National Institute for Health and Care Excellence

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Subarachnoid haemorrhage

[J] Evidence review for managing intracranial hypertension

NICE guideline <number>

Evidence review underpinning

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

1.1 Review question: What is the clinical and cost effectiveness of options for managing intracranial hypertension?

1.2 Introduction

In people with subarachnoid haemorrhage, intracranial pressure may be increased by hydrocephalus, haematoma, infection, or cerebral oedema. Raised intracranial pressure (intracranial hypertension) can impede blood flow to the brain and contribute to brain injury, in spite of a normal systemic blood pressure.

Several treatments for intracranial hypertension are in clinical use but there is variation in practice between neurosurgical centres. This review assesses the evidence to support medical and surgical interventions to treat intracranial hypertension.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (16 and older) with intracranial hypertension and a confirmed subarachnoid haemorrhage caused by a suspected or confirmed ruptured aneurysm.

Intervention	• Diuretics
	• Hypertonic saline
	• Surgical interventions:
	  ○ Decompressive Craniectomy
	  ○ External ventricular drain
	• Sedation
	• Hypertensive therapy

Comparison	Comparators: • To each other (within and between class comparison) • To no treatment
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) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work, driving) • Complications of intervention (any) • Change in intracranial pressure
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

Two studies were included in the review;[6, 38] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

1.4.2 Excluded studies

See the excluded studies list in Appendix J:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bentsen 2006[6]	**Hypertonic saline** - was a 7.2% saline in 6% hydroxyethyl starch 200/0.5 solution (HyperHAES, Fresenius Kabi AG) The observation period lasted from 10 min before until 210 min after the start of the infusion. Need for rescue treatment was defined by treatment failure limits for ICP and CPP, which were an ICP of >20> 20 mm HG and a CPP of 60 <60 mmHG. Unless these limits were reached during the observation period, the ventilation variables were kept unaltered, the infusion rates vasopressors, analgesics, sedatives, and fluids were stable, the resistance in the external ventricular drainage (EVD) was unchanged, and the patients were neither stimulated or moved. N=11 **Control** (placebo) - was 0.9% saline solution (Fresenius Kabi AG, Bad Homburgh v.d.h), Germany. The observation period lasted from 10 mins before until 210 mins after the	Included intensive care patients with an acute spontaneous SAH with stable ICP in the range 10 - 20 mmHg. They needed to be >18 years of age, sedated, mechanically ventilated, have stable hemodynamics and serum sodium of <160 mmol/L Age: Intervention Group – 50.1 (10.5) Placebo group – 55.2 (10.8)	• Intracranial pressure	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	start of the infusion. Need for rescue treatment was defined by treatment failure limits for ICP and CPP, which were an ICP of >20> 20 mm HG and a CPP of 60 <60 mmHG. Unless these limits were reached during the observation period, the ventilation variables were kept unaltered, the infusion rates vasopressors, analgesics, sedatives, and fluids were stable, the resistance in the external ventricular drainage (EVD) was unchanged, and the patients were neither stimulated or moved. N=11 Follow-up: 210 minutes			
Nagel 2009[38]	**Decompressive craniectomy** - Hemicraniectomy was performed in median on day 4(2-6) after SAH, in 2 of the 7 patients early after SAH. In 4 patients (57%) a dilating pupil was observed shortly before hemicraniectomy. N=7 **Control**: Patients who did not received decompressive craniectomy N=11	Any SAH patient developing intracranial hypertension with ICP values ≥20 mmHg for at least >6h after SAH and requiring treatment of elevated ICP was included. aSAH confirmed by CT; cerebral angiogram demonstrating intracranial aneurysm; patients underwent clipping followed by intraoperative insertion of the micro-dialysis catheter or patients underwent endovascular therapy of an aneurysm from the anterior	• Mortality • GOS (Glasgow outcome scale) 1-2 • GOS (Glasgow outcome scale) 3 • GOS (Glasgow outcome scale) 4-5	Retrospective cohort study Mean age of patients was not significantly different between groups.

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 1 year	circulation and additionally had an external ventricular drainage placed, so catheter placement through the existing burr hole allowed monitoring of the anterior cerebral artery territory. Age: Intervention group - 48(3.4) Control group 52(3.5)		

1 See Appendix D: for full evidence tables.

2 ### 1.4.4 Quality assessment of clinical studies included in the evidence review

3 **Table 3: Clinical evidence summary: Hypertonic saline vs placebo**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Hypertonic Saline (95% CI)
Change in intracranial pressure	22 (1 study) 210 minutes	⨁⨁⨁⨁ HIGH		The mean change intracranial hypertension in the control groups was -0.3 mmHg	The mean change intracranial hypertension in the intervention groups was 3 lower mmHg (4.72 to 1.28 lower)

1 **Table 4: Clinical evidence summary: Decompressive craniectomy vs no decompressive craniectomy**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no additional treatment	Risk difference with decompressive craniectomy (95% CI)
Mortality -	18 (1 study) death during hospitalisation	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.79 (0.38 to 1.64)	727 per 1000	153 fewer per 1000 (from 451 fewer to 465 more)
Mortality - (12 months)	18 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 13.08 (0.23 to 729.15)	0 per 1000	140 more per 1000 (from 150 fewer to 440 more)
GOS grade 1-2 (12 months) scale 1-5; high score represents positive outcome	16 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.04 (0.65 to 1.67)	800 per 1000	32 more per 1000 (from 280 fewer to 536 more)
GOS grade 3 (12 months) scale 1-5; high score represents positive outcome	16 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.67 (0.13 to 22)	100 per 1000	67 more per 1000 (from 87 fewer to 1000 more)
GOS grade 4-5 (12 months) scale 1-5; high score represents positive outcome	16 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1 due to risk of bias	Peto OR 0.2 (0 to 11.57)	100 per 1000	78 fewer per 1000 (from 100 fewer to 462 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

2 See Appendix G: for full GRADE tables.

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 H:.

1.5.3 Unit costs

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

Table 5: UK costs of treatments for decompressive craniectomy

Procedure	Description	Average cost
Decompressive craniectomy/ hemicraniotomy	Very Major Intracranial Procedures, 19 years and over [weighted average of NHS Reference Cost code AA52A-D]	£10,574

Source: NHS Reference Costs 2018/19[40]

1.6 Evidence statements

1.6.1 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee considered mortality, quality of life (Glasgow outcome scale) and degree of disability or dependence in daily activities to be critical outcomes for decision-making. Other important outcomes included subsequent subarachnoid haemorrhage, return to daily activity, complications of intervention and reduction in intracranial pressure.

1.7.1.2 The quality of the evidence

No evidence was identified for managing intracranial hypertension using diuretics, sedation, external ventricular drain or hypertensive therapy.

Limited evidence was identified from two studies for hypertonic saline and decompressive craniectomy. The very small size of the studies (ranging from 18 to 22 participants) limited confidence in the strength of the evidence. The quality of evidence varied from high to very low; most of the evidence was downgraded due to risk of bias and/or imprecision. The RCT reported high quality evidence for the outcome of intracranial pressure, however the committee agreed that the evidence from this small study was insufficiently powered for clinical outcomes and could not support a recommendation. The outcomes from the

retrospective cohort study were at a high risk of bias due to their study design and were also downgraded due to imprecision.

1.7.1.3 Benefits and harms

The anticipated benefit of treating intracranial hypertension is to reduce the risk of mortality and subsequent neurological deterioration.

Hypertonic saline vs placebo

The committee were aware that administration of hypertonic saline may reduce intracranial pressure but is associated with a risk of metabolic derangement. The committee noted evidence from 1 small RCT that hypertonic saline lowers intracranial pressure when compared with normal saline, but the quality and quantity of the evidence was too low to draw any conclusions on the benefits or harms of this treatment and so no clinical recommendation was made.

Decompressive craniectomy vs no additional treatment

Evidence from 1 small cohort study showed a reduction in mortality (during hospitalisation) and less disability (GOS) with decompressive craniectomy compared with no decompressive craniectomy. This benefit was not sustained and at twelve months the study reported an increase in mortality with decompressive craniectomy compared to no decompressive craniectomy. The committee considered that the quality and quantity of the evidence was too low to draw any firm conclusions.

The committee noted from their clinical experience that a lower rate of mortality, but a higher rate of disability might be expected with decompressive craniectomy. The committee highlighted that there are recognised risks to an invasive procedure such as decompressive craniectomy, including haemorrhagic, infective, and CSF related complications. The committee agreed that no recommendation could be made for decompressive craniectomy.

The committee agreed that raised intracranial pressure is common in patients with aSAH, but intracranial hypertension that impedes blood flow to the brain and contributes to brain injury is generally only seen in the sickest group. These patients are usually unconscious or require ventilation on an intensive care unit, and the anticipated benefit of treating intracranial hypertension in these patients is to reduce the risk of death and disability. However, the committee acknowledged that management of this heterogeneous population varies widely in current practice, with some clinicians advocating routine monitoring of intracranial pressure to guide intervention to lower intracranial pressure and maintain cerebral perfusion (such as CSF drainage, hypertonic saline, or vasopressor therapy). By contrast, other clinicians favour management without intracranial pressure measurement.

The committee discussed the options for monitoring intracranial pressure and managing intracranial hypertension but could not agree whether intracranial pressure should be routinely measured or how raised intracranial pressure should be managed. The committee was therefore unable to make a consensus recommendation.

As the evidence available for this review and for the review on monitoring intracranial pressure (evidence review I) was 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 people 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 this review. Unit costs were presented to the committee for consideration of cost effectiveness. However, due to a lack of clinical

evidence the committee could not determine the clinical effectiveness of interventions to manage intracranial hypertension and therefore the cost effectiveness could not be assessed.

Due to the lack of evidence the committee made a research recommendation and therefore there will be no resource impact.

1.7.3 Other factors the committee took into account

There was no consensus within the committee whether intracranial pressure should be routinely measured or how raised intracranial pressure should be managed. The committee recognised the difference in management between traumatic brain injury and primary vascular injuries of the brain. It was noted by the committee that in traumatic brain injury, measuring intracranial pressure is a routine practice whereas in vascular injuries it is seldom performed. The committee added that there is significant variation in how intracranial hypertension is managed. A number of centres monitor and manage intracranial hypertension in aSAH in a manner similar to that for traumatic brain injury.

Due to the lack of evidence available for this review and for the review on monitoring intracranial pressure, the committee made a research recommendation to assess the clinical and cost effectiveness of interventions to monitor and reduce intracranial pressure in unconscious or ventilated people with aSAH, in whom the poor clinical condition is attributed at least partly to raised intracranial pressure.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 6: Review protocol: Managing intracranial hypertension**

ID	Field	Content
0.	PROSPERO registration number	CRD42019146786
1.	Review title	What is the clinical and cost effectiveness of options for managing intracranial hypertension?
2.	Review question	What is the clinical and cost effectiveness of options for managing intracranial hypertension?
3.	Objective	To determine which intervention to manage 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 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 intracranial hypertension and a confirmed subarachnoid haemorrhage caused by a suspected or confirmed ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
7.	Intervention/Exposure/Test	• Diuretics • Hypertonic saline • Surgical interventions:

		○ Decompressive Craniectomy ○ External ventricular drain • Sedation • Hypertensive therapy
8.	Comparator/Reference standard/Confounding factors	Comparators: • To each other (within and between class comparison) • To no treatment
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Intracranial hypertension due to hydrocephalus. • Non- English language studies • Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
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, driving) • Complications of intervention (any) • Change in intracranial pressure 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 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • Subgroups will be investigated separately if meta-analysed results show heterogeneity.
17.	Analysis of sub-groups	Strata: • n/a Subgroups: • Patient grade: ○ Good grade

<table>
<tr><td></td><td></td><td colspan="3">○ Poor grade
• Cause of intracranial hypertension:
○ Haemotoma
○ Cerebral oedema</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3"></td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">3 February 2021</td></tr>
<tr><td rowspan="8">23.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☑</td><td>☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☑</td><td>☑</td></tr>
<tr><td>Data analysis</td><td>☑</td><td>☑</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

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

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</td></tr>
<tr><td>25.</td><td>Review team members</td><td colspan="3">From the National Guideline Centre:</td></tr>
</table>

		• 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, intracranial hypertension, raised intracranial pressure

33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

1
2

1 **Table 7: 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.[39] **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 reviews;

- What is the clinical and cost effectiveness of options for managing intracranial hypertension?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[39]

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 8: Database date parameters and filters used

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

Database	Dates searched	Search filter used
		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 9: 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**

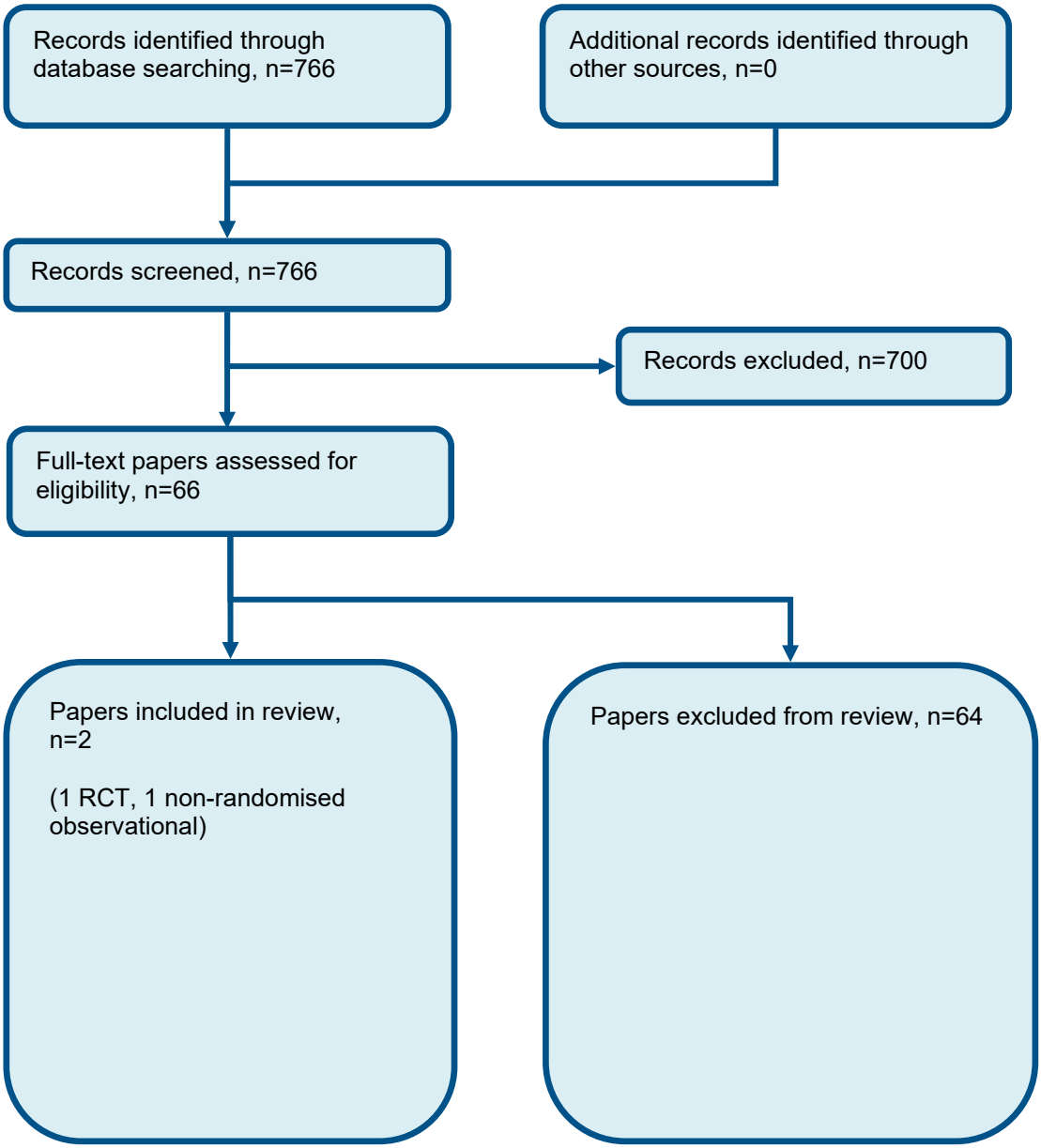
#1.	MeSH DESCRIPTOR Subarachnoid Hemorrhage EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#3.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)))
#4.	((SAH or aSAH))
#5.	#1 OR #2 OR #3 OR #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 managing intracranial hypertension



Appendix D: Clinical evidence tables

Study	Bentsen 2006[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in Norway; Setting: single centre study, intensive care
Line of therapy	1st line
Duration of study	Intervention time : 210 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Included intensive care patients with an acute spontaneous SAH with stable ICP in the range 10 -20 mmHg. They needed to be >18 yrs of age, sedated, mechanically ventilated, have stable hemodynamics and serum sodium of <160 mmol/L
Exclusion criteria	Not specified
Age, gender and ethnicity	Age - Mean (SD): Intervention group - 50.1(10.5); placebo - 55.2(10.8). Gender (M:F): 4/18. Ethnicity: not stated
Further population details	1. Cause of intracranial hypertension: Not stated / Unclear (spontaneous SAH). 2. Patient grade: Poor grade (Hunt and Hess median (range) intervention group - 5(3-5); place (2 -5)).
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Hypertonic saline. Hypertonic saline - was a 7.2% saline in 6% hydroxyethyl starch 200/0.5 solution (HyperHAES, Fresenius Kabi AG) The observation period lasted from 10 min before until 210 min after the start of the infusion. Need for rescue treatment was defined by treatment failure limits for ICP and CPP, which were an ICP of >20> 20 mm HG and a CPP of 60 <60 mmHG. Unless these limits were reached during the observation period, the ventilation variables were kept unaltered, the infusion rates vasopressors, analgesics, sedatives, and fluids were stable, the resistance in the external ventricular drainage (EVD) was unchanged, and the patients were neither stimulated or moved.. Duration 10 minutes before to 210 minutes after the infusion. Concurrent medication/care: n/a. Indirectness: No indirectness (n=11) Intervention 2: No treatment. Placebo - was 0.9% saline solution (Fresenius Kabi AG, Bad Homburgh v.d.h),

	Germany. The observation period lasted from 10 mins before until 210 mins after the start of the infusion. Need for rescue treatment was defined by treatment failure limits for ICP and CPP, whichwere an ICP of >20> 20 mm HG and a CPP of 60 <60 mmHG. Unless these limits were reached during the observation period, the ventilation variables were kept unaltered, the infusion rates vasopressors, analgesics, sedatives, and fluids were stable, the resistance in the external ventricular drainage (EVD) was unchanged, and the patients were neither stimulated or moved.. Duration 10 minutes before to 210 minutes after the infusion. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYPERTONIC SALINE versus NO TREATMENT Protocol outcome 1: Complications of procedure (any) - Actual outcome: intracranial pressure change score at 210 min after trhe intervention; Group 1: mean -3.3 (SD 2.6); n=11, Group 2: mean -0.3 (SD 1.3); n=11 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Mortality ; Health and social quality of life ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work)

1

2

Study	**Nagel 2009[38]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in Germany; Setting: n/a
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: n/a
Subgroup analysis within study	Not applicable: n/a

Inclusion criteria	Any SAH patient developing intracranial hypertension with ICP values ≥20 mmHg for at least >6h after SAH and requiring treatment of elevated ICP was included. aSAH confirmed by CT; cerebral angiogram demonstrating intracranial aneurysm; patients underwent clipping followed by intraoperative insertion of the microdialysis catheter or patients underwent endovascular therapy of an aneurysm from the anterior circulation and additionally had an external ventricular drainage placed, so catheter placement through the existing burrhole allowed monitoring of the anterior cerebral artery territory.
Exclusion criteria	Patients were excluded if they were hemodynamically instable, presented with fixed and dilated pupils on admission or died within 24 hours after admission
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): intervention group - 48(3.4) control group 52(3.5). Gender (M:F): 4/14. Ethnicity: not stated
Further population details	1. Cause of intracranial hypertension: Not applicable (SAH). 2. Patient grade: Not applicable (WFNS grade: intervention/comparison:(grade1 - 2/1; grade2 - 0/0; grade3 - 2/0; grade4 - 0/4; grade5 - 3/6) Fisher grade - intervention/comparison: (grade1 - 0/0; grade2 - 0/0; grade3 - 4/1; grade4 - 3/10).
Indirectness of population	No indirectness
Interventions	(n=7) Intervention 1: Surgical interventions - Decompressive Craniectomy . decompressive craniectomy - Hemicraniectomy was performed in median on day 4(2-6) after SAH, in 2 of the 7 patients early after SAH. in 4 patients (57%) a dilating pupil was observed shortly before hemicraniectomy.. Duration n/a. Concurrent medication/care: All patients underwent first line treatment. Second line treatment included barbiturate coma and forced hyperventilation in both groups. Moderate hyperventilation was performed in most patients (n=16, 89%) while forced hyperventilation was rare (n=5, 28%) most frequently, moderate hyperventilation was started on day 3 (10 out of 16 patients, 63 %, range 1-9 days) and forced hyperventilation on day 6 (4 of 5 patients, 80%, 1-8 days). Indirectness: No indirectness (n=11) Intervention 2: No treatment. no decompressive craniectomy. Duration n/a. Concurrent medication/care: All patients underwent first line treatment. Second line treatment included barbiturate coma and forced hyperventilation in both groups. Moderate hyperventilation was performed in most patients (n=16, 89%) while forced hyperventilation was rare (n=5, 28%) most frequently, moderate hyperventilation was started on day 3 (10 out of 16 patients, 63 %, range 1-9 days) and forced hyperventilation on day 6 (4 of 5 patients, 80%, 1-8 days). Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DECOMPRESSIVE CRANIECTOMY versus NO TREATMENT

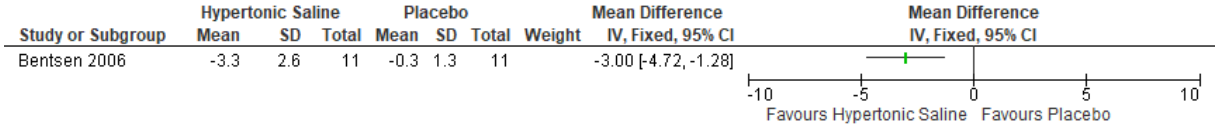
Protocol outcome 1: Mortality
- Actual outcome: Mortality - Death while clinical stay at while clinical stay; Group 1: 4/7, Group 2: 8/11

Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Mortality - Death 12 months at 12 months; Group 1: 5/7, Group 2: 8/11 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Health and social quality of life - Actual outcome: GOS (global outcome score (4-5) at 12 months; Group 1: 0/6, Group 2: 1/10 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 - Actual outcome: GOS (global outcome score 3 at 12 months; Group 1: 1/6, Group 2: 1/10 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 - Actual outcome: GOS (global outcome score 1-2 at 12 months; Group 1: 5/6, Group 2: 8/10 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work) ; Complications of procedure (any)

Appendix E: Forest plots

E.1 Hypertonic saline vs placebo

Figure 2: Change in intracranial pressure



E.2 Decompressive craniectomy vs no decompressive craniectomy

Figure 3: Mortality (death during hospitalisation)

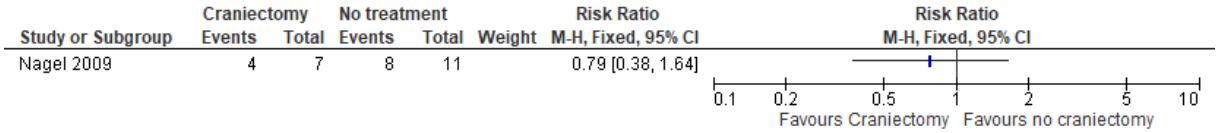


Figure 4: Mortality (12 months)

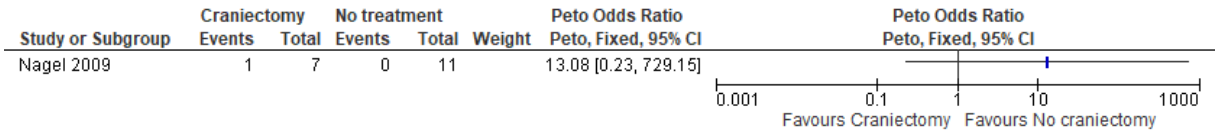


Figure 5: GOS grade 1 – 2 (12 months). Scale 1-5; high score represents positive outcome

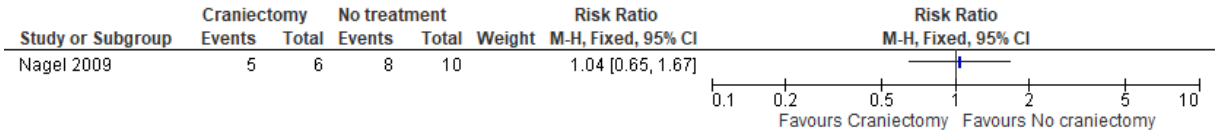


Figure 6: GOS grade 3 (12 months). Scale 1-5; high score represents positive outcome

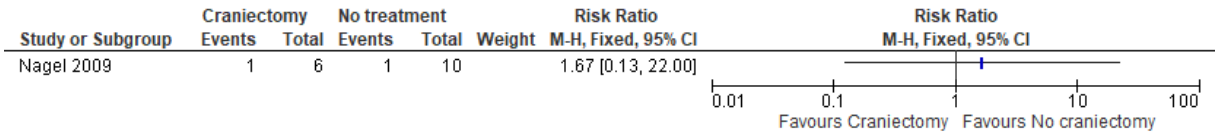
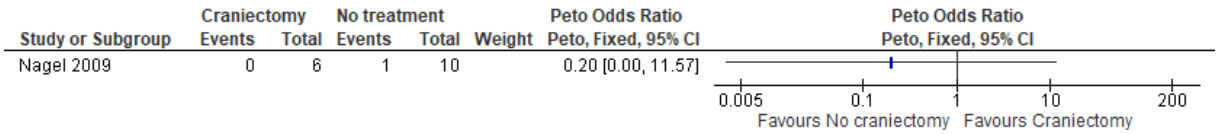


Figure 7: GOS grade 4 – 5 (12 months). Scale 1-5; high score represents positive outcome



Appendix F: Minimal Important Difference for continuous outcomes

Table 10: Minimal important differences: Hypertonic saline versus placebo

Outcomes	Minimally important difference (MID)
Change in intracranial pressure	0.65

Appendix G: GRADE tables

Table 11: Clinical evidence profile: Hypertonic saline vs placebo (RCT)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypertonic Saline	Placebo	Relative (95% CI)	Absolute		
Intracranial Hypertension (follow-up mean 210 minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11	11	-	MD 3 lower (4.72 to 1.28 lower)	⊕⊕OO LOW	IMPORTANT

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence profile: Decompressive craniectomy vs no decompressive craniectomy (Observational study)

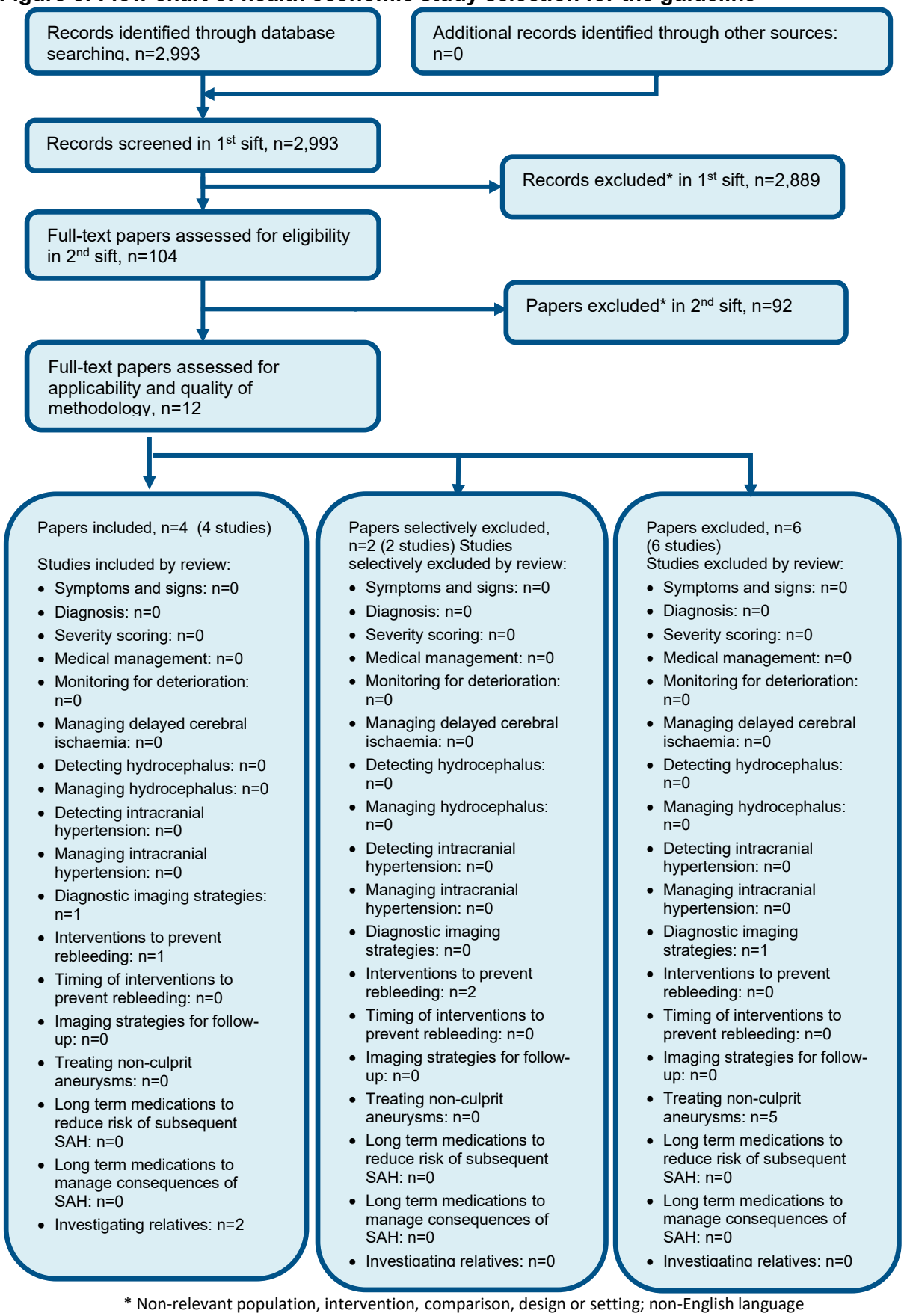
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery (decompressive craniectomy)	No surgery	Relative (95% CI)	Absolute		
mortality - death while clinical stay												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	study design[3]	4/7 (57.1%)	8/11 (72.7%)	RR 0.79 (0.38 to 1.64)	153 fewer per 1000 (from 451 fewer to 465 more)	⊕OOO VERY LOW	CRITICAL
Mortality - death 12 months (follow-up mean 12 months)												

1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	study design[3]	5/7 (71.4%)	8/11 (72.7%)	Peto OR 13.08 (0.23 to 729.15	not estimable	⊕OOO VERY LOW	CRITICAL
GOS grade 1-2 after 12 months (follow-up mean 12 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	study design[3]	5/6 (83.3%)	8/10 (80%)	RR 1.04 (0.65 to 1.67)	32 more per 1000 (from 280 fewer to 536 more)	⊕OOO VERY LOW	CRITICAL
GOS grade 3 after 12 months (follow-up mean 12 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	study design[3]	1/6 (16.7%)	1/10 (10%)	RR 1.67 (0.13 to 22)	67 more per 1000 (from 87 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
GOS grade 4-5 after 12 months (follow-up mean 12 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	study design[3]	0/6 (0%)	1/10 (10%)	Peto OR 0.2 (0 to 11.57)	78 fewer per 1000 (from 100 fewer to 462 more)	⊕OOO VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix H: Health economic evidence selection

Figure 8: Flow chart of health economic study selection for the guideline



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

1

Appendix I: Health economic evidence tables

None.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 13: Studies excluded from the clinical review

Study	Exclusion reason
Al-Rawi 2010[1]	Inappropriate study design – no comparison group
Alotaibi 2017[2]	Systematic review - references checked
Asaad 2019[3]	Inappropriate comparison – different EVD techniques
Bakar 2012[4]	Inappropriate population – traumatic brain injury
Battison 2005[5]	Inappropriate population – majority non SAH
Bentsen 2004[7]	Inappropriate study design - no comparison group
Bundgaard 2001[8]	Inappropriate population – brain tumours
Burger 2008[9]	Inappropriate population – traumatic brain injury
Buschmann 2007[10]	Inappropriate comparison – decompressive hemicraniectomy
Carandini 2018[11]	Systematic review - references checked
Cole 2007[12]	Systematic review - references checked
Cossu 2016[13]	Systematic review - references checked
Dai 2005[15]	Inappropriate intervention – nimodipine
D'Ambrosio 2005[14]	Inappropriate comparison – hemicraniectomy
Dorfer 2010[16]	Inappropriate comparison - retrospective study comparing clipping + decompressive hemicraniectomy to embolization + decompressive hemicraniectomy or insufficient decompressive hemicraniectomy
Eide 2011[17]	Inappropriate comparison – different ICP management techniques
Froelich 2009[18]	Inappropriate population – neuro-critically ill people
Graetz 2010 [19]	Inappropriate comparison – ICP management
Hauer 2011[20]	Inappropriate population – cerebrovascular disease
Hayashi 1988[21]	Inappropriate study design – same intervention between groups
Helbok 2011[22]	Inappropriate study design – before and after study
Heuer 2004[23]	Inappropriate study design - no comparison group
Horn 1999[24]	Inappropriate population – traumatic brain injury
Infanti 2008[25]	Inappropriate study design - literature review
Jagersberg 2010[26]	Inappropriate population – traumatic brain injury
Karnatovskaia,2014[27]	Inappropriate comparison - comparison of temperature management
Kim, 2015[28]	Inappropriate population – traumatic brain injury
Lewandowski-Belfer 2014[29]	Inappropriate study design – no comparison group
Lewis 2014 [30]	Inappropriate study design - no comparison group
Lo 2017[31]	Inappropriate population – cerebrovascular disease
Malmivaara 2011[32]	Inappropriate study design - no comparison group
Munch 1998[33]	Inappropriate population – severe head injury
Murad 2008[34]	Inappropriate population – traumatic brain injury
Murad 2011[35]	Inappropriate study design – no comparison group
Myles 1996[36]	Inappropriate study design – review article

Study	Exclusion reason
Nagel 2009[37]	Inappropriate comparison – same intervention for all groups
Otani 2008[42]	Inappropriate study design – before and after study
Otani 2013[41]	Inappropriate study design – no comparison group
Pasarikovski 2017[43]	Systematic review - references checked
Qureshi, 2000[44]	Inappropriate study design - literature review
Ravishankar 2020[45]	Literature review - references checked
Reddy 2009[46]	Systematic review - references checked
Roitberg 2008[47]	Inappropriate population – mixed population (ICH or SAH)
Schirmer 2007[48]	Inappropriate study design – before and after study
Schwarz 1998[49]	Inappropriate study design – no relevant outcomes
Shi 2000[50]	Not in English
Stocchetti 2000[51]	Inappropriate population – head injury
Takeuchi 2011[52]	Inappropriate comparison/ inappropriate population – prognostic study for non traumatic ICH
Tanrikulu 2015[53]	Inappropriate population – mixed population (MCA infarction/haemorrhage/trauma)
Thenier-Villa 2020[54]	Inappropriate comparison – rebleed versus no rebleed, all participants had EVD
Tietjen, 1996[55]	Inappropriate study design - literature review
Tuettenberg 2009[56]	Inappropriate population - mixed population (traumatic brain injury and SAH)
Tuteja, 2019[57]	inappropriate population/inappropriate comparison – spontaneous ICH
Uozumi 2014[58]	Inappropriate population – no raised ICP
Villa 2012[59]	Inappropriate population – raised ICP excluded
Wang 2017[60]	Inappropriate comparison – nursing assessment
Witherspoon, 2017[61]	Inappropriate study design - literature review
Won 2008[62]	Inappropriate study design – no comparison group
Woodcock 1982[63]	Inappropriate study design/ inappropriate intervention – before and after study for barbiturates
Wykes 2015[64]	Inappropriate study design - literature review
Xu 2018[65]	Inappropriate population – subdural haematoma
Yang 2016[66]	Inappropriate comparison – craniotomy techniques
Zahid 2012[67]	Inappropriate comparison – temperature control compared to surgery
Zhao 2015[68]	Inappropriate population – no raised ICP

J.21 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 14: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

1