity analysis conducted in the Ward study showed that cost-effectiveness of no follow up improved as the sensitivity of CT increased.[79]

The results of the Taylor study, which did not consider costs, however, stands in contradiction to the findings of both Malhotra and Ward. This study suggested that the harms associated with LP are highly likely to outweigh the clinical benefits and that no follow up is likely to be the most beneficial diagnostic strategy. This led Taylor to conclude that the use of CT followed by LP should be revisited as the procedure may be doing more harm than good.[76]

The results reported by Taylor *et al.* are primarily driven by the consequences of over-diagnosis which can lead to surgery-related morbidity and mortality in otherwise healthy patients. Examination of the Malhotra and Ward studies suggests this is an issue which may have been overlooked, thus explaining the difference in results. Malhotra appears to only account for the possibility of traumatic LP, while Ward assumes 100% specificity of LP, which does not appear to be supported by published estimates of the diagnostic accuracy of LP.

Comparisons of alternative active diagnostic strategies compared with LP suggest that LP after negative CT is likely to be both the most clinically effective and cost-effective diagnostic strategy. In the Malhotra/Wu *et al.* study this is primarily a consequence of false positives associated with CTA

and MRA which both increase costs while leading to overtreatment.[77, 78] In Ward *et al.*, the superiority of LP appears to be due to the higher complication rates associated with CTA and MRA; over-diagnosis was not considered by Ward *et al.*[79] Both Malhotra/Wu *et al.* and Ward *et al.* conclude that LP should be retained as a diagnostic strategy for SAH.[77-79]

3.4.3 Systematic reviews

The good quality systematic review by Carpenter *et al.* included 20 studies assessing various aspects of the management of patients with acute headache or other symptoms or signs suggestive of spontaneous SAH; only studies that reported sufficient data to construct 2x2 tables were included.[25] Eleven of the included studies did not meet the inclusion criteria for our review as they did not restrict their inclusion criteria to neurologically intact sudden onset severe headache patients (n=8), did not include a relevant intervention (n=2) or assessed outdated CT technology (n=1). Therefore, the findings of this review may not be entirely applicable to neurologically intact acute headache patients presenting in current NHS practice.

Eight of the included studies described the diagnostic accuracy of 22 components of patients' clinical history and six studies described the diagnostic accuracy of four physical examination tests for SAH; a history of subjective neck stiffness (likelihood ratio [LR]+ 4.12; 95% CI 2.24 to 7.59, 5 studies, I^2=86%), and neck stiffness on physical examination (LR+ 6.59; 95% CI 3.95 to 11.0, 3 studies, I^2=65%) were the individual findings most strongly associated with SAH. However, there was significant statistical heterogeneity for most of the pooled results. There was more consistency in positive likelihood ratio results for altered mental status (LR+ 2.18; 95% CI 1.33 to 3.56, 4 studies, I^2=0%) and focal neurological deficit (LR+ 3.26; 95% CI 1.93 to 5.52, 4 studies, I^2=9%). Other aspects of history and physical examination assessed include blurred vision, burst or explode at onset, exertion at onset, loss of consciousness, nausea, photophobia and vomiting.

The review also assessed the four related Canadian clinical decision rules, although only one study by Perry *et al.* was included,[31] therefore, there were insufficient studies to undertake meta-analysis. The review reported that Rule 1 appears sufficient to rule out SAH (LR- 0.06; 95% CI 0.01 to 0.22), was uncomfortable to use for only 18% of surveyed emergency physicians, was misinterpreted in 4.7% cases and would theoretically decrease CT and/or LP testing rates from 84% to 74%. However, the Ottawa SAH Rule more accurately rules out SAH (LR- 0.02; 95% CI 0.00 to 0.39) but could increase CT and/or LP testing rates if strictly applied. The authors concluded that existing SAH clinical decision rules await external validation, but offer the potential to identify subsets most likely to benefit from post-CT LP, angiography or no further testing.

Five of the included studies assessed the diagnostic accuracy of non-contrast CT (at any time interval from headache onset); pooled sensitivity was 94% (95% CI 91 to 96, I^2=74%), specificity was 100% (95% CI 100 to 100, I^2=33%) and the negative likelihood ratio was 0.07 (95% CI 0.03 to 0.17, I^2=78%). Two studies reported the diagnostic accuracy of non-contrast CT performed within 6 hours of symptom onset; pooled sensitivity was 100% (95% CI 98 to 100, I^2=0%), specificity was 100% (95% CI 99 to 100, I^2=81%) and the negative likelihood ratio was 0.01 (95% CI 0 to 0.04, I^2=0%). Two studies assessed CT beyond 6 hours of symptom onset; pooled sensitivity was 89% (95% CI 83 to 93, I2=89%), specificity was 100% (95% CI 100 to 100, I^2=96%) and the negative likelihood ratio was 0.07 (95% CI 0.01 to 0.61, I^2=63%).

Six studies assessed CSF analysis for xanthochromia using variable methods (including visual inspection and spectrophotometry). Spectrophotometry, rather than visual inspection of CSF, is used in current NHS practice. Two studies assessed spectrophotometric bilirubin using the UK NEQAS

algorithm with pooled sensitivity of 100% (95% CI 59 to 100, I^2=0%), specificity was 95% (95% CI 93 to 96, I^2=98%), LR+ was 15.23 (95% CI 1.58 to 146.73, I^2=97%) and LR- was 0.13 (95% CI 0.02 to 0.83, I^2=0%). Using the pooled estimates of diagnostic accuracy and testing risks and benefits, the authors estimated that LP only benefits CT negative patients when the pre-LP probability of SAH is on the order of 5%, which corresponds to a pre-CT probability greater than 20%.

The systematic review by Dubosh *et al*., with an unclear risk of bias, aimed to determine the sensitivity of non-contrast CT using modern scanners (16-slice technology or greater) when performed within 6 hours of headache onset to exclude SAH in neurologically intact adult patients presenting with a history concerning for spontaneous SAH.[21] The review included five studies, although two of the studies did not meet the inclusion criteria for our review as they did not restrict their inclusion criteria to neurologically intact sudden onset severe headache patients (peaking within one hour of onset). Therefore, the findings of this review may not be entirely applicable to neurologically intact acute headache patients presenting in NHS practice. The pooled sensitivity of CT was 98.7% (95% CI 97.1 to 99.4, I^2=31%), specificity was 99.9% (95% CI 99.3 to 100) and the negative likelihood ratio was 0.01 (95% CI 0.003 to 0.034, I^2=0%).

The systematic review conducted to derive American College of Emergency Physicians (ACEP) clinical policy, with a high overall risk of bias, assessed four clinical questions; three of which were relevant to our review.[80] The review included eleven studies between these three clinical questions, four of which did not meet the inclusion criteria for our review as they did not restrict their inclusion criteria to neurologically intact sudden onset severe headache patients or did not include a relevant intervention. Therefore, the findings of this review may not be entirely applicable to neurologically intact acute headache patients presenting in NHS practice.

The ACEP review assessed whether there are risk-stratification strategies that reliably identify the need for emergent neuroimaging in the adult ED patient presenting with acute headache. The authors concluded that the only risk stratification that currently reliably identifies the need for neuroimaging is the Ottawa SAH Rule, but because of its poor specificity, many patients will have negative workups exposing them to radiation and additional testing. Additional protocols using biomarkers and validated decision rules should be investigated to provide clinicians with both the necessary sensitivity and specificity in this workup. A recommendation was made to use the Ottawa SAH Rule for patients presenting to the ED with a normal neurologic examination result and peak headache severity within one hour of onset. Although the presence of neck pain and stiffness on physical examination is strongly associated with SAH, the review recommended not using a single physical sign and/or symptom to rule out SAH.

The review also assessed whether normal non-contrast CT performed within 6 hours of headache onset precludes the need for further diagnostic workup for SAH in adult ED patients presenting with acute headache. The authors concluded that with the addition of newer studies incorporating advanced CT scanning capabilities, the clinical strategy for evaluating SAH has evolved to provide clinicians an alternative to the previously suggested protocol of head CT followed by LP. They concluded that through a careful history and physical examination, clinicians can use the high sensitivity of non-contrast head CT within the first 6 hours of symptom onset to reliably rule out SAH in neurologically intact patients, without the performance of LP, and that a normal non-contrast head CT performed within 6 hours is sufficient to preclude further diagnostic workup for SAH. If clinical suspicion remains high despite the negative findings, further evaluation may be pursued.

Finally, the review assessed whether CTA of the head is as effective as LP to safely rule out SAH in the adult ED patient who is still considered to be at risk of SAH after a negative non-contrast head CT. The review stated that the main argument in favour of LP is that it is very sensitive for detecting SAH. However, limitations include a very low testing yield, a high rate of traumatic tap, high rates of uninterpretable LP test results, physician time to perform the procedure, patient preference, and the high rate of post-LP headache. CTA avoids many of the negatives associated with LP and appears to be an excellent test for detecting cerebral aneurysms. However, the major disadvantage is that it diagnoses aneurysms rather than bleeding; the aneurysm may be an incidental finding and may lead to unnecessary invasive cerebral procedures. CTA also exposes the patient to additional radiation risk and decreased LP diagnosis of certain other medical diseases. The review concluded that CTA appears to be a reasonable alternative to LP to safely rule out SAH from an intracranial source and recommended that clinicians should use shared decision making to select the best diagnostic testing modality after weighing potential pros and cons of LP versus CTA.

3.4.4 Clinician surveys

A UK-based survey of consultants in emergency medicine and neuroscience specialties from four major neuroscience centres in London, which was of unclear quality, aimed to establish whether the different clinical specialties had different risk tolerances for the investigation of suspected spontaneous SAH and to establish if their risk-benefit appraisals concur with current guidelines.[27] Seventeen ED clinicians and 30 neurospecialists indicated their risk tolerance for missed SAH diagnosis by recording the highest post-test probability at which they would stop investigations to diagnose SAH; ED clinicians accepted almost 3 times the risk of a missed SAH diagnosis compared with the neuroscience specialists (2.8% vs 1.1%; p=0.03). Neurospecialists were more likely to advocate routine LPs compared with ED clinicians (74% vs 39%; p=0.01). Only 39% of ED clinicians agreed with the current guidelines that LP is mandatory in suspected SAH when initial CT is negative, compared with 89% of neurospecialists (p=0.0001). ED clinicians were more inclined to omit the LP if a negative CT had been obtained within 6 hours of headache onset (35% vs 3%; p=0.002). Fewer than 10% respondents in each group indicated a willingness to substitute LP in favour of a cheaper or quicker test if it carried an increased risk of missed diagnosis; however, ED clinicians were more likely to accept an increased risk of misdiagnosis for the benefit of a non-invasive test (38% vs 11%; p=0.02). 91% of clinicians in both groups reported direct personal experience of missed SAH due to incomplete investigation; 65% of ED clinicians and 55% of neurospecialists had given evidence in a medicolegal capacity. 22% clinicians reported that they would feel obliged to investigate SAH if it had been raised and documented as a potential diagnosis, irrespective of their own clinical judgement.

The other two UK-based clinician surveys were poor quality. One surveyed 62 doctors at a teaching hospital (the title of the paper suggests that they surveyed acute medicine clinicians, although it was not explicitly stated) to assess knowledge of acute headache management and the need for a guideline.[83] Almost all clinicians indicated that they would assess neck stiffness (98.4%), upper and lower limb power (93.5%), presence of rash (87.1%), sensation (79%) and test plantars and reflexes (77.4%). Clinicians indicated that they were confident in recognising meningitis, SAH, acute migraine and encephalitis as causes of headache and were confident in the initial management of meningitis, temporal arteritis, encephalitis and SAH. 94.6% respondents indicated that they would find a Trust acute headache guideline useful. The other UK-based survey used a clinical vignette of a 45-year-old man presenting with thunderclap headache, with a pristine neurological examination, to explore the approach of 160 emergency medicine and acute medicine clinicians in Scotland.[85] 89% clinicians elected to perform non-contrast CT as their first investigation, 1% chose CT/MR angiogram, 6% would refer elsewhere and 3% would discharge the patient without investigation. If the initial imaging

was negative, 84% would then proceed to LP, 1% would proceed to CT/MR angiogram, 9% would refer elsewhere and 6% would discharge the patient home without performing a second investigation. Of those patients who chose LP as their second investigation, 94% would be content that no further investigation was required if LP was also normal; 57% would refer elsewhere and 37% would discharge the patient. Only 36% respondents stated that they always transported CSF samples protected from light; 21% sometimes protected from light and 43% never protected from light. 22% respondents were aware of a local protocol for the investigation of acute headache.

A large, good quality survey of 1149 emergency physicians from Australia, Canada, the UK and the USA aimed to determine ED practice for investigating acute headache patients, whether emergency physicians would consider using a clinical decision rule for acute headache and what the required sensitivity of such a rule would be for SAH.[82] 49.5% respondents thought all acute headache patients should be investigated with CT. 57.4% thought that if CT was normal, all such patients should have LP (highest in the UK: 66.0%, lowest in the USA: 51.4%). 32.5% thought that performing LP in such patients without first getting a CT was a safe practice (highest in Canada: 45.3%, lowest in UK: 11.1%). 59.7% respondents manage these patients with CT and/or LP always or most of the time. 95.7% reported they would consider using a well-validated clinical decision rule in acute headache patients to determine the need for investigations to rule out SAH. Physicians in the UK were willing to accept a slightly lower sensitivity than those in Australia, Canada and the US. Overall, the median sensitivity deemed to be required by such a rule was 99% (interquartile range 98-99%).

A good quality survey of 168 emergency medicine clinicians at two academic hospitals and four community hospitals in urban and suburban settings in USA and Canada aimed to assess physician knowledge on imaging and LP test performance and used case-based scenarios to assess practice pattern, variation and adherence to clinical policy.[86] 89% clinicians indicated that CT has high sensitivity (defined as 91-100%) for SAH within 6 hours of symptom onset, although there were significant differences observed by site, academic setting and experience level. 60% indicated that CT has a lower sensitivity (defined as 81-90%) for SAH between 6-12 hours of symptom onset; 21% still rated CT sensitivity as high between 6-12 hours. 40% clinicians indicated that xanthochromia has a high sensitivity for SAH after 6 hours of symptom onset and 63% indicated that spectrophotometry has a high sensitivity for SAH after 6 hours. Most clinicians were able to list the high-risk clinical features of SAH, however, only 55% indicated that they used validated clinical decision rules in their practice (clinicians from an academic setting were more likely than those from a non-academic setting: 69% vs 33%). For the four case presentations within 6 hours of symptom onset, 66% clinicians indicated that they would perform a CTA after negative CT in at least one case, 34% indicated that they would perform LP after negative CT in at least one case, and 10% indicated both CTA and LP after negative CT in at least one case.

An Australian study, which was of unclear quality, conducted semi-structured interviews with 15 emergency medicine clinicians to identify factors that influence their decisions about diagnostic testing for headache patients, suspicious for SAH, after a normal brain CT.[81] Sixteen factors were identified, grouped into six categories: patient interaction, practice evidence, patient profile, consulting, external influences and experiential factors. Patient interaction was at the forefront of the identified factors; when the best diagnostic approach is uncertain, patient interaction/preference appeared to be the most important factor in deciding an approach. Patient risk profile, practice evidence and guidelines were also important. Other influencing factors included experiential factors of the clinician (past outcomes), consultation with colleagues and external influences where practice location and work processes impose constraints on test ordering external to the preferences of the clinician or patient. Participants did not consider that fear of litigation influenced their practice.

A poor quality Australian study surveyed 878 emergency medicine physicians and trainees to establish current clinical practice on several aspects of the investigation of 'acute headache'.[84] 47.3% respondents agreed or strongly agreed that brain CT (3rd generation or later) within 6 hours of headache onset is sufficient to exclude a diagnosis of SAH, whilst 42.1% disagreed or strongly disagreed. 14.4% agreed or strongly agreed that brain CT within 12 hours of headache onset is sufficient to exclude SAH, whilst 71.3% disagreed or strongly disagreed; trainees were more likely to be satisfied with a 12 hour CT than emergency physicians (17.6% vs 11.8%). 79.8% agreed or strongly agreed that CT images are required to be reported by a consultant radiologist (not necessarily a neuroradiologist); qualified emergency physicians were significantly more likely to agree or strongly agree with this statement than trainees (83.7% vs 75%; p=0.002). 72.4% respondents disagreed or strongly disagreed that 'a decreasing RBC count excludes SAH'; only 14.7% agreed or strongly agreed. For detection of xanthochromia in the CSF, 57.7% of respondents felt that spectrophotometry (vs visual inspection) is necessary to accurately diagnose SAH, 25% were unsure and 17.3% disagreed or strongly disagreed. After a negative CT scan, 88% of respondents preferred LP to CTA for further investigation of SAH.

4 Qualitative study

The purpose of the qualitative study was to explore patients' views and experiences of the management of headache in the ED and the acceptability of different care pathways. Originally, we aimed to conduct three focus groups with patients that had attended an ED at a single NHS Trust in the North of England. However, the qualitative study was severely impacted by the COVID-19 pandemic. In particular, changes to the patient pathway, the reduced number of patients attending hospital at this time and the conversion of admission wards to COVID-19 wards significantly affected the recruitment of patients, as well as the time that clinical teams had available to support the study. As a result, we were unable to complete the qualitative study and stopped identifying patients in November 2020.

In this chapter we outline our original research plan and the changes that we made in response to the COVID-19 pandemic. In doing so, we aim to not only provide a transparent account of the methods we adopted, but hope that the strategies we employed to try to identify and recruit patients are helpful to those planning or undertaking qualitative research during the COVID-19 pandemic or in other challenging environments.

4.1 Ethical approval

The qualitative study was categorised as a service evaluation and was approved by Leeds Teaching Hospitals NHS Trust on 31st July 2020 and the University of York Health Sciences Research Governance Committee on 3rd August 2020. Due to the difficulties that the clinical teams faced in trying to identify potentially eligible patients to the qualitative study during the COVID-19 pandemic (see below), we sought approval to also conduct semi-structured interviews. Adopting this change meant that we could schedule interviews as soon as potentially eligible patients were identified and avoid any delays associated with having to wait for sufficient numbers of patients to conduct a focus group.

4.2 Sampling and recruitment

We were interested in inviting neurologically intact patients who presented to hospital with sudden onset severe headache (peaking within one hour), who had undergone CT and in some cases LP to rule out SAH to our qualitative study. Patients that indicated an interest in taking part in the qualitative study were provided with a participant information sheet (Appendix 5, Section 8) and asked to complete a consent to contact form (Appendix 6, Section 8), which was then transferred to the qualitative research team. All participants who expressed an interest in the qualitative study were informed that a qualitative researcher would contact them via telephone or email, depending on the preferences of the interviewee, to arrange a time for the interview/focus group to take place. We planned for participants to either complete and return a hardcopy of the consent form (Appendix 7, Section 8) to the qualitative researcher via post or to complete an e-consent form depending on their preferences. We also planned to obtain verbal consent at the start of each interview/focus group.

We aimed to purposively sample 20-25 patients to ensure maximum variation across the sample according to age, gender and diagnosis. However, due to recruitment to the qualitative study being far lower than anticipated, we adopted a convenience sample frame, with selection based on those who indicated an interest to take part and completed consent to contact forms at the study site.

Originally, we planned for a research nurse to identify potentially eligible patients from the ED to the qualitative study. However, changes to the clinical pathway and resourcing issues at the study site meant this was not possible. Instead, patients were identified by a consultant and/or trainee(s) from

neurology and acute medicine. In anticipation of the challenges associated with recruiting patients to a primary research study during the COVID-19 pandemic, we adopted a range of additional methods to try to maximise recruitment. We held meetings via Zoom with staff from acute medicine and neurology departments to ensure that they understood what was involved in approaching patients to the qualitative study. A staff manual was also developed and distributed to staff which outlined: the aim of the qualitative study, which patients should be approached, how staff should approach patients and processes for storing and sending study documents to the qualitative research team. Regular emails and/or telephone calls were also held between the qualitative team and clinical staff that were involved in identifying patients throughout our recruitment period to discuss any challenges with identifying patients and the implications of COVID-19. Upon receipt of patients' details, the qualitative team attempted to make contact with patients three times by telephone and email before a patient was considered a 'decliner.' It was agreed that any further attempts to contact patients could be considered coercion.

4.3 Data collection

Due to the need for social distancing, we planned for all data to be collected via telephone or the videoconferencing programme 'Zoom.' A topic guide (Appendix 8, Section 8) for the interviews and focus groups was developed by the research team. We planned to ask patients about their experiences of presenting to the hospital with sudden onset severe headache and their experiences of diagnosis and treatment. More specifically, we aimed to understand patients' views on different care pathways for managing sudden onset severe headache, the acceptability of not having a LP in the event of a negative CT scan, the level of risk patients would find acceptable if they were, or were not, given a LP and their views on receiving LP as an outpatient.

Regular changes in local and national restrictions that were put in place and the implications of these on staff time, patient pathways and the likelihood of patients attending hospital with sudden onset severe headache made it difficult to judge when staff should start to approach patients about the qualitative study and how long to continue to try to identify patients. Following discussions with the clinical co-applicants and site staff, participating departments began approaching patients about taking part in the qualitative study in September 2020. On 5th November 2020, England entered a second national lockdown. At this time, only two patients had agreed to take part in a qualitative interview (seven consent to contact forms had been received by the qualitative team). Previous research considers 10-12 participants to be the minimum number of interviews that can be conducted to draw meaningful conclusions.[87] When considering our recruitment rate, which meant we would not have reached our initial target of 20-25 patients within 6 months, and the tightening of COVID-19 restrictions nationally, a decision was made to stop recruitment and to not conduct the two interviews that we had scheduled.

5 Patient and clinician engagement

The project team included four clinicians with expertise in emergency medicine, acute medicine, neurology, stroke and headache, and a patient collaborator with experience of presenting to the ED with sudden onset severe headache. Three additional patients who presented to the ED at Leeds Teaching Hospitals NHS Trust with sudden onset severe headache and additional clinicians with expertise in emergency medicine, acute medicine, neurology, neuroradiology and an NHS commissioner were recruited to our advisory group (advisory group members are listed on page 2 of this report).

The patients' and clinicians' perspectives were collected at various points through the project including at team and advisory group meetings and during protocol development. The patients' and clinicians' perspectives were used to help with the interpretation of the results of the systematic review.

Discussions at team meetings highlighted a lack of consistency regarding inpatient versus ambulatory LP; practice varied between (a) undertaking LP on an ambulatory basis, (b) undertaking LP while the patient is still in hospital, but then discharging the patient to the ambulatory care unit while the result is awaited (which can take 2-3 days at a district general hospital) or (c) keeping the patient in hospital until the LP has been undertaken and the result is received.

In November 2020, meetings were held with members of the project team and advisory group to discuss the findings of the project, draw conclusions and make recommendations for further research. Due to COVID-19 restrictions, meetings had to be held via Zoom, Microsoft Teams or telephone, rather than face to face.

Clinical and patient members of the project team and advisory group were unsurprised by the findings relating to the diagnostic accuracy of CT, LP and the Ottawa SAH Rule in neurologically intact adults presenting with non-traumatic sudden onset severe headache (peaking within one hour). They highlighted the importance of involving the patient in the decision of whether additional testing is required after a negative CT result; communicating the level of certainty in the diagnostic test result and possible adverse effects of subsequent diagnostic tests to aid the decision-making process.

Clinicians discussed the variation in practice regarding inpatient versus ambulatory LP, when LP is required for reassurance; two patient advisors and the patient collaborator expressed a preference for ambulatory LP. Owing to the lack of studies assessing the setting for LP, it was felt that further primary research may be useful to address this question.

The difficulties associated with diagnosing SAH in patients who present several days after headache onset was also discussed; there is a lack of guidance and consistency in how these patients are assessed. It was concluded that further primary research would be informative in order to develop guidance for this patient subgroup.

6 Discussion

6.1 Summary of findings

Fifty-one studies were included in the systematic review; 37 cohort/before and after studies, four cost-effectiveness studies, three systematic reviews and seven clinician surveys. Twelve of the cohort/before and after studies had a low risk of bias for all domains, the other 25 were at risk of bias. All four of the cost-effectiveness studies had specific quality issues and were undertaken from a US Medicare perspective, limiting their reliability and relevance to UK decision makers. The systematic reviews and clinician surveys were of variable quality.

Evidence on the accuracy of the Ottawa SAH Rule for ruling out SAH in alert patients with atraumatic sudden onset severe headache demonstrated that it is highly sensitive, but lacks specificity, suggesting that it's use would result in a high proportion of SAH-negative patients undergoing further investigation with CT and/or LP unnecessarily.

Evidence on the diagnostic accuracy of CT demonstrated that it is highly accurate when undertaken within 6 hours of headache onset and when images are assessed by a neuroradiologist or radiologist who routinely interprets brain CT images. Around 1018 patients may need to undergo additional testing to identify one case of SAH in patients who were classed as negative by CT undertaken within 6 hours. This suggests that a CT-only strategy could reduce the burden of adverse events and resource use associated with potentially unnecessary LP and CTA procedures in patients who receive CT within 6 hours of headache onset, with only a very minimal increase in the risk of missed diagnoses. Therefore, the additional costs associated with the procedures and treatment of adverse events following up all negative CT scans in this population may outweigh the benefits of identifying additional cases. Nevertheless, it is likely that the risk tolerance of individual clinicians and patients will ultimately determine whether further investigations are undertaken in the absence of guidelines based on UK validation studies. The diagnostic accuracy of CT beyond 6 hours from headache onset was shown to be considerably lower, therefore, LP is more likely to be of benefit to patients who have CT beyond 6 hours from headache onset, where a clinical suspicion of SAH remains.

The diagnostic accuracy of LP, using spectrophotometric assessment of CSF samples, was highly sensitive but had a false negative rate of 5%. Very few studies reported rates of LP-related complications resulting in patients returning to the ED; where reported these ranged from 5.3-9.5%.

The pathway of non-contrast CT followed by LP was highly sensitive for detecting SAH, although specificity was quite low in some studies, owing to the high false-positive rate for LP. The CT-LP pathway also identified other significant pathologies, such as intracerebral haemorrhage, brain tumour, and meningitis. This may mean the value of this pathway could extend beyond SAH in a way that makes LP cost-effective in the acute headache population as a whole, even if not the case when considering only the identification of SAH.

The four cost-effectiveness studies modelled different diagnostic strategies (LP, CT angiography, MRI/MRA or no further follow-up) for patients presenting with thunderclap headache who had a negative CT result. The results suggest that LP is likely to be the most clinically effective and cost-effective strategy, however, all four studies had specific quality issues and were undertaken from a US Medicare perspective, limiting their reliability and relevance to UK decision makers.

Our findings were consistent with the three relatively recent systematic reviews that were identified; all three SRs concluded that CT within 6 hours of symptom onset was highly accurate and may be considered sufficient to preclude further diagnostic workup for SAH. Two of the SRs assessed clinical

decision rules to identify subsets of headache patients most likely to benefit from testing and concluded that the Ottawa SAH Rule accurately rules out SAH but could increase CT and/or LP testing rates if strictly applied.

Seven surveys explored clinicians' approach to the investigation of patients with sudden onset severe headache. The survey findings suggest that decisions relating to the management of patients with acute headache vary according to clinician specialty and experience level, academic setting and country. Patient interaction/preference was also an important factor influencing decision making.

Patient and clinician engagement

Project team and advisory group members were unsurprised by the findings of the systematic review relating to the diagnostic accuracy of CT, LP and the Ottawa SAH Rule. They highlighted the importance of involving the patient in the decision of whether additional testing is required after a negative CT result; communicating the level of certainty in the diagnostic test result and possible adverse effects of subsequent diagnostic tests to aid the decision-making process. Clinicians also discussed the variation in practice regarding inpatient versus ambulatory LP; two patient advisors and the patient collaborator expressed a preference for ambulatory LP, when LP is necessary.

6.2 Strengths and limitations

Strengths

The systematic review used a comprehensive search strategy to identify all relevant evidence on the assessment of patients with sudden onset severe headache, suspicious of SAH. Several studies reported sufficient data to reconstruct 2x2 tables and were synthesised using bivariate meta-analysis. Where appropriate, subgroups were identified and analysed separately to account for underlying differences in diagnostic strategies; the diagnostic accuracy of CT conducted within 6 hours of headache onset was analysed separately from CT at any timepoint from headache onset and the accuracy of different methods of CSF analysis (visual inspection and spectrophotometry) was also assessed. Studies that did not report sufficient data to be included in meta-analyses were described narratively and their results compared with results of the meta-analyses, where appropriate.

In addition to the primary studies assessing diagnostic accuracy, up to date systematic reviews, cost-effectiveness studies and clinician surveys were also identified and summarised in a narrative synthesis. The quality of all included studies was assessed using criteria relevant to the study design and the applicability of studies to UK practice was assessed.

The project team consisted of researchers with extensive experience in systematic review methods, clinicians with expertise in emergency medicine, acute medicine, neurology, stroke and headache, and a patient collaborator with experience of presenting to the ED with sudden onset severe headache. The research was also informed by the views of an advisory group, consisting of additional emergency medicine, acute medicine, neurology and neuroradiology clinicians, an NHS commissioner and three additional patients who presented to Leeds Teaching Hospitals NHS Trust with sudden onset severe headache. The systematic review results were presented to the project team and advisory group towards the end of the project and their input was combined with the results to inform the conclusions and recommendations for further research.

Limitations

Despite the precisely defined inclusion criteria in this review, there remained substantial heterogeneity in the study methods and population characteristics of included studies. The evidence base included too few patients, given the rarity of SAH events and missed diagnoses, to provide definitive estimates of the diagnostic accuracy of the strategies discussed. This led to considerable heterogeneity in the

results of some meta-analyses, and potentially meant uncertainty was underestimated in others. Furthermore, the prevalence of SAH was higher in most included studies than in normal NHS practice, which has implications for the applicability of pre- and post-test probability estimates, and the NNT figures presented here.

Despite employing a range of strategies to try to maximise recruitment to the qualitative study, restrictions put in place as a result of the COVID-19 pandemic meant we were unable to recruit a sufficient number of patients to draw meaningful conclusions. Therefore, we were unable to complete the qualitative study.

6.3 Gaps in the evidence base

There were no studies assessing the diagnostic accuracy of other clinical decision rules for SAH; only the Ottawa SAH Rule, along with earlier rules developed by Perry and colleagues that were refined to develop the Ottawa SAH Rule, have been validated.

No studies were identified assessing the setting for LP, therefore, further primary research would be useful to determine the safety and acceptability of ambulatory LP in those patients who require further assessment after negative non-contrast CT.

The difficulties associated with diagnosing SAH in patients who present several days after headache onset was highlighted by clinicians at the project team/advisory group meeting held in November 2020; there is a lack of guidance and consistency in how these patients are assessed. It was concluded that further primary research would be beneficial in order to develop guidance for the assessment of this small patient subgroup.

Evidence on the diagnostic accuracy of CT within 6 hours of headache onset was assessed in studies undertaken in Canada, the Netherlands and Spain, including a total of 2377 patients. A large 100-centre UK-based study plans to assess the accuracy of CT within 6 hours of headache onset and at different time points at hourly intervals (from 6 to 24 hours) after headache onset (SHED). This study is being undertaken between February and August 2021 by the Royal College of Emergency Medicine Trainee Emergency Research Network (Co-chief investigators: Professor Dan Horner from Salford Royal NHS Foundation Trust and Dr Tom Roberts, Musgrove Park Hospital, Taunton). Results are expected early in 2022 and will inform the diagnostic accuracy of CT within 6 hours and at different time points from headache onset. A comparison of the UK results with those of the earlier non-UK based studies will be very informative.

All the existing cost-effectiveness studies assessing diagnostic strategies for sudden onset severe headache patients were undertaken from a US Medicare perspective. A cost-effectiveness analysis undertaken from a UK perspective, bringing together the latest available data on benefits, harms and costs (including the planned UK-based SHED study), would be useful to inform decision makers on the value of further testing.

6.4 Conclusions

The evidence suggests that in view of its high false positive rate, the Ottawa SAH Rule does little to aid clinical decision making for sudden onset severe headache patients. Use of the tool would potentially result in around 76% SAH-negative patients undergoing further investigation with CT and/or LP unnecessarily, resulting in greater healthcare resource use and higher rates of adverse events. There was a lack of data to assess the accuracy of the Ottawa SAH Rule in patient subgroups by time to headache peak. The Ottawa SAH Rule was developed for use in patients whose headache peaked within one hour of onset, however patients who present with ‘thunderclap headache’, which

peaks within one minute, are more likely to have suffered a SAH. There were no studies of other clinical decision rules for SAH. Clinical advisors indicated that a variety of clinical decision rules are used in current NHS practice.

Non-contrast CT undertaken within 6 hours of headache onset, with CT images assessed by a neuroradiologist or radiologist who routinely interprets brain CT images, is highly accurate for identifying SAH. However, in centres without specialist neuroradiology expertise, the accuracy is likely to be lower; studies included in the meta-analysis benefited from neuroradiology expertise. CT undertaken beyond 6 hours from headache onset is much less sensitive for detecting SAH (sensitivity ≤90%). LP (with spectrophotometric CSF analysis using the UK NEQAS protocol) following negative CT was highly sensitive, although there was a 5% rate of false positives. Only two studies reported the rates of LP-related complications resulting in patients returning to the ED or hospitalisation; 5.3% and 9.5%. The pathway of non-contrast CT followed by LP was highly sensitive for detecting SAH, although specificity was quite low in some studies, owing to the high false-positive rate for LP. In view of the reduced sensitivity of CT beyond 6 hours from headache onset, LP may be beneficial in patients who have CT beyond 6 hours, where a clinical suspicion of SAH remains. The pathway also identified other significant pathologies, such as intracerebral haemorrhage, brain tumour, and meningitis. Clinician and patient advisory group members emphasised the importance of shared decision making when considering whether subsequent tests should be undertaken after receiving a negative CT result.

6.5 Recommendations for further research

Further primary research is recommended to compare inpatient LP versus LP on an ambulatory basis and to assess which patients may be suitable for ambulatory LP. This could be investigated by retrospectively reviewing the medical records of patients at different Trusts, comparing characteristics and outcomes of patients who underwent LP on an inpatient basis with those who underwent LP on an ambulatory basis.

Qualitative research would also be useful to understand the acceptability of different care pathways for managing sudden onset severe headache. Particular priority should be given to exploring patient views on not having LP in the event of a negative CT scan result, and of receiving LP on an ambulatory basis. However, it should be considered that patients who attend hospital during pandemics may not be representative of the 'usual' patient population and it is important that this work is undertaken at a time when the effects of COVID-19 are reduced and recruitment is achievable. In particular, it is important to ensure that changes to patient pathways and the reduced number of patients that attended hospital during the COVID-19 pandemic do not negatively affect recruitment to future qualitative studies.

Further research would also be beneficial in order to develop guidance for the assessment of the subgroup of patients who present several days after headache onset.

A decision model and cost-effectiveness analysis would allow existing evidence on diagnostic accuracy, harms and resource use to be drawn together and allow an appropriate assessment of the value of alternative decision rules and/or diagnostic strategies. In this regard, it is notable that no economic evaluations have been conducted from a UK perspective, with existing studies making substantively different assumptions about the diagnostic accuracy of alternative strategies and the harms associated with follow-up testing to CT. An up-to-date and comprehensive economic analysis may therefore be appropriate, and would enable the value of alternative diagnostic strategies to be considered in a coherent and well-established framework to allow a more definitive judgment of the

value of alternative strategies. An economic analysis could also offer other advantages to decision-makers as it could be extended to include analyses of both the value of information and value of implementation. The former quantifies the economic worth of future research to resolve decision uncertainty, while the latter considers the value of increasing adherence to guidelines and would thus help decision-makers judge the appropriateness of investing in policy initiatives to encourage uptake and best practice. This may be of particular value in this context in future, given the variability of current practice and the potential need for discouragement and disinvestment from follow-up testing.

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8 Appendices

Appendix 1: Literature search strategies

Database search strategies

MEDLINE ALL
(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)
via Ovid http://ovidsp.ovid.com/
1946 to February 07, 2020
Searched on: 10th February 2020
Records retrieved: 5141

1 Headache Disorders, Primary/ (771)
2 Headache/ (27331)
3 Vascular Headaches/ (1301)
4 Headache Disorders, Secondary/ (604)
5 Headache Disorders/ (2300)
6 (headache$ or head ache$).ti,ab. (81511)
7 LASH.ti,ab. (377)
8 (thunderclap$ or thunder clap$).ti,ab. (483)
9 (cephalalgi$ or cephalgi$).ti,ab. (1088)
10 (cranial adj2 pain$).ti,ab. (180)
11 (hemicrania or cephalea or cranialgia).ti,ab. (1015)
12 or/1-11 (91905)
13 Subarachnoid Hemorrhage/ (20706)
14 (Subarachnoid$ adj2 hemorr?ag$).ti,ab. (20324)
15 (Subarachnoid$ adj2 haemorr?ag$).ti,ab. (4429)
16 (Subarachnoid$ adj2 (bleed$ or blood)).ti,ab. (796)
17 (arachnoid$ adj2 (haemorr?ag$ or hemorr?ag$ or bleed$ or blood)).ti,ab. (210)
18 (SAH or SAHs).ti,ab. (10673)
19 or/13-18 (32469)
20 12 and 19 (2380)
21 Emergencies/ (39849)
22 Emergency Service, Hospital/ (66056)
23 exp Emergency Medical Services/ (136120)
24 Triage/ (11201)
25 ((emergency or emergencies or casualty) adj3 (room$ or department$ or service$ or unit$ or ward$ or centre$ or center$ or hospital$ or setting$ or clinic or clinics or care or healthcare or medical)).ti,ab. (149559)
26 triage$.ti,ab. (17352)
27 (accident$ adj2 (emergency or emergencies)).ti,ab. (4771)
28 21 or 22 or 23 or 24 or 25 or 26 or 27 (259901)
29 12 and 28 (3064)
30 20 or 29 (5154)
31 exp animals/ not humans/ (4671979)
32 30 not 31 (5141)

EMBASE
via Ovid http://ovidsp.ovid.com/
1974 to 2020 February 07
Searched on: 10th February 2020
Records retrieved: 13950

1 "headache and facial pain"/ (1630)
2 secondary headache/ (1161)
3 headache/ (208066)
4 vascular headache/ (574)
5 thunderclap headache/ (788)
6 exertional headache/ (102)
7 stabbing headache/ (226)
8 exp tension headache/ (7654)
9 (headache$ or head ache$).ti,ab. (129375)
10 LASH.ti,ab. (554)
11 (thunderclap$ or thunder clap$).ti,ab. (838)
12 (cephalalgi$ or cephalgi$).ti,ab. (1810)
13 (cranial adj2 pain$).ti,ab. (250)
14 (hemicrania or cephalea or cranialgia).ti,ab. (1411)
15 or/1-14 (253856)
16 subarachnoid hemorrhage/ (42006)
17 (Subarachnoid$ adj2 hemorr?ag$).ti,ab. (26796)
18 (Subarachnoid$ adj2 haemorr?ag$).ti,ab. (6005)
19 (Subarachnoid$ adj2 (bleed$ or blood)).ti,ab. (1037)
20 (arachnoid$ adj2 (haemorr?ag$ or hemorr?ag$ or bleed$ or blood)).ti,ab. (403)
21 (SAH or SAHs).ti,ab. (15683)
22 16 or 17 or 18 or 19 or 20 or 21 (50197)
23 15 and 22 (5697)
24 Emergency/ (52475)
25 Emergency health service/ (94019)
26 Hospital emergency service/ (4243)
27 Emergency ward/ (138545)
28 Emergency care/ (43804)
29 Emergency patient/ (3295)
30 ((emergency or emergencies or casualty) adj3 (room$ or department$ or service$ or unit$ or ward$ or centre$ or center$ or hospital$ or setting$ or clinic or clinics or care or healthcare or medical)).ti,ab. (227136)
31 triage$.ti,ab. (27449)
32 (accident$ adj2 (emergency or emergencies)).ti,ab. (6037)
33 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (380671)
34 15 and 33 (8994)
35 23 or 34 (13959)
36 (rat or rats or mouse or mice).ti. (1445465)
37 35 not 36 (13950)

Cochrane Central Register of Controlled Trials (CENTRAL)
via Wiley http://onlinelibrary.wiley.com/
Issue 2 of 12, February 2020
Searched on: 10th February 2020
Records retrieved: 581

The strategy below was used to search both CENTRAL and CDSR.

#1 MeSH descriptor: [Headache Disorders] this term only 135
#2 MeSH descriptor: [Headache] this term only 2318
#3 MeSH descriptor: [Vascular Headaches] this term only 40
#4 MeSH descriptor: [Headache Disorders, Secondary] this term only 55
#5 MeSH descriptor: [Headache Disorders, Primary] this term only 17
#6 (headache* or head next ache*):ti,ab,kw 31430
#7 LASH:ti,ab,kw 90
#8 (thunderclap* or thunder next clap*):ti,ab,kw 4
#9 (cephalalgi* or cephalgi*):ti,ab,kw 76
#10 (cranial near/2 pain*):ti,ab,kw 13
#11 (hemicrania or cephalea or cranialgia):ti,ab,kw 46
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 31574
#13 MeSH descriptor: [Subarachnoid Hemorrhage] this term only 579
#14 (Subarachnoid* near/2 hemorr?ag*):ti,ab,kw 1819
#15 (Subarachnoid* near/2 haemorr?ag*):ti,ab,kw 470
#16 (Subarachnoid* near/2 (bleed* or blood)):ti,ab,kw 55
#17 (arachnoid* near/2 (haemorr?ag* or hemorr?ag* or bleed* or blood)):ti,ab,kw 32
#18 (SAH or SAHs):ti,ab,kw 1011
#19 #13 or #14 or #15 or #16 or #17 or #18 2336
#20 #12 and #19 90
#21 MeSH descriptor: [Emergencies] this term only 1318
#22 MeSH descriptor: [Emergency Service, Hospital] this term only 2111
#23 MeSH descriptor: [Emergency Medical Services] explode all trees 3734
#24 MeSH descriptor: [Triage] this term only 285
#25 ((emergency or emergencies or casualty) near/3 (room* or department* or service* or unit* or ward* or centre* or center* or hospital* or setting* or clinic or clinics or care or healthcare or medical)):ti,ab,kw 18260
#26 triage*:ti,ab,kw 1717
#27 (accident* near/2 (emergency or emergencies)):ti,ab,kw 355
#28 #21 or #22 or #23 or #24 or #25 or #26 or #27 20016
#29 #12 and #28 509
#30 #20 or #29 592
#31 #20 or #29 in Trials 581
#32 #20 or #29 in Cochrane Reviews, Cochrane Protocols 11

Cochrane Database of Systematic Reviews (CDSR)
via Wiley http://onlinelibrary.wiley.com/
Issue 2 of 12, February 2020
Searched on: 10th February 2020
Records retrieved: 11

See above under CENTRAL for search strategy used.

Science Citation Index
via Web of Science, Clarivate Analytics https://clarivate.com/
1900 – 7th February 2020
Searched on: 10th February 2020
Records retrieved: 3758

21 3,758 #19 not #20
20 1,684,685 TI=(rat or rats or mouse or mice)
19 3,765 #18 OR #13
18 2,204 #17 AND #6
17 142,684 #16 OR #15 OR #14
16 3,670 TS=(accident* NEAR/2 emergenc*)
15 16,817 TS=triage*
14 131,101 TS=((emergency or emergencies or casualty) NEAR/3 (room* or department* or service* or unit* or ward* or centre* or center* or hospital* or setting* or clinic or clinics or care or healthcare or medical))
13 1,787 #12 AND #6
12 32,430 #11 OR #10 OR #9 OR #8 OR #7
11 9,617 TS=(SAH or SAHs)
10 416 TS=(arachnoid* NEAR/2 (haemorr$ag* or hemorr$ag* or bleed* or blood))
9 856 TS=(Subarachnoid* NEAR/2 (bleed* or blood))
8 3,745 TS=(Subarachnoid* NEAR/2 haemorr$ag*)
7 26,313 TS=(Subarachnoid* NEAR/2 hemorr$ag*)
6 73,503 #5 OR #4 OR #3 OR #2 OR #1
5 1,111 TS=(hemicrania or cephalea or cranialgia)
4 219 TS=(cranial NEAR/2 pain*)
3 1,139 TS=(cephalalgi* or cephalgi*)
2 584 TS=(thunderclap* or "thunder clap*")
1 72,669 TS=(headache* or "head ache*" or LASH)

Database of Abstracts of Reviews of Effects (DARE)
via http://www.crd.york.ac.uk/CRDWeb/
Inception – 31st March 2015
Searched on: 10th February 2020
Records retrieved: 19

The strategy below was used to search all three of the CRD databases - DARE, the HTA database and NHS EED.

1 MeSH DESCRIPTOR Headache Disorders, Primary 1
2 MeSH DESCRIPTOR Headache 81
3 MeSH DESCRIPTOR Vascular Headaches 0
4 MeSH DESCRIPTOR Headache Disorders, Secondary 2
5 MeSH DESCRIPTOR Headache Disorders 21
6 (headache* or "head ache" or "head aches") 806
7 (thunderclap* or thunder clap*) 1
8 (cephalalgi* or cephalgi*) 36
9 (cranial NEAR2 pain*) 0
10 (pain* NEAR2 cranial) 0
11 (hemicrania or cephalea or cranialgia) 2
12 (LASH) 3
13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 819
14 MeSH DESCRIPTOR Subarachnoid Hemorrhage 96
15 (Subarachnoid* NEAR2 (haemorrhag* or hemorrhag* or haemorrag* or hemorrag*)) 158
16 ((haemorrhag* or hemorrhag* or haemorrag* or hemorrag*) NEAR2 subarachnoid*) 5
17 (Subarachnoid* NEAR2 (bleed* or blood)) 0
18 ((bleed* or blood) NEAR2 Subarachnoid*) 1
19 (arachnoid* NEAR2 (haemorrhag* or hemorrhag* or haemorrag* or hemorrag* or bleed* or blood)) 6
20 ((haemorrhag* or hemorrhag* or haemorrag* or hemorrag* or bleed* or blood) NEAR2 arachnoid*) 0
21 (SAH or SAHs) 44
22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 168
23 #13 AND #22 4
24 MeSH DESCRIPTOR Emergencies 86
25 MeSH DESCRIPTOR Emergency Service, Hospital 442
26 MeSH DESCRIPTOR Emergency Medical Services EXPLODE ALL TREES 825
27 MeSH DESCRIPTOR Triage 111
28 ((emergency or emergencies or casualty) NEAR3 (room* or department* or service* or unit* or ward* or centre* or center* or hospital* or setting* or clinic or clinics or care or healthcare or medical)) 1927
29 ((room* or department* or service* or unit* or ward* or centre* or center* or hospital* or setting* or clinic or clinics or care or healthcare or medical) NEAR3 (emergency or emergencies or casualty)) 727
30 (triage*) 258
31 (accident* NEAR2 (emergency or emergencies)) 121
32 ((emergency or emergencies) NEAR2 accident*) 2
33 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 2279
34 #13 AND #33 44
35 #23 OR #34 46

Health Technology Assessment (HTA) database
via http://www.crd.york.ac.uk/CRDWeb/
Inception – 31st March 2018
Searched on: 10th February 2020
Records retrieved: 1

See above under DARE for search strategy used.

NHS Economic Evaluations Database (NHS EED)
via http://www.crd.york.ac.uk/CRDWeb/
Inception – 31st March 2015
Searched on: 10th February 2020
Records retrieved: 26

See above under DARE for search strategy used.

EconLit
via Ovid http://ovidsp.ovid.com/
1886 to January 30, 2020
Searched on: 10th February 2020
Records retrieved: 1

1 (headache$ or head ache$).ti,ab. (57)
2 LASH.ti,ab. (9)
3 (thunderclap$ or thunder clap$).ti,ab. (0)
4 (cephalalgi$ or cephalgi$).ti,ab. (0)
5 (cranial adj2 pain$).ti,ab. (0)
6 (hemicrania or cephalea or cranialgia).ti,ab. (0)
7 or/1-6 (66)
8 (Subarachnoid$ adj2 hemorr?ag$).ti,ab. (1)
9 (Subarachnoid$ adj2 haemorr?ag$).ti,ab. (1)
10 (Subarachnoid$ adj2 (bleed$ or blood)).ti,ab. (0)
11 (arachnoid$ adj2 (haemorr?ag$ or hemorr?ag$ or bleed$ or blood)).ti,ab. (0)
12 (SAH or SAHs).ti,ab. (52)
13 8 or 9 or 10 or 11 or 12 (53)
14 7 and 13 (0)
15 ((emergency or emergencies or casualty) adj3 (room$ or department$ or service$ or unit$ or ward$ or centre$ or center$ or hospital$ or setting$ or clinic or clinics or care or healthcare or medical)).ti,ab. (667)
16 triage$.ti,ab. (78)
17 (accident$ adj2 (emergency or emergencies)).ti,ab. (22)
18 15 or 16 or 17 (732)
19 7 and 18 (1)
20 14 or 19 (1)

On-going, unpublished or grey literature searches

ClinicalTrials.gov
https://clinicaltrials.gov/
Searched on: 11th February 2020
Records retrieved: 139

1. 20 Studies found for: headache AND (subarachnoid haemorrhage OR subarachnoid haemorrhage OR sub-arachnoid haemorrhage OR sub-arachnoid hemorrhage)

2. 1 Study found for: thunderclap AND (subarachnoid haemorrhage OR subarachnoid haemorrhage OR sub-arachnoid haemorrhage OR sub-arachnoid hemorrhage)

3. 2 Studies found for: headache AND (arachnoid haemorrhage OR arachnoid hemorrhage)

4. No Studies found for: thunderclap AND (arachnoid haemorrhage OR arachnoid hemorrhage)

5. 116 Studies found for: headache AND (emergency OR casualty OR triage)

6. No Studies found for: thunderclap AND (emergency OR casualty OR triage)

WHO International Clinical Trials Registry Platform
http://www.who.int/ictrp/search/en/
Searched on: 11th February 2020
Records retrieved: 84

Basic search interface used.

1. 13 records for 13 trials found for: headache AND subarachnoid

2. 1 trial found for: headache AND sub-arachnoid

3. 1 trial found for: headache AND arachnoid

4. No results were found for: thunderclap OR thunder clap

5. 68 records for 68 trials found for: headache AND emergenc*

6. No results were found for: headache AND casualty

7. 1 trial found for: headache AND triag*

EU Clinical Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search
Searched on: 11th February 2020
Records retrieved: 16

1. 3 result(s) found for: headache* AND (subarachnoid* haemorrhag* OR subarachnoid* haemorrhag* OR sub-arachnoid* haemorrhage* OR sub-arachnoid* hemorrhage*)

2. thunderclap OR "thunder clap" – 0 results

3. 2 result(s) found for: headache* AND (arachnoid* haemorrhag* OR arachnoid* hemorrhag*)

4. 11 result(s) found for: headache* AND (emergenc* OR casualty OR triag*)

Conference Proceedings Citation Index: Science
via Web of Science, Clarivate Analytics https://clarivate.com/
1990 – 7th February 2020
Searched on: 10th February 2020
Records retrieved: 251

# 19	251	#18 OR #13
# 18	193	#17 AND #6
# 17	18,714	#16 OR #15 OR #14
# 16	511	TS=(accident* NEAR/2 emergenc*)
# 15	2,397	TS=triage*
# 14	16,654	TS=((emergency or emergencies or casualty) NEAR/3 (room* or department* or service* or unit* or ward* or centre* or center* or hospital* or setting* or clinic or clinics or care or healthcare or medical))
# 13	70	#12 AND #6
# 12	3,066	#11 OR #10 OR #9 OR #8 OR #7
# 11	990	TS=(SAH or SAHs)
# 10	22	TS=(arachnoid* NEAR/2 (haemorr$ag* or hemorr$ag* or bleed* or blood))
# 9	44	TS=(Subarachnoid* NEAR/2 (bleed* or blood))
# 8	388	TS=(Subarachnoid* NEAR/2 haemorr$ag*)
# 7	2,317	TS=(Subarachnoid* NEAR/2 hemorr$ag*)
# 6	7,771	#5 OR #4 OR #3 OR #2 OR #1
# 5	94	TS=(hemicrania or cephalea or cranialgia)
# 4	8	TS=(cranial NEAR/2 pain*)
# 3	92	TS=(cephalalgi* or cephalgi*)
# 2	56	TS=(thunderclap* or "thunder clap*")
# 1	7,652	TS=(headache* or "head ache*" or LASH)

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 11th February 2020

Records retrieved: 60

#1 MeSH DESCRIPTOR Headache Disorders, Primary 3
#2 MeSH DESCRIPTOR Headache 62
#3 MeSH DESCRIPTOR Vascular Headaches 0
#4 MeSH DESCRIPTOR Headache Disorders, Secondary 4
#5 MeSH DESCRIPTOR Headache Disorders 18
#6 headache* or (head adj1 ache*) 865
#7 headache* or "head ache" or "head aches" 865
#8 LASH 7
#9 thunderclap* or (thunder adj1 clap*) 1
#10 cephalalgi* or cephalgi* 31
#11 cranial adj2 pain* 2
#12 hemicrania or cephalea or cranialgia 7
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #8 OR #9 OR #10 OR #11 OR #12 876
#14 MeSH DESCRIPTOR Subarachnoid Hemorrhage 62
#15 Subarachnoid* adj2 (hemorrhag* or hemorrag* or haemorrhag* or haemorrag*) 221
#16 Subarachnoid* adj2 (bleed* or blood) 14
#17 arachnoid* adj2 (haemorrhag* or haemorrag* or hemorrhag* or hemorrag* or bleed* or blood) 4
#18 SAH or SAHs 95
#19 #14 OR #15 OR #16 OR #17 OR #18 247
#20 #13 AND #19 8
#21 MeSH DESCRIPTOR Emergencies 81
#22 MeSH DESCRIPTOR Emergency Service, Hospital 303
#23 MeSH DESCRIPTOR Emergency Medical Services EXPLODE ALL TREES 493
#24 MeSH DESCRIPTOR Triage 50
#25 (emergency or emergencies or casualty) adj3 (room* or department* or service* or unit* or ward* or centre* or center* or hospital* or setting* or clinic or clinics or care or healthcare or medical) 2230
#26 triage* 230
#27 accident* adj2 (emergency or emergencies) 184
#28 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 2477
#29 #28 AND #13 53
#30 #20 OR #29 60

ECRI Guidelines Trust

https://guidelines.ecri.org/

Searched on: 17th February 2020

Records retrieved: 5

1. headache OR thunderclap OR “thunder clap” – 39 results – filtered to diagnosis – 16 results browsed for relevance – 5 potentially relevant.

Clinical Knowledge Summaries
https://cks.nice.org.uk/
Searched on: 17th February 2020
Records retrieved: 4

Browsed topic list for headache – 4 relevant records found.

NHS Evidence
https://www.evidence.nhs.uk/
Searched on: 17th February 2020
Records retrieved: 69

The following search strings were entered into the search box with the inbuilt guidance filters box checked to limit results to guidelines.

1. headache* AND "subarachnoid haemorrhage" – filtered to guidance - 26 results

2. headache* AND "subarachnoid hemorrhage" – filtered to guidance – 19 results

3. (intitle: headache*) AND emergenc* - filtered to guidance – 24 results

Trip
https://www.tripdatabase.com/
Searched on: 25th February 2020
Records retrieved: 17

1. (title:headache) AND ("subarachnoid haemorrhage" OR "subarachnoid hemorrhage") – filtered to guidance – 7 results

2. (title:headache) AND emergency – filtered to guidance – 10 results

Appendix 2: Studies excluded at full paper stage with rationale

Study details	Reason for exclusion
Abu-Habsa, 2016[88]	Not a SR or primary study (abstract based on unclear quality SR)
Acosta, 2019[89]	No relevant outcome assessed
Ahmad, 2008[90]	No relevant outcome assessed
Alexiu, 2017[91]	No relevant intervention (care pathway/test for SAH)
American College of Emergency Physicians, 2002[92]	Outdated SR
Anonymous, 1996[93]	Outdated SR
Anonymous, 2004[94]	Not a SR or primary study
Anonymous, 2010[95]	Not a SR or primary study
Anonymous, 2014[96]	Not a SR or primary study
Anonymous, 2018[97]	Not a SR or primary study
Apok, 2009[98]	No relevant intervention (care pathway/test for SAH)
Arora, 2010[99]	Not neurologically intact sudden onset severe headache patients
Asghar, 2013[100]	No relevant outcome assessed
Ashraf, 2019[101]	Not neurologically intact sudden onset severe headache patients
BASH, 2019[102]	Not a SR or primary study
Bashir, 2018[103]	Not neurologically intact sudden onset severe headache patients
Bateman, 2012[104]	No relevant intervention (care pathway/test for SAH)
Beck, 2006[105]	No relevant intervention (care pathway/test for SAH)
Becker, 1993[106]	No relevant outcome assessed
Bent, 2015[107]	Not neurologically intact sudden onset severe headache patients
Bledsoe, 2010[108]	Not neurologically intact sudden onset severe headache patients
Blum, 2017[109]	No relevant intervention (care pathway/test for SAH)
Bo, 2008[110]	Not neurologically intact sudden onset severe headache patients
Boesiger, 2005[111]	Not neurologically intact sudden onset severe headache patients
Breen, 2008[112]	Not neurologically intact sudden onset severe headache patients
Budweg, 2016[113]	Not neurologically intact sudden onset severe headache patients
Byyny, 2008[114]	Not neurologically intact sudden onset severe headache patients
Cahill, 2016[115]	Not neurologically intact sudden onset severe headache patients
Carley, 2005[116]	Outdated SR
Carstairs, 2006[117]	Not neurologically intact sudden onset severe headache patients
Ceppi, 2008[118]	Outdated SR
Chalouhi, 2013[119]	Not neurologically intact sudden onset severe headache patients
Chaudhry, 2011[120]	Not neurologically intact sudden onset severe headache patients (conference abstract only)
Chin, 2016[121]	Not a SR or primary study

Chu, 2014a[122]	Not neurologically intact sudden onset severe headache patients
Chu, 2014b[123]	No relevant intervention (to UK NHS)
Chu, 2016a[124]	Not neurologically intact sudden onset severe headache patients
Chu, 2016b[125]	Not neurologically intact sudden onset severe headache patients
Chu, 2017[126]	Not neurologically intact sudden onset severe headache patients
Chu, 2018[127]	Duplicate report
Clarke, 2010[128]	No relevant outcome assessed
Claveau, 2014[129]	Not a SR or primary study
Clerc, 2011[130]	Outdated SR
Cortelli, 2004[131]	Not a SR or primary study (consensus statement based on outdated SR)
Cortnum, 2010[132]	Not neurologically intact sudden onset severe headache patients
Crossley, 2011[133]	Not neurologically intact sudden onset severe headache patients
Czuczman, 2011[134]	Duplicate report
Czuczman, 2013[135]	No relevant intervention (to UK NHS)
Dachs, 2011[136]	Not a SR or primary study
Da Rocha, 2006[137]	Not neurologically intact sudden onset severe headache patients
Davies, 2013[138]	Not neurologically intact sudden onset severe headache patients (conference abstract only)
DeGood, 2014[139]	No relevant intervention (care pathway/test for SAH)
Del Sette, 2003[140]	Not a SR or primary study
Detsky, 2006[141]	Outdated SR
Diagnostic Imaging Pathways, 2014[142]	Not a SR or primary study
Diagnostic Imaging Pathways, 2017[143]	Not a SR or primary study
Diaz, 2007[144]	No relevant outcome assessed
Dolezil, 2010[145]	No relevant intervention (care pathway/test for SAH)
Douglas, 2014[146]	Not a SR or primary study
Dubin, 2015[147]	No relevant outcome assessed
Dubosh, 2018[148]	No relevant intervention (care pathway/test for SAH)
Dubosh, 2019[149]	No relevant intervention (care pathway/test for SAH)
Edlow, 2000a[150]	Not a SR or primary study
Edlow, 2000b[151]	Not a SR or primary study
Edlow, 2008[152]	Outdated SR
Edlow, 2010[153]	Outdated SR
Eggers, 2011[154]	Not neurologically intact sudden onset severe headache patients
Ejaz, 2015[155]	Not a SR or primary study
Elyas, 2016[156]	No relevant intervention (care pathway/test for SAH)
Eryigit, 2017[157]	Not neurologically intact sudden onset severe headache patients
European Stroke Organisation, 2013[158]	Not a SR or primary study
Fargen, 2013[159]	Not a SR or primary study
Farzad, 2013[160]	Not a SR or primary study
Fearon, 2019[161]	Not neurologically intact sudden onset severe headache patients

Ferrante, 2013[162]	Not neurologically intact sudden onset severe headache patients
Fodden, 1989[163]	No relevant intervention (care pathway/test for SAH)
Foot, 2001[164]	Outdated CT technology (patients recruited >20 years ago)
Fridriksson, 2001[165]	Not neurologically intact sudden onset severe headache patients
Gaughran, 2014[166]	Not neurologically intact sudden onset severe headache patients
Gee, 2012[167]	Not neurologically intact sudden onset severe headache patients
Ghosh, 2012[168]	No relevant intervention (care pathway/test for SAH)
Gilbert, 2011[169]	No relevant outcome assessed
Gilbert, 2012[170]	Not neurologically intact sudden onset severe headache patients
Gill, 2014[171]	Duplicate report
Gill, 2018[172]	Not neurologically intact sudden onset severe headache patients
Goldstein, 2006[6]	Not neurologically intact sudden onset severe headache patients
Goldstein, 2018[173]	No relevant intervention (care pathway/test for SAH)
Gordon, 2015[174]	No relevant intervention (care pathway/test for SAH)
Gould, 2011[175]	No relevant intervention (care pathway/test for SAH)
Goyale, 2016[176]	Not neurologically intact sudden onset severe headache patients
Graham, 2014[177]	Not neurologically intact sudden onset severe headache patients
Gray, 2015[178]	Not a SR or primary study
Grayson, 2005[179]	Not a SR or primary study
Grimaldi, 2008[180]	Not a SR or primary study
Grimaldi, 2009[3]	Not neurologically intact sudden onset severe headache patients
Grooters, 2014[181]	No relevant intervention (care pathway/test for SAH)
Grory, 2018[182]	Duplicate report
Han, 2013[183]	No relevant intervention (not assessing for SAH)
Hann, 2014[184]	Duplicate report
Hann, 2015[185]	Not neurologically intact sudden onset severe headache patients
Hart, 2007[186]	Not neurologically intact sudden onset severe headache patients
Hasan, 2018[187]	Not neurologically intact sudden onset severe headache patients
Headache, 2006[188]	Not a SR or primary study
Heasley, 2005[189]	Not neurologically intact sudden onset severe headache patients
Hennessy, 2015[190]	Not neurologically intact sudden onset severe headache patients (conference abstract only)
Hewett, 2010[191]	No relevant outcome assessed
Holdgate, 2001[192]	Not a SR or primary study
Hussain, 2013[193]	Duplicate report
Hylleraas, 2010[194]	Not neurologically intact sudden onset severe headache patients

Imao, 2015[195]	Not neurologically intact sudden onset severe headache patients
Jakobsson, 1996[196]	Not neurologically intact sudden onset severe headache patients
Jang, 2019[197]	Not neurologically intact sudden onset severe headache patients
Jehle, 2012[198]	Not neurologically intact sudden onset severe headache patients
Johnson, 2017[199]	Not neurologically intact sudden onset severe headache patients
Kashefiolasl, 2017[200]	Not neurologically intact sudden onset severe headache patients
Kasper, 2011[201]	Not neurologically intact sudden onset severe headache patients
Khan, 2014a[202]	Duplicate report
Khan, 2014b[203]	Duplicate report
Khan, 2014c[204]	Duplicate report
Khan, 2014d[205]	Duplicate report
Kilian, 2012[206]	No relevant outcome assessed
Kilic, 2017[207]	Not neurologically intact sudden onset severe headache patients
Kim, 2014[208]	Not neurologically intact sudden onset severe headache patients
Kimura, 2016[209]	Not neurologically intact sudden onset severe headache patients
Knaus, 1980[210]	Not neurologically intact sudden onset severe headache patients
Knaus, 1981[211]	Outdated CT technology (patients recruited >20 years ago)
Knox, 2012[212]	Not neurologically intact sudden onset severe headache patients
Kowalski, 2004[14]	Not neurologically intact sudden onset severe headache patients
Landtblom, 2002[11]	Not neurologically intact sudden onset severe headache patients
Lansen, 1993[213]	Not neurologically intact sudden onset severe headache patients
Lau, 2011[214]	Not a SR or primary study
Lawton, 2017[215]	Not a SR or primary study
Lee, 2014[216]	No relevant intervention (care pathway/test for SAH)
Lin, 2019[217]	Not neurologically intact sudden onset severe headache patients
Linn, 1994a[218]	Not neurologically intact sudden onset severe headache patients
Linn, 1994b[219]	Duplicate report
Linn, 1998[220]	No relevant intervention (care pathway/test for SAH)
Linn, 2000[221]	Not neurologically intact sudden onset severe headache patients
Ljubisavljevic, 2016[222]	Not neurologically intact sudden onset severe headache patients
Ljubisavljevic, 2017a[223]	Not neurologically intact sudden onset severe headache patients

Ljubisavljevic, 2017b[224]	Not neurologically intact sudden onset severe headache patients
Ljubisavljevic, 2018[225]	Not neurologically intact sudden onset severe headache patients
Lledo, 1994[226]	Outdated CT technology (patients recruited >20 years ago)
Locker, 2006[2]	Not neurologically intact sudden onset severe headache patients
Long, 2016[227]	Not a SR or primary study
Luda, 1995[228]	No relevant intervention (care pathway/test for SAH)
Lui, 2008[229]	No relevant intervention (care pathway/test for SAH)
MacGrory, 2018[230]	No relevant intervention (care pathway/test for SAH)
Majed, 2009[231]	Not neurologically intact sudden onset severe headache patients
Manella, 2018[232]	Not a SR or primary study
Mapoure Njankouo, 2016[233]	No relevant intervention (care pathway/test for SAH)
Mark, 2012[234]	Not neurologically intact sudden onset severe headache patients
Mark, 2013[235]	Not neurologically intact sudden onset severe headache patients
Mark, 2015a[236]	Not neurologically intact sudden onset severe headache patients
Mark, 2015b[237]	Not neurologically intact sudden onset severe headache patients
Mark, 2015c[238]	Not neurologically intact sudden onset severe headache patients
Mark, 2016[239]	Not neurologically intact sudden onset severe headache patients
Mark, 2017[240]	Not neurologically intact sudden onset severe headache patients
Martin, 2015[241]	Not neurologically intact sudden onset severe headache patients
Mastrandrea, 2019[242]	Not neurologically intact sudden onset severe headache patients
Matloob, 2012[243]	Duplicate report
Mayabi, 2012[244]	Not neurologically intact sudden onset severe headache patients
Mayer, 1996[245]	Not neurologically intact sudden onset severe headache patients
McCarron, 2015[246]	Not neurologically intact sudden onset severe headache patients
McCormack, 2010[247]	Decision model based on outdated SR
McCormack, 2012[248]	Not a SR or primary study
Medina, 2003[249]	Outdated SR
Menon, 2016[250]	Not neurologically intact sudden onset severe headache patients
Mert, 2008[251]	Not neurologically intact sudden onset severe headache patients
Meurer, 2016[252]	Not a SR or primary study (guidelines based on poor quality SR)
Migdal, 2015[253]	Duplicate report

Moeller, 2008[254]	Not neurologically intact sudden onset severe headache patients
Morgenstern, 2001[1]	Not neurologically intact sudden onset severe headache patients
Muehlschlegel, 2013[255]	Not neurologically intact sudden onset severe headache patients
Muhammed, 2010[256]	No relevant outcome assessed
Mushtaq, 2014[257]	Not neurologically intact sudden onset severe headache patients
Narayan, 2015[258]	Not neurologically intact sudden onset severe headache patients
Narita, 1994[259]	Not neurologically intact sudden onset severe headache patients
National Study of Subarachnoid Haemorrhage, 2006[12]	Not a SR or primary study
NICE, 2019[260]	Not a SR or primary study
Oda, 2015[261]	Not neurologically intact sudden onset severe headache patients
Oh, 2018[262]	Not neurologically intact sudden onset severe headache patients
Ois, 2019[263]	Not neurologically intact sudden onset severe headache patients
O'Neill, 2005[264]	Not neurologically intact sudden onset severe headache patients
Page, 1994[265]	Not neurologically intact sudden onset severe headache patients
Pancu, 2004[266]	No relevant intervention (to UK NHS)
Pari, 2015[7]	No relevant intervention (care pathway/test for SAH)
Parker, 2018[267]	No relevant outcome assessed
Pascual, 2008[268]	Not neurologically intact sudden onset severe headache patients
Pashapour, 2012[269]	No relevant outcome assessed
Patterson, 2016[270]	No relevant intervention (care pathway/test for SAH)
Pavlovic, 2018[271]	No relevant intervention (care pathway/test for SAH)
Peker, 2014[272]	Not neurologically intact sudden onset severe headache patients
Peretz, 2020[273]	Not a SR or primary study
Perry, 2012[274]	Duplicate report
Perry, 2013a[275]	Duplicate report
Perry, 2013b[276]	Duplicate report
Perry, 2014a[277]	Duplicate report
Perry, 2014b[278]	Duplicate report
Perry, 2018[279]	Duplicate report
Powell, 2018[280]	Not a SR or primary study
Petzold, 2011[281]	Not neurologically intact sudden onset severe headache patients
Quon, 2015[282]	No relevant intervention (care pathway/test for SAH)
Raffaelli, 2017[283]	Not neurologically intact sudden onset severe headache patients
Ramakrishnan, 2018[284]	Not neurologically intact sudden onset severe headache patients
Razazian, 2013[285]	No relevant intervention (care pathway/test for SAH)
Reeve, 2016[286]	No relevant intervention (to UK NHS)

Rizk, 2013[287]	Not neurologically intact sudden onset severe headache patients
Robba, 2016[288]	Not neurologically intact sudden onset severe headache patients
Rogers, 2014[289]	Duplicate report
Royuela, 2019[290]	Not neurologically intact sudden onset severe headache patients
Sahai-Srivastava, 2008[291]	Not neurologically intact sudden onset severe headache patients
Sahraian, 2019[292]	Not neurologically intact sudden onset severe headache patients
Samaniego, 2019[293]	Not neurologically intact sudden onset severe headache patients
Savitz, 2009[294]	Outdated SR
Sayer, 2015[26]	Not neurologically intact sudden onset severe headache patients
Schull, 1999[295]	Outdated CT technology (patients recruited >20 years ago)
Schwartz, 2009[296]	Not a SR or primary study
Schwartz, 2013[297]	Not a SR or primary study
Scott-King, 2018[298]	Not neurologically intact sudden onset severe headache patients
Scott-King, 2019[299]	Not neurologically intact sudden onset severe headache patients
Sjulstad, 2019[300]	Not a SR or primary study
Smith, 2013[301]	No relevant intervention (to UK NHS)
Sonne, 2019[302]	Not neurologically intact sudden onset severe headache patients
Stevenson, 1998[4]	Not neurologically intact sudden onset severe headache patients
Swenson, 2013[303]	Not neurologically intact sudden onset severe headache patients
Takagi, 2018[304]	Not neurologically intact sudden onset severe headache patients
Tantarattanapong, 2019[305]	No relevant intervention (care pathway/test for SAH)
Tarnutzer, 2017[306]	Not neurologically intact sudden onset severe headache patients
Taylor, 2014[307]	Duplicate report
Thomas, 2011[308]	Not neurologically intact sudden onset severe headache patients
Thomas, 2014[309]	Not neurologically intact sudden onset severe headache patients
Tieu, 2018[310]	Not neurologically intact sudden onset severe headache patients
Tolias, 1996[311]	No relevant intervention (care pathway/test for SAH)
TOP Headache Working Group, 2016[312]	Not a SR or primary study
Torzewski, 2011[313]	No relevant intervention (care pathway/test for SAH)
Tulla, 2019[314]	Not neurologically intact sudden onset severe headache patients
Tumani, 2010[315]	Not a SR or primary study
Tung, 2014[316]	Not neurologically intact sudden onset severe headache patients

Uotila, 2012[317]	Not neurologically intact sudden onset severe headache patients
Van der Wee, 1995[318]	Outdated CT technology (patients recruited >20 years ago)
Van Gijn, 2005[319]	Not a SR or primary study
Vergouwen, 2013[320]	Not a SR or primary study
Vermeulen, 1989[321]	Outdated CT technology (patients recruited >20 years ago)
Vermeulen, 2007[322]	Not neurologically intact sudden onset severe headache patients
Vernetti, 2017[323]	No relevant intervention (care pathway/test for SAH)
Vidal-Castello, 2019[324]	Not neurologically intact sudden onset severe headache patients
Visser, 2012[325]	Not neurologically intact sudden onset severe headache patients
Vu, 2018[326]	No relevant intervention (care pathway/test for SAH)
Waldman, 2017[327]	No relevant outcome assessed
Ward, 2011[328]	Not a SR or primary study (NHS EED abstract based on Ward et al.[79])
Webb, 2003[329]	Outdated CT/LP technology (patients recruited >20 years ago)
Westafer, 2016[330]	Not a SR or primary study
Williams, 2014[331]	No relevant outcome assessed
Wood, 1990[332]	Not neurologically intact sudden onset severe headache patients
Wood, 2005[333]	Not neurologically intact sudden onset severe headache patients
Wu, 2016[334]	Duplicate report
Yesilaras, 2017[335]	Not neurologically intact sudden onset severe headache patients
Zahar, 2010[336]	Not neurologically intact sudden onset severe headache patients
Zammit, 2018[337]	No relevant intervention (care pathway/test for SAH)
Zavala, 2008[338]	Not a SR or primary study
Zhao, 2019[339]	No relevant intervention (care pathway/test for SAH)
Zuzek, 2019[340]	Not neurologically intact sudden onset severe headache patients

Abbreviations: CT, computed tomograph; EED, Economic Evaluations Database; SAH, subarachnoid haemorrhage; SR, systematic review.

Appendix 3: Study details and results tables

Cohort/before and after studies (n=37)

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Canadian Clinical Decision Rules					
Perry, 2010[43] Prospective cohort study Emergency Departments at six university affiliated tertiary care teaching hospitals, Canada *Also reported in CT Scan section*	1999 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within 1 hour) or syncope associated with headache. An additional 1050 potentially eligible patients were identified who were not enrolled 'missed eligible patients'. Patient recruitment: November 2000 – November 2005 (patient overlap with Perry, 2011[59]).	Third generation CT scanner, results verified by the local attending radiologist (either neuroradiologists or general radiologists who routinely interpret head CT). Identification of high risk clinical characteristics for SAH in order to develop clinical decision rules based on variables collected on history or examination. Rule 1: age >40; complaint of neck pain or stiffness; witnessed loss of consciousness; onset with exertion.	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or $>5x10^6$/L RBCs in the final tube of CSF with aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (telephone follow-up at 1 month and 6 months and medical record review).	**Diagnostic accuracy results** **CT (SAH):** Sensitivity: 93.1% (calculated by CRD) Specificity: 100% (calculated by CRD) Positive predictive value: 100% (calculated by CRD) Negative predictive value: 99.4% (calculated by CRD) Overall accuracy: 99.4% (calculated by CRD) Prevalence: 6.5% **Clinical decision rules (SAH):** Retrospective sensitivity: Rule 1-3: 100% (95% CI 97.1 to 100) Specificity: Rule 1: 28.4% (95% CI 26.4 to 30.4); Rule 2: 36.5% (95% CI 34.4 to 38.8); Rule 3: 38.8% (95% CI 36.7 to 41.1). 1606 (80.3%) patients had a CT scan and 905 (45.3%) had LP; 854 (42.7%) had CT scan and LP. 8.4% patients had a CT angiogram. Use of any one of the rules assessed would have lowered rates of investigation (CT, LP or both) from 82.9% to between 63.7-73.5%. 48 patients had other serious conditions diagnosed on CT or LP, such as transient ischaemic attack/acute ischaemic stroke, other	Patient selection: Unclear Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
		Rule 2: arrival by ambulance; age >45; vomiting at least once; diastolic BP >100 mm Hg. Rule 3: arrival by ambulance; systolic BP >160 mm Hg; complaint of neck pain or stiffness; age 45-55.		type of haemorrhagic stroke, bacterial meningitis, hypertensive emergency or cerebral neoplasm.	
Matloob, 2013[44] Retrospective cohort study Emergency Department at one teaching hospital, UK	112 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within 1 hour). Patient recruitment: August 2011 – October 2011.	UK validation of 3 Canadian clinical decision rules. Rule 1: age >40; complaint of neck pain or stiffness; witnessed loss of consciousness; onset with exertion. Rule 2: arrival by ambulance; age >45; vomiting at least once; diastolic BP >100 mm Hg. Rule 3: arrival by ambulance; systolic BP >160 mm Hg; complaint of neck	Diagnosis on discharge. SAH was defined using CT and LP (xanthochromia). In patients not fully investigated the authors searched for admission to regional neurosurgical centre within 6 months of discharge.	**Diagnostic accuracy results** **Rule 1 (SAH):** Sensitivity: 100% (95% CI 40 to 100) Specificity: 43% (95% CI 33 to 52) Positive predictive value: 6.1% (calculated by CRD) Negative predictive value: 100% (95% CI 90 to 100) Overall accuracy: 44.6% (calculated by CRD) **Rule 2 (SAH):** Sensitivity: 100% (95% CI 40 to 100) Specificity: 27% (95% CI 19 to 36) Positive predictive value: 4.8% (calculated by CRD) Negative predictive value: 100% (95% CI 85 to 100) Overall accuracy: 29.5% (calculated by CRD) **Rule 3 (SAH):** Sensitivity: 100% (95% CI 40 to 100)	Patient selection: Low Index test: Unclear Reference standard: Unclear Flow/timing: High

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
		pain or stiffness; age 44-55. Comparator: Current UK practice (defined as clinical assessment without the use of a formal decision rule).		Specificity: 37% (95% CI 28 to 47) Positive predictive value: 5.6% (calculated by CRD) Negative predictive value: 100% (95% CI 89 to 100) Overall accuracy: 39.3% (calculated by CRD) **Current UK practice (SAH):** Sensitivity: 100% (95% CI 40 to 100) Specificity: 66% (95% CI 56 to 74) Positive predictive value: 9.8% (calculated by CRD) Negative predictive value: 100% (95% CI 94 to 100) Overall accuracy: 67.0% (calculated by CRD) Prevalence: 3.6% 41 (36.6%) patients had a CT scan and 9 (8.0%) had LP (after –ve CT). The investigation rate of 36.6% would have increased with the use of the Canadian decision rules (59%, 74% and 64% for rules 1-3 respectively).	
MacDonald, 2012[45] Retrospective cohort study Emergency department at one District	280 neurologically intact, acute headache patients who had head CT. Patient recruitment: 2 year period.	Perry's three decision rules to aid investigation of suspected SAH.	CT. LP results were searched for patients with suspected SAH but no evidence on CT.	8/280 (2.9%) patients had SAH. None would have been missed using the clinical decision rules suggested by Perry *et al.* However, there were nine cases of other significant pathologies such as intra-parenchymal bleeds, tumours and infarction that would have been missed by employing the rules.	Patient selection: Unclear Index test: Unclear Reference standard: Low Flow/timing: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
General Hospital, UK					(limited reporting, as only a conference abstract was available)
Kelly, 2014[46] Retrospective cohort study Emergency Departments at two teaching hospitals, Australia	59 non-traumatic neurologically intact (GCS 15) sudden onset headache patients with confirmed SAH (all were confirmed with CT). Patient recruitment: 2000 – 2011.	3 Canadian clinical decision rules. Rule 1: age >40; complaint of neck pain or stiffness; witnessed loss of consciousness; onset with exertion. Rule 2: arrival by ambulance; age >45; vomiting at least once; diastolic BP >100 mm Hg. Rule 3: arrival by ambulance; systolic BP >160 mm Hg; complaint of neck pain or stiffness; age 45-55.	CT, CT angiography, conventional angiography, MRI, or LP supported by specialist neurosurgical opinion.	**Diagnostic accuracy results** **Rule 1 (SAH):** Sensitivity: 96.6% (95% CI 88.5 to 99.1); 2 cases missed. **Rule 2 (SAH):** Sensitivity: 100% (95% CI 93.9 to 100) **Rule 3 (SAH):** Sensitivity: 89.8% (95% CI 79.5 to 95.3); 6 cases missed. The addition of vomiting to rule 1 and 3 increased sensitivity to 100%.	Patient selection: Low Index test: High Reference standard: Low Flow/timing: High
Perry, 2013[31] Prospective cohort study	2131 non-traumatic, neurologically intact (GCS 15) headache patients	3 clinical decision rules and development of the Ottawa SAH Rule.	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or >1x10^6/L RBCs in the final tube of CSF with	**Diagnostic accuracy results** **Rule 1 (SAH):** Sensitivity: 98.5% (95% CI 94.6 to 99.6) Specificity: 27.6% (95% CI 25.7 to 29.6)	Patient selection: Low Index test: Low Reference standard: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency Departments at ten university hospitals, Canada	(peaking within 1 hour). Patient recruitment: April 2006 – July 2010 (appears to be patient overlap with Perry, 2011[59]).	Rule 1: age >40; complaint of neck pain or stiffness; witnessed loss of consciousness; onset with exertion. Rule 2: arrival by ambulance; age >45; vomiting at least once; diastolic BP >100 mm Hg. Rule 3: arrival by ambulance; systolic BP >160 mm Hg; complaint of neck pain or stiffness; age 45-55. Ottawa SAH Rule: age >40; complaint of neck pain or stiffness; witnessed loss of consciousness; onset with exertion; thunderclap headache (instantly peaking pain); limited neck flexion on examination.	aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (telephone follow-up at 1 month and 6 months and medical record review).	**Rule 2 (SAH):** Sensitivity: 95.5% (95% CI 90.4 to 97.9) Specificity: 30.6% (95% CI 28.6 to 32.6) **Rule 3 (SAH):** Sensitivity: 97.0% (95% CI 92.5 to 98.8) Specificity: 35.6% (95% CI 33.6 to 37.7) **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 97.2 to 100) Specificity: 15.3% (95% CI 13.8 to 16.9) Positive predictive value: 7.2% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 20.5% (calculated by CRD) Prevalence: 6.2% Physicians were 'uncomfortable' or 'very uncomfortable' using rule 1 in 18.2% patients, rule 2 in 23.7% patients and rule 3 in 23.6% patients. Physicians misinterpreted the clinical decision rule as not requiring investigation in 4.7% patients using rule 1, 6.0% using rule 2 and 4.6% using rule 3 – the most frequently misinterpreted variables were neck pain and stiffness for rules 1 and 3 and arrival by ambulance for rule 2. 1767 (82.9%) patients had a CT scan and 833 (39.1%) had LP. 15.1% patients had a CT angiogram. 84.3% patients had CT, LP or both;	Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				use of rule 1 would have decreased this rate to 74.0%, rule 2 to 71.0% and rule 3 to 66.4%. The Ottawa SAH Rule would have slightly increased the investigation rate to 85.7%.	
Yiangou, 2017[47] Retrospective cohort study Emergency Department at one university hospital, UK	162 fully alert, neurologically intact patients presenting with acute headache. Patient recruitment: 1 January 2013 – 1 March 2013.	Four Canadian SAH decision rules: Rule 1, Rule 2, Rule 3 and the Ottawa SAH Rule (full results only presented for the Ottawa SAH Rule). Comparator: Current practice at the North-West England University Hospital.	Final diagnosis (CT, LP and re-admission with SAH).	**Diagnostic accuracy results** **Ottawa SAH Rule:** Sensitivity: 100% (95% CI 31.0 to 100) Specificity: 38.9% (95% CI 31.5 to 47.1) Positive predictive value: 3% (calculated by CRD) Negative predictive value: 100% (95% CI 92.7 to 100) Overall accuracy: 40.1% (calculated by CRD) **Current practice:** Sensitivity: 100% (95% CI 31.0 to 100) Specificity: 58.5% (95% CI 50.5 to 66.2) Positive predictive value: 4.3% (calculated by CRD) Negative predictive value: 100% (95% CI 95.1 to 100) Overall accuracy: 59.3% (calculated by CRD) Prevalence: 1.9% Based on current practice 42.6% patients were investigated with CT and no patients with SAH were missed. Retrospective application of the Canadian SAH rules to this cohort would have increased the CT investigation rate to 54.3%, 64.8%, 50% and 61.7% for Rule 1, Rule 2, Rule 3 and the Ottawa SAH Rule, respectively	Patient selection: Unclear Index test: Unclear Reference standard: Low Flow/timing: Low (limited reporting, as only a conference poster was available)

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				(p<0.001). One patient that suffered a SAH would have been missed if Rule 3 was applied. 3 patients (1.9%) were diagnosed with SAH by CT, 11 (6.8%) were diagnosed with other cerebral pathologies and 148 (91.4%) were diagnosed with benign causes of headaches.	
Perry, 2017[48] Prospective cohort study Emergency Departments at six tertiary care university hospitals, Canada	1153 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within 1 hour). Patient recruitment: January 2010 – January 2014 (may be patient overlap with Perry, 2010[43]).	Ottawa SAH Rule.	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or >1x10^6/L RBCs in the final tube of CSF with aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (telephone follow-up at 1 month and 6 months and medical record review).	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 94.6 to 100) Specificity: 13.6% (95% CI 13.1 to 15.8) Positive predictive value: 6.7% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 18.6% (calculated by CRD) Prevalence: 5.8% 89.1% patients had a CT scan and 39.2% had LP; 37.8% had CT scan and LP. 18% patients had a CT angiogram. 8.6% were admitted to hospital. Final diagnosis: 67 (5.8%) SAH, 8 (0.7%) intracerebral haemorrhage, 6 (0.5%) ischemic stroke or TIA, 3 (0.3%) brain tumour, 3 (0.3%) bacterial meningitis, 2 (0.2%) subdural hematoma. The most common diagnoses were benign headache (53.7%), migraine (19.3), other benign cause (10.4%).	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low
Bellolio, 2015[32]	454 non-traumatic, neurologically intact (GCS 15)	Ottawa SAH Rule.	Subarachnoid blood on CT, LP (xanthochromia or RBCs in the final tube	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 62.9 to 100)	Patient selection: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Retrospective cohort study Emergency Department at one academic hospital, USA	headache patients (peaking within 1 hour). Patient recruitment: January 2011 – November 2013.		of CSF with aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (medical record review).	Specificity: 7.6% (95% CI 5.4 to 10.6) Positive predictive value: 2.1% (95% CI 1.0 to 4.2) Negative predictive value: 100% (95% CI 87.4 to 100) Overall accuracy: 9.5% (calculated by CRD) Prevalence: 2.0% 79% patients had a CT scan, 17% had LP; 21.9% had LP after negative CT. 10% patients had CT angiogram. Application of the Ottawa SAH Rule at the time of investigation in this cohort would have prevented 13 CTs but would have indicated additional workup in 71 patients with no further yield of SAH cases. Final diagnosis: 9 SAH, 7 ischemic stroke or TIA, 1 intracerebral haemorrhage, 1 brain tumour, 1 bacterial meningitis, 1 subdural hematoma.	Index test: Unclear Reference standard: Unclear Flow/timing: Low
Wu, 2019[49] Retrospective cohort study Emergency Department at one tertiary academic medical centre, Taiwan	913 non-traumatic, neurologically intact patients with a principal diagnosis of headache (time to peak intensity not stated; 8.2% had thunderclap headache).	Ottawa SAH Rule.	Final diagnosis. The authors defined headache secondary to SAH or ICP based on a new neuroimaging finding, such as brain MRI, CT, CSF study, or diagnosed by a neurologist at hospital discharge.	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 78.2 to 100) Specificity: 37% (95% CI 33.8 to 40.2) Positive predictive value: 2.6% (95% CI 1.5 to 4.2) Negative predictive value: 100% (95% CI 98.9 to 100) Overall accuracy: 38% (calculated by CRD) Prevalence: 1.6% **Ottawa SAH Rule (SAH or intracranial haemorrhage):**	Patient selection: Low Index test: Unclear Reference standard: High Flow/timing: High

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
	Patient recruitment: January 2016 – March 2017.			Sensitivity: 100% (95% CI 84.6 to 100) Specificity: 37.3% (95% CI 34.1 to 40.5) Positive predictive value: 3.8% (95% CI 2.4 to 5.7) Negative predictive value: 100% (95% CI 98.9 to 100) Overall accuracy: 38.8% (calculated by CRD) Prevalence: 2.4% 33.1% patients had a CT scan taken during their ED visit, with an average time to CT ordered of 42.4 ± 73.6 minutes. Patients who received a CT scan had a longer ED length of stay (p<0.001) Final diagnosis: 15 (1.6%) SAH, 46 (5.0%) intracranial pathology (including 24 non-haemorhagic intracranial pathology).	
Chu, 2018[50] Retrospective cohort study (sub-study of Chu *et al.*, 2017, a prospective snapshot of 34 EDs, which was excluded as it also included non-neurologically intact patients)	137 non-traumatic headache patients (peaking within 1 hour) with no neurological deficit. The study included 847 patients in total, 137 of which met the Ottawa SAH Rule criteria (and our inclusion criteria). Patient recruitment: September 2014.	Ottawa SAH Rule.	Discharge diagnosis (CT or review of state-wide electronic records ≥3 months after presentation).	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (calculated by CRD) Specificity: 22.4% (calculated by CRD) Positive predictive value: 2.8% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 24.1% (calculated by CRD) Prevalence: 2.2% (calculated by CRD) 107 (78.1%) patients had at least one high risk feature on the Ottawa SAH Rule (met work-up criteria); of which 49 had CT head with 3 CTs positive for SAH. Of the 58 patients who met the work-up criteria but did not have CT, none	Patient selection: Unclear Index test: Unclear Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
34 Emergency Departments in Queensland, Australia				had SAH within 3 months. 30 (21.9%) patients did not meet work-up criteria, of which 5 had CT head and 25 did not have CT; none of which had SAH within 3 months. 54 (39.4%) patients underwent CT.	
Pathan, 2018 [51] Retrospective cohort study Emergency Department at one university hospital, UK	145 non-traumatic, alert headache patients (peaking within 1 hour) with no new neurological deficits. The study included 737 patients in total, 145 of which met the Ottawa SAH Rule criteria (and our inclusion criteria) and were included in the analysis of the Ottawa SAH Rule. Patient recruitment: 1 January 2016 – 31 December 2016.	Ottawa SAH Rule. Comparator: Current practice without a rule assessed in all headache patients (including those not meeting our inclusion criteria).	CT and/or LP (subarachnoid blood on CT or xanthochromia in the CSF).	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 46.3 to 100) Specificity: 44.2% (95% CI 36 to 53) Positive predictive value: 6% (95% CI 2.2 to 14.1) Negative predictive value: 100% (95% CI 92.7 to 100) Overall accuracy: 46.2% (calculated by CRD) Prevalence: 3.4% Diagnostic accuracy results were also presented for current practice without a rule, but not all patients met our inclusion criteria. 87 (60%) patients who met Ottawa SAH Rule criteria had a CT scan. 35 (24%) patients who met Ottawa SAH Rule criteria had a LP. According to the Ottawa SAH Rule 62 patients required no further investigations and 83 required further work-up with CT ± LP.	Patient selection: Low Index test: Unclear Reference standard: Low Flow/timing: Unclear
Cheung, 2018[52] Retrospective cohort study	500 non-traumatic, neurologically intact (GCS 15), acute headache patients (peaking within 1 hour).	Ottawa SAH Rule (validation in Asian Chinese patients). Comparator: Modified Ottawa	Subarachnoid blood on CT (films reviewed by both an experienced emergency physician and radiology fellow), LP (xanthochromia or RBCs	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 94% (95% CI 82.5 to 98.4) Specificity: 32.9% (95% CI 28.6 to 37.5) Positive predictive value: 13.5% (95% CI 10.2 to 17.6)	Patient selection: Low Index test: Unclear/High Reference standard: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency Department at one regional hospital, Hong Kong	Patient recruitment: July 2013 – June 2016.	SAH Rule including both vomiting and SBP >160 mmHg.	in the final tube of CSF with aneurysm or arteriovenous malformation seen on angiography).	Negative predictive value: 98% (95% CI 93.9 to 99.5) Overall accuracy: 39% (calculated by CRD) **Modified Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 91.1 to 100) Specificity: 13.1% (95% CI 10.2 to 16.7) Positive predictive value: 11.3% (95% CI 8.6 to 14.8) Negative predictive value: 100% (95% CI 92.4 to 100) Overall accuracy: 21.8% (calculated by CRD) Prevalence: 10% 96.2% patients had a CT scan and 10% had LP. 34/50 SAH patients had aneurysmal SAH.	Flow/timing: Low
Perry, 2020[53] Prospective before/after implementation study Emergency Departments at six academic hospitals, Canada *Also reported in CT Scan section*	3672 non-traumatic, alert patients (GCS 15) with acute headache or headache-associated syncope (peaking within 1 hour). Patient recruitment: January 2010 – June 2013 (before implementation) and June 2013 –	Physician education to use Ottawa SAH Rule and 6-hour-CT rule. Comparator: Control period (before implementation).	Subarachnoid blood on CT (3rd generation or better using thin slices), LP (xanthochromia on visual inspection or >1x10^6/L RBCs in the final tube of CSF with aneurysm seen on angiography) and clinical follow-up (electronic health record review at 6 months and study end).	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 98.1 to 100) Specificity: 12.7% (95% CI 11.7 to 13.9) Positive predictive value: 5.8% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 17.2% (calculated by CRD) Prevalence: 5.1% **6-hour-CT Rule (SAH):** 1204 patients received CT within 6 hours Sensitivity: 95.5% (95% CI 89.8 to 98.5)* Specificity: 100% (95% CI 99.7 to 100)	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
	January 2016 (after implementation).			Positive predictive value: 100% (calculated by CRD) Negative predictive value: 99.5% (calculated by CRD) Overall accuracy: 99.6% (calculated by CRD) Prevalence: 9.2% (calculated by CRD) *5 patients had SAH with CT reported as normal: 2 unruptured aneurysms on CTA and presumed traumatic LP; 1 missed by the radiologist on initial interpretation; 1 dural vein fistula (i.e. nonaneurysmal); and 1 patient with sickle cell anaemia with profound anaemia (Hgb, 63 g/L) with a 3mm aneurysm. The rate of CT use remained constant; 88.0% in the control phase vs 87.5% in the intervention phase. The LP rate decreased from 38.9% to 25.9% (p<0.0001). The CTA rate increased from 18.8% to 21.7% (p=0.029). Admission rates decreased from 9.8% to 7.4% (p=0.011). Time from Emergency Physician assessment to discharge/referral was slightly longer (4.9 hours vs 5.2 hours; p=0.053). Mean length of stay in the ED was similar 6.3 vs 6.4 hours; p=0.685). Final diagnosis: 188 (5.1%) SAH, 26 (0.7%) ischemic stroke or TIA, 24 (0.7%) intracerebral haemorrhage, 10 (0.3%) brain tumour, 7 (0.2%) bacterial meningitis.	
Pathway of CT followed by LP					
Perry, 2002[10]	891 non-traumatic, alert patients (GCS	Pathway of CT followed by LP.	Not applicable.	Mean ED length of stay was 239 minutes (SD 148.3, range 17-1438 minutes). The mean ED	Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Retrospective cohort study Emergency Department at one tertiary care university centre, Canada	15) with acute headache or syncope (peaking within 1 hour). Patient recruitment: 1 January 2000 – 31 October 2000.			length of stay was 4 hours (95% CI 3.8 to 4.1) if no diagnostic testing was performed, 5 hours (95% CI 4.7 to 5.4) if CT was performed and 7.1 hours (95% CI 6.3 to 7.9) if LP was performed. 313 (35.1%) patients underwent CT; 9 were positive for SAH and 8 were positive for other acute processes (neoplasm or infarct). 85/891 (9.5%) patients underwent LP; 2 were positive for SAH (one of which had a positive CT result before LP, the other had LP without CT). 64/296 (21.6%) underwent LP after negative CT. 32 (3.6%) patients had potentially dangerous conditions: 10 (1.1%) SAH, 9 ischemic event, 6 brain tumour, 4 bacterial meningitis, 3 temporal arteritis. The most common diagnoses were migraine (43.7%), other benign headache (33.1%) and other/not determined (10.7%). 426 (2.9%) patients were referred to the neurosurgical service and 33 (3.7%) were admitted.	
Perry, 2008[54] Prospective cohort study Emergency departments at two tertiary care hospitals, Canada	592 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within 1 hour) or syncope associated with headache.	CT (using final neuroradiology report), followed by LP if CT negative (visual inspection of CSF for xanthochromia or $>5x10^6$ RBCs/L in the final tube).	SAH defined by CT (using final neuroradiology report), LP (xanthochromia on visual inspection or $>5x10^6$/L RBCs in the final tube of CSF with aneurysm seen on angiography) or autopsy report confirming SAH.	**Diagnostic accuracy results** **CT followed by LP (SAH):** Sensitivity: 100% (95% CI 94 to 100) Specificity: 67% (95% CI 63 to 71) Positive predictive value: 25.8% (calculated by CRD) Negative predictive value: 100% (95% CI 98 to 100) Overall accuracy: 70.4% (calculated by CRD) Prevalence: 10.3%	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
	Patient recruitment: November 2000 – November 2003 (appears to be patient overlap with Perry, 2011[59]).		Patients were contacted via telephone to verify that they had not had subsequent adverse events or diagnosis of SAH.	55/61 SAH cases were diagnosed on CT, 6 by presence of xanthochromia. 100% patients underwent CT, 91% underwent LP and 13% underwent angiography. 68 patients (11.5%) had an abnormal CT result and 183 (34.0%) had an abnormal LP result; xanthochromia was detected in the CSF of 7 patients (1.2%). Other significant pathologies detected were transient ischemic attack (0.8%), bacterial meningitis (0.2%), CNS tumour (0.2%) and intracerebral haemorrhage (0.2%). The most common diagnoses were benign headache (46.5%) and migraine (26.4%).	
Valle Alonso, 2018[55] Retrospective cohort study Emergency Department at one regional hospital, Spain *Also reported in CT Scan section and Lumbar puncture section*	85 non-traumatic, sudden headache patients (peaking within 1 hour) without unconsciousness or neurological focus, presenting to the ED within 6 hours of symptom onset. Patient recruitment: March 2012 – March 2013.	CT (within 6 hours) followed by LP, if CT negative for SAH. The CT used was multi-slice (4-320 slices/rotation) with slices of 5 - 7.5 mm for the brain and 2.5 – 5 mm for the posterior fossa. The CT report was made by deputies of the radiology service, with over 5 years of	LP was performed in all patients with a negative CT scan. Clinical follow-up at 6 months using medical records or phone calls where there was no conclusive data in medical records.	**Diagnostic accuracy results** **CT within 6 hours (SAH):** Sensitivity: 100% (calculated by CRD) Specificity: 98.7% (calculated by CRD) Positive predictive value: 90.9% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 98.8% (calculated by CRD) Prevalence: 11.8% (calculated by CRD) 74 (87%) patients underwent LP; LP was positive in 1 patient and inconclusive in 2 patients. However, bleeding was ruled out with later images; thus no cases of SAH were identified by LP. No cases of SAH were	Patient selection: Unclear Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
		experience and in consultation with the neuroradiologist when there was doubt.		reported during the 6 months of follow-up. 7 patients experienced post puncture headache, going back to the ED and admission was necessary for 2 of them for pain control. The most frequent final diagnosis was migraine (38.8%). 9.4% had a severe diagnosis, such as meningitis (4.7%) and reversible cerebral vasoconstriction syndrome (4.7%). SAH patients were more likely to arrive at ED by ambulance (p=0.010) and have occipital headache location (p=0.012). Among the clinical signs highlighted, the presence of syncope (p=0.036), neck pain or stiffness (p=0.010), photophobia (p=0.001), nausea or vomiting (p=0.000), as well as higher numbers of systolic (mean 153 vs 126) and diastolic blood pressure (mean of 100 vs 80) (p=0.000).	
Cooper, 2016[9] Retrospective cohort study Clinical Decision Unit at one teaching hospital, UK *Also reported in CT Scan section and Lumbar puncture section*	517 non-traumatic, neurologically pristine (GCS 15) patients with acute sudden onset severe headache managed on a CDU pathway for exclusion of SAH. Patient recruitment: January 2004 – December 2006.	CDU pathway of CT followed by LP. Initial and verified non-contrast CT reports (performed on third-generation scanners) and LP results (all taken >12 hours from the index headache).	Subarachnoid blood on CT (verified by a consultant radiologist), LP (CSF positive for bilirubin on spectrophotometry or a uniformly blood-stained CSF sample across four bottles and positive angiography). If CT/LP strategy was not completed, sudden death or subsequent SAH was assessed at 12 months by	**Diagnostic accuracy results** **CT (SAH):** Sensitivity: 92.9% (95% CI 79.5 to 100) Specificity: 100% (95% CI 99.6 to 100) Positive predictive value: 100% (95% CI 98.2 to 100) Negative predictive value: 99.8% (95% CI 99.4 to 100) Overall accuracy: 99.8% (calculated by CRD) Prevalence: 2.7% (14/510 who had CT) **LP after negative CT (SAH):** Sensitivity: 100% (95% CI 93.7 to 100) Specificity: 96.8% (95% CI 94.8 to 98.8)	Patient selection: Low Index test: Unclear Reference standard: Low Flow/timing: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
			analysing attendance and investigations (electronic hospital database).	Positive predictive value: 9.1% (95% CI 0 to 26.1) Negative predictive value: 100% (95% CI 99.5 to 100) Overall accuracy: 96.8% (calculated by CRD) Prevalence: 0.3% (1/309 who had LP) CT was positive for SAH in 13 patients; 6 had an underlying lesion on angiography and 7 had perimesencephalic SAH. 4 CT scans were initially reported as 'normal' making patients eligible for LP, only to be subsequently altered in 3 cases to SAH positive after neuroradiological interpretation of the CT scan. LP was positive for SAH in 11 patients; 10 patients were LP positive but angiography negative (false positives). 510 (98.6%) patients had a CT scan and 309 had LP. 491 patients were eligible for LP (490 initially negative on CT + 1 patient who went straight to LP without CT); 182 eligible patients did not have LP due to procedure failure (n=18), patient refusal or contraindication (n=65) or decision of attending doctor (n=99). CT was positive for other significant aetiology in a further 14 patients: 4 cerebral infarction, 2 venous sinus thrombosis, 2 incidental cerebral aneurysm, 1 arachnoid cyst, 1 metastatic disease, 1 haemangioma, 1 subdural haemorrhage, 1 meningioma, 1 bleed into	

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				glioblastoma. LP was positive for other significant aetiology in a further 17 patients: 16 viral meningitis and 1 nonocclusive sagital sinus thrombosis.	
Blok, 2015[56] Retrospective cohort study Emergency Departments at eleven non-academic hospitals, Netherlands *Also reported in CT Scan section*	760 neurologically intact (GCS 15) 'spontaneous' acute headache patients with suspected SAH, who underwent CT within 6 hours of onset (judged negative by radiologist) and subsequent LP. Patient recruitment: January 2007 – January 2013.	CT (third generation scanner) <6 hours from headache onset (assessed by a staff radiologist), followed by LP >12 hours after onset (CSF was analysed using spectrophotometry).	Review of admission CTs in patients with bilirubin positive CSF by two neuroradiologists and one stroke neurologist. Lumbar puncture >12 hours after onset (CSF was analysed using spectrophotometry using a number of methods across the 11 sites: oxyhaemoglobin/bilirubin concentration, UK NEQAS, qualitative assessment of absorption curve, Leiden method, and bilirubin excess).	52 (7%) CSF samples were initially considered positive for SAH, but only one CT was positive for subarachnoid blood (in the basal cisterns) on review by two neuroradiologists and one stroke neurologist; angiography did not identify an aneurysm and the patient was diagnosed with non-aneurysmal perimesencephalic haemorrhage (with a benign clinical course and no readmission for SAH during 26 month follow-up). No subarachnoid blood was identified in the other 51 patients with positive CSF findings. 28/51 patients had angiography; aneurysm was identified in 8 patients (3 previously coiled). In those with an aneurysm it was considered that aneurysm rupture was unlikely and the aneurysm was considered incidental (4 were treated and 4 were not). The negative predictive value for detection of subarachnoid blood on CT by staff radiologists working in a non-academic hospital was 99.9% (95% CI 99.3 to 100). SAH prevalence was 0.13% (1/760).	Patient selection: Low Index test: Low Reference standard: Unclear Flow/timing: Unclear
Dutto, 2009[57] Before and after study	70 non-traumatic, neurologically intact (GCS 15), alert patients with headache (25 before and 45 after	Diagnostic protocol for non-traumatic acute headache in the ED, there was a different flow chart for each of the 3	Not applicable.	43/45 (95.5%) patients underwent CT scan after implementation of the diagnostic protocol versus 24/25 (96%) before. 2 patients received LP; both were negative. Neurological consultations were performed in 30/45 (66.6%)	Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency Department at one urban non-teaching hospital, Italy	implementation of the intervention). The study included 686 patients in total, patients were retrospectively assigned to 3 subgroups based on headache characteristics; subgroup 1 comprised patients with suspected SAH; thunderclap headache, 'worst headache ever', neurological signs, syncope, vomiting/nausea or onset following exertion (who met our inclusion criteria). Patient recruitment: April – September 2005 (before) and April – September 2006 (after).	subgroups. The flow chart recommended LP (if deemed necessary) for patients who had a negative CT scan result but who were suspected of SAH. Where SAH was not suspected or where LP results were normal, the attending physician could consult a neurologist for further clinical decisions. Comparator: Normal practice pre-implementation.		patients after the intervention versus 19/25 (76.0%) before. In the full population, the protocol was strictly applied in 247/374 (66%) patients after implementation. A higher proportion of patients received neither a CT scan nor a neurological consultation after implementation of the protocol than before (40.9% versus 34%). Patients spent less time in the ED after implementation of the protocol than before (170.6 ± 102 minutes versus 180 ± 105 minutes). Malignant secondary headaches (including SAH, neoplasm, intracranial haemorrhage and ischemic stroke) were diagnosed in 30/686 (4.37%) patients in the full population, with SAH accounting for 10 cases (1.5%); 5 before and 5 after implementation of the protocol. There was 1 misdiagnosis (cerebral neoplasm) after the intervention and two misdiagnoses (1 SAH, 1 intracerebral haemorrhage) before the intervention.	
CT Scan					
Perry, 2010[43]	1999 non-traumatic, alert, neurologically	Third generation CT scanner, results verified by the local	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or	**Diagnostic accuracy results** **CT (SAH):** Sensitivity: 93.1% (calculated by CRD)	Patient selection: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Prospective cohort study Emergency Departments at six university affiliated tertiary care teaching hospitals, Canada *Also reported in Canadian Clinical Decision Rules section*	intact (GCS 15) headache patients (peaking within 1 hour) or syncope associated with headache. An additional 1050 potentially eligible patients were identified who were not enrolled 'missed eligible patients'. Patient recruitment: November 2000 – November 2005 (patient overlap with Perry, 2011[59])	attending radiologist (either neuroradiologists or general radiologists who routinely interpret head CT). Identification of high risk clinical characteristics for SAH in order to develop clinical decision rules based on variables collected on history or examination. Rule 1: age >40; complaint of neck pain or stiffness; witnessed loss of consciousness; onset with exertion. Rule 2: arrival by ambulance; age >45; vomiting at least once; diastolic BP >100 mm Hg. Rule 3: arrival by ambulance; systolic BP >160 mm Hg;	>5x10^6/L RBCs in the final tube of CSF with aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (telephone follow-up at 1 month and 6 months and medical record review).	Specificity: 100% (calculated by CRD) Positive predictive value: 100% (calculated by CRD) Negative predictive value: 99.4% (calculated by CRD) Overall accuracy: 99.4% (calculated by CRD) Prevalence: 6.5% **Clinical decision rules (SAH):** Retrospective sensitivity: Rule 1-3: 100% (95% CI 97.1 to 100) Specificity: Rule 1: 28.4% (95% CI 26.4 to 30.4); Rule 2: 36.5% (95% CI 34.4 to 38.8); Rule 3: 38.8% (95% CI 36.7 to 41.1). 1606 (80.3%) patients had a CT scan and 905 (45.3%) had LP; 854 (42.7%) had CT scan and LP. 8.4% patients had a CT angiogram. Use of any one of the rules assessed would have lowered rates of investigation (CT, LP or both) from 82.9% to between 63.7-73.5%. 48 patients had other serious conditions diagnosed on CT or LP, such as transient ischaemic attack/acute ischaemic stroke, other type of haemorrhagic stroke, bacterial meningitis, hypertensive emergency or cerebral neoplasm.	Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
		complaint of neck pain or stiffness; age 45-55.			
Khan, 2017[58] A priori planned secondary analysis of two sequential prospective cohort studies Emergency Departments at eleven university affiliated hospitals, Canada	2412 non-traumatic, neurologically intact (GCS 15) acute headache patients (peaking within 1 hour). 3315 patients were recruited in total, but only 2412 had complete information. Same cohort of patients as Perry, 2010[43] and Perry, 2011.[59] Patient recruitment: 2000 – 2010.	CT, results determined by an experienced radiologist (either a neuroradiologist or general radiologist who regularly interprets head CT images).	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or $>5x10^6$/L RBCs in the final tube of CSF with aneurysm seen on angiography) and clinical follow-up (telephone follow-up at 14 days and medical record review).	194 (8.0%) patients had a final diagnosis of SAH; 178/194 cases (91.8%) were identified using CT (91.8% sensitivity). 727 patients had CT within 6 hours of headache onset; 91 (12.5%) had SAH; all cases were identified using CT (100% sensitivity). 1685 patients had CT over 6 hours from headache onset; 103 (6.1%) had SAH; 87/103 (84.5%) were identified using CT (84.5% sensitivity). 100% patients had a CT scan, 1222 (50.7%) patients had LP and 206 (8.5%) had angiography. 273 (11.3%) patients were admitted to hospital; 180 SAH patients and 93 non-SAH patients. 11 (0.5%) patients died; all had SAH. Median time from headache onset to CT was significantly shorter for patients with SAH; 6.4 hours (IQR 3.5 – 27.1) versus 12.6 hours (IQR 5.5 – 48.0) for those without SAH ($p<0.001$). Most of this difference was due to SAH patients presenting to hospital earlier on average than non-SAH patients (4.5 hours (IQR 1.7-22.7) vs 9.6 hours (IQR 2.8-46.0), $p<0.001$). The in-hospital interval from registration to imaging was also significantly shorter in SAH patients	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				(1.9 hours (IQR 1.2-2.8) vs 2.5 hours (IQR 1.5-3.9), p<0.001). Patients with SAH were older (52.7 vs 44.2 years, p<0.001), were more likely to have arrived by ambulance (56.2% vs 21.7%, p<0.001), vomited (65.5% vs 26.8%, p<0.001) and experienced witnessed loss of consciousness (7.7% vs 3.2%, p<0.001).	
Perry, 2011[59] Prospective cohort study (part of a larger project on clinical decision rules: Perry, 2010[43]) Emergency Departments at eleven university affiliated tertiary care teaching hospitals, Canada	3132 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within 1 hour) or syncope associated with headache, who underwent CT as part of their diagnostic intervention. Patient recruitment: November 2000 – December 2009 (patient overlap with Perry, 2010[43]).	Third generation multi-slice CT scanner (from 4 to 320 slices/rotation), interpreted by local radiologists (either neuroradiologists or general radiologists who routinely interpret head CT). The final local 'sign off' report was used, even though it might be created the next day, especially when the scan was obtained during the evening or weekend. The protocols at the beginning of the study (2000-2002) used 5 mm slices for the posterior fossa and 10 mm for the	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or >5x10^6/L RBCs in the final tube of CSF with aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (telephone follow-up at 1 month and 6 months and medical record review).	**Diagnostic accuracy results** **CT overall (SAH):** Sensitivity: 92.9% (95% CI 89.0 to 95.5) Specificity: 100% (95% CI 99.9 to 100) Positive predictive value: 100% (95% CI 98.3 to 100) Negative predictive value: 99.4% (calculated by CRD) Overall accuracy: 99.5% (calculated by CRD) Prevalence: 7.7% **CT within 6 hours of symptom onset (SAH):** Sensitivity: 100% (95% CI 97.0 to 100) Specificity: 100% (95% CI 99.5 to 100) Positive predictive value: 100% (95% CI 96.9 to 100) Negative predictive value: 100% (95% CI 99.5 to 100) Overall accuracy: 100% (calculated by CRD) Prevalence: 12.7% **CT >6 hours from symptom onset (SAH):** Sensitivity: 85.7% (95% CI 78.3 to 90.9) Specificity: 100% (95% CI 99.8 to 100)	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
		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.		Positive predictive value: 100% (calculated by CRD) Negative predictive value: 99.2% (calculated by CRD) Overall accuracy: 99.2% (calculated by CRD) Prevalence: 4.7% 3132 (100%) patients had a CT scan; 953 (30.4%) within 6 hours of symptom onset. 1546/3132 (49.4%) had LP. 3 SAH patients were discharged after misinterpretation of the CT scan by emergency physicians, but were recalled after review of the CT by radiologists. One CT was initially misinterpreted as normal by the emergency physician and radiology trainee; the patient had blood in the CSF attributed to traumatic LP and was found to have an aneurysm on follow-up MR angiogram 5 days later.	
Backes, 2012[60] Retrospective cohort study Emergency department at one university hospital, Netherlands	250 non-traumatic, alert, neurologically intact (GCS 15) headache patients with a clinical suspicion of SAH. Patients were identified from databases of SAH patients and patients in whom SAH was ruled out	Plain head CT scan (16-256 slices per rotation multidetector row third-generation scanner with a slice thickness of 5 mm). CT scans were interpreted by an experienced neuroradiologist. Head CT was performed within 6	LP performed ≥12 hours after ictus (CSF was examined using visual inspection and spectrophotometry for the presence of bilirubin).	**Diagnostic accuracy results** **CT overall (aSAH):** Sensitivity: 95.4% (95% CI 89.5 to 98.5) Specificity: 100% (95% CI 97.4 to 100) Positive predictive value: 100% (95% CI 96.5 to 100) Negative predictive value: 96.6% (95% CI 92.2 to 98.9) Overall accuracy: 98.4% (calculated by CRD) Prevalence: 35.2% (calculated by CRD) **CT within 6 hours of symptom onset (aSAH or other significant pathology*):**	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
	using CT and LP. 247/250 (98.8%) experienced headache. Patient recruitment: 1 January 2005 – 1 January 2012 (likely patient overlap with Backes, 2015[75]).	hours of symptom onset in 137 patients (54.8%) and >6 hours in 113 patients (45.2%).		Sensitivity: 98.5% (95% CI 92.1 to 100) Specificity: 100% (95% CI 94.8 to 100) Positive predictive value: 100% (95% CI 94.6 to 100) Negative predictive value: 98.6% (95% CI 92.3 to 100) Overall accuracy: 99.3% (calculated by CRD) Prevalence: 50.5% (calculated by CRD) *perimesencephalic haemorrhage, cerebral venous sinus thrombosis or cervical arteriovenous malformation **CT >6 hours from symptom onset (aSAH or other significant pathology*):** Sensitivity: 90.0% (95% CI 76.3 to 97.2) [88.1% (calculated by CRD)] Specificity: 100% (95% CI 95.1 to 100) Positive predictive value: 100% (95% CI 90.3 to 100) Negative predictive value: 94.8% (95% CI 87.2 to 98.6) [93.4% (calculated by CRD)] Overall accuracy: 95.6% (calculated by CRD) Prevalence: 37.2% (calculated by CRD) *perimesencephalic haemorrhage, acute ischemic stroke or thoracic arteriovenous malformation Final diagnosis in those who had CT scan within 6 hours of symptom onset (n=137): 56 aSAH, 11 perimesencephalic haemorrhage and 1 cerebral venous sinus thrombosis. 69 patients with negative/inconclusive CT results had LP;	

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				no further aSAH diagnoses but 1 patient was diagnosed with cervical arteriovenous malformation. Final diagnosis in those who had CT scan >6 hours from symptom onset (n=113): 28 aSAH, 8 perimesencephalic haemorrhage, 1 acute ischaemic stroke. 76 patients with negative/inconclusive CT results had LP; there were 4 further aSAH diagnoses and 1 cervical arteriovenous malformation. The 4 patients with negative or inconclusive CT results and aSAH on LP had been scanned between 27 hours and 10 days of symptom onset. In headache patients (n=247/250), sensitivity of head CT in patients scanned within 6 hours of symptom onset was 100% (95% CI 94.6 to 100), specificity was 100% (95% CI 94.8 to 100). Sensitivity of head CT >6 hours after symptom onset was 92.3% (95% CI 79.1 to 98.4), specificity was 100% (95% CI 95.1 to 100).	
Perry, 2020[53] Prospective before/after implementation study Emergency Departments at six academic	3672 non-traumatic, alert patients (GCS 15) with acute headache or headache-associated syncope (peaking within 1 hour).	Physician education to use Ottawa SAH Rule and 6-hour-CT rule. Comparator: Control period (before implementation).	Subarachnoid blood on CT (3rd generation or better using thin slices), LP (xanthochromia on visual inspection or >1x10^6/L RBCs in the final tube of CSF with aneurysm seen on angiography) and clinical follow-up (electronic	**Diagnostic accuracy results** **Ottawa SAH Rule (SAH):** Sensitivity: 100% (95% CI 98.1 to 100) Specificity: 12.7% (95% CI 11.7 to 13.9) Positive predictive value: 5.8% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 17.2% (calculated by CRD) Prevalence: 5.1% (calculated by CRD)	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
hospitals, Canada *Also reported in Canadian Clinical Decision Rules section*	Patient recruitment: January 2010 – June 2013 (before implementation) and June 2013 – January 2016 (after implementation).		health record review at 6 months and study end).	**6-hour-CT Rule (SAH):** 1204 patients received CT within 6 hours Sensitivity: 95.5% (95% CI 89.8 to 98.5) Specificity: 100% (95% CI 99.7 to 100) Positive predictive value: 100% (calculated by CRD) Negative predictive value: 99.5% (calculated by CRD) Overall accuracy: 99.6% (calculated by CRD) Prevalence: 9.2% (calculated by CRD) The rate of CT use remained constant; 88.0% in the control phase vs 87.5% in the intervention phase. The LP rate decreased from 38.9% to 25.9% (p<0.0001). The CTA rate increased from 18.8% to 21.7% (p=0.029). Admission rates decreased from 9.8% to 7.4% (p=0.011). Time from Emergency Physician assessment to discharge/referral was slightly longer (4.9 hours vs 5.2 hours; p=0.053). Mean length of stay in the ED was similar 6.3 vs 6.4 hours; p=0.685). Final diagnosis: 188 (5.1%) SAH, 26 (0.7%) ischemic stroke or TIA, 24 (0.7%) intracerebral haemorrhage, 10 (0.3%) brain tumour, 7 (0.2%) bacterial meningitis.	
Valle Alonso, 2018[55] Retrospective cohort study	85 non-traumatic, sudden headache patients (peaking within 1 hour) without unconsciousness or neurological focus,	CT (within 6 hours) followed by LP, if CT negative for SAH. The CT used was multi-slice (4-320	LP was performed in all patients with a negative CT scan. Clinical follow-up at 6 months using medical records or phone calls where there was no	**Diagnostic accuracy results** **CT within 6 hours (SAH):** Sensitivity: 100% (calculated by CRD) Specificity: 98.7% (calculated by CRD) Positive predictive value: 90.9% (calculated by CRD)	Patient selection: Unclear Index test: Low Reference standard: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency Department at one regional hospital, Spain *Also reported in Pathway of CT followed by LP section and Lumbar puncture section*	presenting to the ED within 6 hours of symptom onset. Patient recruitment: March 2012 – March 2013.	slices/rotation) with slices of 5 - 7.5 mm for the brain and 2.5 – 5 mm for the posterior fossa. The CT report was made by deputies of the radiology service, with over 5 years of experience and in consultation with the neuroradiologist when there was doubt.	conclusive data in medical records.	Negative predictive value: 100% (calculated by CRD) Overall accuracy: 98.8% (calculated by CRD) Prevalence: 11.8% (calculated by CRD) 74 (87%) patients underwent LP; LP was positive in 1 patient and inconclusive in 2 patients. However, bleeding was ruled out with later images; thus no cases of SAH were identified by LP. No cases of SAH were reported during the 6 months of follow-up. 7 patients experienced post puncture headache, going back to the ED and admission was necessary for 2 of them for pain control. The most frequent final diagnosis was migraine (38.8%). 9.4% had a severe diagnosis, such as meningitis (4.7%) and reversible cerebral vasoconstriction syndrome (4.7%). SAH patients were more likely to arrive at ED by ambulance (p=0.010) and have occipital headache location (p=0.012). Among the clinical signs highlighted, the presence of syncope (p=0.036), neck pain or stiffness (p=0.010), photophobia (p=0.001), nausea or vomiting (p=0.000), as well as higher numbers of systolic (mean 153 vs 126) and diastolic blood pressure (mean of 100 vs 80) (p=0.000).	Flow/timing: Low
Cooper, 2016[9] Retrospective cohort study	517 non-traumatic, neurologically pristine (GCS 15) patients with acute	CDU pathway of CT followed by LP.	Subarachnoid blood on CT (verified by a consultant radiologist), LP (CSF positive for	**Diagnostic accuracy results** **CT (SAH):** Sensitivity: 92.9% (95% CI 79.5 to 100) Specificity: 100% (95% CI 99.6 to 100)	Patient selection: Low Index test: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Clinical Decision Unit at one teaching hospital, UK *Also reported in Pathway of CT followed by LP section and Lumbar puncture section*	sudden onset severe headache managed on a CDU pathway for exclusion of SAH. Patient recruitment: January 2004 – December 2006.	Initial and verified non-contrast CT reports (performed on third-generation scanners) and LP results (all taken >12 hours from the index headache).	bilirubin on spectrophotometry or a uniformly blood-stained CSF sample across four bottles and positive angiography). If CT/LP strategy was not completed, sudden death or subsequent SAH was assessed at 12 months by analysing attendance and investigations (electronic hospital database).	Positive predictive value: 100% (95% CI 98.2 to 100) Negative predictive value: 99.8% (95% CI 99.4 to 100) Overall accuracy: 99.8% (calculated by CRD) Prevalence: 2.7% (14/510 who had CT) **LP after negative CT (SAH):** Sensitivity: 100% (95% CI 93.7 to 100) Specificity: 96.8% (95% CI 94.8 to 98.8) Positive predictive value: 9.1% (95% CI 0 to 26.1) Negative predictive value: 100% (95% CI 99.5 to 100) Overall accuracy: 96.8% (calculated by CRD) Prevalence: 0.3% (1/309 who had LP) CT was positive for SAH in 13 patients; 6 had an underlying lesion on angiography and 7 had perimesencephalic SAH. 4 CT scans were initially reported as 'normal' making patients eligible for LP, only to be subsequently altered in 3 cases to SAH positive after neuroradiological interpretation of the CT scan. LP was positive for SAH in 11 patients; 10 patients were LP positive but angiography negative (false positives). 510 (98.6%) patients had a CT scan and 309 had LP. 491 patients were eligible for LP (490 initially negative on CT + 1 patient who went straight to LP without CT); 182 eligible patients	Reference standard: Low Flow/timing: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				did not have LP due to procedure failure (n=18), patient refusal or contraindication (n=65) or decision of attending doctor (n=99). CT was positive for other significant aetiology in a further 14 patients: 4 cerebral infarction, 2 venous sinus thrombosis, 2 incidental cerebral aneurysm, 1 arachnoid cyst, 1 metastatic disease, 1 haemangioma, 1 subdural haemorrhage, 1 meningioma, 1 bleed into glioblastoma. LP was positive for other significant aetiology in a further 17 patients: 16 viral meningitis and 1 nonocclusive sagital sinus thrombosis.	
Blok, 2015[56] Retrospective cohort study Emergency Departments at eleven non-academic hospitals, Netherlands *Also reported in Pathway of CT followed by LP section*	760 neurologically intact (GCS 15) 'spontaneous' acute headache patients with suspected SAH, who underwent CT within 6 hours of onset (judged negative by radiologist) and subsequent LP. Patient recruitment: January 2007 – January 2013.	CT (third generation scanner) <6 hours from headache onset (assessed by a staff radiologist), followed by LP >12 hours after onset (CSF was analysed using spectrophotometry).	Review of admission CTs in patients with bilirubin positive CSF by two neuroradiologists and one stroke neurologist. Lumbar puncture >12 hours after onset (CSF was analysed using spectrophotometry using a number of methods across the 11 sites: oxyhaemoglobin/bilirubin concentration, UK NEQAS, qualitative assessment of absorption curve, Leiden method, and bilirubin excess).	52 (7%) CSF samples were initially considered positive for SAH, but only one CT was positive for subarachnoid blood (in the basal cisterns) on review by two neuroradiologists and one stroke neurologist; angiography did not identify an aneurysm and the patient was diagnosed with non-aneurysmal perimesencephalic haemorrhage (with a benign clinical course and no readmission for SAH during 26 month follow-up). No subarachnoid blood was identified in the other 51 patients with positive CSF findings. 28/51 patients had angiography; aneurysm was identified in 8 patients (3 previously coiled). In those with an aneurysm it was considered that aneurysm rupture was unlikely and the aneurysm was considered incidental (4 were treated and 4 were not).	Patient selection: Low Index test: Low Reference standard: Unclear Flow/timing: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				The negative predictive value for detection of subarachnoid blood on CT by staff radiologists working in a non-academic hospital was 99.9% (95% CI 99.3 to 100). SAH prevalence was 0.13% (1/760).	
Austin, 2018[61] Interim analysis of a retrospective cohort study Emergency department at one academic hospital, UK	250 patients attending the ED with suspected SAH who underwent CT. Patient recruitment: January – December 2016.	Interpretation of CT scans for SAH by emergency physicians (images were viewed on desktop screens). Average timeframe from symptom onset to scan was 48 hours (range 2 – 288).	Interpretation of CT scans for SAH by neuroradiologists (images were viewed using dedicated high definition screens for interpretation).	20 (8%) patients had SAH. A further 5 scans had other positive findings; 3 intracranial haemorrhage, 1 subdural haematoma, 1 venous sinus thrombosis. **Diagnostic accuracy results** **Emergency physician interpretation of CT (intracranial pathologies):** Sensitivity: 84% (95% CI 63.9 to 95.5) Specificity: 95% (95% CI 90.9 to 97.2) Three scans showing subarachnoid blood and one case of venous sinus thrombosis were interpreted as negative by Emergency Physicians. There was no difference in false negative interpretation between registrars and consultants. Gold standard was the final neuroradiologist report; neuroradiologists used dedicated high definition screens for interpretation. 69 patients (30.6%) were further investigated; 59 (26.2%) had LP (3 had a positive result).	Patient selection: Unclear Index test: High* Reference standard: Unclear Flow/timing: Low (limited reporting, as only a correspondence article was available) *Bias was considered high due to interpretation of index test on desktop screens, rather than high definition screens, as per

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
					reference standard
Lumbar Puncture					
Migdal, 2015[62] Retrospective cohort study Emergency Department at one academic hospital, USA	245 non-traumatic headache patients who presented with 'worst ever' or thunderclap headache and underwent LP to evaluate for SAH after normal CT. The study included 302 patients in total, 245 of which were included in a subgroup analysis of patients with 'low risk clinical features', with normal mental status, no known aneurysm at the time of LP and no known prior SAH (who met our inclusion criteria). Patient recruitment: 1 July 2010 – 30 June 2013.	LP after normal CT (64-slice CT scanner, interpreted by board-certified radiologists). Diagnosis of SAH on LP was defined as xanthochromia in the CSF or RBCs $>1x10^6/mm^3$ in the final tube with aneurysm or arteriovenous malformation subsequently identified on cerebral angiography.	Not applicable.	There were no cases of SAH in the low risk subgroup. 13/245 (5.3%) of these patients had LP-related complications. 2/302 (0.66%) patients in the full population had SAH diagnoses based on LP; both had high-risk characteristics for SAH (i.e. altered mental status or known aneurysm), but no signs of intracranial haemorrhage on CT. 18/302 (6%) had LP-related complications that resulted in a return visit to the ED or hospitalisation, including 12 patients with low-pressure headache (4 patients treated with a blood patch), 4 patients with severe LP site pain and 2 patients with contaminated CSF cultures. No patients had an infectious or haemorrhagic complication arising from LP. 32/302 (10.6%) patients in the full population had an alternative diagnosis identified from LP; 19 had viral meningitis, 5 had bacterial meningitis, 1 had chemical meningitis from recent contrast exposure. Head CTA identified 22 aneurysms in the 100 patients tested from the full population (22%).	Unclear
Perry, 2015[63]	1739 non-traumatic, alert	LP with CSF analysis (5 sites used visual	Blood in the subarachnoid space on	641/1739 patients had an abnormal LP result (red blood cells in the final tube or	Patient selection: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Sub-study of a prospective cohort study Emergency Departments at twelve academic centres, Canada	(GCS 15) headache patients (peaking within 1 hour) with suspected SAH and an initial negative CT scan. The analysis included the 641 patients with an abnormal LP result. Patient recruitment: November 2000 – December 2009 (appears to be patient overlap with Perry, 2011[59]).	inspection, 1 used spectrophotometry). Risk threshold based on concentration of RBCs in sample. Median time from headache onset to LP was 18 hours.	plain CT or xanthochromia or red blood cells in the final tube of CSF with aneurysm on cerebral angiography (digital subtraction, magnetic resonance, or CT) requiring neurovascular intervention or resulting in death.	xanthochromia). 15 of which had aneurysmal SAH; 7 cases were identified by presence of xanthochromia and 8 had abnormal erythrocyte count in CSF. Optimal RBC count cut-off to differentiate traumatic tap from SAH was $\leq 2000 \times 10^6$/L. Sensitivity was 93.3% (95% CI 66.0 to 99.7) and specificity was 92.8% (95% CI 90.5 to 94.6%) at this cut-off. Visual inspection of xanthochromia had sensitivity of 46.7% (95% CI 22.3 to 72.6) and specificity of 97.3% (95% CI 95.6 to 98.4). **Diagnostic accuracy results** **Risk classification based on threshold of $<2000 \times 10^6$/L RBC and no xanthochromia (aneurysmal SAH):** Sensitivity: 100% (95% CI 74.7 to 100) Specificity: 91.2% (calculated by CRD) Positive predictive value: 21.4% (95% CI 12.9 to 33.2) Negative predictive value: 100% (95% CI 99.2 to 100) Overall accuracy: 91.4% (calculated by CRD) Prevalence: 2.3% (15/641)	Index test: High Reference standard: Low Flow/timing: Unclear
Dupont, 2008[64] Retrospective cohort study	152 non-traumatic, alert, neurologically intact (GCS 15) thunderclap headache patients	LP with CSF analysis. CSF analysis of cell count, protein, glucose content and appearance was	Four-vessel catheter angiography was performed in all patients with xanthochromic CSF (n=18). If no aneurysm was detected, the	**Diagnostic accuracy results** **CSF xanthochromia (cerebral aneurysm):** Sensitivity: 93% Specificity: 95% Positive predictive value: 72% Negative predictive value: 99%	Patient selection: Low Index test: Low Reference standard: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency department at one academic medical centre, USA	(sudden and severe headache with maximal intensity at onset) with normal results on non-contrast CT. Mean time from headache onset to CT was 29.5 hours (range 1 hour to 10 days). Interpretation of CT results was performed by a radiologist or neuroradiologist. Patient recruitment: 1 January 1998 – 1 January 2008.	conducted in the hospital laboratory facility. Xanthochromia was determined by visual inspection of centrifuged samples on a background of white paper and under full-spectrum light. Mean time from headache onset to CSF analysis was 35.9 hours (range 2 hours to 10 days). Results were reported to the treating physician within 90 minutes of the LP procedure.	procedure was performed again within 7-14 days. Patients with an unruptured aneurysm, deemed to be an incidental finding, were noted. Patients with non-xanthochromic CSF (n=99) and patients who refused LP (n=35) were followed up clinically. A magnetic resonance angiographic study (1.5 T, gadolinium-enhanced) was performed in patients who were initially discharged from the ED but returned with symptoms of a second sudden-onset headache (n=35).	Overall accuracy: 94.9% (calculated by CRD) CSF xanthochromia was present in 18/117 (15%) patients who underwent LP; 13/18 (72%) had a ruptured cerebral aneurysm detected. 3/5 (60%) patients in whom aneurysm was not detected had a history of migraine, vs 2/13 (15%) of those with aSAH. Of the 99 patients without xanthochromia detected in the CSF, 35/99 (35%) underwent additional MR angiography on recurrence of their headaches; all were negative. 98/99 (99%) had no bleeding event at clinical follow-up. However, 1/99 (1%) patient who tested negative for xanthochromia was subsequently found to have a ruptured middle cerebral artery aneurysm (false negative result); this patient had (negative) CT performed 6 hours after headache onset and LP performed 9 hours after headache onset – whilst CSF was not deemed xanthochromic, the CSF RBC count remained between 20,000 and 30,000/µL in 4 successive collection tubes. Patients with aneurysm had significantly higher red blood cell counts (mean 85,779 [SD 43,245]/µL) than patients without aneurysm (mean 98.7 [SD 646.2]/µL); $p<0.001$. Patients with aneurysm also had significantly higher total nucleated blood cell counts (mean 64.7 [SD 49.7]/µL) than patients without aneurysm (mean 1.47 [SD 1.18]/µL); $p=0.02$.	Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				152 (100%) patients had a negative CT scan and 117 (77%) underwent LP. 23% patients refused LP despite strong recommendations (none of which had bleeding events at clinical follow-up). Prevalence: 9.2% (14/152 of the total cohort; calculated by CRD)	
Sansom, 2014[65] Retrospective cohort study Emergency department at one teaching hospital, UK	60 thunderclap headache patients with a negative CT scan result (mean time from headache onset to CT was 32.1 hours, range 2-170). 323 patients presented with thunderclap headache during the recruitment period, only the 60 patients who had a negative CT result and underwent LP were included in the analysis. Patient recruitment: 1 May 2013 – 31 October 2013.	LP with CSF analysis (national guidelines for CSF analysis for xanthochromia were used).	Not applicable.	None of the 60 cases of thunderclap headache with negative CT were positive for xanthochromia. 52/60 CSF examinations were normal for all CSF parameters (protein, glucose, cells, microscopy and xanthochromia). 5 of 8 abnormal examinations were positive for oxyhaemoglobulin; 3 were associated with mild pleocytosis (<10 WBC x 10^6/L). Cerebral infarction was confirmed in 2 of the 8 patients with subsequent scans. CSF examination showed pleocytosis in the remaining case. Aneurysm was excluded in 5 patients with vascular imaging. Prevalence of SAH in the full population was 5.6% (18/323).	High (limited reporting, as only a conference poster was available)
Horstman, 2012[66]	30 patients with sudden severe headache or neck	Bilirubin in the CSF (>0.05 at wavelength 458 nm). CSF was	Not applicable.	Aneurysms were detected in 13/30 (43%) patients with bilirubin in their CSF, all of whom presented between 4 and 14 days after symptom	Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Retrospective cohort study Emergency department at one university hospital, Netherlands	pain and negative head CT but bilirubin detected in CSF. WFNS score of 1 in all but one patient (WFNS 2, equivalent to 13-14 on GCS). Patient recruitment: 2002 – 2007.	protected from light by wrapping in foil, then centrifuged at 1,500 rpm for 10 minutes. The supernatant was stored at 4◦C until analysis. CSF investigations were performed using a Beckman DU 650 spectrophotometer (Beckman Coulter, The Netherlands).		onset. CT scans from patients from outside hospitals referred to our hospital were judged as normal by the radiologist at the outside hospital, but slight abnormalities were found in 4/30 (13.3%) after revision by the neuroradiologist at our hospital; 2 were positive for SAH, 2 were ambiguous (suspicion of small amount of blood in the pentagon). Aneurysms were treated by coiling in 9 patients and clipping in 2; 2 patients were not treated due to poor clinical condition or refusal of further tests. 2/13 patients died within 3 months; 1 due to a re-bleed, the other due to secondary ischaemia. One further SAH patient had a poor outcome with major neurological deficits because of secondary ischeaemia. All patients without an aneurysm detected were alive after 2-7 years of follow-up with no further SAH episodes.	
Brunell, 2013[67] Retrospective cohort study Emergency department or outpatient clinics in neurology or infectious diseases at one	453 patients over 10 years of age who underwent LP to exclude SAH, including 400 patients with thunderclap headache (88%) and 53 patients where the treating physician wanted to perform LP to	LP with CSF analysis. An automated quantitative measurement of bilirubin in the CSF was used. The CSF and plasma bilirubin and CRP measurements were performed on a high-throughput automatic	Not applicable.	295/453 (65%) LPs resulted in completely normal CSF-analysis and 138 (30%) were pathological in a way that was deemed insignificant by the treating physician, e.g. very mild pleocytosis or raised protein. 14 (3%) patients had an alternative diagnosis (most commonly aseptic meningitis) and 5 (1.1%) had SAH. 4/5 SAH patients presented with thunderclap headache and had non-aneurysmal SAH not requiring surgical intervention. The other patient	Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
university hospital, Sweden	exclude SAH (e.g. patients with previous SAH or cases of severe headache with unclear onset). Patient recruitment: January 2009 – December 2011.	analyser: Abbott Architect c8000 (Abbott Laboratories, Illinois, USA). Above the cut-off 350 nmol/L the CSF-bilirubin determinations were regarded as positive. Hemoglobin in CSF was measured by spectrophotometry at a fixed wavelength 415 nm, on a Hitatch U-1100, utilising 0.040 arbitrary units (AU) as a cut-off. Samples are routinely protected from light before analysis.		had decreased level of consciousness and prior history of SAH; due to poor general condition no further investigations or treatment were performed. All patients with SAH detected by LP underwent LP >12 hours after headache onset and CT >6 hours after headache onset. One patient was not CT-negative, but underwent LP prior to CT, which demonstrated bleeding. 11/14 patients with an alternative diagnosis presented with thunderclap headache and all diagnoses were based on LP performed >12 hours after headache onset. 6 patients had normal neurological examination and 3 had only discrete signs of meningism. 2 patients received antiviral treatment for herpex simplex virus, 12 had no treatment and all patients made a full recovery. 153/453 (34%) patients were admitted for their LP after negative CT, including patients admitted to await the 12 hour time limit or because time could not be spared to perform the LP in the ED (additional patients were admitted for medical reasons, e.g. pain relief). All patients had a CT scan and LP.	
Gangloff, 2015[68] Some results also taken from duplicate report[341]	706 non-traumatic, neurologically intact (GCS 15) acute headache patients with suspected SAH and	Visual and spectrophotometric inspection of xanthochromia. LP was undertaken >12 hours after symptom	Angiography (catheter angiogram, CT-angiogram). To avoid misclassifying incidental aneurysm with a traumatic tap as aSAH,	**Diagnostic accuracy results** **UK NEQAS CSF analysis (aneurysmal SAH):** Sensitivity: 100% (95% CI 47.8 to 100) Specificity: 98.1% (95% CI 96.7 to 99.0) Positive predictive value: 27.8% (calculated by CRD)	Patient selection: Low Index test: Low Reference standard: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Retrospective cohort study Emergency Department at one university hospital, Canada	an initial negative CT scan (Siemens Sensation 4 between 2003-2008 and Sensation 16 from 2008 onwards; CT scan read by a radiologist). Patient recruitment: 2003-2009 (may be patient overlap with Perry, 2011[59]).	onset in 466 patients (67.5%), median 13 hours. Visual analysis was performed on fresh CSF by the technologist on duty, immediately after arrival to the laboratory. Spectrophotometry was performed after visual assessment, using a quartz cuvette compared against a blank made of ultra-pure water and scanned from 350 nm to 700 nm using a Cary100 spectrophotometer (Varian). Resulting scans were analysed using the UK NEQAS 2008 approach and the Hendrik Duiser iterative approach.	positive cases were further reviewed by two physicians using a standardised data collection sheet – in case of disagreement medical charts were sent to a neurosurgeon for a third opinion. The study had a safety-net for possible missed SAH; it is the only neurosurgical referral centre covering more than half the province of Quebec, a false-negative patient would eventually be picked up on a follow-up visit or readmission, or in the event of any sudden death through coroner investigation.	Negative predictive value: 100% (calculated by CRD) Overall accuracy: 98.2% (calculated by CRD) Prevalence: 0.7% 13 (1.8%) false positive results; 9 of which had non-aneurysmal SAH. **Iterative spectrophotometry method (aneurysmal SAH):** Sensitivity: 100% (95% CI 47.8 to 100) Specificity: 91.9% (95% CI 89.6 to 93.9) 56 (7.9%) false positive results; 18 of which were due to other indications (10 non-aneurysmal SAH, 7 meningitis, 1 hyperbilirubinemia disease). **Visual xanthochromia (aneurysmal SAH):** Sensitivity: 80% (95% CI 28.4 to 99.5) Specificity: 98.7% (95% CI 97.5 to 99.4) LP identified 5 aneurysmal SAH patients who had a negative CT; all had high red blood cell count (from 1310 to 63,000 x 10^6/L) and positive spectrophotometric xanthochromia; 4/5 were positive on visual inspection for xanthochromia. All 5 patients received coiling or clipping and had a good outcome. 4/5 SAH patients had delays longer than 24 hours prior to CT, the other patient received CT 2.5 hours after symptom onset.	Flow/timing: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Perry, 2006[69] Sub-study of a prospective cohort study Emergency Departments at three tertiary care university hospitals, Canada	220 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within 1 hour) or syncope associated with headache. Patient recruitment: July 2002 – January 2004 (appears to be patient overlap with Perry, 2011[59] and Perry, 2015[63]).	LP with CSF examined using spectrophotometry (Milton Roy Spectronic 1001plus). After routine analysis for cell count and visible xanthochromia, any remaining CSF in the final tube was centrifuged and frozen for later spectrophotometry. Absorbances were measured across a 1-cm light path at 360 nm, 415 nm, 440 nm, 476 nm and 530 nm relative to a saline blank. Four different definitions of positive spectrophotometry were selected a priori: Traditional, Chalmers and Kiley, Chalmers revised and UK NEQAS. The interval between headache onset and LP was >12 hours in 55% patients.	Subarachnoid blood on CT, LP (xanthochromia on visual inspection or >5x10^6/L RBCs in the final tube of CSF with aneurysm or arteriovenous malformation seen on angiography) and clinical follow-up (telephone follow-up at 30 days).	**Diagnostic accuracy results** **Visual inspection (SAH):** Sensitivity: 50% (95% CI 3.0 to 81) Specificity: 97% (95% CI 92 to 99) **Traditional definition (SAH):** Sensitivity: 100% (95% CI 16 to 100) Specificity: 29% (95% CI 23 to 35) **Chalmers and Kiley definition (SAH):** Sensitivity: 0% (95% CI 0 to 16) Specificity: 89% (95% CI 84 to 92) **Chalmers revised definition (SAH):** Sensitivity: 100% (95% CI 3.0 to 100) Specificity: 29% (95% CI 23 to 35) **UK NEQAS definition (SAH):** Sensitivity: 100% (95% CI 3.0 to 100) Specificity: 83% (95% CI 76 to 87) Prevalence: 1 patient had aneurysmal SAH and 1 patient had an incidental unruptured aneurysm. One patient with aneurysm had normal CT 8 hours after headache onset; LP demonstrated high levels of RBCs (53,500x10^6/L) and visible xanthochromia, with aneurysm (11x8mm) confirmed on CT angiography. The other patient had normal CT 3 days after headache onset; CSF contained RBCs (41x10^6/L) but no visual xanthochromia and was classed as traumatic tap	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
		Comparator: Visual inspection of the centrifuged CSF for xanthochromia against a white paper background under full spectrum light.		by the treating physician. Aneurysm (5mm) was confirmed on CT angiography but was considered incidental and not treated; the patient remained well 1 year later. 87.7% patients had a CT scan and 100% had LP. 5.9% patients had a CT angiogram. If presence of visible xanthochromia (visual inspection) were the only indication for angiography, the angiography rate would reduce by 85%. However, using any of the 3 sensitive spectrophotometric definitions of xanthochromia would increase angiography rates from 254% to 1208% compared with current practice.	
Cooper, 2016[9] Retrospective cohort study Clinical Decision Unit at one teaching hospital, UK *Also reported in Pathway of CT followed by LP section and CT Scan section*	517 non-traumatic, neurologically pristine (GCS 15) patients with acute sudden onset severe headache managed on a CDU pathway for exclusion of SAH. Patient recruitment: January 2004 – December 2006.	CDU pathway of CT followed by LP. Initial and verified non-contrast CT reports (performed on third-generation scanners) and LP results (all taken >12 hours from the index headache).	Subarachnoid blood on CT (verified by a consultant radiologist), LP (CSF positive for bilirubin on spectrophotometry or a uniformly blood-stained CSF sample across four bottles and positive angiography). If CT/LP strategy was not completed, sudden death or subsequent SAH was assessed at 12 months by analysing attendance and investigations (electronic hospital database).	**Diagnostic accuracy results** **CT (SAH):** Sensitivity: 92.9% (95% CI 79.5 to 100) Specificity: 100% (95% CI 99.6 to 100) Positive predictive value: 100% (95% CI 98.2 to 100) Negative predictive value: 99.8% (95% CI 99.4 to 100) Overall accuracy: 99.8% (calculated by CRD) Prevalence: 2.7% (14/510 who had CT) **LP after negative CT (SAH):** Sensitivity: 100% (95% CI 93.7 to 100) Specificity: 96.8% (95% CI 94.8 to 98.8) Positive predictive value: 9.1% (95% CI 0 to 26.1) Negative predictive value: 100% (95% CI 99.5 to 100)	Patient selection: Low Index test: Unclear Reference standard: Low Flow/timing: Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				Overall accuracy: 96.8% (calculated by CRD) Prevalence: 0.3% (1/309 who had LP) CT was positive for SAH in 13 patients; 6 had an underlying lesion on angiography and 7 had perimesencephalic SAH. 4 CT scans were initially reported as 'normal' making patients eligible for LP, only to be subsequently altered in 3 cases to SAH positive after neuroradiological interpretation of the CT scan. LP was positive for SAH in 11 patients; 10 patients were LP positive but angiography negative (false positives). 510 (98.6%) patients had a CT scan and 309 had LP. 491 patients were eligible for LP (490 initially negative on CT + 1 patient who went straight to LP without CT); 182 eligible patients did not have LP due to procedure failure (n=18), patient refusal or contraindication (n=65) or decision of attending doctor (n=99). CT was positive for other significant aetiology in a further 14 patients: 4 cerebral infarction, 2 venous sinus thrombosis, 2 incidental cerebral aneurysm, 1 arachnoid cyst, 1 metastatic disease, 1 haemangioma, 1 subdural haemorrhage, 1 meningioma, 1 bleed into glioblastoma. LP was positive for other significant aetiology in a further 17 patients: 16 viral meningitis and 1 nonocclusive sagital sinus thrombosis.	

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Valle Alonso, 2018[55] Retrospective cohort study Emergency Department at one regional hospital, Spain *Also reported in Pathway of CT followed by LP section and CT Scan section*	85 non-traumatic, sudden headache patients (peaking within 1 hour) without unconsciousness or neurological focus, presenting to the ED within 6 hours of symptom onset. Patient recruitment: March 2012 – March 2013.	CT (within 6 hours) followed by LP, if CT negative for SAH. The CT used was multi-slice (4-320 slices/rotation) with slices of 5 - 7.5 mm for the brain and 2.5 – 5 mm for the posterior fossa. The CT report was made by deputies of the radiology service, with over 5 years of experience and in consultation with the neuroradiologist when there was doubt.	LP was performed in all patients with a negative CT scan. Clinical follow-up at 6 months using medical records or phone calls where there was no conclusive data in medical records.	**Diagnostic accuracy results** **CT within 6 hours (SAH):** Sensitivity: 100% (calculated by CRD) Specificity: 98.7% (calculated by CRD) Positive predictive value: 90.9% (calculated by CRD) Negative predictive value: 100% (calculated by CRD) Overall accuracy: 98.8% (calculated by CRD) Prevalence: 11.8% (calculated by CRD) 74 (87%) patients underwent LP; LP was positive in 1 patient and inconclusive in 2 patients. However, bleeding was ruled out with later images; thus no cases of SAH were identified by LP. No cases of SAH were reported during the 6 months of follow-up. 7 patients experienced post puncture headache, going back to the ED and admission was necessary for 2 of them for pain control. The most frequent final diagnosis was migraine (38.8%). 9.4% had a severe diagnosis, such as meningitis (4.7%) and reversible cerebral vasoconstriction syndrome (4.7%). SAH patients were more likely to arrive at ED by ambulance (p=0.010) and have occipital headache location (p=0.012). Among the clinical signs highlighted, the presence of syncope (p=0.036), neck pain or stiffness (p=0.010), photophobia (p=0.001), nausea or vomiting (p=0.000), as well as higher numbers	Patient selection: Unclear Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				of systolic (mean 153 vs 126) and diastolic blood pressure (mean of 100 vs 80) (p=0.000).	
Heiser, 2015[70] Retrospective cohort study Emergency departments at two academic hospitals, USA	676 non-traumatic, alert, acute headache patients who underwent LP to rule out SAH and had an abnormal result on CSF. Patient recruitment: Not reported. 6 year study period.	Validation of a clinical prediction rule to differentiate between traumatic LP and SAH, based on CSF findings (RBC count >2000 x 10^6/L and the presence of xanthochromia, if neither criteria present, aSAH can be excluded).	SAH was confirmed in 49 patients using diagnostic imaging. Demographics, co-morbidity, clinical findings, diagnostic testing and final diagnosis were obtained from ED records. Unclear whether all patients had diagnostic testing and/or other reference standard.	**Diagnostic accuracy results** **Clinical prediction rule (RBC count >2000 x 10^6/L and presence of xanthochromia) (SAH):** Sensitivity: 81.6% (95% CI 68.0 to 91.2) Specificity: 97.3% (95% CI 95.7 to 98.4) Positive predictive value: 70.2% (calculated by CRD) Negative predictive value: 98.5% (calculated by CRD) Overall accuracy: 96.2% (calculated by CRD) Prevalence: 7.2% (49/676) The incidence of traumatic LP was 24.4%. The range of values in tube 4 for the SAH group was 120 to 521,500 RBCs, suggesting that there is not a CSF RBC cut-off value at which one can safely exclude SAH. We found no risk factor or combination of clinical factors that would improve ED provider sensitivity without markedly decreasing specificity.	Patient selection: Low Index test: Unclear Reference standard: Unclear Flow/timing: Unclear (limited reporting, as only a conference presentation was available)
CT Angiography					
Alons, 2015[71] Retrospective cohort study Emergency department at one teaching	70 non-traumatic, neurologically intact, acute severe headache patients with normal non-contrast CT (evaluated by specialised neuroradiologists)	CT angiogram using GE Lightspeed 64-slice CT scanner. All but 1 scan was made within a week of the occurrence of the headache; 1 scan was made after 3 weeks.	Not applicable.	There were no cases of SAH. 13/70 (19%) patients had a vascular abnormality identified on CTA; 8 (11%) had aneurysms (3 were coiled, 3 were clipped and 2 received follow-up CTA to monitor aneurysm size), 2 cerebral venous thrombosis, 2 reversible cerebral vasoconstriction syndrome and 1	Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
hospital, Netherlands	and CSF findings (all patients had CT and LP). Patient recruitment: January 2008 – May 2011.	MRI was also used in 15 patients.		patient had ischemia of the posterior circulation in the right occipital area.	
Alons, 2018[72] Retrospective cohort study and meta-analysis Emergency departments at two university affiliated secondary referral centres, Netherlands	88 neurologically intact, acute headache patients (developing within 5 minutes and lasting ≥1 hour) with normal non-contrast CT and CSF findings, when performed (LP performed in 35% patients). The meta-analysis also included 641 patients identified from the literature. Patient recruitment: 2011 – 2014.	CT angiography using Aquilion One (Toshiba Medical Systems), Aquilion 64 (Toshiba Medical Systems) or GE Lightspeed 64-slice CT scanners.	Not applicable.	There were no cases of SAH. 5/88 patients had a vascular abnormality identified on CTA; 1 aneurysm (a small unruptured aneurysm with a normal LP, not considered to be the cause of the headache), 1 cerebral venous thrombosis, 2 reversible cerebral vasoconstriction syndrome and 1 cervical dissection. The aneurysm was treated with clip ligation, the reversible cerebral vasoconstriction syndrome patients were followed up clinically and the other two patients were followed up with medication change. 1 patient experienced an adverse event associated with CTA; a short-term allergic reaction to iodinated contrast media.	Unclear
History and Examination					
Locker, 2004[73] Retrospective cohort study	353 non-traumatic, neurologically intact (GCS ≥14) headache patients. 36/353 patients presented with	Adequacy of history, examination and investigation (CT and LP).	Not applicable.	7/353 (2%) patients were diagnosed with SAH; 4 had abnormal neurological examination, 3 presented with 'first or worst' headache (3/36; 8.3%).	Unclear

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency department at one teaching hospital, UK	'first or worst' headache and normal neurological examination (who met our inclusion criteria). Patient recruitment: 1 January 2000 – 31 December 2000.			Other secondary headaches identified in the full study population were: 1 intracranial bleed, 8 cerebral/cerebellar infarct, 3 meningitis, 18 systemic infection, 28 'other' secondary headache. 280 patients were diagnosed with primary headaches (migraine, tension headache, cluster headache or 'other' primary headache). The final diagnosis was not known for 8 patients. 1 patient was re-admitted within 3 months with SAH, it is unclear whether this was originally missed or new. 4 characteristics were selected as predictors of secondary headache: age >65 years, temperature >38◦C, systolic BP >160 mmHg, presence of neck stiffness. The presence of at least one of these features in the study population predicted secondary headache with a sensitivity of 37.8% and a specificity of 82.1%. Only 1 patient had an adequate history recorded and no patient had a complete examination recorded.	
Perry, 2005[74] Prospective cohort study Emergency departments at three university-	747 non-traumatic, alert, neurologically intact (GCS 15) acute headache patients (peaking within 1 hour) or	Patient assessment made by attending physicians certified in emergency medicine or supervised residents in an emergency medicine training	Subarachnoid blood on CT (3rd generation or higher, verified by a neuroradiologist), LP (xanthochromia on visual inspection or >$5x10^6$/L RBCs in the final tube of CSF with aneurysm or	50/747 (6.7%) patients had SAH. 7 patients (0.94%) had other serious illnesses; 4 CNS neoplasm, 2 other type of cerebral haemorrhage, 1 bacterial meningitis. 71.8% were diagnosed as having benign headache or migraine. The emergency physicians' pre-test probability that their patient had a SAH was assessed using	Patient selection: Low Index test: Low Reference standard: Low Flow/timing: Low

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
affiliated tertiary care teaching hospitals, Canada	syncope associated with headache. Patient recruitment: November 2000 – March 2003 (appears to be patient overlap with Perry, 2011[59]).	program (without the use of a clinical decision rule).	arteriovenous malformation seen on angiography).	a receiver operating characteristic (ROC) curve; the area under the ROC curve was 0.85 (95% CI 0.80 to 0.91) (data available for 639 cases). There were 3 SAH patients for whom the physician pre-test probability was ≤2%; these patients had perimesencephalic bleed (n=1), vasculitis with SAH (n=1) and a 4.5mm right superior hypophyseal artery aneurysm (n=1, although unclear whether the patient had an SAH or a benign headache with an incidental aneurysm – CT was normal and LP was equivocal). Using the pre-test probability of ≥2% as the threshold to use diagnostic tests for headache patients, the sensitivity of clinical suspicion was 93% (95% CI 81 to 97) and specificity was 49% (95% CI 45 to 53). Physicians reported being "uncomfortable" (47.3% cases) or "very uncomfortable" (28.1% cases) with performing no test in 75.4% of cases (data available for 659 cases) and being "uncomfortable" (37.6% cases) or "very uncomfortable" (12.0% cases) with performing LP without CT in 49.6% cases (data available for 625 cases). 79.9% patients had a CT scan and 45.9% had LP; 42.6% had CT and LP.	
Backes, 2015[75] Retrospective cohort study	247 non-traumatic, alert, neurologically intact (GCS 15) headache patients (peaking within	Neurologic examination for neck stiffness as a predictor of SAH. The time interval between symptom	Subarachnoid blood on CT or presence of bilirubin at CSF absorption spectrophotometry.	114 (46%) patients had SAH; in 2 patients head CT was negative for SAH but CSF tested positive for bilirubin and aneurysm was confirmed using CT angiogram.	Patient selection: Low Index test: Low Reference standard: High

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
Emergency department at one university hospital, Netherlands	minutes and lasting ≥1 hour). Patients were identified from databases of SAH patients and patients in whom SAH was ruled out using CT and LP. Diagnostic accuracy results were presented for 223 patients, as information on neck stiffness was missing for 24 patients. Patient recruitment: 1 January 2005 – 1 September 2013 (likely patient overlap with Backes, 2012[60]).	onset and neurological examination was dichotomised into ≤6 hours and 6-72 hours.		82 patients had neck stiffness at neurological examination, although this was mild or ambiguous for 18 of these patients. **Diagnostic accuracy results** **Neck stiffness (SAH):** Sensitivity: 67.0% (95% CI 57.9 to 76.1) Specificity: 89.2% (95% CI 83.6 to 94.7) Positive predictive value: 84.1% (95% CI 74.4 to 91.3) Negative predictive value: 75.9% (95% CI 68.8 to 82.9) Overall accuracy: 78.9% (calculated by CRD) Prevalence: 46% **Neck stiffness assessed within 6 hours (SAH):** Sensitivity: 59.5% (95% CI 47.4 to 70.7) Specificity: 93.1% (95% CI 84.5 to 97.7) Positive predictive value: 89.8% (95% CI 77.8 to 96.6) Negative predictive value: 69.1% (95% CI 58.9 to 78.1) **Neck stiffness assessed between 6-72 hours (SAH):** Sensitivity: 86.2% (95% CI 68.3 to 96.1) Specificity: 83.3% (95% CI 69.8 to 92.5) Positive predictive value: 75.8% (95% CI 57.7 to 88.9) Negative predictive value: 90.9% (95% CI 78.3 to 97.5)	Flow/timing: High

Study details	Patient characteristics	Intervention(s)	Reference standard	Main results	Risk of bias
				The presence of neck stiffness at neurological examination was more strongly predictive of SAH in subgroups with other high-risk clinical characteristics such as being ≥40 years old, vomiting and transient loss of consciousness.	

Abbreviations: aSAH, aneurysmal subarachnoid haemorrhage; BP, blood pressure; CDU, Clinical Decision Unit; CI, confidence interval; CNS, central nervous system; CRD, Centre for Reviews and Dissemination; CSF, cerebrospinal fluid; CT, computed tomography; CTA, computed tomography angiography; ED, Emergency Department; GCS, Glasgow Coma Scale; LP, lumbar puncture; MRI, Magnetic resonance imaging; RBC, red blood cell; ROC, receiver operating characteristic; SAH, subarachnoid haemorrhage.

Cost-effectiveness studies (n=4)

Study details	**Malhotra, 2016[78]**
Country	USA
Year of cost analysis	2014
Currency	US Dollar
Aim of study	Cost utility analysis considering the cost-effectiveness of alternative testing strategy in patients with suspected subarachnoid haemorrhage but a negative non-contrast CT
Decision analysis model overview	Decision tree considering aneurysm risk under alternative test strategies.
Perspective	Societal payers' perspective
Discount rate - benefits and costs	No discounting was applied
Time horizon	1 year
Population details	Patients presenting with thunderclap headache with a negative non-contrast CT.
Intervention vs. comparator/s	CT angiography vs. lumbar puncture vs. no follow-up.
Primary effectiveness data	Prevalence of SAH in this population was assumed to be 8.41%, and the sensitivity and specificity of a non-contrast head CT scan were 98% and 100% respectively (Boesiger 2005, Byyny 2008, Perry 2011). CTA was assigned a sensitivity of 99.2% for the detection of aneurysms and a specificity of 100% , with values taken from Carstairs *et al*. (2006) and Westerlaan *et al*. (2011). Sensitivity of LP was 100%, and specificity was 86.7% (Gorchynski 2007, Perry 2010, Menke 2011). Probabilities of complications were based on literature values. Cancer was not included as a complication of CTA, nor were other contrast related complications.
Utilities applied	Patients were utilities based on outcome achieved using a uniform distribution. Utilities applied were as follow: good outcome (0.6 to 1.0 QALY), poor outcome (0.2 to 0.5 QALY), and death (0 QALY).
Utilities source	Samsa *et al.* (1999)
Costs considered	Procedure costs, hospitalisations costs (including bed costs, blood tests and IV caffeine) Costs of treatment (coiling of unruptured aneurysms), care costs associated with treated and untreated aneurysm, and AE costs
Costs source	Procedure costs and AE costs were derived from Medicare reimbursement. Other costs were derived from published sources.
Results	In the base-case analysis, CTA was dominated by doing nothing and LP. LP had an expected cost of $570 and total QALYs of 0.7992, while CTA had an expected cost of $596 and QALYs of 0.7986. Doing nothing had a cost of $1,019 and 0.7989 QALYs. LP therefore generated more QALYs at a lower cost than the CTA and no follow-up strategies. LP was also the most cost-effective strategy in 85% of PSA iterations.
Sensitivity analysis undertaken and results	The sensitivity threshold at which CT with no follow-up was found to be the most cost-effective strategy was 99.2%, when CT sensitivity was between 73.7% and 99.2%, LP was the most cost-effective follow-up

	strategy. If the pre-test probability of SAH was 3.2 – 54.6%, LP was the most cost-effective follow-up strategy.
Study details	**Taylor, 2016[76]**
Country	USA
Year of cost analysis	NA
Currency	NA
Aim of study	Decision analytic model to ascertain the optimum testing strategy in patients with suspected subarachnoid haemorrhage but a negative SAH result.
Decision analysis model overview	Decision tree considering aneurysm risk, surgical complications and AE's associated with LP and CTA. A Markov node also considered the outcomes of patients who develop malignancies resulting from radiation exposure.
Perspective	Not stated
Discount rate - benefits and costs	3% discount rate applied to benefits
Time horizon	Not stated
Population details	Patients presenting with thunderclap headache with normal neurological function and a negative non-contrast CT.
Intervention vs. comparator/s	Lumbar puncture vs. no follow-up.
Primary Effectiveness measure(s)	The diagnostic accuracy of LP was derived from Perry *et al.* (2008), and Claveau and Dankoff (2013), which for the base-case analysis used a sensitivity of 100% (94 – 100) and specificity of 67% (63 – 71) for SAH. The sensitivity and specificity of CT angiography for detecting aneurysm were 98% and 100% respectively, with values taken from Carstairs *et al.* (2006) and Westerlaan *et al.* (2011). A range of adverse events were considered in the model, including mortality and long-term morbidity arising from lumbar puncture and aneurysm surgery, from missed cases of SAH, and death resulting from other factors related to aneurysm and treatment/diagnosis.
Utilities applied	Health states were each assigned a utility. Utilities modelled for patients SAH and testing related AE were as follows: RF requiring RRT (0.84), LP morbidity (0.7), and long-term morbidity associated with SAH were applied (0.74). Where patients were modelled to experience multiple source of morbidity utility values were generated by multiplying individual values. It is not clear on what utility value was applied to patients who experience no long-term morbidity.
Utilities source	Tengs and Wallace (2000)
Costs considered	No costs were considered in the model.
Costs source	NA
Results	The testing threshold in the base-case analysis was 4.3%. The probabilistic mean testing threshold was 4.3% (95% CI 1.4 to 9.3%).

	The authors conclude that in the majority of patients scanned with newer-generation CT scanners, LP would cause more harm than good.
Sensitivity analysis undertaken and results	In the two-way sensitivity analysis considering x and y the testing threshold was found to vary from 1.9% to 15.6%. Uncertainty was driven primarily by probability of death from initial missed SAH, other drivers included probability of non-aneurysmal SAH following negative head CT, and probability of renal failure.
Study details	**Ward, 2012[79]**
Country	USA
Year of cost analysis	2009
Currency	US Dollar
Aim of study	To determine the relative cost-effectiveness of diagnostic strategies for SAH.
Decision analysis model overview	Decision tree considering the outcome of the testing strategy, with a Markov node used to consider the outcomes of patients who develop malignancies resulting from radiation exposure. The decision tree considered aneurysm risk and complications associated with CTA. The Markov model consisted of three states – healthy, cancer, and death.
Perspective	Not stated
Discount rate - benefits and costs	Costs and benefits were both discounted at a rate of 3%
Time horizon	37 years
Population details	Neurological normal patients presenting to the ED more than 12 hours after onset of acute severe headache.
Intervention vs. comparator/s	CT-alone vs. CT followed by LP vs. CT followed by CT angiography vs. CT followed by MRI/MRA.
Primary Effectiveness measure(s)	Prevalence of SAH in the modelled patient population was 12%. Sensitivity of non-contrast head CT was 95.6% for SAH (McCormack 2010) sensitivity of CTA was 97%, of LP was 100%, and MRI/MRA was 86%. Specificity of non-contrast CT was 100%, CTA was 98%, LP was 85%, and MRI/MRA was 85%. The model considered malignancy, contrast-induced nephropathy, and anaphylactoid reactions as consequences of CT and CTA. Patients receiving LP had a 20.5% incidence of postdural puncture headache (PDHA), and 4.1% of all LP patients returned to the ED for PDHA evaluation.
Utilities applied	Health states were each assigned a utility, with normal health assigned a value of 1 and death 0. Utilities modelled for patients SAH and testing related AE were as follows: cancer or CIN (0.7) other disability (0.85), dialysis 0.84, and severe disability (0.26).
Utilities source	Tengs and Wallace (2000).
Costs considered	Costs included procedure costs, hospitalisation and facilities costs, staff costs, care costs associate with SAH related morbidity and costs of AEs including cancer treatment.

Costs source	Costs associated with procedures, facilities, and staff were based on Medicare data. Other costs were drawn from relevant published sources.
Results	In the base case analysis, the CT-only strategy had a cost of $10,339 and generated 20.25 QALYs, which dominated CT/CTA and CT/MRA strategies, which generated 20.24 and 20.27 QALYs respectively at a greater cost. The CT/LP strategy had an ICER of $41,239 versus CT-only, with an incremental cost of $4,781 and generating an additional 0.116 QALYs.
Sensitivity analysis undertaken and results	Sensitivity analysis showed that higher CT sensitivity results in the CT-only strategy becoming cost-effective, however, in the >12 hour since headache onset group, CT followed by LP was the most cost-effective strategy.
Study details	**Wu, 2016[77]**
Country	USA
Year of cost analysis	2014
Currency	US dollar
Aim of study	Cost utility analysis considering the cost-effectiveness of alternative testing strategy in patients with suspected subarachnoid haemorrhage but a negative non-contrast CT.
Decision analysis model overview	Decision tree considering aneurysm risk a under alternative test strategies and AEs associated with CTA.
Perspective	US Medicare reimbursement perspective.
Discount rate - benefits and costs	Costs only
Time horizon	1 year
Population details	Patients presenting to the ED with thunderclap headache but a negative non-contrast CT scan.
Intervention vs. comparator/s	CT angiography vs. lumbar puncture
Primary Effectiveness measure(s)	Prevalence of SAH in this population was assumed to be 8.41%, and the sensitivity and specificity of a non-contrast head CT scan were 98% and 100% respectively (Boesiger 2005, Byyny 2008, Perry 2011). CTA was assigned a sensitivity of 99.2% for the detection of aneurysms, while the sensitivity of LP was 100%, and specificity was 86.7% (Gorchynski 2007, Perry 2010, Menke 2011). Rates of complications associated with each procedure were taken from literature sources, post-LP headache was included but radiation-associated risks from CTA administration were not.
Utilities applied	Utilities were assigned to each terminal node, and reflected either a ‘good’ or ‘poor’ outcome according to the modified Rankin Scale score they achieved. Utility inputs for a ‘poor’ mRS outcome, and described as 0.2 – 0.5, increasing to 0.6 – 1.0 for a ‘good’ outcome.
Utilities source	Samsa *et al.* (1999)
Costs considered	Costs included procedure costs, costs associate with SAH related morbidity and costs of AEs.
Costs source	Costs were derived from 2014 Medicare reimbursement values where available, with other costs obtained from published sources.

Results	In the base-case analysis, CTA was associated with a total cost of $747 and an expected utility of 0.798603029, while LP was associated with a cost of $504 and utility of 0.799259526, i.e. LP dominated CTA. The authors conclude that LP should be used to evaluate patients with thunderclap headache following a negative CT. However, the difference in QALYs generated by each of the technologies was extremely small, reflecting the high sensitivity value for non-contrast CT in the baseline analysis.
Sensitivity analysis undertaken and results	Sensitivity analysis showed LP to be the most cost-effective approach until its cost exceeded $364.45 (baseline $87.17).

Abbreviations: AE, adverse event; CIN, contrast-induced nephropathy; CT, computed tomography; CTA, computed tomography angiography; ED, Emergency Department; ICER, incremental cost effectiveness ratio; IV, intravenous; LP, lumbar puncture; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; PDHA, postdural puncture headache; QALY, quality adjusted life year; RF, renal failure; RRT, renal replacement therapy; SAH, subarachnoid haemorrhage.

Systematic Reviews (n=3)

Study details	Patient characteristics	Intervention	Main results	Risk of bias
Dubosh, 2016[21] Systematic review and meta-analysis (4 databases were searched to April 2015)	Neurologically intact patients presenting with a history concerning for spontaneous non-traumatic SAH.	Non-contrast brain CT using modern generation multidetector scanner (16-slice technology or greater) within 6 hours of headache onset to exclude SAH.	5 studies were included with an estimated 8907 patients who underwent CT within 6 hours. Pooled sensitivity: 98.7% (95% CI 97.1 to 99.4) Pooled specificity: 99.9% (95% CI 99.3 to 100) It was estimated that in the worse-case scenario 13/8907 patients who underwent CT within 6 hours had a missed SAH (incidence 1.46/1000).	Unclear
Carpenter, 2016[25] Systematic review and meta-analysis (3 databases were searched to June 2015, along with abstracts presented at relevant scientific meetings)	ED patients with acute headache or other symptoms or signs (such as syncope, acute mental status change or otherwise unexplained nausea) in whom spontaneous (non-traumatic) SAH was a diagnostic consideration.	History, physical examination, CSF analysis, CT and clinical decision rules for spontaneous SAH.	20 studies were included; prevalence of SAH ranged from 0.91-68%. **History and physical examination** 8 studies described the diagnostic accuracy of 22 components of history and 6 studies described the diagnostic accuracy of 4 physical examination tests for SAH. No single element of history had a very high pooled LR+. Findings on history that increased the probability of SAH the most included subjective neck stiffness (LR+: 4.12 [95% CI 2.24 to 7.59]), while the absence of 'worst headache of life' (LR-: 0.36 [95% CI 0.01 to 14.22]) or onset of headache over more than one hour (LR-: 0.06 [95% CI 0 to 0.95]) each reduced the probability of SAH. On physical examination, neck stiffness (LR+: 6.59 [95% CI 3.95 to 11.0]) was strongly associated with SAH. Most elements of history and physical examination demonstrated significant statistical heterogeneity. **Clinical decision rules** 4 related SAH clinical decision rules have been described, 3 of which were prospectively validated in a subsequent study by the same investigators (Perry *et al.*). Rule 1 appears sufficient to rule-out SAH (LR-: 0.06 [95% CI 0.01 to 0.22]), was uncomfortable to use for only 18% of surveyed emergency physicians, was misinterpreted in 4.7% cases and would theoretically decrease CT	Low

Study details	Patient characteristics	Intervention	Main results	Risk of bias
			and/or LP testing rates from 84% to 74%. The Ottawa SAH Rule more accurately rules out SAH (LR-: 0.02 [95% CI 0.00 to 0.39]) but could increase CT and/or LP testing rates if strictly applied. **CT** 5 studies assessed CT. Pooled sensitivity: 94% (95% CI 91 to 96, I^2=74%), pooled negative LR-: 0.07 (95% CI 0.03 to 0.17, I^2=78%). 2 studies assessed CT within 6 hours of symptom onset. Pooled sensitivity: 100% (95% CI 98 to 100, I^2=0%), pooled LR-: 0.01 (95% CI 0 to 0.04, I^2=78%). Beyond 6 hours pooled sensitivity: 89% (95% CI 83 to 93, I^2=89%), pooled LR-: 0.07 (95% CI 0.01 to 0.61, I^2=63%). **CSF analysis** 6 studies assessed CSF analysis for xanthochromia using variable methods (including visual inspection and spectrophotometry). Visible xanthochromia (5 studies, results from Figure 5 of paper) pooled sensitivity: 71% (95% CI 56 to 83, I^2=53%), specificity: 93% (95% CI 91 to 94, I^2=98%), LR+: 12.56 (95% CI 2.03 to 77.67, I^2=97%), LR-: 0.30 (95% CI 0.09 to 1.06, I^2=78%). Different results were reported in the text of paper: pooled sensitivity: 85% (95% CI 66 to 96, I^2=0%), specificity: 97% (95% CI 96 to 98, I^2=13%), LR+: 24.67 (95% CI 12.13 to 50.14, I^2=64%), LR-: 0.22 (95% CI 0.09 to 0.54, I^2=13%). 2 studies assessed spectrophotometric bilirubin using the UK National External Quality Assessment Service (UKNEQAS) algorithm with pooled sensitivity: 100% (95% CI 59 to 100, I^2=0%), specificity: 95% (95% CI 93 to 96, I^2=98%), LR+: 15.23 (95% CI 1.58 to 146.73, I^2=96%), LR- 0.13 (95% CI 0.02 to 0.83, I^2=0%).	

Study details	Patient characteristics	Intervention	Main results	Risk of bias
			Test-treatment threshold Using the pooled estimates of diagnostic accuracy and testing risks and benefits, we estimate LP only benefits CT negative patients when the pre-LP probability of SAH is on the order of 5%, which corresponds to a pre-CT probability greater than 20%.	
Writing Subcommittee of the American College of Emergency Physicians, 2019[80] Systematic review conducted to derive American College of Emergency Physicians clinical policy (6 databases were searched to July 2017)	ED patients with acute non-traumatic headache.	4 different clinical questions were addressed (3 questions are relevant for our review) relating to risk-stratification strategies, non-opioids for primary headache, non-contrast head CT performed within 6 hours of headache onset, and CT angiography.	**Risk-stratification strategies** 2 class II studies and 2 class III studies were included. The only risk stratification that currently reliably identifies the need for neuroimaging is the Ottawa SAH Rule, but because of its poor specificity, many patients will have negative workups exposing them to radiation and additional testing. Additional protocols using biomarkers and validated decision rules should be investigated to provide clinicians with both the necessary sensitivity and specificity in this workup. **Non-contrast head CT within 6 hours of headache onset** 1 class II study and 1 class III study were included. With the addition of newer studies incorporating advanced CT scanning capabilities, the clinical strategy for evaluating SAH has evolved to provide clinicians an alternative to the previously suggested protocol of head CT followed by LP. Through a careful history and physical examination, clinicians can use the high sensitivity of non-contrast head CTs within the first 6 hours of onset of symptoms to reliably rule out SAH without the performance of LP. As a result, a normal non-contrast head CT performed within 6 hours of symptom onset in neurologically intact patients is sufficient to preclude further diagnostic workup for SAH. If clinical suspicion remains high despite the negative findings, further evaluation may be pursued.	High

Study details	Patient characteristics	Intervention	Main results	Risk of bias
			CT angiography vs LP to safely rule out SAH in patients still considered to be at risk after negative non-contrast CT 6 class III studies were included. Few studies directly compare CT/LP vs CT/CTA in ED patients still considered at risk of SAH after negative non-contrast head CT. The one quality study that does directly compare these diagnostic workup options is limited by low patient numbers and sensitivity point estimates with wide CIs. The main argument in favour of LP is that it is very sensitive for detecting SAH. However, limitations include a very low testing yield, a high rate of traumatic tap, high rates of uninterpretable LP test results, physician time to perform the procedure, patient preference, and the high rate of post-LP headache. CTA avoids many of the negatives associated with LP and appears to be an excellent test for detecting cerebral aneurysms. However, the major disadvantage is that it diagnoses aneurysms rather than bleeding; the aneurysm may be an incidental finding and may lead to unnecessary invasive cerebral procedures. CTA also exposes the patient to additional radiation risk and decreased LP diagnosis of certain other medical diseases. CTA appears to be a reasonable alternative to LP to safely rule out SAH from an intracranial source. Clinicians should use shared decision making to select the best diagnostic testing modality after weighing potential pros and cons of LP versus CTA.	

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; CT, computed tomography; CTA, computed tomography angiography; ED, Emergency Department; LP, lumbar puncture; LR, likelihood ratio; SAH, subarachnoid haemorrhage.

Clinician surveys (n=7)

Study details	Survey respondents	Research question	Main results	Study quality
Chu, 2019[81] Semi-structured interviews with emergency medicine clinicians from 6 EDs across Queensland, Australia	15 fellows of the Australasian College for Emergency Medicine (ranging from a new fellow to a department director). Dates of recruitment not reported.	To identify factors that influence emergency physicians' decisions about diagnostic testing after a normal CT brain scan for ED patients with a headache suspicious of a SAH.	Sixteen factors that influenced the ordering of diagnostic tests for suspected SAH following a negative CT brain scan were identified, which were grouped into 6 categories: patient interaction, practice evidence, patient profile, consulting, external influences and experiential factors. Patient interaction was at the forefront of the identified factors. This shared decision-making process incorporated 'what the patient wants' but may be biased by the clinician's own preferences and the way they communicate the benefits and harms of the diagnostic options to the patient. When the best diagnostic approach is uncertain, patient interaction/preference appeared to be the most important factor in deciding an approach. Patient risk profile, practice evidence and guidelines were also important. Other influencing factors included experiential factors of the clinician (past outcomes), consultation with colleagues and external influences where practice location and work processes impose constraints on test ordering external to the preferences of the clinician or patient. Participants did not consider that fear of litigation influenced their practice.	Unclear
Perry, 2009[82] Survey of emergency physicians from Australia, Canada, UK and USA	1149 emergency physicians from Australia, Canada, UK and USA. 77% practiced in a teaching hospital and 23% in a non-teaching hospital setting. Dates of	To determine what the ED current practice is for investigating acute headache patients, whether emergency physicians would consider using a clinical decision rule for acute headache and what the required sensitivity of such a rule would be for SAH.	49.5% respondents thought all acute headache patients should be investigated with CT. 57.4% thought that if CT is normal, all such patients should have LP (highest in UK 66.0%, lowest in US 51.4%). 32.5% thought that performing a LP in such patients without first getting a CT was a safe practice (highest in Canada 45.3%, lowest in UK 11.1%). 59.7% manage these patients with CT and/or LP always or most of	Good

	recruitment: July 2005 – April 2006.		the time. 95.7% reported they would consider using a well-validated clinical decision rule in acute headache patients to determine the need for investigations to rule out SAH. Physicians in the UK were willing to accept a slightly lower sensitivity than those in Australia, Canada and the US. Overall, the median sensitivity deemed to be required by such a rule was 99% (IQR 98-99%).	
Lansley, 2016[27] Survey of consultants in emergency medicine and neuroscience specialties from 4 major neuroscience centres in London, UK	23 consultants in emergency medicine and 35 consultant neurosurgeons, neurologists or neuroradiologists from 4 large NHS Trusts with tertiary neuroscience services in London. Dates of data collection: October 2015 – February 2016.	To establish if emergency medicine and neuroscience specialist consultants have different risk tolerances for investigation of suspected spontaneous SAH, and to establish if their risk-benefit appraisals concur with current guidelines.	17 ED clinicians and 30 neurospecialists indicated their risk tolerance for missed SAH diagnosis by recording the highest post-test probability at which they would stop investigations to diagnose SAH; ED clinicians accepted almost 3 times the risk of a missed SAH diagnosis compared with the neuroscience specialists (2.8% vs 1.1%; p=0.03). Neurospecialists were more likely to advocate routine LPs compared with ED clinicians (74% vs 39%; p=0.01). Only 39% ED clinicians agreed with the current guidelines that LP is mandatory in suspected SAH when initial CT is negative, compared with 89% of neurospecialists (p=0.0001). ED clinicians were more inclined to omit the LP if a negative CT had been obtained within 6 hours of headache onset (35% vs 3%; p=0.002). Fewer than 10% respondents in each group indicated a willingness to substitute LP in favour of a cheaper or quicker test if it carried an increased risk of missed diagnosis; however, ED clinicians were more likely to accept an increased risk of misdiagnosis for the benefit of a non-invasive test (38% vs 11%; p=0.02). 91% of clinicians in both groups reported direct personal experience of missed SAH due to incomplete investigation; 65% ED clinicians and 55% neurospecialists had given evidence in a medicolegal capacity. 22% clinicians reported that they would feel obliged to investigate SAH if it had been raised and	Unclear

			documented as a potential diagnosis, irrespective of their own clinical judgement.	
Binks, 2017[83] Survey of doctors of all grades at a teaching hospital in the UK	62 doctors at a teaching hospital in the UK (the title of the paper suggests it is doctors in acute medicine, although it is not explicitly stated). Respondents included 6 consultants, 16 registrars, 11 core medical trainees, 11 foundation year 2 doctors and 16 foundation year 1 doctors. Dates of recruitment: 24 April – 5 May 2015.	To develop an easy to follow, practical headache guideline for doctors of all grades. Before launch, we performed a survey of the Trust's doctors to assess knowledge of acute headache management and the need for a guideline.	Q: Which of the following would you routinely examine in patients presenting with acute headache (items include neck stiffness, reflexes, rash, etc)? Almost all doctors indicated that they would interrogate neck stiffness (98.4%) and upper and lower limb power (93.5%). Most would look for rash (87.1%), complete a thorough cranial nerve assessment (83.9%), examine sensation (79%) and test plantars and reflexes (77.4%). Only 40.3% agreed they would do fundoscopy, with free text comments suggesting that difficulty accessing equipment was a key factor. Q: How confident do you feel recognising different presentations of headache and how confident do you feel in the initial management of different causes of headache (items include SAH, stroke, meningitis, etc)? Confidence was high in recognition of meningitis, SAH, acute migraine and encephalitis and for initial management of meningitis, temporal arteritis, encephalitis and SAH (score of 4 or 5 out of 5). However, confidence was lower for other conditions including cerebral venous sinus thrombosis, cervical artery dissection, carbon monoxide poisoning and acute glaucoma. Confidence levels were not only decreased among juniors, but other grades too. Q: Would you find a Trust acute headache guideline useful? 94.6% respondents indicated that they would find a headache guideline useful. Q: If you are a senior grade (registrar/consultant) indicate how you think junior knowledge/clerking of headache compares to the following presentations (items include acute coronary syndrome, sepsis, etc)?	Poor

			50% or more consultants and registrars (≥11/22) thought headache knowledge was 'not as good' as the other presentations listed, with the exception of acute kidney injury and seizure. Q: Case vignette asking what the next appropriate stage of management was (discharge, keep under investigation, discharge with outpatient referral to neurology). 43/56 (77%) doctors chose the 'correct' answer to the clinical scenario (keep under investigation), whilst 12 doctors would have discharged the patient with outpatient neurology follow-up.	
Rogers, 2014[84] Survey of emergency medicine physicians and trainees in Australia	878 members of the Australasian College for Emergency Medicine. 52% practiced in a major referral centre, 27% in an urban district centre, 19% in a rural/regional area and 2% in private or 'other' centres. Dates of recruitment: January 2013.	To establish current clinical practice among Australasian emergency physicians and trainees on several aspects of the investigation of 'acute headache'.	47.3% respondents agreed or strongly agreed that a CT brain (3rd generation or later) within 6 hours of headache onset is sufficient to exclude a diagnosis of SAH, compared with 42.1% who disagreed or strongly disagreed. For a CT performed within 12 hours of ictus, 14.4% agreed or strongly agreed that SAH could be excluded, whilst 71.3% disagreed or strongly disagreed that a sub-12 hour CT is sufficient; trainees were more likely to be satisfied with a 12 hour CT than emergency physicians (17.6% vs 11.8%). 79.8% agreed or strongly agreed that CT images are required to be reported by a consultant radiologist (not necessarily a neuroradiologist); qualified emergency physicians were significantly more likely to agree or strongly agree with this statement than trainees (83.7% vs 75%; p=0.002). 72.4% respondents disagreed or strongly disagreed that 'a decreasing RBC count excludes SAH'; only 14.7% agreed or strongly agreed. For detection of xanthochromia in the CSF, 57.7% of respondents felt that spectrophotometry (vs visual inspection) is necessary to accurately diagnose SAH, 25% were unsure and 17.3% disagreed or strongly disagreed.	Poor

			64.6% respondents indicated that LP should wait until 12 hours after headache onset, 25.2% thought a 6 hour wait was necessary, 5.0% thought it should be performed immediately and 5.1% felt that the timing does not matter. After a negative CT scan, for further investigation of SAH, 88% of respondents preferred LP to CT angiography.	
Dobb, 2013[85] Survey of emergency medicine and acute medicine clinicians in Scotland, UK	160 consultants, staff specialists and senior trainees (ST3+) in Emergency Medicine and Acute Medicine working in Scotland. 69% respondents worked in Emergency Medicine, 28% worked in Acute Medicine and 4% covered both specialties. 86% were consultants or specialty doctors and 14% were trainees, ranging from ST3 to ST6. Dates of recruitment: June – August 2010.	To explore the approach of emergency medicine and acute medicine clinicians to the investigation of a patient with thunderclap headache.	The online survey was based on a clinical vignette of a 45-year-old man presenting with thunderclap headache who had a pristine neurological examination. Respondents were asked which initial investigation (if any) they would perform. Subsequent information was then revealed according to their answer. Respondents were then asked what further investigations (if any) they would perform and how they would manage the patient. 139 clinicians (89%) elected to perform a non-contrast CT brain as their first investigation; 2 (1%) chose CT/MR angiogram; 10 (6%) would refer elsewhere; and 5 (3%) would discharge the patient without investigation. If the initial imaging (CT or CT/MR angiogram) was negative, 119 (84%) would then proceed to LP (although 20% would undertake this investigation before 12 hours from headache onset, with 80% waiting until 12 hours had elapsed); 1 (1%) would proceed to CT/MR angiogram; 13 (9%) would refer elsewhere; and 8 (6%) clinicians would discharge the patient home without performing a second investigation. Of the 119 clinicians who would perform LP as their second investigation after negative brain imaging, 112 (94%) would be content that no further investigation was required if LP was normal, although 68 (57%) would refer elsewhere; and 44 (37%) would discharge	Poor

			home. 8 clinicians would perform a third investigation: 7 clinicians (4%) would refer for MRI or non-invasive angiography; and the single clinician who would perform non-invasive angiography as a second investigation would proceed to LP if this was normal. No respondent elected to perform a fourth investigation or requested investigations that were not listed. Only 36% respondents always transported CSF samples protected from light (21% sometimes and 43% never). Samples always arrived at the lab within one hour for 78% respondents, sometimes within an hour for 20% respondents and never within an hour for 2% respondents. Data were also collected on patient position when undertaking LP, preference for type and gauge of spinal needle. Only 35 (22%) respondents were aware of a local protocol for investigation of acute headache.	
Kumar, 2019[86] Survey of emergency medicine clinicians at 2 academic hospitals and 4 community hospitals in urban and suburban settings in USA and Canada	168 emergency physicians between the age of 20 and 80 years at Stanford Healthcare (California), Intermountain Healthcare (Utah) and the Ottawa Hospital (Toronto). 59% respondents identified their practice setting as academic. Dates of recruitment not reported.	To assess physician knowledge on imaging and LP test performance. We also used case-based scenarios to assess their practice pattern, variation, and adherence to clinical policy.	150 physicians (89%) indicated that non-contrast CT has high sensitivity (defined as 91-100%) for SAH within 6 hours of symptom onset, although statistically significant differences were observed by site, academic setting and experience level. 100 physicians (60%) indicated that non-contrast CT has a lower sensitivity (defined as 81-90%) for SAH between 6 and 12 hours of symptom onset; 35 physicians (21.1%) still rated CT sensitivity as high between 6 and 12 hours of symptom onset. Only 68 physicians (40%) indicated that xanthochromia has a high sensitivity (defined as 91-100%) for SAH after 6 hours of symptom onset. 104 physicians (63%) indicated that spectrophotometry has a high sensitivity (defined as 91-100%) after 6 hours.	Good

			Most physicians were able to list the high-risk clinical features of SAH; however, only half of the physicians (54.9%) indicated that they use validated clinical decision rules in their practice. Physicians from an academic setting were more likely to use a clinical decision rule than those from a non-academic setting (69.2% vs 33.3%). For the four case presentations within 6 hours of symptom onset, 110 physicians (66%) indicated that they would perform a CTA after negative CT in at least one case, 57 physicians (34%) indicated that they would perform LP after negative CT in at least one case, and 16 (10%) indicated both a CTA and a LP after negative CT in at least one case. We also observed practice site variation in the proportion of physicians who indicated that they would use CTA.	

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; CTA, computed tomography angiography; ED, Emergency Department; IQR, interquartile range; LP, lumbar puncture; MR, magnetic resonance; MRI, magnetic resonance imaging; Q, question; SAH, subarachnoid haemorrhage; ST, senior trainee.

Appendix 4: Quality assessment results tables

Cohort/before and after studies assessed using QUADAS-2 (n=28)

Study	Study design	Risk of bias level of concern				Applicability level of concern		
		Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Perry, 2010[43]	Prospective cohort study	Unclear	Low concern	Low concern	Low concern	Low concern	Low concern	High concern
Matloob, 2013[44]	Retrospective cohort study	Low concern	Unclear	Unclear	High concern	Low concern	Unclear	Low concern
MacDonald, 2012[45]	Retrospective cohort study	Unclear	Unclear	Low concern	Unclear	Unclear	Unclear	Low concern
Kelly, 2014[46]	Retrospective cohort study	Low concern	High concern	Low concern	High concern	High concern	Unclear	Low concern
Perry, 2013[31]	Prospective cohort study	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Yiangou, 2017[47]	Retrospective cohort study	Unclear	Unclear	Low concern	Low concern	Low concern	Unclear	Low concern
Perry, 2017[48]	Prospective cohort study	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Bellolio, 2015[32]	Retrospective cohort study	Unclear	Unclear	Unclear	Low concern	Unclear	Unclear	Low concern
Wu, 2019[49]	Retrospective cohort study	Low concern	Unclear	High concern	High concern	Unclear	Unclear	Unclear
Chu, 2018[50]	Retrospective cohort study	Unclear	Unclear	Low concern	Low concern	Unclear	Unclear	Low concern
Pathan, 2018[51]	Retrospective cohort study	Low concern	Unclear	Low concern	Unclear	Low concern	Unclear	Low concern
Cheung, 2018[52]	Retrospective cohort study	Low concern	Unclear (Ottawa SAH Rule) High concern (modified Ottawa SAH Rule)	Low concern	Low concern	Low concern	High concern	Low concern
Perry, 2020[53]	Prospective before/after implementation study	Low concern	Low concern	Low concern	Low concern	Low concern	Unclear	Low concern

Study	Study design	Risk of bias level of concern				Applicability level of concern		
		Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Perry, 2008[54]	Prospective cohort study	Low concern	Low concern	Low concern	Low concern	Low concern	High concern	Low concern
Valle Alonso, 2018[55]	Retrospective cohort study	Unclear	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern
Cooper, 2016[9]	Retrospective cohort study	Low concern	Unclear	Low concern	Unclear	Low concern	Low concern	Low concern
Blok, 2015[56]	Retrospective cohort study	Low concern	Low concern	Unclear	Unclear	High concern	Low concern	Low concern
Khan, 2017[58]	A priori planned secondary analysis of two sequential prospective cohort studies	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	High concern
Perry, 2011[59]	Prospective cohort study	Low concern	Low concern	Low concern	Low concern	Low concern	Low concern	High concern
Backes, 2012[60]	Retrospective cohort study	Low concern	Low concern	Low concern	Low concern	High concern	Unclear	Low concern
Austin, 2018[61]	Retrospective cohort study	Unclear	High concern (index test was interpreted on inferior screens to reference standard)	Unclear	Low concern	High concern	Unclear	Unclear
Perry, 2015[63]	Sub-study of a prospective cohort study	Low concern	High concern	Low concern	Unclear	High concern	High concern	High concern
Dupont, 2008[64]	Retrospective cohort study	Low concern	Low concern	Low concern	Low concern	Low concern	High concern	Low concern
Gangloff, 2015[68]	Retrospective cohort study	Low concern	Low concern	Low concern	Unclear	Unclear	Low concern	Low concern
Perry, 2006[69]	Sub-study of a prospective cohort study	Low concern	Low concern	Low concern	Low concern	High concern	High concern	High concern

Study	Study design	Risk of bias level of concern				Applicability level of concern		
		Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Heiser, 2015[70]	Retrospective cohort study	Low concern	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Perry, 2005[74]	Prospective cohort study	Low concern	Low concern	Low concern	Low concern	Low concern	Unclear	Low concern
Backes, 2015[75]	Retrospective cohort study	Low concern	Low concern	High concern	High concern	High concern	Unclear	Low concern
Total	6 prospective cohort studies 18 retrospective cohort studies 1 before/after study 1 secondary analysis 2 sub-studies	21 low concern 7 unclear 0 high concern	15 low concern 10 unclear 3 high concern	21 low concern 5 unclear 2 high concern	17 low concern 7 unclear 4 high concern	15 low concern 6 unclear 7 high concern	9 low concern 14 unclear 5 high concern	20 low concern 3 unclear 5 high concern

Cohort/before and after studies not eligible for QUADAS-2 (n=9)

Study	Study design	Clearly defined inclusion criteria	Representative sample*	Groups similar at baseline	Clearly described & consistent delivery of intervention*	Reliable and consistent outcome assessment*	Blinded outcome assessment	Outcome data complete/attrition low*	Adequate follow-up duration*	Overall judgement of risk of bias
Perry, 2002[10]	Retrospective cohort study	Yes	Yes	N/A	Unclear	Unclear	N/A	Yes	Yes	Unclear
Dutto, 2009[57]	Before and after study	Yes	Yes	Yes	Yes	Unclear	N/A	Yes	Yes	Unclear
Migdal, 2015[62]	Retrospective cohort study	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Unclear	Unclear
Sansom, 2014[65]	Retrospective cohort study	Unclear	Yes	N/A	Unclear	Unclear	N/A	No	Unclear	High
Horstman, 2012[66]	Retrospective cohort study	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Low
Brunell, 2013[67]	Retrospective cohort study	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Low
Alons, 2015[71]	Retrospective cohort study	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Unclear	Unclear
Alons, 2018[72]	Retrospective cohort study	No	Unclear	N/A	Yes	Yes	N/A	Yes	Unclear	Unclear
Locker, 2004[73]	Retrospective cohort study	Yes	Yes	N/A	Unclear	Yes	N/A	Yes	Yes	Unclear

* Key domains. Abbreviations: N/A, not applicable.

Cost-effectiveness studies (n=4)

Studies	Malhotra, 2016[78]	Taylor, 2016[76]	Ward, 2012[79]	Wu, 2016[77]
Study question				
1. Costs and effects examined	Yes	No	Yes	Yes
2. Alternatives compared	Yes	Yes	Yes	Yes
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	Yes	No	No	Yes
Selection of alternatives				
4. All relevant alternatives are compared (including do-nothing if applicable)	Yes	No	Yes	No
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	Yes	Yes	Yes	Yes
6. The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	Yes
Form of evaluation				
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	N/A	Yes	Yes
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	N/A	N/A	N/A
Effectiveness data				
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	Yes	Yes	Yes	Yes
10. Effectiveness data from RCT or review of RCTs	No	No	No	No
11. Potential biases identified (especially if data not from RCTs)	No	Yes	Yes	Yes
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	N/A	N/A	N/A
Costs				
13. All the important and relevant resource use included	Unclear	N/A	Unclear	Unclear
14. All the important and relevant resource use measured accurately (with methodology)	No	N/A	No	No

15. Appropriate unit costs estimated (with methodology)	Yes	N/A	Yes	Yes
16. Unit costs reported separately from resource use data	Yes	N/A	Yes	Yes
17. Productivity costs treated separately from other costs	N/A	N/A	N/A	N/A
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	No	N/A	No	No
Benefit measurement and valuation				
19. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Yes	Yes	Yes
20. Methods to value health states and other benefits are stated	Yes	No	Yes	Yes
21. Details of the individuals from whom valuations were obtained are given	No	No	No	No
Decision modelling				
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Yes	Yes	Yes	Yes
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Yes	Yes	Yes	Yes
24. All model outputs described adequately	Yes	Yes	Yes	Yes
Discounting				
25. Discount rate used for both costs and benefits	No	N/A	Yes	No
26. Do discount rates accord with NHS guidance?	No	N/A	Yes	No
Time horizon				
27. Is the time horizon of the model sufficient to reflect all important differences between options?	Unclear	N/A	Yes	Unclear
28. Are the time horizon of the model, the duration of treatment and the duration of the treatment effect described and justified?	No	No	Yes	No
Allowance for uncertainty				
29. Details of statistical tests and confidence intervals are given for stochastic data	No	Yes	No	No
30. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	Yes	N/A	Yes	Yes
31. Are all appropriate input parameters included with uncertainty?	No	Yes	No	No

32. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	No	Yes	No	No
33. Are the probability distributions adequately detailed and appropriate?	Yes	Yes	Yes	Yes
34. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	Yes	Yes	Yes	Yes
Deterministic analysis				
35. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc.)	Yes	Yes	Yes	Yes
36. The choice of variables for sensitivity analysis is justified	Yes	Yes	Yes	Yes
37. The ranges over which the variables are varied are stated	Yes	Yes	Yes	Yes
Presentation of results				
38. Incremental analysis is reported using appropriate decision rules	Yes	N/A	Yes	Yes
39. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	N/A	Yes	Yes
40. Applicable to the NHS setting	No	No	No	No

Abbreviations: ICER, incremental cost-effectiveness ratio; RCT, randomised controlled trial.

Systematic reviews (n=3)

Study	Study design	Clear research question	Adequate search strategy*	Clear study selection/reasons for rejection*	Adequate study details reported	Study quality appropriately assessed*	Appropriate synthesis*	Appropriate conclusions drawn*	Overall judgement of risk of bias
Dubosh, 2016[21]	Systematic review and meta-analysis	No	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Carpenter, 2016[25]	Systematic review and meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
American College of Emergency Physicians, 2019[80]	Systematic review	No	Yes	No	Yes	Yes	Yes	Yes	High

* Key domains

Clinician surveys (n=7)

Study	Study design	Clear objective	Representative sample	Systematic approach to survey development	Survey tested/piloted	Survey administered appropriately	Sample size justified & response rate reported	Clear and transparent reporting of results	Overall judgement of quality
Chu, 2019[81]	Semi-structured interviews with emergency medicine clinicians	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Perry, 2009 [82]	Survey of emergency medicine clinicians	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lansley, 2016[27]	Survey of emergency medicine and neuroscience specialist clinicians	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Binks, 2017[83]	Survey of clinicians	No	Unclear	No	Yes	Yes	No	No	Poor
Rogers, 2014[84]	Survey of emergency medicine clinicians and trainees	Yes	Unclear	No	Yes	Yes	Yes	Yes	Poor
Dobb, 2013[85]	Survey of emergency medicine and acute medicine clinicians	Yes	Yes	No	No	Yes	Yes	Yes	Poor
Kumar, 2019[86]	Survey of emergency medicine clinicians	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Appendix 5: Qualitative study participant information sheet

Participant Information Sheet

Study Title: Management of sudden onset severe headache presenting to the Emergency Department: a qualitative study

We invite you to take part in a research study evaluating how sudden, severe headaches are managed in the Emergency Department

Can you help?

We would like to know about your experiences of going to the Emergency Department with a severe headache which came on suddenly. Before you decide whether to take part, it is important that you understand why we are doing the study and what we will ask you to do. Please take time to read this information sheet. You may wish to discuss it with a family member or the researcher before you make your decision.

What is the study about?

We would like to find out patients' views and experiences of going to the emergency department with a sudden, severe headache. We also want to discuss the different ways of diagnosing, testing for and managing sudden, severe headaches and find out how acceptable these are to patients. We hope that the results of the study will help to improve patient care for people with sudden, severe headaches in Emergency Departments across the NHS.

Why have I been invited to take part?

We are inviting you to be involved in this research because you have attended the Emergency Department with a sudden, severe headache. In order for us to understand patients' experiences and find out how acceptable different ways of managing these symptoms are to patients, we need to speak to patients about their views and experiences of their care.

What happens if I take part?

You will be invited to take part in a group discussion with other patients who have experienced this kind of headache. We would like to find out about your experiences and your thoughts about how these experiences could be improved. There are different ways of managing sudden, severe headaches and we would like your opinions about how acceptable these may be to patients.

Due to restrictions in place during the COVID-19 pandemic the group discussion will take place virtually via the video conferencing program 'Zoom'. If you choose to take part, the

research team will send you a virtual invitation to join the meeting through Zoom, which can be accessed freely via a smartphone, tablet or computer. The discussion will consist of approximately 8 patients and 2 researchers who will help with the discussion. The discussion will be recorded and the recording made anonymous and stored securely. It is expected that the discussion will last for approximately one hour. If you agree to be involved in the study you will be asked to sign an e-consent form.

Your current and future care will not be affected in any way by your decision to be involved, or not, in the study.

What are the advantages of taking part?

There is no direct benefit of taking part to you personally, but your contribution will help us to understand how care can be improved from patients' perspectives.

What are the disadvantages of taking part?

The group discussion will take up approximately one hour of your time.

While we do not expect this to happen, you might discuss topics which are sensitive or may upset you. You can decline to discuss anything which you find uncomfortable.

Do I have to take part?

No. It is for you to decide and is completely voluntary. If you decide to take part, you will be given this information sheet to keep and be asked to sign an e-consent form.

What if I change my mind about being involved?

You can withdraw from the study at any point, without giving a reason. Data collected from you up to the time of your withdrawal from the study will be kept. We are happy to provide more information on this.

What if I have any questions or concerns?

If you have any concerns or questions about this study, please contact us using the contact details listed at the end of this leaflet. Please feel free to ask any further questions before deciding whether to take part, or at any time during the study.

If you would like independent advice about whether or not to take part, the Patient Advice and Liaison Service (PALS) can be contacted by e-mailing:

patientexperience.leedsth@nhs.net or telephoning 01132066261

If you have any concerns about the way you have been approached or treated during the course of the study, or if you wish to make a formal complaint, please contact the study manager:

Dr Arabella Scantlebury
York Trials Unit
Department of Health Sciences
ARRC Building
University of York
York
YO10 5DD
Tel: 01904321105

Who is organising and funding the study?

The study has been designed by a team based at Leeds Teaching Hospitals NHS Trust, the Centre for Reviews and Dissemination (CRD) and York Trials Unit (within the Department of Health Sciences) at the University of York. The Sponsor is Leeds Teaching Hospitals NHS Trust. Group discussions will be run by researchers from the University of York.

This service evaluation is funded by the National Institute for Health Research (NIHR 200486) and does not require ethical approval.

What will happen to the study findings?

Once the study is completed, we will write up a summary of the findings. Results from this study may be published in journals for researchers, health professionals and policy makers, or may be presented at scientific meetings so that other healthcare professionals caring for similar patients can learn from your experiences. However, you will not be identified in any reports, publications or presentations. We will also write a summary for patients and are happy to share the findings with you on completion of the study. Please let the researcher know if you would like a summary. Information you provide may be used to support other research in the future. Anonymised data that you provide may be shared with authorised researchers.

Will my information be kept confidential?

What you say in the group discussion will be kept strictly confidential in that the recordings will not be shared with anyone other than the research team and transcription services. We may quote some of the things you have said in writing about the research, but these would be anonymous – your name and any identifiable information will not appear in any reports, publications or presentations.

Data Storage

The University of York is responsible for looking after your information and using it properly. Your data will be held securely at the York Trials Unit, University of York and identifiable information will be kept for five years after the study has finished. To safeguard your rights, we will use the minimum personally identifiable information possible. Hard copies of identifiable information will be destroyed when no longer required by the research team. Data will be anonymised using a Patient Identification Number generated specifically for this study by the research team. Group discussions will be recorded on an encrypted Dictaphone and will be deleted once they have been moved to a computer.

Hard-copy data will be stored at the University of York in a lockable filing cabinet. E-Consent forms and identifiable information will be stored separately from study data. All electronic participant data will be stored on password protected, encrypted university computers. Participant contact information will be stored only as long as is necessary, on password protected, encrypted computers.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained.

How to contact us

If you would like any further information, please contact us:

Dr Helen Anderson
Tel: 01904 321399

Or

Dr Heather Leggett
Tel: 01904 326387

York Trials Unit
Department of Health Sciences
ARRC Building
University of York
York
YO10 5DD

Thank you for reading this information sheet and for considering taking part

Appendix 6: Qualitative study consent to contact form

Management of sudden onset severe headache presenting to the Emergency Department: a qualitative study

Permission for release of personal details

I agree that my personal details be given to researchers carrying out this study. I have filled in my contact details and I understand that a researcher will now contact me. This will enable them to explain the study in more detail so that I can then decide whether or not to take part.

(BLOCK CAPITALS PLEASE)

Name:	……	……..	…….
	Mr/Mrs/Miss	Forename	Surname
Address:	……..		
	……..		
	……..		
Postcode:	……..		
Tel No:	……..		
Mobile No:	……..		
Email:	……@……..		
How would you prefer to be contacted (please circle)?		Telephone/ Mobile/ Email	
At what time of day would you prefer to be contacted (please circle)?		Morning/Afternoon/ Evening/ Don't Mind	

……. ……/……../2020

Signature of patient Date

Please hand this form in to the Research Nurse who approached you about this study or the ward reception before you leave.

If you have any questions, please contact
Heather Leggett at Heather.leggett@york.ac.uk or
Helen Anderson at Helen.anderson@york.ac.uk or on 01904 321399

Appendix 7: Qualitative study consent form

Title of Project: Management of sudden onset severe headache presenting to the Emergency Department: a qualitative study

Please read the statements below and initial each box to indicate that you understand and agree with each statement. For any queries please contact: Contact details: Dr Helen Anderson: helen.anderson@york.ac.uk or Heather Leggett: heather.leggett@york.ac.uk

1. I confirm that I have read and understand the information sheet version[1.2], dated [11.08.2020] for the above study and have had the opportunity to ask questions about the study and any questions have been answered to my satisfaction. ☐
2. I understand that my participation is voluntary and that I am free to withdraw from the focus group at any time without giving any reason, and without my medical care or legal rights being affected. ☐
3. I understand that the interview will be recorded on an encrypted digital voice recorder and that the sound file will be stored on a secure computer at the University of York. ☐
4. I understand that the interview transcript will be strictly confidential and that I will be anonymous in any written reports from the research. ☐
5. I understand that anonymised written quotations from the interview may be used in publications, presentations and teaching. ☐
6. I understand that my details (eg name, address), this consent form and other data collected as part of this research study will be strictly confidential, stored at the University of York. ☐
7. I agree to participate in this research ☐

Name of participant Signature Date

Name of researcher Signature Date

Appendix 8: Qualitative study topic guide

Topic Guide: Interviews with patients who have presented to the Emergency Department after a sudden onset severe headache

At the beginning of all interviews

- The qualitative researcher will introduce themselves to the participants as part of the research team.
- The qualitative researcher will explain the study and the purposes of the interview.
- The qualitative researcher will explain that we would like to audio-record the interview and explain the processes for ensuring anonymity and confidentiality of interview data.
- The qualitative researcher will explain how interview data will be used.
- The qualitative researcher will determine if the participants would like to take part in the study and if so, will obtain final verbal consent. If the participant would no longer like to take part they will be thanked for their time and the interview will not continue.
- The qualitative researcher will describe key features of zoom (video and mute buttons and raising hand?). Participants may leave the call at any point and may choose to join using video or audio or both.
- Participants will be provided with the opportunity to ask any questions.

This topic guide summarises the main areas to be explored during interviews. As with any interview, these headings are intended as a starting point to ensure the primary issues are covered, whilst allowing flexibility for new issues to emerge.

1. To explore patients experience of managing headache in hospital
    a. Who did you see, what care did you receive, how long did you have to wait, what treatment options were you given and how were any potential risks associated with them communicated to you, how was your diagnosis, or possible diagnoses communicated to you? Were you informed of the reasons for needing specific tests? Were you involved in any decisions about your treatment options?
    b. were there any issues during treatment and diagnosis
    c. Potential impact of COVID on preference for attending hospital and remaining in hospital whilst awaiting tests.

2. We would now like to get your thoughts on some of the different ways that headache could be managed in hospital.
    - Option 1: Patients are discharged home after a negative CT result without lumbar puncture
    - Option 2: Patients receive a lumbar puncture as an inpatient after having a negative CT
    - Option 3: Patients are discharged as an outpatient following a negative CT and are asked to return for a lumbar puncture as an outpatient.

Prompt: are they all acceptable? Are any ‘better’ than another? If so why? Do any of these feel risky or unclear? Feelings on possibility of negative outcomes from lumbar puncture?

3. Explore patient's views on the use of lumbar puncture for management of sudden onset headache

- Ask patient if they had a lumbar puncture?
- How does the patient feel about the idea of not having a lumbar puncture in the event of a negative CT scan?
- How does the patient feel about having a lumbar puncture as an outpatient. i.e being sent home after diagnosis and initial assessment and returning to hospital for a separate appointment.
    - Explore potential influence on COVID-19 on this.

End interview

- Thank participants and ask if they have any comments.

- Explain again about how data will be used and reiterate information about their own anonymity and confidentiality.

- Provide opportunity for questions and state that the lead researcher is contactable after the interview, should questions arise.