National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[F] Evidence review for management of delayed cerebral ischemia

NICE guideline NG228

Methods, evidence and recommendations

November 2022

Final

National Institute for Health and Care Excellence

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ISBN: 978-1-4731-4815-4

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1 Management of delayed cerebral ischemia (DCI)

Evidence review underpinning recommendation 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 delayed cerebral ischaemia?

1.2 Introduction

Delayed cerebral ischaemia (DCI) is a major cause of poor outcome in people with aneurysmal subarachnoid haemorrhage. The pathophysiology of DCI is incompletely understood but the condition is characterised by global or focal ischaemic brain injury. Focal injury often occurs in the vicinity of the ruptured aneurysm and cerebral angiography may show severe arterial narrowing due to vasospasm. Some patients improve with treatment but the brain injury can progress to cerebral infarction and death.

DCI usually presents 5-10 days after aneurysm rupture with a reduction in consciousness or new neurological deficit and the diagnosis is confirmed by exclusion of other causes of deterioration (including hypoxia, metabolic disturbance, hypotension, hydrocephalus, intracranial bleeding, cerebral oedema). Current practice is to induce hypertension with inotropic agents on the presumption that an elevated blood pressure will drive more blood through the brain, and so improve ischaemia. Some patients do not respond to medical treatment and intra-arterial vasodilators and cerebral artery angioplasty are sometimes used in these cases.

This review assessed the clinical and cost-effectiveness of treatments for delayed cerebral ischaemia.

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 delayed cerebral ischemia following a subarachnoid haemorrhage caused by a suspected or confirmed ruptured aneurysm.

Intervention	• Vasopressors (hypertensive treatment)
	  ○ Noradrenaline
	  ○ Metaraminol
	• Inotrope
	  ○ Adrenaline
	  ○ Dobutamine
	  ○ Milrinone
	• Fluid therapy (crystalloid, colloid, albumin)
	  ○ Hypervolemia
	  ○ Euvolemia
	• Intra-arterial vasodilator medication
	• Angioplasty

	• Combination of above
Comparison	Comparators: • To each other • Within class • To no treatment
Outcomes	Critical: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important: • Subsequent subarachnoid haemorrhage • Return to usual daily activity e.g. work • Cerebral infarction • Intracranial bleed • Cardiopulmonary complications • Length of stay in hospital
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

Three studies were included in the review,[47, 102, 103] these are summarised in Table 2 below. These included 1 RCT and 2 retrospective cohort sub-studies of a single RCT. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

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

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

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
Gathier 2018[47]	**Induced hypertension:** Hypertension needed to be started within 3 hours after the start of clinical symptoms of DCI. Hypertension was induced with fluids and norepinephrine over a central venous line placed for this purpose in the intensive care unit (ICU) according to the local protocol of the participating centre. The treatment was continued until improvement of neurological deficits, occurrence of a complication, a maximum MAP of 130 mmHg, or a systolic blood pressure of 230 mmHg. In case of clinical improvement, norepinephrine was continued for at least 48 hours and then slowly tapered. In case of recurrence of symptoms during tapering, norepinephrine was restarted and tapering was attempted 24 hours later. In the absence of clinical improvement within 24 hours, norepinephrine was tapered. (n=21) **Control (no hypertension):**	Patients who have had a subarachnoid haemorrhage, above 18 years of age who developed delayed cerebral ischemia Mean age (SD): Hypertension: 63 (12); Control: 57 (10) Netherlands Randomised controlled trial	• Degree of disability (mRS at 3 months) • Activity of daily living (Barthel Index) • Quality of life (stroke specific quality of life scale) • Anxiety and Depression (Hospital anxiety and depression scale)	Trial stopped prematurely due to difficulties with participant recruitment and lack of clinical efficacy

Study	Intervention and comparison	Population	Outcomes	Comments
	In the no hypertension group, hypertension was not induced, but a minimal MAP of 80 mmHg was maintained with fluids and, when necessary, with vasopressors. In the latter case, a central venous line was placed, but otherwise, no central venous lines were used in the no hypertension group (n=20) All patients were treated with oral nimodipine and fluid administration aimed at normovolemia. Follow-up: 3 months			
Polin 1998[103]	**Intra-arterial vasodilator medication (papaverine):** Patients were treated with intra-arterial infusions of 0.09% (90mg in 100ml) up to a higher dose of 0.8% (800mg in 100ml) papaverine for each vascular territory (n=31) **Control:** Patients were matched to the papaverine cohort by gender, same dose of study drug (tirilazad), age within 10 years and degree of arterial narrowing (n=62)	Patients who have been treated for subarachnoid haemorrhage that have symptomatic vasospasm Mean age: 56.7 years (range 40-70) USA Retrospective cohort study	• Degree of disability (mRS ≤2)	Study is a subgroup analysis from the North American Tirilizad trial of 54 medical centres, of patients with subarachnoid haemorrhage. Participants were matched with patients from the same trial who exhibited similar clinical characteristics (including age, degree of vasospasm and the GCS scores) but received medical management alone for vasospasm.

Study	Intervention and comparison	Population	Outcomes	Comments
	Trial protocol: As part of the main clinical trial, 14 patients had received placebo (vehicle), 6 received 2mg/kg/day Tirilizad and 11 received 6mg/kg/day Tirilizad. For Vasospasm, Nimodipine 60mg every 4 hours was also given. Follow-up: 3 months			
Polin 2000[102]	**Angioplasty:** Group consisted of patients who had been treated with Angioplasty alone or Angioplasty plus papaverine if symptomatic of cerebral vasospasm (n=38) **Control:** Patients were matched to the Angioplasty cohort by gender, same dose of study drug, age within 10 years and degree of arterial narrowing (n=83) **Trial protocol:** As part of the main clinical trial, 14 patients had received placebo (vehicle), 6 received 2mg/kg/day Tirilizad and 11 received 6mg/kg/day Tirilizad. For Vasospasm, Nimodipine 60mg every 4 hours was also given.	Patients who have been treated for subarachnoid haemorrhage that have symptomatic vasospasm Mean age: 48.1 years (range 30-77) USA Retrospective cohort study	• Degree of disability (mRS ≤2)	Study is a subgroup analysis from the North American Tirilizad trial of 54 medical centres, of patients with subarachnoid haemorrhage. A conditional logistic regression analysis was performed in which patients were compared with individuals matched for age, sex, dose of study drug, admission neurological grade, and GCS score at the time of angioplasty.

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 3 months			

See Appendix D: for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Intra-arterial vasodilator medication (Papaverine) versus control (no papaverine)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Papaverine (95% CI)
Degree of disability (mRS ≤2) scale 0-6; high score represents poor outcome	93 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.78 (0.5 to 1.21)	Moderate	
				581 per 1000	128 fewer per 1000 (from 290 fewer to 122 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					

Table 4: Clinical evidence summary: Angioplasty versus control (no angioplasty)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Angioplasty (95% CI)
Degree of disability (mRS ≤2) scale 0-6; high score represents poor outcome	121 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.92 (0.66 to 1.28)	Moderate	
				602 per 1000	48 fewer per 1000 (from 205 fewer to 169 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Angioplasty (95% CI)
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					

Table 5: Clinical evidence summary: Norepinephrine + Fluids (Hypertension) versus control (no induced hypertension)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Norepinephrine + Fluids (95% CI)
mRS 0 – no symptoms	41 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	Peto OR 0.12 (0.01 to 2.02)	Moderate	
				100 per 1000	81 fewer per 1000 (from 99 fewer to 275 more)
mRS 1 – no significant disability	41 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.24 (0.03 to 1.95)	Moderate	
				200 per 1000	152 fewer per 1000 (from 194 fewer to 190 more)
mRS 2 – slight disability	41 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 1.9 (0.55 to 6.6)	Moderate	
				150 per 1000	135 more per 1000 (from 68 fewer to 840 more)
mRS 3 – moderate disability	41 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.63 (0.12 to 3.41)	Moderate	
				150 per 1000	56 fewer per 1000 (from 132 fewer to 362 more)
mRS 4 – moderate/severe disability	41 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.95 (0.22 to 4.18)	Moderate	
				150 per 1000	8 fewer per 1000 (from 117 fewer to 477 more)
mRS 5- severe disability	41 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 2.86 (0.32 to 25.24)	Moderate	
				50 per 1000	93 more per 1000 (from 34 fewer to 1000 more)
mRS 6 - dead				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Norepinephrine + Fluids (95% CI)
	41 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.43 (0.47 to 4.32)	200 per 1000	86 more per 1000 (from 106 fewer to 664 more)

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

Table 6: Evidence not suitable for GRADE: Norepinephrine + Fluids (Hypertension) versus control

Outcome	Study (no. of participants)	Risk of bias	Comparison results (Median, IQR)	Intervention results	*P* value
Activities of Daily Living (Barthel Index) Scale 0 – 20	Gathier 2018 n=41	Low	Normotension: 20 (16-20)	Hypertension: 20 (10-20)	-
Quality of Life (Stroke specific quality of life scale)	Gathier 2018 n=41	Low	Normotension: 49 (35-55)	Hypertension: 47 (35-55)	-
Anxiety & Depression (Hospital Anxiety & Depression scales) Scale 0 – 21 (each)	Gathier 2018 n=41	Low	Normotension: 8 (4-11)	Hypertension: 13 (3-13)	-

Data reported as median value and IQR and so was not suitable for inclusion in GRADE analysis

See Appendix F: 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 G:.

1.5.3 Unit costs

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

Table 7: UK costs of treatments for angioplasty

Procedure	Description	Average cost
Angioplasty	Percutaneous Transluminal Angioplasty, including stenting, of Intracranial or Extracranial Blood Vessel [NHS Reference Cost code YA10Z]	£4,390
Placement of central venous catheter	(Peripheral) Insertion of (Non-Tunnelled or Tunnelled) Central Venous Catheter, 19 years and over [weighted average of NHS Reference Cost codes YR40A, YR41A, YR42A]	£1,239

Source: NHS Reference Costs 2018/19[96]

Table 8: UK costs of norepinepherine

Drug	Cost/unit (£)
Noradrenaline (2mg/2ml) solution	£ 2.40
Noradrenaline (4mg/4ml) concentrate for solution	£ 5.80
Noradrenaline (4mg/4ml) solution	£ 4.40
Noradrenaline (8mg/8ml) concentrate for solution	£ 11.60

Source: British National Formulary, August 2020[65]

Table 9: UK costs of drugs for fluid management

Solution	Preparation	Dose	Cost per unit
Albumin	Infusion	50mg per 1ml	£13.50 - £67.50
Fresh frozen plasma	Infusion	200ml	£75.00
Tetrastarch	Infusion	6% 500ml	£10.63 - £15.30

Source: British National Formulary, August 2020[65]

1.6 Evidence statements

1.6.1 Clinical evidence statements

Three outcome measures for health related quality of life from 1 study were not suitable for inclusion in the GRADE summary tables.

The study found no significant difference between people receiving norepinephrine and fluids (hypertension) or no treatment (normotension) in activities of daily living, quality of life, or anxiety and depression. (n=41, low risk of bias).

1.6.2 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 critical outcomes for this review were mortality; health and social-related quality of life (any validated measure); and degree of disability or dependence in daily activities (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures). The committee also considered subsequent subarachnoid haemorrhage; return to usual daily activity e.g. work; cerebral infarction; intracranial bleed; cardiopulmonary complications; and length of stay in hospital to be important outcomes.

Evidence was identified for degree of disability or dependence in daily activities. No evidence was found for the remaining outcomes.

1.7.2 The quality of the evidence

The evidence in this review included data from 1 RCT and 2 retrospective cohort sub-studies of a single RCT. The 2 observational studies compared the intervention groups with matched control groups to account for key confounders, including age.

The evidence ranged from low to very low quality, with the majority of the evidence of low quality due to the risk of bias and imprecision. The committee noted a risk of selection bias and a lack of blinding in treatment provision and outcome assessment. There was a high level of uncertainty due to significant statistical imprecision for most outcomes. Imprecision was indicated by wide confidence intervals crossing the thresholds for clinical significance, with which the committee would typically judge if an intervention shows benefit or harm. This reflected the small size of the studies and the low event rate of some outcomes. The committee agreed that a clinical recommendation could not be based on the evidence available due to its insufficient quality and quantity. Instead, the committee agreed a consensus recommendation based on their own clinical experience and understanding, recommending the use of vasopressor therapy to raise blood pressure in euvolaemic patients with delayed cerebral ischaemia.

1.7.3 Benefits and harms

The committee highlighted that delayed cerebral ischaemia is a serious complication of aSAH and is associated with significant morbidity and mortality. Delayed cerebral ischaemia can cause catastrophic deterioration in a patient who has previously been stable, and an effective treatment could have significant benefit.

The committee agreed that patients with suspected delayed cerebral ischaemia should be assessed clinically and investigated with CT brain imaging to exclude other causes of neurological deterioration. Treatments to target DCI can be started once it is determined that DCI is the most likely cause of neurological deterioration.

Norepinephrine + fluids vs Control (no induced hypertension):

One randomised controlled trial assessed norepinephrine and intravenous fluids compared to routine fluid management in people with delayed cerebral ischaemia. Norepinephrine (a vasopressor) and intravenous fluid were used to increase blood pressure with the objective of improving cerebral blood flow to limit or prevent cerebral infarction. Administration of norepinephrine and fluids was not associated with lower disability (mRS) at 3 months. There were significantly fewer participants with the lowest level of disability (mRS 0 or 1) with intervention, although there were significantly more people with an mRS of 2 (slight levels of disability) and mRS 5 (severe disability) with intervention. There was no clinically important difference between groups for those with mRS of 3 or 4. The committee noted that there was a clinically significant increase in mortality rate in the norepinephrine and fluids group compared to routine fluid management, although the evidence was of low quality with very serious imprecision around the point estimate. The committee agreed that the quantity and quality of evidence on norepinephrine was insufficient to support a recommendation.

The committee recognised that the use of norepinephrine to increase blood pressure is established practice for people with a clinical diagnosis of delayed cerebral ischaemia and may result in acute improvement in the patient's condition. The committee agreed that the historical practice of maintaining hypervolaemia (an artificially high blood volume) can result in adverse events such as pulmonary oedema, dilutional hyponatremia, coagulopathy, and aneurysm rebleeding. In current practice most clinicians therefore administer intravenous fluid to ensure euvolaemia and if symptoms persist a vasopressor (such as norepinephrine) is administered to raise systemic blood pressure. The committee acknowledged that many patients benefit in the short-term from these measures but there is no evidence of impact on longer-term outcome. Nevertheless, the committee agreed a consensus recommendation that people with delayed cerebral ischaemia after an aneurysmal subarachnoid haemorrhage should be given intravenous fluid to ensure euvolaemia (normal blood volume) and treatment with a vasopressor should be considered if symptoms persist, accepting that clinical improvement with a vasopressor may be temporary. The committee also agreed to make a research recommendation on the role of vasopressors in people with delayed cerebral ischaemia.

The management of patients who do not improve with a vasopressor varies widely but some clinicians recommend cerebral angiography and intra-arterial therapies, including intra-arterial vasodilators and angioplasty.

Angioplasty vs Control (no angioplasty):

One small retrospective cohort study compared intra-cranial arterial angioplasty with no intervention in patients with delayed cerebral ischaemia. Angioplasty showed no clinically important difference in the degree of disability, as measured by the number of patients with a favourable outcome (mRS ≤2). The committee agreed that the evidence on angioplasty was insufficient to support a recommendation.

From their experience the committee were aware that use of angioplasty varies widely and practice varies between centres. Although the procedure can lead to immediate clinical improvement in some patients, it is associated with procedural risks including stroke, bleeding from arterial access sites, and complications of anaesthesia. The committee were not able to reach a consensus on the use of angioplasty and concluded that further research reviewing the efficacy of intra-arterial therapies is required.

Intra-arterial vasodilator medication (Papaverine) versus control (no papaverine):

Evidence from 1 retrospective cohort study showed that fewer patients achieved a favourable outcome (mRS ≤2 at follow-up) with intra-arterial papaverine compared to a control group. This difference was deemed to be clinically significant. The committee also noted that papaverine is not commonly used in current practice. The committee agreed that the evidence on papaverine was insufficient to support a recommendation.

The committee made a research recommendation on the role of intra-arterial therapies in the management of patients with delayed cerebral ischaemia (see Appendix J).

The committee noted the evidence available on the clinical and cost effectiveness of interventions to manage DCI in people who have experienced an aSAH, was of insufficient quality and quantity to inform any recommendations. The committee therefore referred to their clinical experience to form a consensus recommendation. The committee agreed that in people with a clinical diagnosis of delayed cerebral ischaemia, treatment with vasopressors along with close monitoring is established practice and could be considered once euvolemia is ensured. The committee highlighted that short-term clinical improvement with vasopressors may not translate into better longer-term clinical outcomes. The committee made a research recommendation on the role of vasopressors in the management of patients with delayed cerebral ischaemia (see Appendix K).

1.7.4 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.

With the aid of unit costs the committee made a consensus recommendation for a vasopressor in euvolaemic people with delayed cerebral ischaemia. The recommendation is not expected to have a substantial resource impact as it is reflective of current practice in England.

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Appendices

Appendix A: Review protocols

Table 10: Review protocol: Managing DCI

ID	Field	Content
0.	PROSPERO registration number	CRD42019146783
1.	Review title	What is the clinical and cost effectiveness of options for managing delayed cerebral ischaemia?
2.	Review question	What is the clinical and cost effectiveness of options for managing delayed cerebral ischaemia?
3.	Objective	To determine which intervention to manage delayed cerebral ischaemia is the most clinically and cost-effective. Delayed cerebral ischemia is recognised as a serious complication of aneurysmal subarachnoid haemorrhage associated with increased morbidity and mortality.
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 delayed cerebral ischemia following a 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	• Vasopressors (hypertensive treatment)

		○ Noradrenaline ○ Metaraminol • Inotrope ○ Adrenaline ○ Dobutamine ○ Milrinone • Fluid therapy (crystalloid, colloid, albumin) ○ Hypervolemia ○ Euvolemia • Intra-arterial vasodilator medication • Angioplasty • Combination of above
8.	Comparator/Reference standard/Confounding factors	Comparators: • To each other • Within class • 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: • 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. e.g. Modified Rankin Scale and patient-reported outcome measures)
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to usual daily activity e.g. work • Cerebral infarction • Intracranial bleed • Cardiopulmonary complications • Length of stay in hospital 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/

<table>
<tr><td></td><td></td><td colspan="3">• Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.
• Subgroups will be investigated separately if meta-analysed results show heterogeneity.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Strata:
• n/a
Subgroups:
• Grade
○ Good grade
○ Bad grade</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></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></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

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

5e Organisational affiliation of the review</td></tr>
</table>

		National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms 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; delayed cerebral ischaemia	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Table 11: 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.[95] **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 clinical and cost effectiveness of options for managing delayed cerebral ischaemia?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[95]

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 12: Database date parameters and filters used

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

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

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or 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.	randomized controlled trial.pt.
30.	controlled clinical trial.pt.
31.	randomi#ed.ti,ab.
32.	placebo.ab.
33.	randomly.ti,ab.
34.	Clinical Trials as topic.sh.
35.	trial.ti.
36.	or/29-35

37.	Meta-Analysis/
38.	exp Meta-Analysis as Topic/
39.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
40.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
41.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43.	(search* adj4 literature).ab.
44.	(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.
45.	cochrane.jw.
46.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
47.	or/37-46
48.	Epidemiologic studies/
49.	Observational study/
50.	exp Cohort studies/
51.	(cohort adj (study or studies or analys* or data)).ti,ab.
52.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
53.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	Controlled Before-After Studies/
55.	Historically Controlled Study/
56.	Interrupted Time Series Analysis/
57.	(before adj2 after adj2 (study or studies or data)).ti,ab.
58.	exp case control study/
59.	case control*.ti,ab.
60.	Cross-sectional studies/
61.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	or/48-61
63.	exp "Sensitivity and Specificity"/
64.	(sensitivity or specificity).ti,ab.
65.	((pre test or pretest or post test) adj probability).ti,ab.
66.	(predictive value* or PPV or NPV).ti,ab.
67.	likelihood ratio*.ti,ab.
68.	likelihood function/
69.	((area under adj4 curve) or AUC).ti,ab.
70.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
71.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
72.	gold standard.ab.
73.	or/63-72
74.	28 and (36 or 47 or 62 or 73)
75.	Vasospasm, Intracranial/
76.	delayed cerebral isch?emia.ti,ab.

77.	((cerebral or cerebrovascular or intracranial or intra-cranial) adj (spasm* or angiospasm* or vasospasm*)).ti,ab.
78.	(Cerebral adj (artery or arterial) adj (spasm* or angiospasm* or vasospasm*)).ti,ab.
79.	((intracranial or intra-cranial) adj vascular adj (spasm* or angiospasm* or vasospasm*)).ti,ab.
80.	DCI.ti,ab.
81.	or/75-80
82.	74 and 81

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.	brain vasospasm/
81.	delayed cerebral isch?emia.ti,ab.
82.	((cerebral or cerebrovascular or intracranial or intra-cranial) adj (spasm* or angiospasm* or vasospasm*)).ti,ab.
83.	(Cerebral adj (artery or arterial) adj (spasm* or angiospasm* or vasospasm*)).ti,ab.
84.	((intracranial or intra-cranial) adj vascular adj (spasm* or angiospasm* or vasospasm*)).ti,ab.
85.	DCI.ti,ab.
86.	or/80-85
87.	79 and 86

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: [Vasospasm, Intracranial] this term only
#8.	delayed cerebral isch*emia:ti,ab
#9.	((cerebral or cerebrovascular or intracranial or intra-cranial) NEXT (spasm* or angiospasm* or vasospasm*)):ti,ab
#10.	(Cerebral adj (artery or arterial) NEXT (spasm* or angiospasm* or vasospasm*)):ti,ab
#11.	((intracranial or intra-cranial) NEXT vascular NEXT (spasm* or angiospasm* or vasospasm*)):ti,ab
#12.	dci:ti,ab
#13.	(or #7-#12)

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 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003 – 23 June 2020	Exclusions Health economics studies

Database	Dates searched	Search filter used
Embase	2003 – 23 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 23 June 2020 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

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

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

Embase (Ovid) search terms

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

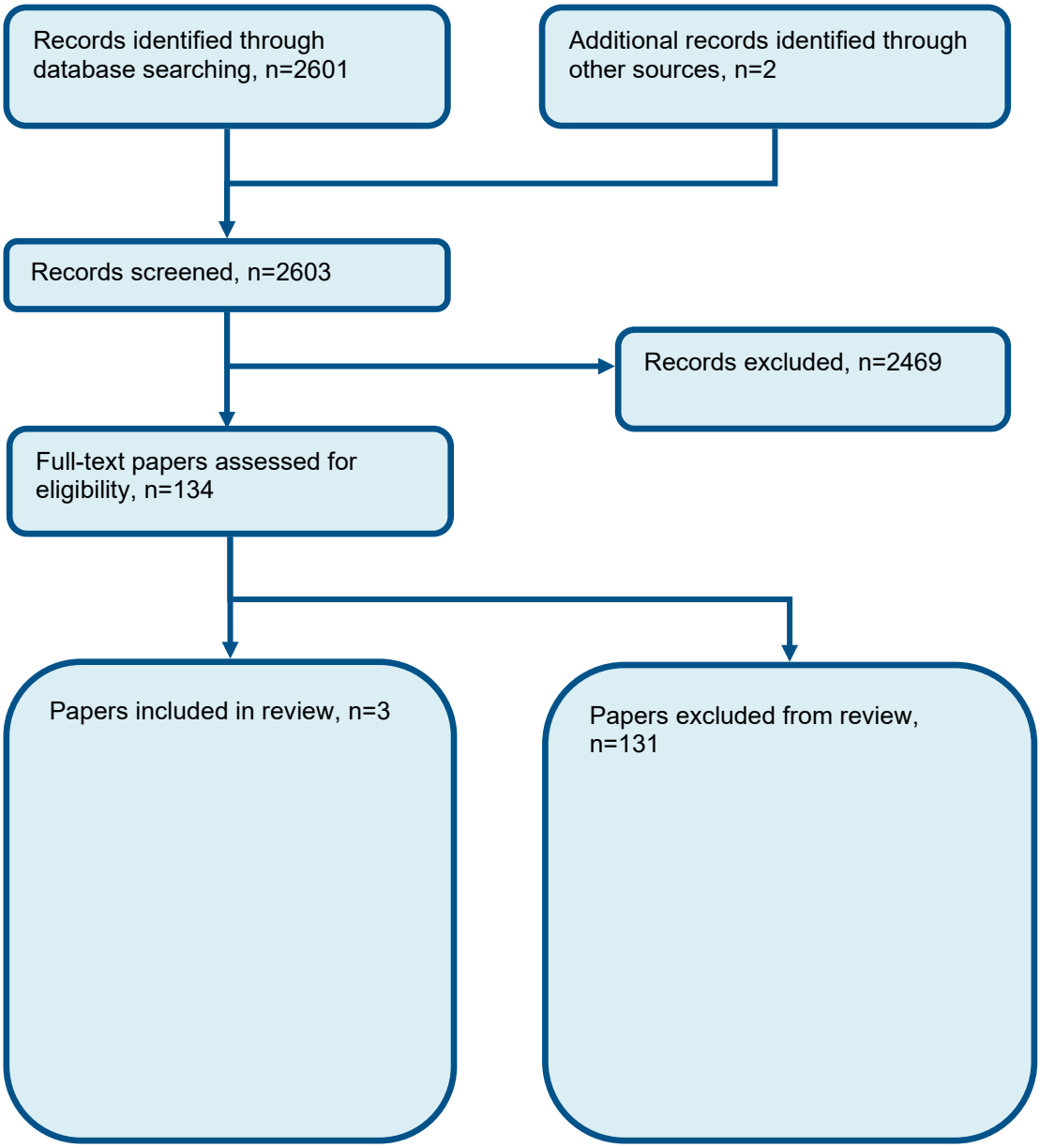
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of management of DCI



Appendix D: Clinical evidence tables

Study	**Gathier 2018[47]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=41)
Countries and setting	Conducted in Netherlands; Setting: Magnus Institute of Neurosciences, Department of Neurosurgery and Neurology, University Medical Centre Utrecht, The Netherlands
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients for trial participation include all patients above 18 years with an aneurysmal SAH who develop delayed cerebral ischemia (DCI based on a decrease of at least one point on the Glasgow Coma Scale sum-score, and/or the development of new focal neurological deficits according to the NIHSS, diagnosed by a neurologist, neurosurgeon, or intensivist, unless the deterioration does not reflect DCI as evaluated by the treating physician)
Exclusion criteria	Coexisting severe head injury, Perimesencephalic haemorrhage, A history of a ventricular cardiac rhythm disorder or heart failure necessitating medical treatment, Likely transfer to another hospital, not participating in the trial, soon after treatment for the aneurysm, Moribund, Pregnancy No informed consent; Another cause for neurological deterioration, e.g.: (Increasing) hydrocephalus, Recurrent bleeding, Clinical signs of epilepsy, Severe infectious disease with associated decrease in level of consciousness, Hypoglycaemia, defined as serum glucose <3.0 mmol/l, Hyponatremia, defined as serum sodium <125 mmol/l, Metabolic encephalopathy due to renal or

	hepatic failure, An untreated symptomatic aneurysm, A spontaneous mean arterial pressure above 120 mmHg at the moment of randomization, Any contraindication for induced hypertension.
Recruitment/selection of patients	Patients with aneurysmal subarachnoid haemorrhage who go on to develop delayed cerebral ischemia.
Age, gender and ethnicity	Age - Mean (SD): Hypertension: 63 (12); Control: 57 (10). Gender (M:F): 10/31.
Further population details	1. Patient grade: Poor grade (Admission WFNS score >3 - Hypertension: 12; No hypertension: 8).
Extra comments	This trial was prematurely terminated based on the evidence of the Data safety Monitoring Board because of lack of effect on overall cerebral perfusion and slow recruitment resulting in the conclusion that it would be unfeasible to obtain sufficient numbers of included subjects within a reasonable time frame.
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Vasopressors (hypertensive treatment) - Noradrenaline. Hypertension needed to be started within 3 hours after the start of clinical symptoms of DCI. Hypertension was induced with fluids and norepinephrine over a central venous line placed for this purpose in the intensive care unit (ICU) according to the local protocol of the participating centre. The treatment was continued until improvement of neurological deficits, occurrence of a complication, a maximum MAP of 130 mmHg, or a systolic blood pressure of 230 mmHg. Clinical improvement within 24 hours was judged by the unblinded treating clinician. In case of clinical improvement, norepinephrine was continued for at least 48 hours and then slowly tapered. In case of recurrence of symptoms during tapering, norepinephrine was restarted and tapering was attempted 24 hours later. In the absence of clinical improvement within 24 hours, norepinephrine was tapered. Duration As required . Concurrent medication/care: All patients were treated with oral nimodipine and fluid administration aimed at normovolemia (n=20) Intervention 2: No treatment. In the no hypertension group, hypertension was not induced, but a minimal MAP of 80 mmHg was maintained with fluids and, when necessary, with vasopressors. In the latter case, a central venous line was placed, but otherwise, no central venous lines were used in the no hypertension group. Duration As required. Concurrent medication/care: All patients were treated with oral nimodipine

	and fluid administration aimed at normovolemia
Funding	Academic or government funding (C.S. Gathier is supported by the Dutch Heart Foundation (grant 2009B046) and the Brain Foundation Netherlands (grant 2009(1)-72).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NOREPINEPHRINE + FLUIDS versus NO HYPERTENSIVES

Protocol outcome 1: Health and social quality of life
- Actual outcome: Activities of daily living (Barthel Index) at 3 months postintervention; Median (IQR): Hypertension: 20 (10-20); Control: 20 (16-20) Barthel Index 0-20 Top=High is good outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome: Quality of life (Stroke specific Quality of life) at 3 months postintervention; Median (IQR): Hypertension: 47 (35-55); Control: 49 (35-55) Stroke specific Quality of life Scale Different scales for different domains within questionnaire Top=Unclear;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome: Anxiety & Depression (HADS scale) at 3 months postintervention; Median IQR : Hypertension: 13 (3-13); Control: 8 (4-11));
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: mRS 0 at 3 months postintervention; Group 1: 0/21, Group 2: 2/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome: mRS 1 at 3 months postintervention; Group 1: 1/21, Group 2: 4/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome: mRS 2 at 3 months postintervention; Group 1: 6/21, Group 2: 3/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome: mRS 3 at 3 months postintervention; Group 1: 2/21, Group 2: 3/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement -

Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: mRS 4 at 3 months postintervention; Group 1: 3/21, Group 2: 3/20 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: mRS 5 at 3 months postintervention; Group 1: 3/21, Group 2: 1/20 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: mRS 6 at 3 months postintervention; Group 1: 6/21, Group 2: 4/20 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Mortality ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work) ; Cerebral infarction ; Intracranial bleed ; Cardiopulmonary complication ; Length of hospital stay
Comments	Trial stopped prematurely due to difficulties with participant recruitment and lack of clinical efficacy.

Study	Polin 1998[103]
Study type	Retrospective cohort analysis – sub-study of RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=31)
Countries and setting	Conducted in USA; Setting: 14 medical centres across northern America
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who have been treated for subarachnoid haemorrhage that have symptomatic vasospasm
Exclusion criteria	prophylactic treatment with papaverine for angiographic vasospasm without clinical symptoms
Age, gender and ethnicity	Age - Mean (range): 56.7 years (40-70). Gender (M:F): 12/19.
Further population details	1. Patient grade: Not stated / Unclear ((Papaverine group only): WFNS I - II: 19; III - V: 12).
Extra comments	All patients were part of the North American Tirilizad Trial. Participants were matched with patients from the same trial who exhibited similar clinical characteristics (including age, degree of vasospasm and the GCS scores) but received medical management alone for vasospasm.
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Combination of interventions. Patients were treated with 0.09% (90mg in 100ml) to a higher dose of 0.8% (800mg in 100ml) for each vascular territory. Duration Unclear. Concurrent medication/care: As part of the main clinical trial, 14 patients had received placebo (vehicle), 6 received 2mg/kg/day Tirilizad and 11 received 6mg/kg/day Tirilizad. For Vasospasm, Nimodipine 60mg every 4 hours was also given. . Indirectness: No indirectness (n=62) Intervention 2: No treatment. Patients were matched to the Papaverine cohort by gender, same dose of study drug, age within 10 years and degree of arterial narrowing.. Duration Unclear .

	Concurrent medication/care: As part of the main clinical trial, 14 patients had received placebo (vehicle), 6 received 2mg/kg/day Tirilizad and 11 received 6mg/kg/day Tirilizad. For Vasospasm, Nimodipine 60mg every 4 hours was also given. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PAPAVERINE versus NO TREATMENT Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Favourable outcome (mRS ≤ 2) at 3 months; Group 1: 14/31, Group 2: 36/62; Comments: results given as percentages (45% papaverine and 56% control had favourable outcome) Risk of bias: All domain - Very high, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Mortality ; Health and social quality of life ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work) ; Cerebral infarction ; Intracranial bleed ; Cardiopulmonary complication ; Length of hospital stay

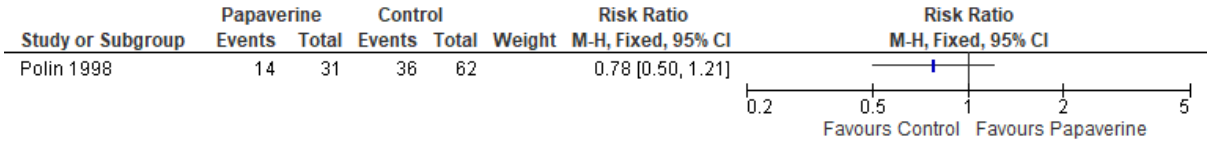
Study	Polin 2000[102]
Study type	Retrospective cohort analysis – sub-study of RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in USA; Setting: 15 medical centres across northern America
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who have been treated for subarachnoid haemorrhage that have symptomatic vasospasm
Exclusion criteria	Patients who may have received papaverine alone for treatment of cerebral vasospasm
Age, gender and ethnicity	Age - Mean (range): 48.1 years (30-77). Gender (M:F): 15/23.
Further population details	1. Patient grade: Not stated / Unclear ((Angioplasty group only) WFNS I or II: 18; III: 8; IV - V: 12).
Extra comments	All patients were part of the North American Tirilizad Trial.. A conditional logistic regression analysis was performed in which patients were compared with individuals matched for age, sex, dose of study drug, admission neurological grade, and GCS score at the time of angioplasty.
Indirectness of population	No indirectness
Interventions	(n=83) Intervention 1: No treatment. Patients were matched to the Angioplasty cohort by gender, same dose of study drug, age within 10 years and degree of arterial narrowing. Duration Unclear. Concurrent medication/care: As part of the main clinical trial, 15 patients had received placebo (vehicle), 10 received 2mg/kg/day Tirilizad and 13 received 6mg/kg/day Tirilizad. For Vasospasm, Nimodipine 60mg every 4 hours was also given. . Indirectness: No indirectness (n=38) Intervention 2: Combination of interventions - (to be reported). Group consisted of patients who had been treated with Angioplasty alone or Angioplasty plus papaverine if symptomatic of

	cerebral vasospasm. Duration Unclear. Concurrent medication/care: As part of the main clinical trial, 14 patients had received placebo (vehicle), 6 received 2mg/kg/day Tirilizad and 11 received 6mg/kg/day Tirilizad. For Vasospasm, Nimodipine 60mg every 4 hours was also given. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANGIOPLASTY + PAPAVERINE versus NO TREATMENT Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Favourable outcome (mRS ≤ 2) at 3 months; Group 1: 21/38, Group 2: 50/83; Comments: results given as percentages (53% angioplasty and 60% control had favourable outcome) Risk of bias: All domain - Very high, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Mortality ; Health and social quality of life ; Subsequent subarachnoid haemorrhage ; Return to daily activity (e.g. work) ; Cerebral infarction ; Intracranial bleed ; Cardiopulmonary complication ; Length of hospital stay

Appendix E: Forest plots

E.1 Intra-arterial vasodilator medication (papaverine) vs Control (no papaverine)

Figure 2: Favourable outcome (mRS ≤2) (3 months). scale 0-6; high score represents poor outcome



E.2 Angioplasty vs Control (no angioplasty)

Figure 3: Favourable outcome (mRS ≤2) (3 months). Scale 0-6; high score represents poor outcome

E.3 Norepinephrine + fluids vs Control (no induced hypertension)

Figure 4: mRS 0 – no symptoms (3 months)

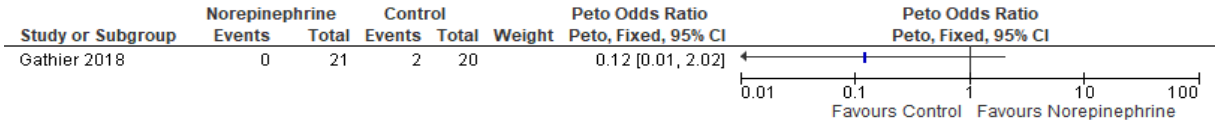


Figure 5: mRS 1 – no significant disability (3 months)

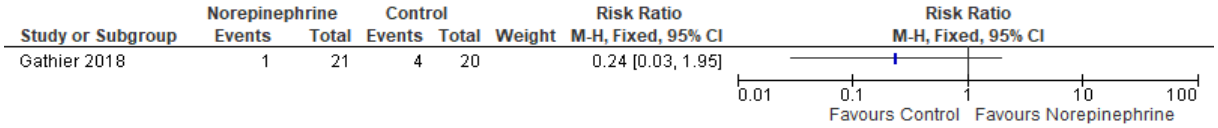


Figure 6: mRS 2 – slight disability (3 months)

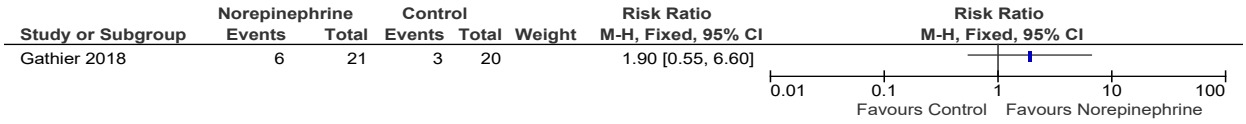


Figure 7: mRS 3 – moderate disability (3 months)

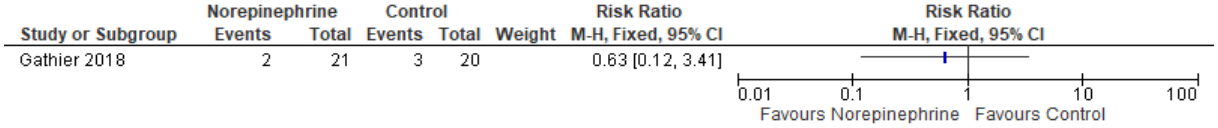


Figure 8: mRS 4 – moderate/severe disability (3 months)

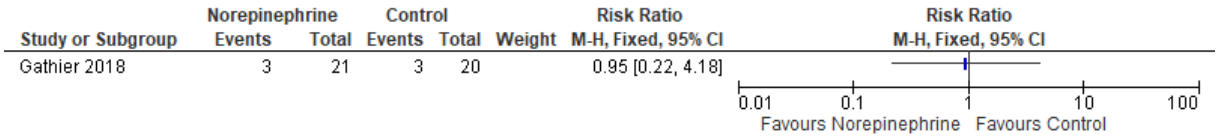


Figure 9: mRS 5 – severe disability (3 months)

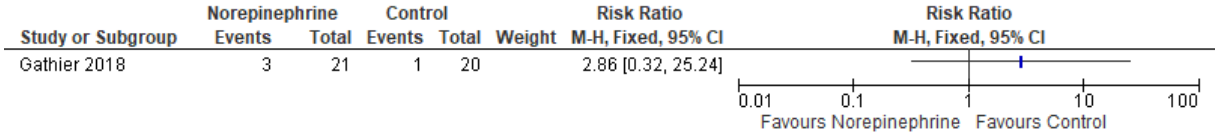
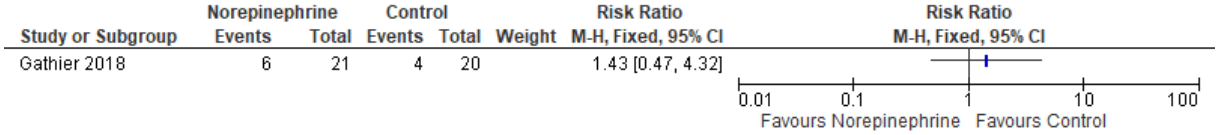


Figure 10: mRS 6 – dead (3 months)



Appendix F: GRADE tables

Table 14: Clinical evidence profile: Intra-arterial vasodilator medication (Papaverine) vs control (no papaverine)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Papaverine	Control	Relative (95% CI)	Absolute		
Favourable outcome (mRS ≤2)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/31 (45.2%)	58.1%	RR 0.78 (0.5 to 1.21)	128 fewer per 1000 (from 290 fewer to 122 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

Table 15: Clinical evidence profile: Angioplasty vs control (no angioplasty)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angioplasty	Control	Relative (95% CI)	Absolute		
Favourable outcome (mRS ≤2)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/38 (55.3%)	60.2%	RR 0.92 (0.66 to 1.28)	48 fewer per 1000 (from 205 fewer to 169 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

Table 16: Clinical evidence profile: Norepinephrine + fluids vs control (no induced hypertension)

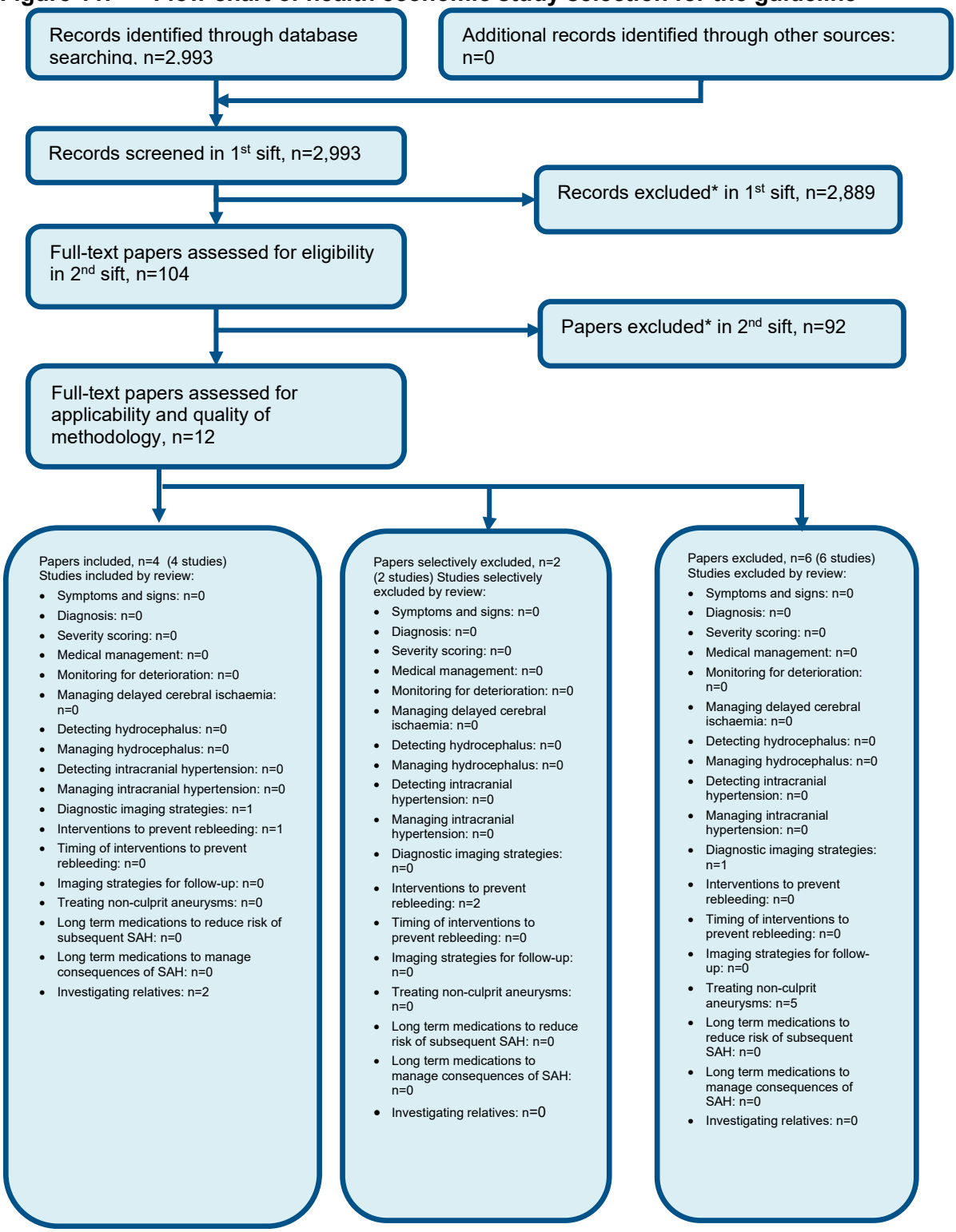
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Norepinephrine + Fluids**	**Control**	**Relative (95% CI)**	**Absolute**		
mRS 0 (3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/21 (0%)	10%	Peto OR 0.12 (0.01 to 2.02)	81 fewer per 1000 (from 99 fewer to 275 more)	⊕⊕OO LOW	CRITICAL
mRS 1 (3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/21 (4.8%)	20%	RR 0.24 (0.03 to 1.95)	152 fewer per 1000 (from 194 fewer to 190 more)	⊕⊕OO LOW	CRITICAL
mRS 2 (3 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/21 (28.6%)	15%	RR 1.9 (0.55 to 6.6)	135 more per 1000 (from 68 fewer to 840 more)	⊕⊕OO LOW	CRITICAL
mRS 3 (3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/21 (9.5%)	15%	RR 0.63 (0.12 to 3.41)	56 fewer per 1000 (from 132 fewer to 362 more)	⊕⊕OO LOW	CRITICAL
mRS 4 (3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/21 (14.3%)	15%	RR 0.95 (0.22 to 4.18)	8 fewer per 1000 (from 117 fewer to 477 more)	⊕⊕OO LOW	CRITICAL
mRS 5 (3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/21 (14.3%)	5%	RR 2.86 (0.32 to 25.24)	93 more per 1000 (from 34 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
mRS 6 (3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/21 (28.6%)	20%	RR 1.43 (0.47 to 4.32)	86 more per 1000 (from 106 fewer to 664 more)	⊕⊕OO LOW	CRITICAL

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

Appendix G: Health economic evidence selection

Figure 11: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 17: Studies excluded from the clinical review

Study	Reason for exclusion
Aburto-Murrieta 2012[1]	Inappropriate study design - Patients not matched and results not adjusted by age
Adami 2018[2]	Inappropriate study design – no relevant outcomes
Ades 1987[3]	Citation only
Akdemir 2009[4]	Inappropriate intervention – prophylactic treatment
Allen 1983[6]	Inappropriate intervention – prophylactic treatment
Allen 1985[5]	Inappropriate population – animal and human study
Andaluz 2002[7]	Inappropriate study design – no useable outcomes
Arakawa 2004[8]	Inappropriate study design – non comparative / no useable outcomes
Badjatia 2004[9]	Inappropriate study design – no relevant outcomes
Barbarawi 2009[10]	Inappropriate intervention – prophylactic treatment
Bashir 2016[11]	Inappropriate study design – non comparative
Biondi 2004[12]	Inappropriate study design – non comparative
Boet 2005[13]	Inappropriate study design – prophylactic treatment
Boet 2000[14]	Inappropriate study design – no relevant outcomes
Boulouis 2017[15]	Systematic review: references checked
Bradford 2013[16]	Inappropriate intervention – prophylactic treatment
Brandt 1986[17]	Inappropriate study design – narrative report
Brathwaite 2014[18]	Inappropriate study design – literature review
Brewer 2001[19]	Inappropriate study design – no relevant outcomes
Buchheit 1988[20]	Inappropriate study design – no relevant outcomes
Chalouhi 2014[21]	Inappropriate study design - Patients not matched and results not adjusted by age
Chaudhry 2017[22]	Inappropriate study design – non comparative
Chen 2011[24]	Systematic review: references checked
Chen 2020[23]	Inappropriate population – patients with vasospasm
Cho 2011[25]	Inappropriate study design – no comparison group
Choi 2011[26]	Inappropriate study design – no comparison group
Coyne 1994[27]	Inappropriate study design – no comparison group
Crespy 2019[28]	Inappropriate intervention – non randomized study
Curran 2006[29]	Inappropriate study design – literature review
Dehdashti 2011[30]	Inappropriate study design – non comparative
Desbordes 1989[31]	Paper not available
Duman 2017[32]	Inappropriate study design – non comparative
Ehlert 2016[33]	Inappropriate study design – unclear methodology and outcomes
Etminan 2015[34]	Inappropriate study design – no comparison group / no relevant outcomes
Feigin 1998[36]	Systematic review: references checked
Feigin 2000[35]	Systematic review: references checked

Study	Reason for exclusion
Feng 2002[37]	Inappropriate study design – no comparison group
Firlik 1997[38]	Inappropriate study design – no comparison group
Fountas 2008[39]	Inappropriate population – vasospasm compared to no vasospasm
Francoeur 2016[40]	Inappropriate study design – literature review
Fraticelli 2008[41]	Inappropriate study design – non comparative
Friedlich 2009[42]	Inappropriate intervention – prophylactic treatment
Frontera 2010[43]	Inappropriate study design – non comparative
Frontera 2011[44]	Inappropriate study design – non comparative
Gathier 2014[46]	Inappropriate study design – trial protocol
Gathier 2017[45]	Inappropriate study design -abstract only
Goel 2016[48]	Inappropriate study design - Patients not matched and results not adjusted by age
Goodson 2008[49]	Inappropriate study design – non comparative
Gross 2017[50]	Inappropriate study design – non comparative
Guggiari 1987[51]	Inappropriate study design -abstract only
Haegens 2018[52]	Inappropriate study design – no relevant outcomes
Hafeez 2019[53]	Systematic review: references checked
Hanggi 2008[54]	Inappropriate study design- non comparative
Harada 1995[55]	Paper not available
Hasegawa 2016[56]	Inappropriate study design – literature review
Hockel 2016[57]	Inappropriate study design – non comparative
Hongo 1993[58]	Inappropriate study design – literature review
Hosmann 2018[59]	Inappropriate study design – no relevant outcomes
Huang 2010[60]	Systematic review: references checked
Hui 2005[61]	Inappropriate study design – non comparative
Iwabuchi 2011[62]	Inappropriate study design – non comparative
Jan 1988[63]	Inappropriate study design - Patients not matched and results not adjusted by age
Jestaedt 2008[64]	Inappropriate intervention – no medical intervention
Jun 2010[66]	Inappropriate study design -abstract only
Kasuya 2011[67]	Inappropriate study design – non comparative
Katoh 1999[68]	Inappropriate study design – non comparative
Kerz 2008[69]	Inappropriate intervention - statin
Khatri 2011[70]	Inappropriate study design – non comparative
Khatri 2011[71]	Inappropriate study design – non comparative
Kim 2009[72]	Inappropriate study design – non comparative
Kimball 2011[73]	Inappropriate study design – literature review
Kirchengast 2005[74]	Inappropriate study design – literature review
Kiser 2013[75]	Systematic review: references checked
Koos 1985[76]	Inappropriate study design – non comparative
Koyanagi 2018[77]	Inappropriate intervention – prophylactic treatment
Lannes 2012[78]	Inappropriate study design – no comparison group
Lennihan 2000[79]	Inappropriate intervention – prophylactic treatment
Levati 1998[80]	Inappropriate study design – literature review
Li 2015[81]	Inappropriate study design – no relevant outcomes
Liu 2004[83]	Inappropriate study design – no comparison group

Study	Reason for exclusion
Liu-Deryke 2006[82]	Inappropriate study design – literature review
Loan 2018[84]	Systematic review: references checked
Lu 2012[85]	Inappropriate population – vasospasm compared to no vasospasm
Luo 1996[86]	Paper not available
Macdonald 2013[87]	Inappropriate study design – literature review
Maldonado 1990[88]	Not in English
Mortimer 2015[89]	Inappropriate population low or no vasospasm compared to vasospasm
Muroi 2008[90]	Inappropriate intervention – prophylactic treatment
Mutoh 2012[91]	Paper not available
Mutoh 2014[92]	Inappropriate study design -citation only
Mutoh 2014[93]	Inappropriate intervention – prophylactic treatment
Narayan 2018[94]	Inappropriate study design – no comparison group
Nibbelink 1975[97]	Inappropriate study design – literature review
Nogueira 2007[98]	Inappropriate study design – no comparison group
Otten 2008[99]	Inappropriate study design – literature review
Pala 2019[100]	Inappropriate study design – non comparative
Patel 2017[101]	Inappropriate study design – non comparative
Robinson 1990[104]	Systematic review: references checked
Romero 2009[105]	Inappropriate study design – non comparative
Roy 2017[106]	Inappropriate study design - Patients not matched and results not adjusted by age
Sadamasa 2014[107]	Inappropriate study design – non comparative
Samseethong 2018[108]	Inappropriate intervention – prophylactic treatment
Santillan 2011[109]	Inappropriate study design – non comparative
Sehy 2010[110]	Inappropriate study design – non comparative
Shankar 2011[111]	Inappropriate study design – non comparative
Sokolowski 2018[112]	Inappropriate comparison – intraarterial infusions with or without angioplasty
Son 2010[113]	Inappropriate study design -citation only
Stuart 2018[114]	Systematic review: references checked
Suarez 2011[115]	Systematic review: references checked
Tejada 2007[116]	Inappropriate study design – non comparative
Treggiari 2009[117]	Inappropriate study design – literature review
van den Bergh 2008[121]	Paper not available
van den Bergh 2009[119]	Systematic review: references checked
van den Bergh 2011[118]	Systematic review: not review PICO
van den Bergh 2009[120]	Inappropriate intervention – prophylactic treatment
Velat 2011[122]	Inappropriate study design – literature review
Veldeman 2016[123]	Systematic review: references checked
Venkatraman 2018[124]	Systematic review: references checked
Vergouw 2017[125]	Inappropriate study design – non comparative / prophylactic treatment
Vergouwen 2011[126]	Inappropriate study design – discussion article
Webb 2010[127]	Inappropriate study design – no comparison group
Weyer 2006[128]	Systematic review: references checked

Study	Reason for exclusion
Williams 2020[129]	Not review population – patients with SAH (not explicitly DCI)
Wong 2011[130]	Systematic review: not review PICO
Yao 2017[131]	Systematic review: references checked
Zhang 2018[132]	Inappropriate intervention – prophylactic treatment
Zhang 2013[133]	Systematic review: references checked
Zhu 2001[134]	Paper not available

I.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 18: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

J.1 Intra-arterial therapies to manage delayed cerebral ischaemia

Research question: What is the impact of intra-arterial therapies to manage delayed cerebral ischaemia on outcome in people with aneurysmal subarachnoid haemorrhage?

Why this is important:

Delayed cerebral ischaemia (DCI) is a major cause of poor outcome in people with aneurysmal subarachnoid haemorrhage. DCI usually presents 5-10 days after aneurysm rupture with a reduction in consciousness or new neurological deficit and the diagnosis is confirmed by exclusion of other causes of deterioration (including hypoxia, metabolic disturbance, hypotension, hydrocephalus, intracranial bleeding, cerebral oedema). Current practice is to induce hypertension with inotropic agents on the basis that an elevated blood pressure will improve cerebral perfusion, and so reduce ischaemia. Some patients do not respond to medical treatment and intra-arterial vasodilators and cerebral artery angioplasty are sometimes used in these cases.

Criteria for selecting priority research recommendations:

PICO question	Population: Adults (16 and older) with a diagnosis of delayed cerebral ischemia following subarachnoid haemorrhage caused by a suspected or confirmed ruptured aneurysm. Intervention/comparison(s): • Intra-arterial vasodilator medication • Angioplasty • Conservative care/no additional treatment Outcome(s): • 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) • Cerebral infarction • Intracranial bleed • Cardiopulmonary complications • Length of stay in hospital
Importance to patients or the population	Improved care in the management of delayed cerebral ischaemia aims to prevent or limit cerebral infarction and to reduce the subsequent morbidity and mortality.
Relevance to NICE guidance	Current guidance recommends that euvolaemia (normal blood volume) should be ensured in people with delayed cerebral ischaemia after an aneurysmal subarachnoid haemorrhage and treatment with a vasopressor should be considered if symptoms persist. However, the improvements seen after these measures may be temporary, and there is currently no evidence of impact on longer-term outcomes. Evidence for intra-arterial vasodilators and angioplasty was insufficient to support recommendations. Further evidence would better help to define the role of these interventions to manage DCI.
Relevance to the NHS	Treatment for people with DCI following an aSAH whose condition is not improved by vasopressor therapy varies widely. It is hoped that further research will define the role of intra-arterial therapies (such as vasodilator drugs and angioplasty) in the management of patients with DCI, and facilitate more consistent management of these patients across the NHS.
National priorities	This question is relevant to stroke as a national priority area.
Current evidence base	There is currently limited evidence for intra-arterial therapies to manage delayed cerebral ischaemia. One small retrospective cohort study compared intra-cranial arterial angioplasty with no intervention in patients with delayed cerebral ischaemia. Angioplasty showed no clinically important difference in the degree of disability. Evidence from a second retrospective cohort study showed that fewer patients achieved a favourable outcome with intra-arterial papaverine compared to a control group, although the committee agreed that the evidence on papaverine was insufficient to support a recommendation.
Equality	No equality issues
Study design	Registry-based study.
Timeframe	The proposed research could be carried out over 3-5 years to allow for sufficient data collection and follow-up of participants. Patients with SAH and DCI unresponsive to vasopressor treatment are relatively rare and it may be challenging to recruit the requisite number of patients, so additional time to recruit may be required.
Feasibility	The conduct of a registry study is considered to be feasible.
Other comments	The committee noted that currently clinicians do not have equipoise between interventions to randomise patients to treatment in an RCT, and so a RCT in this area currently may not be feasible. The committee added that a registry-based study could inform practice and might inform the design of a subsequent RCT.
Importance	• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

Appendix K: Research recommendations

K.1 Vasopressors to manage delayed cerebral ischaemia

Research question: What is the clinical and cost effectiveness of vasopressors to manage delayed cerebral ischaemia in people with aneurysmal subarachnoid haemorrhage?

Why this is important:

Delayed cerebral ischaemia (DCI) is a major cause of poor outcome in people with aneurysmal subarachnoid haemorrhage. DCI usually presents 5-10 days after aneurysm rupture with a reduction in consciousness or new neurological deficit and the diagnosis is confirmed by exclusion of other causes of deterioration (including hypoxia, metabolic disturbance, hypotension, hydrocephalus, intracranial bleeding, cerebral oedema). Current practice is to induce hypertension with inotropic agents on the presumption that an elevated blood pressure will drive more blood through the brain, and so improve ischaemia, but evidence to support this practice is lacking.

Criteria for selecting priority research recommendations:

PICO question	Population: Adults (16 and older) with a diagnosis of delayed cerebral ischemia following a subarachnoid haemorrhage caused by a suspected or confirmed ruptured aneurysm.
	
	Intervention(s):
	• Vasopressors (hypertensive treatment)
	  ○ Noradrenaline
	  ○ Metaraminol
	
	Comparison:
	• To no treatment
	
	Outcome(s):
	• 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)
	
	• Subsequent subarachnoid haemorrhage
	• Return to usual daily activity e.g. work
	• Cerebral infarction
	• Cardiopulmonary complications
	• Length of stay in hospital

Importance to patients or the population	Improved care in the management of delayed cerebral ischaemia aims to prevent or limit cerebral infarction and reduce the subsequent risk of morbidity and mortality.
Relevance to NICE guidance	Current guidance recommends that euvolaemia (normal blood volume) should be ensured in people with delayed cerebral ischaemia after an aneurysmal subarachnoid haemorrhage and treatment with a vasopressor should be considered if symptoms persist. However, the improvements seen after these measures may be temporary, and there is no evidence of impact on longer-term outcomes. Further evidence would better define the clinical and cost-effectiveness of vasopressors to manage DCI.

Relevance to the NHS	Treatment for people with DCI following an aSAH whose condition is not improved by vasopressor therapy varies widely. It is hoped that further evidence would reduce variation in practice and allow a consistent approach across the NHS.
National priorities	This question is not relevant to a national priority area.
Current evidence base	One randomised controlled trial assessed norepinephrine (a vasopressor) and intravenous fluids compared to routine fluid management in people with delayed cerebral ischaemia. Administration of norepinephrine and fluids was not associated with lower disability. The committee noted that there was a clinically significant increase in mortality rate in the norepinephrine and fluids group compared to routine fluid management, although the evidence was of low quality with very serious imprecision around the point estimate. The committee agreed that the quantity and quality of evidence on norepinephrine was insufficient to support a recommendation.
Equality	No equality issues
Study design	New research should be carried out using a prospective randomised controlled trial study design.
Timeframe	New research should be conducted within 3-5 years to allow for sufficient data collection and follow-up of participants.
Feasibility	The research is feasible.
Importance	• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.