National Institute for Health and Care Excellence

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Subarachnoid haemorrhage

[I] Evidence review for detecting intracranial hypertension

NICE guideline <number>

Evidence review underpinning

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1 Detecting intracranial hypertension

Evidence review underpinning recommendation 1.3.6 and research recommendations in the NICE guideline.

1.1 Review question: What is the diagnostic accuracy of investigations for detecting intracranial hypertension for the deteriorating or unconscious person?

1.2 Introduction

In people with subarachnoid haemorrhage the pressure inside the skull may be increased by hydrocephalus, haematoma or cerebral oedema. Raised intracranial pressure (intracranial hypertension) can impede blood flow to the brain even if the systemic blood pressure is normal. Raised intracranial pressure can be inferred in people with cerebral oedema or mass lesions on a CT head scan, particularly if focal brain herniation is present, but can only be established definitively by invasive measurement. This can be done by insertion of a pressure sensor into the cranial cavity, or by pressure measurement from a ventricular drain or during a lumbar puncture. An intracranial pressure sensor will give continuous measurements, whereas lumbar puncture measurement will be intermittent and infrequent and is contraindicated if there is a haematoma or brain herniation as it can precipitate significant clinical deterioration.

Recently, attempts have been made to develop non-invasive methods to detect raised intracranial pressure, such as ultrasound measurement of the optic nerve sheath diameter and transcranial Doppler.

This review was carried out to assess the diagnostic accuracy of these techniques for detection of intracranial hypertension in people with aneurysmal SAH and neurological deterioration, using direct measurement of intracranial pressure as the reference standard.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm whose neurological status is deteriorating or is unconscious.
Target condition	Intracranial hypertension
Index tests	• Optic nerve ultrasound (US) • Transcranial Doppler
Reference standard	• Direct pressure measurement/ Intracranial pressure (ICP) monitoring
Statistical measures	• Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
Study design	• Cross-sectional studies • Cohort studies

- Systematic reviews of observational cohort studies will be included

1.4 Clinical evidence

1.4.1 Included studies

Seven cohort studies and 1 case series were included in the review,[4, 6, 8, 23, 31, 32, 40, 41] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C: and study evidence tables in Appendix D:

Studies reporting the diagnostic accuracy of optic nerve ultrasound (US) or transcranial Doppler against a reference standard of direct pressure measurement or intracranial pressure (ICP) monitoring were included. As studies provided insufficient information to conduct a meta-analysis (true positives, true negatives, false positives, false negatives), or too few similar studies were included (≤2 studies) for the same diagnostic outcome, diagnostic accuracy results were reported individually on a per-study basis.

1.4.2 Excluded studies

See the excluded studies list in Appendix G:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Bauerle 2011[4]	Patients with idiopathic intracranial hypertension N=10 Prospective cohort study	Raised intracranial pressure	Ultrasound measurement of the optic nerve sheath diameter (ONSD)	Direct ICP monitoring: lumbar puncture	Not SAH patients
Bellner 2004[6]	Patients admitted to ICU with intracranial disorders. N=81 Prospective cohort study	Raised intracranial pressure (>20 mmHg)	Transcranial Doppler	Direct ICP monitoring: intraventricular catheter	46 (57%) patients had subarachnoid haemorrhage, 21 (26%) patients had closed head injury, and 14 (18%) patients had other neurosurgical disorders.
Bolesch 2015[8]	Outpatients scheduled for LP (20) for benign intracranial hypertension or residual communicating hydrocephalus, and ICU inpatients with SAH receiving invasive ICP monitoring. N=45 Prospective cohort study	Elevated intracranial pressure (>20 cm H_2O)	Ultrasound measurement of the optic nerve sheath diameter (ONSD)	Direct ICP monitoring: lumbar puncture (outpatient cohort)	
Kimberly 2008[23]	Patients with traumatic brain injuries (n=4) or spontaneous Intracerebral haemorrhages (n=11).	Raised intracranial pressure (>20 cm H_2O)	Ultrasound measurement of the optic nerve sheath diameter (ONSD)	Direct ICP monitoring: Extraventricular drain	

Study	Population	Target condition	Index test	Reference standard	Comments
	N=15 Prospective case series				
Moretti 2009[31](Moretti 2009[32])	Adult patients with primary intracerebral haemorrhage (29) or subarachnoid haemorrhage (34) requiring ICP monitoring, sedation, and mechanical ventilation, and 53 control patients with no intracranial pathology, requiring sedation and mechanical ventilation. N=63 Prospective cohort study	Raised intracranial pressure (>20 mmHg)	Ultrasonographic measurement of optic nerve sheath diameter (ONSD)	Direct ICP monitoring: Extraventricular drain (39) or intraparenchymal bolt (24)	Cohort divided into three subgroups: study population (intracranial haemorrhage) with ICP <20mm Hg (37), study population (intracranial haemorrhage) with ICP >20mm Hg (26), and control patients (53).
Ragauskas 2014[40]	Neurological patients requiring lumbar puncture for diagnostic purposes. N=108 Prospective cohort study	Raised intracranial pressure (>14.7 mmHg)	Ultrasonography of the optic nerve sheath diameter (ONSD) Transcranial Doppler	Direct ICP monitoring: lumbar puncture	Patient neurological condition not reported.
Rajajee 2011[41]	Patients who had an external ventricular drain (EVD) or intraparenchymal ICP monitor in place and were judged by the treating clinician to be at	Raised intracranial pressure (>20 mmHg)	Ultrasonography of the optic nerve sheath diameter (ONSD)	Direct ICP monitoring: EVD or intraparenchymal ICP monitor.	Patient diagnoses were SAH (30, TBI (11), ICH (11), brain tumour (5), Ventriculo-peritoneal shunt malfunction (5), ischemic stroke (1), acute liver failure (1).

Study	Population	Target condition	Index test	Reference standard	Comments
	risk for the development of ICP. N=65 Prospective cohort study				

1 See Appendix D:for full evidence tables.

2

1.4.4 3 Quality assessment of clinical studies included in the evidence review

4 **Table 3: Clinical evidence summary: Diagnostic test accuracy for index tests**

Index Test	Number of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
US optic nerve sheath diameter (raised ICP)							
ONSD	10 (1)	Serious[a]	Not serious	Serious[b]	Serious[c]	AUC= 0.92 (0.83-1.01)	VERY LOW
ONSD: ≥5.8mm	10 (1)	Serious[a]	Not serious	Serious[b]	Cannot be assessed	Sensitivity = 90%	LOW
		Serious[a]	Not serious	Serious[b]	Cannot be assessed	Specificity= 84%	LOW
US optic nerve sheath diameter (ICP >14.7mmHg)							
ONSD	92 (1)	Not serious	Not serious	Serious[b]	Serious[c]	AUC = 0.57 (0.47-0.67)	LOW
	16 (1)	Serious[a]	Not serious	Not serious	Serious[c]	AUC = 0.82 (0.61-1.00)	LOW
	15 (1)	Serious[b]	Not serious	Serious[b]	Serious[c]	AUC = 0.93 (0.84-0.99)	VERY LOW

Index Test	Number of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
ONSD: ≥4.5mm	15 (1)	Serious[a]	Not serious	Serious[b]	Cannot be assessed	Sensitivity =100%	LOW
		Serious[a]	Not serious	Serious[b]	Cannot be assessed	Specificity=63%	LOW
ONSD: ≥5.0mm	92 (1)	Not serious	Not serious	Serious[b]	Not serious	Sensitivity =37% (21.5-55.8%)	MODERATE
		Not serious	Not serious	Serious[b]	Serious[c]	Specificity=58.5% (46.3-69.6%)	LOW
	15 (1)	Serious[a]	Not serious	Serious[b]	Very serious[c]	Sensitivity =88% (47-99%)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Serious[c]	Specificity=93% (78-99%)	VERY LOW
ONSD: ≥5.7mm	35 (1)	Serious[a]	Not serious	Serious[b]	Cannot be assessed	Sensitivity =53.5%	LOW
		Serious[a]	Not serious	Serious[b]	Cannot be assessed	Specificity=100%	LOW
US optic nerve sheath diameter (ICP >20mmHg)							
ONSD	63 (2)	Serious[a]	Not serious	Serious[b]	Serious[c]	AUC = 0.93 (0.85-0.97)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	AUC = 0.98 (0.96-0.99)	LOW
ONSD: ≥4.8mm	65 (1)	Serious[a]	Not serious	Serious[b]	Not serious	Sensitivity =96% (91–99%)	LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=94% (92–96%)	LOW
ONSD: ≥5.0mm	65 (1)	Serious[a]	Not serious	Serious[b]	Serious[c]	Sensitivity =86% (79–92%)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=98% (96–99%)	LOW

Index Test	Number of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
ONSD: ≥5.2mm	65 (1)	Serious[a]	Not serious	Serious[b]	Serious[c]	Sensitivity =67% (58–75%)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=98% (97–99%)	LOW
	63 (2)	Serious[a]	Not serious	Serious[b]	Serious[c]	Sensitivity =93.1% (77.2-99%)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=73.9% (61.5-84%)	LOW
ONSD: ≥5.9mm	65 (1)	Serious[a]	Not serious	Serious[b]	Not serious	Sensitivity =19% (13–27%)	LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=100% (99–100%)	LOW
TC Doppler (ICP of >14.7 mmHg)							
TC Doppler	85 (1)	Not serious	Not serious	Serious[b]	Serious[c]	AUC = 0.87 (0.79-0.92)	LOW
		Not serious	Not serious	Serious[b]	Serious[c]	Sensitivity =68% (48.4-82.8%)	LOW
		Not serious	Not serious	Serious[b]	Serious[c]	Specificity=84.3% (74-91%)	LOW
TC Doppler (ICP of >20 mmHg)							
TC Doppler	81 (1)	Serious[a]	Not serious	Serious[b]	Cannot be assessed	Sensitivity =89%	LOW
		Serious[a]	Not serious	Serious[b]	Cannot be assessed	Specificity=92%	LOW

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

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect. Indirectness was due to mixed groups of people with and without aSAH or with unspecified causes of raised intracranial pressure.

(c) *Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. Two clinical decision thresholds were determined at the value above which a test would be recommended (90%), and a second below which a test would be considered of no clinical use (60%).These thresholds were applied for outcomes of sensitivity, specificity, PPV, NPV and AUC. The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold, and downgraded by 2 increments when the range covered two thresholds. Imprecision could not be assessed where there was insufficient data for analysis. Where imprecision cannot be assessed, the outcome was not downgraded.*

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

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

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

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. The committee noted that both an ultrasound of the optic nerve sheath and a transcranial Doppler ultrasound scan would take less than 20 minutes, and would need to be mobile as these scans would be performed on the ward.

Table 4: UK costs of diagnostic investigations

Monitoring technique	NHS Reference cost description	Cost
Optic nerve ultrasound	Ultrasound scan, mobile or intraoperative procedures, with duration of less than 20 minutes	£83
Transcranial Doppler		
Direct pressure monitoring/ intracranial pressure monitoring (ICP)	Minimal Intracranial Procedures (elective inpatient), 19 years and over [NHS Reference cost code: AA57A]	£2,320

Source: NHS Reference costs2018/19[37]

1.6 Evidence statements

1.6.1 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The diagnostic measures that matter most

The committee noted the primary outcome of the evidence review was the accuracy of diagnostic strategies to rule out or confirm a diagnosis of raised intracranial pressure. The committee considered both sensitivity and specificity of investigations to be critical outcomes for this review. The committee agreed that a diagnostic accuracy with sensitivity of ≥90% and specificity of ≥90% would provide value in clinical practice. The committee highlighted that a high sensitivity investigation is important to reliably rule out intracranial hypertension in test negative patients, while a high specificity test can reliably rule in intracranial hypertension in test positive patients. The committee agreed that both sensitivity and specificity were important within this setting, to provide appropriate intervention for those correctly identified with intracranial hypertension, and to seek an alternative diagnosis in people with

neurological deterioration but no intracranial hypertension. The additional important outcomes were positive predictive value, negative predictive value and receiver operating characteristic (ROC) curve or area under the curve.

1.7.1.24 The quality of the evidence

The committee acknowledged the limited quality and number of studies of ultrasound measurement of optic nerve sheath diameter and transcranial Doppler for estimation of intracranial pressure in adults with aSAH. Moreover, several factors varied between the included studies, such as the process of patient selection and the reference threshold used to indicate raised intracranial pressure.

The committee noted that most studies included indirect populations, including mixed groups of people with and without aSAH, or with unspecified causes of raised intracranial pressure. The committee considered that the physiological effects of raised intracranial pressure are unlikely to be significantly different in these populations to people with aSAH, and so agreed that this indirect evidence could inform discussion for the detection of raised intracranial pressure in people with aSAH.

It was also unclear from the studies included whether the patient's clinical state at point of testing was stable or deteriorating. The committee considered this evidence could still inform investigation in people with aSAH but should be downgraded for indirectness.

The committee noted the small size of the studies, ranging from 10 to 108 participants. The data from the included studies could not be meta-analysed, but wide confidence intervals of individual study results indicated imprecision and a further reduction in overall outcome quality.

Due to the low to very low quality of the evidence available, the committee agreed they could not make a recommendation for ultrasound monitoring of the optic nerve sheath diameter or for transcranial Doppler to estimate intracranial pressure.

Because of the limited evidence available for this review and for the review on managing intracranial pressure, the committee decided to make a research recommendation to assess the clinical and cost effectiveness of interventions to monitor and reduce intracranial pressure in unconscious and/or ventilated patients, in whom the poor clinical condition is attributed at least partly to raised intracranial pressure.

1.7.1.31 Benefits and harms

The committee acknowledged that intracranial pressure is often elevated in patients with aSAH, and intracranial hypertension is often unrecognised as it may not be apparent on a brain scan. Moreover, intracranial hypertension that impedes cerebral blood flow and contributes to brain injury is generally only seen in the sickest patients, including those who are unconscious or require ventilation on an intensive care unit. The committee discussed that in current practice intracranial pressure can be monitored in these patients by insertion of an intracranial pressure bolt or from an external ventricular drain inserted for the management of acute hydrocephalus. From the limited, low quality evidence available, the committee agreed that the diagnostic accuracy of optic nerve ultrasound and transcranial Doppler was too varied and, in some studies, too low to confidently replace direct pressure monitoring in patients with aSAH. The consequences of missed detection of intracranial hypertension are uncertain but could include greater disability and death, and the committee agreed it was not appropriate to rely exclusively on these non-invasive tests if an accurate assessment of intracranial pressure is considered necessary.

The committee also acknowledged that insertion of an intracranial pressure bolt is associated with risk, and agreed that monitoring of intracranial pressure will only improve outcome if it leads to effective intervention. The committee were aware that in current practice monitoring

of intracranial pressure is carried out infrequently, with considerable variation in practice between clinicians and neurosurgical centres. Some clinicians advise routine intracranial pressure monitoring in patients with aSAH managed on an intensive care unit, and in patients with intracranial hypertension target treatments to reduce intracranial pressure. Other clinicians only rarely recommend direct measurement of intracranial pressure, arguing that effective treatments for the management of intracranial hypertension are lacking. There was no consensus amongst committee members on the use of intracranial pressure monitoring in patients with aneurysmal subarachnoid haemorrhage and depressed consciousness or need for ventilation, although the committee agreed that intracranial pressure monitoring it is not required in conscious and clinically stable patients. The committee were therefore unable to make a consensus recommendation for intracranial pressure monitoring in patients with aneurysmal subarachnoid haemorrhage who are unconscious or ventilated on an intensive care unit.

As the evidence available for this review and for the review on managing intracranial pressure was very limited, the committee decided to make a research recommendation to assess the clinical and cost effectiveness of interventions to monitor and reduce intracranial pressure in unconscious or ventilated patients with aSAH, in whom the poor clinical condition is attributed at least partly to raised intracranial pressure.

1.7.2 Cost effectiveness and resource use

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

The committee noted that both an individual transcranial Doppler and an ultrasound scan of the optic nerve sheath would take less than 20 minutes and use a mobile ultrasound machine. Therefore, a cost of £71 was considered to be the most appropriate for each scan. The committee noted that, if these scans are to be used to monitor patients, multiple scans throughout the day would be required for several days post ictus. No other accepted protocol or strategy exists so a more thorough cost analysis could not be completed.

The committee noted that if either technique were used to make an initial diagnosis of raised ICP, an intracranial device (reference standard) would still be required to confirm the diagnosis and monitor the pressure in the brain. This is an invasive procedure with attendant risks, most notably subsequent infection, and incurs a high cost of £7,000-£10,000.

A false positive non-invasive test result could lead to an unnecessary invasive procedure to confirm suspected raised intracranial pressure and this also has attendant risks. This might have a significant detriment on quality of life, as well as increased length of stay and therefore cost to the NHS.

A false negative test result might delay further investigations or the placement of an intracranial device to measure pressure. The consequences of missing rising intracranial pressure are likely to vary from person to person and are highly uncertain but are suspected to include death and increased disability.

The committee agreed that these health economic considerations support the decision not to recommend routine monitoring of intracranial pressure using direct or non-invasive techniques.

1.7.3 Other factors the committee took into account

The committee noted that in practice the decision to monitor intracranial pressure and the choice of pressure monitoring device will depend on a number of factors including the person’s clinical condition, interpretation of the CT head scan, and presence of shunts or drains (which can simultaneously be used to measure intracranial pressure). The committee considered that non-invasive measurement of intracranial pressure might have a use in

future as a screening tool, or if the patient has a contraindication for direct pressure monitoring (such as a bleeding disorder). It was accepted that the accuracy of currently available techniques to indirectly measure ICP may vary depending on operator and location. These considerations support the committee decision to make a research recommendation to assess the clinical and cost effectiveness of interventions to monitor and reduce intracranial pressure in unconscious and/or ventilated patients, in whom the poor clinical condition is attributed at least partly to raised intracranial pressure.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Detecting intracranial hypertension

ID	Field	Content
0.	PROSPERO registration number	CRD42019142622
1.	Review title	What is the diagnostic accuracy of investigations for detecting intracranial hypertension for the deteriorating or unconscious person?
2.	Review question	What is the diagnostic accuracy of investigations for detecting intracranial hypertension for the deteriorating or unconscious person?
3.	Objective	To determine the accuracy of investigations in detecting intracranial hypertension. Intracranial hypertension is recognised as a serious complication of aneurysmal subarachnoid haemorrhage associated with increased morbidity.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language only The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm whose neurological status is deteriorating or is unconscious. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.

7.	Intervention/Exposure/Test	• Optic nerve ultrasound (US) • Transcranial doppler
8.	Comparator/Reference standard/Confounding factors	Reference standard: • Direct pressure measurement/ Intracranial pressure (ICP) monitoring
9.	Types of study to be included	• Cross-sectional studies • Cohort studies • Systematic reviews of observational cohort studies will be included.
10.	Other exclusion criteria	Exclusions: • Studies that do not report sensitivity and specificity, or insufficient data to derive these values. • Non English language studies.
11.	Context	
12.	Primary outcomes (critical outcomes)	Statistical measure to detect intracranial hypertension: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Diagnostic test accuracy studies risk of bias was assessed using QUADAS-2. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments

		Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.		
16.	Strategy for data synthesis	Aggregate data on diagnostic accuracy of investigations will be collected and synthesized in a quantitative data analysis. Endnote will be used for bibliography, citations, sifting and reference management. WinBUGS will be used for meta-analysis of diagnostic accuracy studies if included studies are sufficiently homogeneous. Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer.		
17.	Analysis of sub-groups	Not applicable		
18.	Type and method of review	☐	Intervention	
		☒	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date	3 February 2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐ ☑	☐ ☑
		Piloting of the study selection process	☐ ☑	☐ ☑
		Formal screening of search results against eligibility criteria	☐ ☑	☐ ☑
		Data extraction	☐ ☑	☐ ☑
		Risk of bias (quality) assessment	☐ ☑	☐ ☑
		Data analysis	☐ ☑	☐ ☑
24.	Named contact	5a. Named contact		

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

		• notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage; intracranial hypertension	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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2 **(Test and treat protocol)**

ID	Field	Content
0.	PROSPERO registration number	CRD42019143157
1.	Review title	What is the clinical and cost effectiveness of options for detecting intracranial hypertension for the deteriorating or unconscious person?
2.	Review question	What is the clinical and cost effectiveness of options for detecting intracranial hypertension for the deteriorating or unconscious person?
3.	Objective	To determine which diagnostic investigation for detecting intracranial hypertension is the most clinically and cost-effective. Intracranial hypertension is recognised as a serious complication of aneurysmal subarachnoid haemorrhage associated with increased morbidity.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by:

		• English language only The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm whose neurological status is deteriorating or is unconscious. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
7.	Intervention/Exposure/Test	• Optic nerve ultrasound (US) • Transcranial Doppler • Direct pressure measurement/ Intracranial pressure (ICP) monitoring Negative test results must receive no treatment for intracranial hypertension and positive test results should receive some form of treatment for raised intracranial hypertension (directness to be assessed against results of intervention review on management of intracranial hypertension, interventions found to be less effective in this review may be downgraded).
8.	Comparator/Reference standard/Confounding factors	Comparator: • To each other
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, search for non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger. • Non English language studies.
11.	Context	
12.	Primary outcomes (critical outcomes)	• Mortality

		• Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Length of hospital stay • Complications (any) Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction. If not an intervention review, add: A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool • Cross sectional study: JBI checklist for cross sectional study • Case series: Institute of Health Economics (IHE) checklist for case series 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

		• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • CERQual will be used to synthesise data from qualitative studies. • WinBUGS will be used for network meta-analysis, if possible given the data identified. Subgroups will be investigated separately if meta-analysed results show heterogeneity.	
17.	Analysis of sub-groups	Subgroups: • Subsequent treatment following positive diagnosis: ○ Diuretics ○ Hypertonic saline ○ Surgical intervention ○ Sedation ○ Hypertensive therapy ○ Other	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic

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<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="2"></td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="2">3 February 2021</td></tr>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td colspan="2"><table>
<tr><td>Review stage</td><td>Started</td><td>Completed</td></tr>
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<tr><td>Piloting of the study selection process</td><td>☐ ☑</td><td>☐ ☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐ ☑</td><td>☐ ☑</td></tr>
<tr><td>Data extraction</td><td>☐ ☑</td><td>☐ ☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐ ☑</td><td>☐ ☑</td></tr>
<tr><td>Data analysis</td><td>☐ ☑</td><td>☐ ☑</td></tr>
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<tr><td>24.</td><td>Named contact</td><td colspan="2">5a. Named contact
National Guideline Centre

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

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="2">From the National Guideline Centre:
• Ms Gill Ritchie
• Mr Ben Mayer
• Mr Audrius Stonkus
• Mr Vimal Bedia
• Ms Emma Cowles
• Ms Jill Cobb
• Ms Amelia Unsworth</td></tr>
<tr><td>26.</td><td>Funding sources/sponsor</td><td colspan="2">This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</td></tr>
</table>

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage; intracranial hypertension	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		

36.	Details of final publication	www.nice.org.uk

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Table 6: Health economic review protocol

Review question	All questions where health economic evidence applicable
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[34] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will decide based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

This literature search strategy was used for the following review;

- What is the diagnostic accuracy of investigations for detecting intracranial hypertension for the deteriorating or unconscious person?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[34]

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

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
Embase (OVID)	1974 – 24 June 2020	Exclusions Randomised controlled trials

Database	Dates searched	Search filter used
		Systematic review studies Observational studies Diagnostic tests studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None

1 **Medline (Ovid) search terms**

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	limit 27 to English language
29.	exp "Sensitivity and Specificity"/
30.	(sensitivity or specificity).ti,ab.
31.	((pre test or pretest or post test) adj probability).ti,ab.
32.	(predictive value* or PPV or NPV).ti,ab.
33.	likelihood ratio*.ti,ab.
34.	likelihood function/
35.	((area under adj4 curve) or AUC).ti,ab.

36.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
37.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
38.	gold standard.ab.
39.	or/29-38
40.	Epidemiologic studies/
41.	Observational study/
42.	exp Cohort studies/
43.	(cohort adj (study or studies or analys* or data)).ti,ab.
44.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
45.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
46.	Controlled Before-After Studies/
47.	Historically Controlled Study/
48.	Interrupted Time Series Analysis/
49.	(before adj2 after adj2 (study or studies or data)).ti,ab.
50.	exp case control study/
51.	case control*.ti,ab.
52.	Cross-sectional studies/
53.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	or/40-53
55.	Meta-Analysis/
56.	exp Meta-Analysis as Topic/
57.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
58.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
59.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61.	(search* adj4 literature).ab.
62.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/55-64
66.	randomized controlled trial.pt.
67.	controlled clinical trial.pt.
68.	randomi#ed.ti,ab.
69.	placebo.ab.
70.	randomly.ti,ab.
71.	Clinical Trials as topic.sh.
72.	trial.ti.
73.	or/66-72
74.	28 and (39 or 54 or 65 or 73)
75.	exp intracranial hypertension/ or hypertensive encephalopathy/ or pseudotumor cerebri/

76.	(intracranial hypertension or intra-cranial hypertension).ti,ab.
77.	(pseudotumor celebri or hypertensive encephalopathy).ti,ab.
78.	((elevat* or increas*) adj (intracranial or intra-cranial) adj pressure).ti,ab.
79.	intracerebral hypertension.ti,ab.
80.	or/75-79
81.	74 and 80

1 **Embase (Ovid) search terms**

1.	*subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
25.	23 not 24
26.	limit 25 to English language
27.	exp "sensitivity and specificity"/
28.	(sensitivity or specificity).ti,ab.
29.	((pre test or pretest or post test) adj probability).ti,ab.
30.	(predictive value* or PPV or NPV).ti,ab.
31.	likelihood ratio*.ti,ab.
32.	((area under adj4 curve) or AUC).ti,ab.
33.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
34.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
35.	diagnostic accuracy/

36.	diagnostic test accuracy study/
37.	gold standard.ab.
38.	or/27-37
39.	Clinical study/
40.	Observational study/
41.	family study/
42.	longitudinal study/
43.	retrospective study/
44.	prospective study/
45.	cohort analysis/
46.	follow-up/
47.	cohort*.ti,ab.
48.	46 and 47
49.	(cohort adj (study or studies or analys* or data)).ti,ab.
50.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
51.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	(before adj2 after adj2 (study or studies or data)).ti,ab.
53.	exp case control study/
54.	case control*.ti,ab.
55.	cross-sectional study/
56.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
57.	or/39-45,48-56
58.	random*.ti,ab.
59.	factorial*.ti,ab.
60.	(crossover* or cross over*).ti,ab.
61.	((doubl* or singl*) adj blind*).ti,ab.
62.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
63.	crossover procedure/
64.	single blind procedure/
65.	randomized controlled trial/
66.	double blind procedure/
67.	or/58-66
68.	systematic review/
69.	meta-analysis/
70.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
71.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
72.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74.	(search* adj4 literature).ab.
75.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
76.	cochrane.jw.
77.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.

78.	or/68-77
79.	26 and (38 or 57 or 67 or 78)
80.	exp intracranial hypertension/
81.	hypertension encephalopathy/
82.	brain pseudotumor/
83.	(intracranial hypertension or intra-cranial hypertension).ti,ab.
84.	(pseudotumor celebri or hypertensive encephalopathy).ti,ab.
85.	((elevat* or increas*) adj (intracranial or intra-cranial) adj pressure).ti,ab.
86.	intracerebral hypertension.ti,ab.
87.	or/80-86
88.	79 and 87

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#3.	(SAH or aSAH):ti,ab
#4.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#6.	(OR #1-#5)
#7.	MeSH descriptor: [Intracranial Hypertension] explode all trees
#8.	MeSH descriptor: [Hypertensive Encephalopathy] explode all trees
#9.	MeSH descriptor: [Pseudotumor Cerebri] explode all trees
#10.	((intracranial NEXT hypertension) or (intra-cranial NEXT hypertension)):ti,ab
#11.	((pseudotumor NEXT celebri) or (hypertensive NEXT encephalopathy)):ti,ab
#12.	((elevat* or increas*) NEXT (intracranial or intra-cranial) NEXT pressure):ti,ab
#13.	(intracerebral NEXT hypertension):ti,ab
#14.	(or #7-#13)
#15.	#6 and #14

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to subarachnoid haemorrhage population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003 – 23 June 2020	Exclusions Health economics studies
Embase	2003 – 23 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 23 June 2020	None

Database	Dates searched	Search filter used
	NHSEED - Inception to March 2015	

1 **Medline (Ovid) search terms**

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.

39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.

35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

1 **NHS EED and HTA (CRD) search terms**

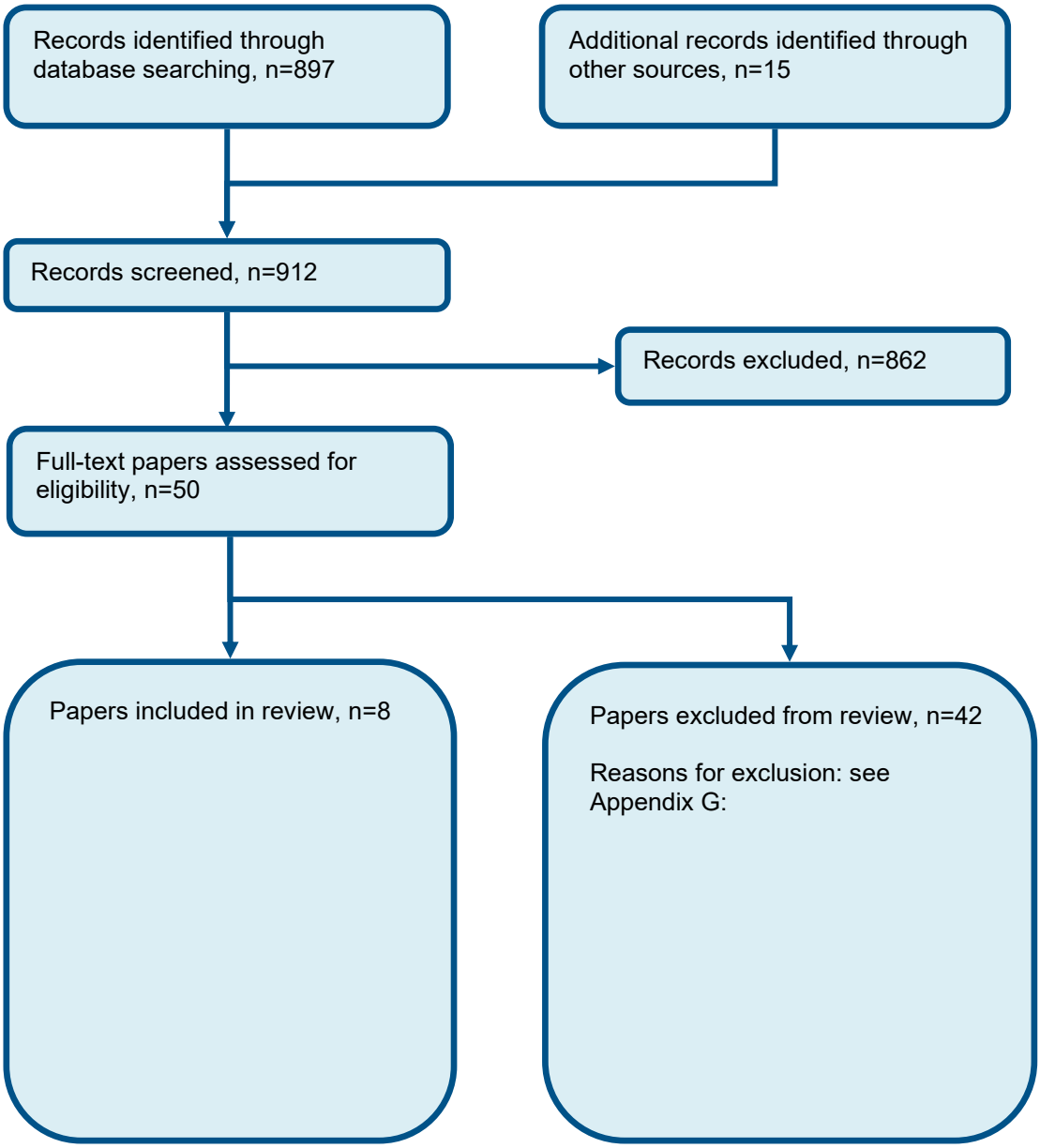
#1.	MeSH DESCRIPTOR Subarachnoid Hemorrhage EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#3.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)))
#4.	((SAH or aSAH))
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Aneurysm EXPLODE ALL TREES
#7.	((aneurysm* or hematoma* or haematoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Intracranial Aneurysm EXPLODE ALL TREES
#10.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (aneurysm* or hematoma* or haematoma*)))
#11.	#9 OR #10
#12.	MeSH DESCRIPTOR Aneurysm, ruptured
#13.	(((ruptur* or weak* or brain or trauma*) adj3 (aneurysm* or hematoma* or haematoma*)))
#14.	#12 OR #13
#15.	(#5 or #8 or #11 or #14)

2

3

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of detection of ICH.



Appendix D: Clinical evidence tables

Reference	**Bauerle 2011[4]**
Study type	Prospective cohort
Study methodology	Data source: Study subjects with idiopathic intracranial hypertension. (The control group consisted of patients who suffered from neurological disorders without signs of elevated intracranial pressure and who had not undergone lumbar puncture in the past) Recruitment: Consecutive patients were enrolled if they granted informed consent.
Number of patients	n = 10
Patient characteristics	Age, mean (SD): 26.2 (5.5) Gender (male to female ratio): 2/8 Ethnicity: Not reported Setting: ICU Country: Germany Inclusion criteria: In all patients, diagnosis was newly established and all individuals had to be naive to treatment. Bilateral papilledema was documented in all probands by an ophthalmological examination including funduscopy. In both groups, patients had to be 18 years old or older. Exclusion criteria: Patients with no history of glaucoma, amblyopia, or diseases of the optic nerve.
Target condition(s)	Elevated intracranial pressure
Index test(s) and reference standard	Index test ONSD: Ultrasound examinations of the eye were carried out in B-mode using a Philips iU22 ultrasound system and a 9–3 MHz linear array transducer. ONSD was assessed 3 mm behind the papilla.

Reference	**Bauerle 2011[4]**
	Reference standard Lumbar puncture. After measuring the CSF opening pressure, therapeutic removal of 30–50 ml of CSF was carried out by the attending physician. Time between measurement of index test and reference standard: measurements were performed before lumbar puncture and the day after the procedure.
Statistical measures	Index text AUC = 0.92; (95% CI = 0.83–1.01; p=0.0001 The sensitivity and the specificity at the optimal cut-off of 5.8mm value were 90 and 84%, respectively.
Source of funding	Not reported
Limitations	Risk of bias: Serious (threshold criteria of raised ICP not reported) Indirectness: Indirect: Patients with idiopathic intracranial hypertension – not SAH patients

1

2

Reference	**Bellner 2004[6]**
Study type	Prospective cohort
Study methodology	Data source: Not reported Recruitment: Not reported
Number of patients	n = 81
Patient characteristics	Age, mean (range): 52 (2-79) Gender (male to female ratio): 37/44 Ethnicity: Not reported

Reference	Bellner 2004[6]
	Setting: Not reported Country: Sweden Inclusion criteria: Patients admitted with intracranial disorders. Exclusion criteria: Not reported
Target condition(s)	Raised intracranial pressure: 0-20 mmHg, 0-40mmHg
Index test(s) and reference standard	Index test The daily TCD measurements were conducted transtemporally using a traditional 2-MHz transducer (EME TC-64 Eden medical records, Uberlingen, Germany). The TCD measurements were routinely performed bilaterally on the middle cerebral artery (MCA). Recordings were documented on a videographic printer for later analysis (Sony VP 850). The depth and angle of insonation giving the highest mean flow velocity (mFV) in MCA was always chosen. Normal mFV in MCA was defined as 62 12 cm/s [1]. Consequently, mFVs were considered subnormal when below 50 cm/s and supernormal when above 74 cm/s. mFVs above 120 cm/s were considered severely elevated indicating vasospasm or hyperemia. Reference standard All patients received an intraventricular catheter for continuous recording of the intracranial pressure (HanniKath, 7F, pvb Medizintechnik Gmbh & Co. kg, Kirchseeon, Germany). Time between measurement of index test and reference standard: TCD measurements were performed parallel to the ICP registration.
Statistical measures	Index text ICP <20 in a population with ICP between 0 and 40, the method had for all measurements a sensitivity of 83% and a specificity of 99%, and for the first measurement only a sensitivity of 89% and a specificity of 92%
Source of funding	Not reported
Limitations	Risk of bias: Serious – Patient selection Indirectness: Indirect: 43% not SAH patients, age range 2 to 79 years

1

Reference	**Bolesch 2015[8]**
Study type	Prospective cohort
Study methodology	Data source: Outpatients scheduled for LP (20) for benign intracranial hypertension, normal pressure hydrocephalus, or residual communicating hydrocephalus, and ICU inpatients with SAH receiving invasive ICP monitoring (25). Recruitment: Not reported
Number of patients	n = 45 total, 25 SAH patients
Patient characteristics	Age, mean (SD): 35 (16) Gender (male to female ratio): 25%/75% Ethnicity: Not reported Setting: Outpatient/ICU Country: Germany Inclusion criteria: Patients aged 19-80 years. Exclusion criteria: Patients with missing or poor transtemporal bone window, contra instability to mydriatic eye drops, trauma of the optic nerve, eye or face preventing or distorting fundoscapy or transtabular
Target condition(s)	Elevated intracranial pressure (>20 cm H_2O)
Index test(s) and reference standard	Index test Ultrasound measurement of the optic nerve sheath diameter (ONSD) Reference standard Direct ICP monitoring: intraventricular catheter or drain (ICU cohort) or ONSD response to lumbar puncture (outpatient cohort) Time between measurement of index test and reference standard: Invasive ICP values taken at the beginning and end of procedure and average values were compared with US values.

Reference	Bolesch 2015[8]
Statistical measures	Index text AUC: 0.82 (0.61-1.00) (results for outpatients SAH patients, n=16) Total cohort, >5.7mm SN 53.5% SP 100% PPV 100% NPV 87%
Source of funding	Not reported
Limitations	Risk of bias: Serious – Patient selection Indirectness: Indirect: 20/45 outpatients scheduled for LP for benign intracranial hypertension or residual communicating hydrocephalus.

1

2

Reference	Kimberly 2008[23]
Study type	Prospective case series
Study methodology	Data source: This research was conducted at a large, urban, academic ED and Level 1 trauma centre with an annual ED patient volume of approximately 75,000 patients. Recruitment: Patients were enrolled as a convenience sample based on availability of study physicians between May 1, 2006, and December 20, 2006.
Number of patients	n = 15
Patient characteristics	Age, mean (range): 60 (27-83) Gender (male to female ratio): 10 male; 5 female Ethnicity: Not reported Setting: ICU

Reference	**Kimberly 2008[23]**
	Country: USA Inclusion criteria: adult ED and neurologic intensive care unit (ICU) patients with invasive intracranial monitoring placed as part of their clinical care. Exclusion criteria: patients less than 18 years of age or patients with significant ocular trauma.
Target condition(s)	ICP > 20 cm H_2O
Index test(s) and reference standard	Index test Ocular US were performed on a Sonosite Micromaxx (SonoSite Inc., Bothell, WA) machine with a 10–5 MHz linear probe using a standard technique. 3 measurements were taken on each eye, averaged to get mean reading Reference standard The patient's nurse clamped the EVD and the ICP was recorded electronically each minute during the US measurements. The ICP measurements were averaged to yield a mean ICP for each subject during the approximately 5 minutes required to perform US measurements for both eyes. Time between measurement of index test and reference standard: Simultaneous
Statistical measures	Index text AUC 0.93 (0.84-0.99) The commonly used cut-off of ONSD > 5.0 mm yielded the most favourable balance of test characteristics, with a resulting sensitivity of 88% (95% CI = 47% to 99%) and specificity of 93% (95% CI = 78% to 99%). Using an ONSD of 4.5 mm gives a sensitivity of 100%, but a specificity of only 63% in this sample.
Source of funding	Not reported
Limitations	Risk of bias: Serious – Patient selection Indirectness: Indirect: Not noted as SAH patients

1

2

Reference	**Moretti 2009[31](Moretti 2009[32])**
Study type	Prospective cohort

Reference	Moretti 2009[31](Moretti 2009[32])
Study methodology	Data source: 10-bed multivalent intensive care unit Recruitment: enrolling 63 adult patients with primary intracerebral haemorrhage (29) or subarachnoid haemorrhage (34), requiring ICP monitoring, sedation, and mechanical ventilation and 53 control patients with no intracranial pathology, requiring sedation and mechanical ventilation.
Number of patients	n = 63 (+53 controls)
Patient characteristics	Age, mean (SD): 52 (11), 52 (12), 58 (19) Gender (male to female ratio): 63/43 Ethnicity: n/a Setting: Intensive care unit Country: Italy Inclusion criteria: patients with primary intracerebral haemorrhage or subarachnoid haemorrhage requiring ICP monitoring, sedation, and mechanical ventilation and control patients with no intracranial pathology, requiring sedation and mechanical ventilation. Exclusion criteria: aged <18 years, obvious ocular pathology, inability to perform ONSD measurement within 1 hour before ICP monitoring.
Target condition(s)	Raised intracranial pressure (>20 mmHg).
Index test(s) and reference standard	Index test Bedside ultrasonographic measurement of optic nerve sheath diameter, measured 3mm behind the globe. Average of ONSD between two eyes was taken. Reference standard Direct ICP monitoring: Extraventricular drain (32) or intraoarenchymal bolt (21) Time between measurement of index test and reference standard: <1 hour

Reference	**Moretti 2009[31](Moretti 2009[32])**
Statistical measures	Index text ONSD: >5.2mm Sensitivity: 93.1% (77.2%-99%) Specificity: 73.9% (61.5%-84%) AUC: 0.93 (0.85-0.97)
Source of funding	Not reported
Limitations	Risk of bias: Serious – Patient selection Indirectness: 34/63 SAH patients

1

Reference	**Ragauskas 2014[40]**
Study type	Prospective cohort
Study methodology	Data source: Department of Neurology at the Hospital of Lithuanian University of Health Sciences patients. Recruitment: Eligible patients from participating hospital were recruited consecutively.
Number of patients	n = 108
Patient characteristics	Age, mean (SD): Gender (male to female ratio): Ethnicity: Not reported Setting: Country: Lithuania Inclusion criteria: Neurological patients requiring lumbar puncture for diagnostic purposes . Exclusion criteria: Aged<18 years, brain lesions, infarcts, or tumours, eye or orbit pathologies, patients with neuro-infections and abnormal cerebrospinal fluid cultures.

Reference	**Ragauskas 2014[40]**
Target condition(s)	Raised intracranial pressure (>14.7 mmHg)
Index test(s) and reference standard	Index test Ultrasound of the ONSD made 3mm behind the eye globe. TC Doppler based on two-depth high resolution technique for simultaneous measurement of blood flow velocity made continuously for up to 10 minutes. Reference standard Lumbar puncture CSF pressure values recorded every 30 seconds. Time between measurement of index test and reference standard: Simultaneous.
Statistical measures	Index text ONSD (n=92) >5.0mm SN 37% (21.5-55.8%) SP 58.5% (46.3-69.6%) AUC 0.57 (0.47-0.67) TC Doppler (n=85) SN 68% (48.4-82.8%) SP 84.3% (74-91%) AUC 0.87 (0.79-0.92)
Source of funding	Supported by the European Commissions Seventh Framework Programme projects.
Limitations	Risk of bias: Low Indirectness: Indirect: Patient neurological condition not reported

1

Reference	**Rajajee 2011[41]**
Study type	Prospective cohort
Study methodology	Data source: Patients admitted who had an external ventricular drain (EVD) or intraparenchymal ICP monitor in place and were judged by the treating clinician to be at risk for the development of ICP.

<table>
<tr><td>Reference</td><td>Rajajee 2011[41]</td></tr>
<tr><td></td><td>Recruitment: Patients admitted to the neurointensive care unit between November 2008 and May 2011. Enrolment was based on investigator availability.</td></tr>
<tr><td>Number of patients</td><td>n = 65</td></tr>
<tr><td>Patient characteristics</td><td>Age, mean (SD): 51 (16), 55 (16)

Gender (male to female ratio):
26/39
Ethnicity:
n/a
Setting:
ICU
Country:
USA
Inclusion criteria: Patients admitted who had an external ventricular drain (EVD) or intraparenchymal ICP monitor in place and were judged by the treating clinician to be at risk for the development of ICP.
Exclusion criteria: age <18 years, known orbital injury and pre-existing optic nerve pathology.</td></tr>
<tr><td>Target condition(s)</td><td>Raised intracranial pressure (>20 mmHg).</td></tr>
<tr><td>Index test(s) and reference standard</td><td><u>Index test</u>
All ONUS scans were performed using a general-purpose, ultrasound machine with a 13–6 MHz linear-array probe with orbital imaging settings and a high resolution optimization setting. The ONSD was measured 3 mm behind the retina.

<u>Reference standard</u>
Invasive monitoring were performed at enrolment and intermittently during the course of the patients' stay in the ICU.

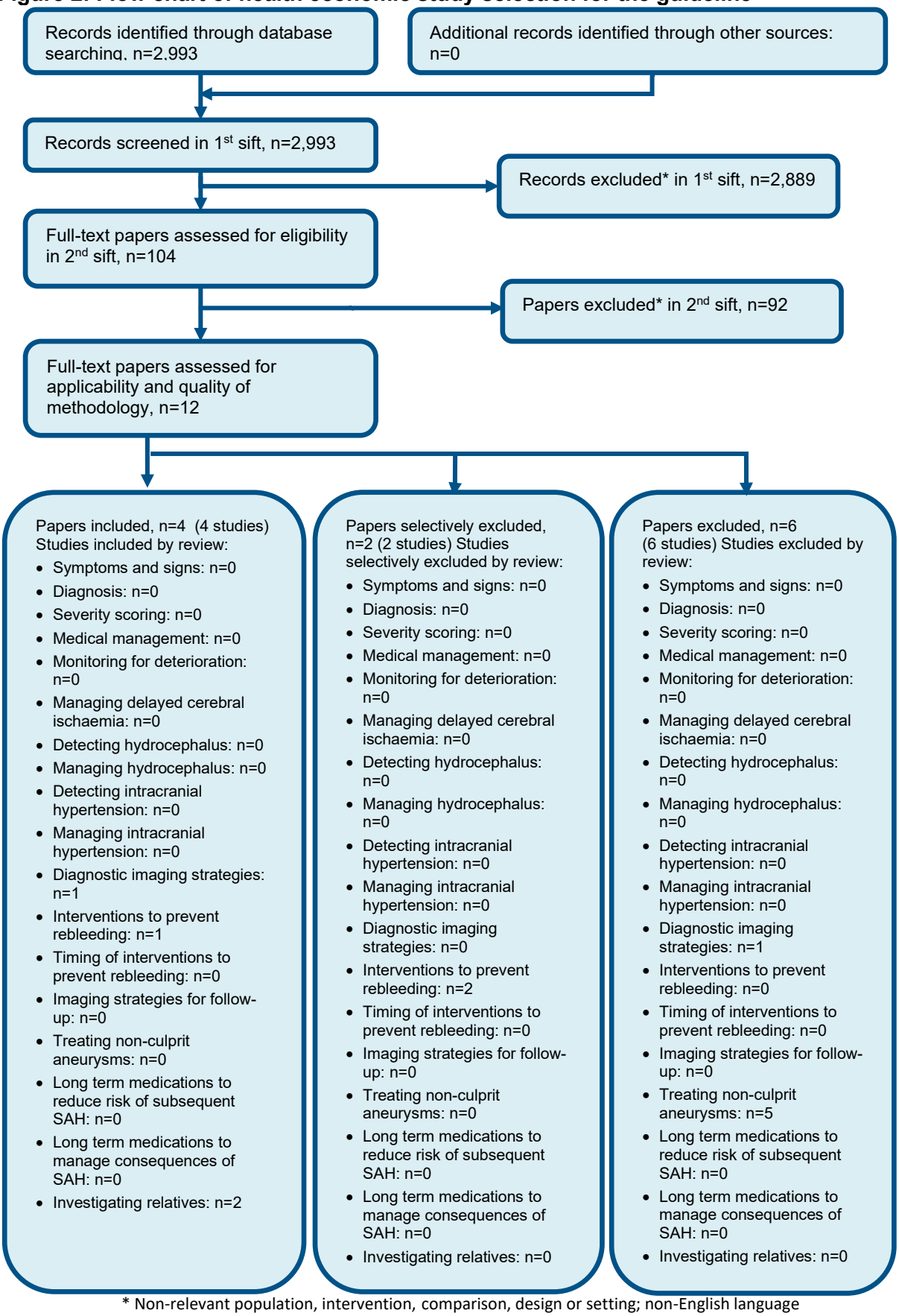
Time between measurement of index test and reference standard: Simultaneous</td></tr>
<tr><td>Statistical measures</td><td><u>Index text</u>
ONSD
<table>
<tr><th>High ICP criterion (mmHg)</th><th>ONSD criterion (mm)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>Positive predictive value (95% CI)</th><th>Negative predictive value (95% CI)</th></tr>
<tr><td>>20</td><td>≥4.8</td><td>96% (91–99%)</td><td>94% (92–96%)</td><td>84% (77–89%)</td><td>99% (97–100%)</td></tr>
<tr><td>>20</td><td>≥5.0</td><td>86% (79–92%)</td><td>98% (96–99%)</td><td>92% (86–96%)</td><td>96% (94–98%)</td></tr>
<tr><td>>20</td><td>≥5.2</td><td>67% (58–75%)</td><td>98% (97–99%)</td><td>93% (86–97%)</td><td>91% (88–93%)</td></tr>
</table></td></tr>
</table>

Reference	**Rajajee 2011[41]**					
	>20	≥5.9	19% (13–27%)	100% (99–100%)	96% (80–100%)	80% (76–84%)
	>25	≥5.2	98% (89–100%)	91% (88–94%)	53% (42–64%)	100% (99–100%)
	AUC: 0.98 (0.96-0.99) p<0.0001					
Source of funding	Funding not stated					
Limitations	Risk of bias: Serious – Patient selection Indirectness: Patients not noted to have SAH					

1

Appendix E: Health economic evidence selection

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



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

1

Appendix F:Health economic evidence tables

None.

1 Appendix G: Excluded studies

G.1 2 Excluded clinical studies

3 **Table 9: Studies excluded from the clinical review**

Reference	Reason for exclusion
Agrawal 2009[1]	Inappropriate intervention – management of ICH
Alvarez-Fernandez 2011[2]	Not in English
Badjatia 2004[3]	Inappropriate intervention – management of ICH
Behrens 2010[5]	Inappropriate study design – validation study
Blaivas 2003[7]	Inappropriate comparison – inappropriate reference standard
Broderick 2007[9]	Inappropriate study design – guideline
Cacciatori 2018[10]	Inappropriate intervention – transcranial Doppler
Carvi y Nievas 2005[11]	Inappropriate study design – no relevant outcomes
Chen 2018[12]	Inappropriate study design – no relevant outcomes
Chieregato 2006[13]	Inappropriate study design – no relevant outcomes
Dalman 1999[14]	Inappropriate population – hyper-perfusion risk
Dubourg 2011[15]	Systematic review: references screened
Edouard 2005[16]	Inappropriate study design – no relevant outcomes
Ehrlich 2016[17]	Inappropriate comparison – monitoring of vasospasm
Geeraerts 2007[18]	Inappropriate outcome - predictor of raised ICP within 48 hours
Geeraerts 2008[19]	Inappropriate population- majority traumatic brain injury
Iacopino 2003[20]	Inappropriate comparison – anaesthetic assessment
Iida 1997[21]	Inappropriate study design – no relevant outcomes
Kim 2013[22]	Inappropriate intervention – algorithm modelling
Klingelhofer 1988[24]	Inappropriate study design
Kofke 1994[25]	Inappropriate study design – no relevant outcomes
Lagreze 2007[26]	Inappropriate comparison – optic nerve imaging
Lang 2003[27]	Inappropriate comparison – inappropriate index and reference standard
Larangeira 2018[28]	Inappropriate study design – no relevant outcomes
Li 2013[29]	Inappropriate study design – surgical intervention
Loncaric-Katusin 2012[30]	Inappropriate study design – narrative review
Naldi 2019[33]	Inappropriate comparison – incorrect reference standard
Newman 2013[35]	Inappropriate study design – no relevant outcomes
Newman 2002[36]	Inappropriate population – paediatric
Pasarikovski 2017[38]	Inappropriate intervention – management of ICH
Qayyum 2013[39]	Inappropriate comparison – incorrect reference standard
Rasulo 2017[42]	Inappropriate population - majority traumatic brain injury
Robba 2016[43]	Inappropriate review population
Schoser 1999[44]	Inappropriate study design – no relevant outcomes
Soldatos 2008[45]	Inappropriate population - majority traumatic brain injury
Strumwasser 2011[46]	Inappropriate population - majority traumatic brain injury
Tarzamni 2016[47]	Inappropriate comparison – incorrect reference standard
Tayal 2007[48]	Inappropriate comparison – incorrect reference standard

Reference	Reason for exclusion
Treib 1997[49]	Inappropriate intervention – management of ICH
Zeiler 2018[50]	Inappropriate review population – animal study
Zhang 2017[51]	Inappropriate study design – literature review
Zoerle 2015[52]	Inappropriate study design – no relevant outcomes

G.2 Excluded health economic studies

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

Table 10: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	