National Institute for Health and Care Excellence

Guideline version (Consultation)

Subarachnoid haemorrhage

[E] Evidence review for monitoring for raised intracranial pressure and vasospasm

NICE guideline <number>

Evidence review underpinning

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Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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ISBN
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Contents

1 Monitoring for raised intracranial pressure and vasospasm

Evidence review underpinning recommendations 1.3.1 to 1.3.2 and research recommendations in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of interventions to monitor for intracranial hypertension or vasospasm in adults with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?

1.2 Introduction

In current practice people with aneurysmal subarachnoid haemorrhage are monitored closely to detect changes in neurological signs, conscious level or overall clinical condition. Clinical deterioration may indicate complications including rebleeding, seizures, acute hydrocephalus, arterial vasospasm, or intracranial hypertension. Arterial vasospasm and intracranial hypertension are associated with the development of delayed cerebral ischaemia and a poor outcome. In some specialist centres, routine monitoring therefore includes techniques to detect early signs of vasospasm or raised intra-cranial pressure that can potentially guide management to prevent cerebral injury.

Transcranial Doppler (TCD) is a non-invasive ultrasound technique usually carried out at the bedside during the first 2-3 weeks following SAH. TCD can monitor patients for evidence of arterial vasospasm and can estimate intracranial pressure. The technique is operator-dependent and may be limited by the ultrasound window in some people (e.g. due to a thick skull vault).

Intracranial pressure (ICP) monitoring requires insertion of a small probe (intracranial pressure bolt) through the skull. The technique provides a continuous direct measurement of ICP on a bedside monitor, and can detect changes in ICP in intubated patients in whom clinical assessment may not be possible (unconscious and/or needing ventilation for more than 48 hours).

The objective of this review is to assess the clinical and cost-effectiveness of routine monitoring for vasospasm or intracranial hypertension to detect ‘early’ signs of deterioration in people with aneurysmal subarachnoid haemorrhage.

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 a confirmed subarachnoid haemorrhage caused by a 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.
Interventions	• Transcranial Doppler

	• Direct pressure monitoring
	  ○ Bolt
	  ○ Drain

Comparisons	Comparators: • To no routine screening • To each other (across class and within class comparison)
Outcomes	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Stroke • DCI • 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 • Length of hospital stay • Complications of investigation • Need for retreatment Outcomes will be grouped at <30 days, 30 days-6 months, 6-12 months, and at yearly time-points thereafter.
Study design	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.

1 **Glasgow Outcome Scale (1975)**

GOS Category	Proposed description of category
Death (1)	Ascribable to particular incident and due to original brain damage. Potentially subcategorize death according to whether occur before or after regaining consciousness to distinguish initial recovery from brain damage
Persistent Vegetative State (2)	Unresponsive and speechless for weeks or months after acute brain damage. Sleep wake cycles after 2-3 weeks
Severe disability (conscious but disabled) (3)	Dependent on daily support because of physical and/or mental causes
Moderate disability (disabled but independent) (4)	Independent in 'daily life' (for example, can use public transport and work in a sheltered environment). Able to maintain self-care and 'activities for daily living'. Considerable family disruption possible
Good recovery (5)	Resumption of normal life, although there may be minor neurological and psychological deficits. Return to work could lead to false impressions in either direction (for example, socioeconomic factors in work availability, attitude of past employers; included here are leisure interests and family relationships.

1.4 2 Clinical evidence

1.4.1 3 Included studies

4 One cross – sectional cohort study was included in the review,[23] this is summarised in Table
5 2 below. Evidence from this study is summarised in the clinical evidence summary below
6 (Table 3).

See also the study selection flow chart in B.2, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix G:.

1.4.2 Excluded studies

See the excluded studies list in Appendix J:

1.4.3 1 Summary of clinical studies included in the evidence review

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

Study	Intervention and comparison	Population	Outcomes	Comments
Hollingworth 2019[23]	**Transcranial Doppler:** centres which routinely screen for vasospasm with transcranial doppler (n=963) **No treatment:** Centres with no routine screening (n=1065) Outcomes were assessed at discharge	aSAH patients treated by surgical clip or coil embolization within 3 days of ictus, >16 of age, who survived into the DCI period (>3 days) with known outcomes, age and WFNS grade were included in the final analysis. Age - Mean (SD): Non screening centres: 54.63 (12.45); Screening centres: 54.91 (12.71) United Kingdom and Ireland (major neurosurgical centres) cross sectional study with prospectively collected data from the UKISAH registry	• Glasgow outcome scale • DCI • Re-bleed • Length of stay	Not all study results adjusted for by age. Comparison between centres and not individual cohorts of patients. Study did model analyses to investigate screening versus non screening: Model B adjusted for age, WFNS, comorbid hypertension, smoking, ischemic heart disease, CSF diversion and re-bleed. Survey part of the study has not been included within the review

3 See Appendix D:for full evidence tables.

4

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Screening vs No screening

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Screening	Risk difference with Screening (95% CI)
Adjusted data					
DCI	2028 (1 study)	⨁⨁⊖⊖ LOW1,2 due risk of bias and imprecision	Adjusted OR 0.9 (0.72 to 1.13)		Not estimable3
GOS 4 or 5	2028 (1 study)	⨁⨁⨁⊖ MODERATE1 due to risk of bias	Adjusted OR 0.56 (0.42 to 0.75)		Not estimable3
Unadjusted data					
Length of stay	2028 (1 study)	⨁⊖⊖⊖ LOW1 due to risk of bias		The mean length of stay in the control groups was 20.8 days	The mean length of stay in the intervention groups was 1.18 days higher (0.45 lower to 2.81 higher)
Rebleed	2028 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias and imprecision	RR 1.14 (0.82 to 1.6)	59 per 1000	8 more per 1000 (from 11 fewer to 35 more)
Delayed Cerebral Ischemia	2028 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	RR 1.02 (0.87 to 1.2)	224 per 1000	4 more per 1000 (from 29 fewer to 45 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Screening	Risk difference with Screening (95% CI)
GOS 1	2028 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias and imprecision	RR 1.17 (0.86 to 1.59)	68 per 1000	12 more per 1000 (from 10 fewer to 40 more)
GOS 2		⨁⨁⊖⊖ LOW1 due to risk of bias	RR 2.95 (1.38 to 6.31)	9 per 1000	18 more per 1000 (from 3 more to 48 more)
GOS 3		⨁⨁⊖⊖ LOW1 due to risk of bias	RR 1.74 (1.43 to 2.11)	129 per 1000	95 more per 1000 (from 55 more to 143 more)
GOS 4		⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias and imprecision	RR 0.9 (0.74 to 1.09)	185 per 1000	19 fewer per 1000 (from 48 fewer to 17 more)
GOS 5		⨁⊖⊖⊖ VERY LOW1,2 risk of bias and imprecision	RR 0.83 (0.77 to 0.9)	610 per 1000	104 fewer per 1000 (from 61 fewer to 140 fewer)

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

3 Risk difference was not estimable due to insufficient data for calculation from the study

1 See Appendix G: for full GRADE tables.

2

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. A single transcranial Doppler ultrasound scan would take less than 20 minutes, and would need to be mobile as these scans would be performed on the ward.

Table 4: UK costs of tests for monitoring

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

Source: NHS Reference costs2018/19[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 that the intended impact of transcranial Doppler (TCD) or intracranial pressure monitoring is to detect and manage vasospasm, thereby preventing complications of aSAH including delayed cerebral ischemia (DCI). As such, the committee agreed outcomes critical for decision making to be mortality; health and social-related quality of life; stroke; DCI; and degree of disability or dependence in daily activity. Other important outcomes were subsequent SAH; return to daily activity; length of hospital stay, complications and the need for treatment.

1.7.1.2 The quality of the evidence

The quality of evidence on transcranial Doppler (TCD) monitoring to detect vasospasm ranged from moderate to very low, due to the risk of bias and imprecision.

The observational study included within the review is a comparison between centres that use TCD for monitoring compared to centres that do not use TCD monitoring. Initially the authors performed a nationwide survey to ascertain which centres do use TCD monitoring and which do not. From the thirteen centres that responded to the survey, cross sectional data from the UKISAH Registry database was extracted.

The data from this study had adjusted data and unadjusted data. The adjusted data was adjusted for age as well as WFNS grade, comorbid hypertension, smoking ischemic heart disease, cerebrospinal fluid diversion and re-bleed. Adjusted data was available for two critical outcomes: DCI and Glasgow Outcome Scale 4 or 5. Age was highlighted as a key confounder, so the adjusted data was considered to be relevant to this review.

Length of stay, rebleed, DCI and Glasgow Outcome Scale 1 – 5 were unadjusted outcomes. The committee agreed to review the unadjusted data alongside the adjusted data as they included critical outcomes.

There was a high level of uncertainty around a number of outcomes due to significant statistical imprecision around the summary effect estimates. This was indicated by wide-ranging confidence intervals crossing the thresholds which demonstrate clinical significance, with which the committee would typically judge if an intervention shows benefit or harm.

The committee considered that despite the large size of the study, the cross-sectional data of specific centres and the quality of the evidence limited the confidence in the evidence and agreed that they could not make a recommendation for routine use of TCD. The committee also highlighted uncertainty around the process and consistency of monitoring of patients provided at the participating centres, and the likelihood that confounding factors between centres influenced outcomes. There is however considerable interest in methods of monitoring and the committee agreed to make a recommendation around the use of TCD.

No evidence was found for direct intracranial pressure monitoring. The committee were aware that high-quality research in this area is difficult given that that intracranial pressure monitoring requires placement of a pressure bolt, which is usually only done in people with ‘poor grade’ subarachnoid haemorrhage and who require ventilation in an intensive care unit. The invasiveness of the technique also makes a general research recommendation inappropriate.

The committee therefore agreed not to make a clinical or research recommendations in relation to intracranial pressure monitoring.

1.7.1.3 Benefits and harms

People with aSAH who develop delayed cerebral ischemia are at increased risk of mortality or poor neurological outcome. One of the challenges in showing benefit for monitoring is the paucity of evidence-based interventions which can then be used to improve outcomes. There is therefore a potential harm where people receive additional interventions which may not result in benefit.

The evidence for transcranial Doppler showed clinically important difference towards increased DCI in centres that screened compared to those centres that did not screen people for vasospasm. However, the committee were uncertain of the reliability of this due to the quality and imprecision of the evidence. There was also a clinically important difference towards better neurological outcomes assessed by Glasgow Outcome Scale and adjusted for age in centres that did not use transcranial Doppler compared to those centres that did.

The results for length of stay, rebleed, DCI and GOS 1 - 5 were not adjusted for age. There was an increase in length of stay in centres that screened people with transcranial Doppler monitoring, however this difference was not considered to be clinically significant. The rates of rebleed and DCI are higher in centres with screening, however were not clinically

significant. The outcome of GOS 1 (mortality) showed a clinically important difference in favour of centres with no screening. Further assessing the quality of life outcomes, GOS 2 (persistent vegetative state), GOS 3 (severe disability) and GOS 4 (moderate disability) were not clinically significant. There was a clinically important difference for GOS 5 (good recovery) which indicates that more people in centres with no screening were likely to have good recovery.

The committee considered that while the results from the investigations are unlikely to have a direct impact on the clinical outcomes observed, they may lead to subsequent investigations or procedures, which could have a greater impact on a person's length of hospital stay, morbidity or mortality.

Given the uncertainty around the evidence available for TCD monitoring and the evidence of potential harm subsequent to routine Doppler monitoring, the committee agreed to make a strong recommendation in that they do not recommend the routine use of TCD but agreed to make a recommendation for TCD monitoring to guide clinical management of an aneurysmal subarachnoid haemorrhage only in the context of clinical research. They therefore developed a research recommendation on the effectiveness of routine transcranial doppler monitoring to guide clinical management.

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.

The committee noted that monitoring with transcranial Doppler would consist of performing an ultrasound scan once or twice a day for around 2 weeks. At £71 per scan this would incur an overall cost of £944 - £1,988.

The committee noted that some centres are currently using transcranial Doppler in routine practice. The committee were concerned that the use of transcranial Doppler for monitoring people post SAH is expensive and there was a lack of high quality clinical evidence to assess its effectiveness; therefore the use of transcranial Doppler may not be clinically or cost effective. The committee agreed to make a recommendation that transcranial Doppler should not be used in routine clinical practice unless part of a research programme due to its high costs and levels of uncertainty concerning its effectiveness.

The committee recognised that transcranial Doppler is a relatively simple non-invasive technique and any future strong evidence supporting its use may have considerable impact.

The committee also noted wide variation in the use of direct intracranial pressure monitoring, and the high cost and lack of clinical evidence for this practice.

1.7.3 Other factors the committee took into account

The committee highlighted that Transcranial Doppler monitoring is operator-dependent and interpretation of TCD measurements can be subjective, which may be a reason for some of the uncertainty around the current evidence base available for its use within SAH. The committee also noted that use of transcranial Doppler for monitoring patients varies considerably across the country. The committee agreed that further research may serve to lessen these uncertainties and provide better direction for future practice.

References

1. Al-Mufti F, Smith B, Lander M, Damodara N, Nuoman R, El-Ghanem M et al. Novel minimally invasive multi-modality monitoring modalities in neurocritical care. Journal of the Neurological Sciences. 2018; 390:184-192

2. Amato A, Britz GW, James ML, Graffagnino C, Zomorodi AR, Zomorodi ME et al. An observational pilot study of CSF diversion in subarachnoid haemorrhage. Nursing in Critical Care. 2011; 16(5):252-260

3. Aminmansour B, Ghorbani A, Sharifi D, Shemshaki H, Ahmadi A. Cerebral vasospasm following traumatic subarachnoid hemorrhage. Journal of Research in Medical Sciences. 2009; 14(6):343-348

4. Aydin HE, Ozbek Z, Aydin N, Bolluk O, Vural M, Arslantas A et al. Application of lumbar drainage in vasospasm after spontaneous subarachnoid hemorrhage and prevention of late cerebral infarction. Acta Neurochirurgica - Supplement. 2015; 120:255-258

5. Bailey RL, Quattrone F, Curtin C, Frangos S, Maloney-Wilensky E, Levine JM et al. The safety of multimodality monitoring using a triple-lumen bolt in severe acute brain injury. World Neurosurgery. 2019; 130:e62-e67

6. Bian LH, Liu LP, Wang WJ, Wang CX, Yang ZH, Song XJ et al. Continual transcranial doppler in the monitoring of hemodynamic change following aneurysmal subarachnoid hemorrhage. CNS Neuroscience & Therapeutics. 2012; 18(8):631-635

7. Biersteker HA, Andriessen TM, Horn J, Franschman G, van der Naalt J, Hoedemaekers CW et al. Factors influencing intracranial pressure monitoring guideline compliance and outcome after severe traumatic brain injury. Critical Care Medicine. 2012; 40(6):1914-1922

8. Can M, Kahyaoglu O, Colak I, Aydin Y. Predictive value of transcranial doppler to detect clinical vasospasm in patients with aneurysmal subarachnoid haemorrhage. 'In:' Kırış T, Zhang JH, editors. Cerebral Vasospasm Acta Neurochirurgica Supplementum. 104. Vienna: Springer. 2008. p. 259-261.

9. Chieregato A, Sabia G, Tanfani A, Compagnone C, Tagliaferri F, Targa L. Xenon-CT and transcranial Doppler in poor-grade or complicated aneurysmatic subarachnoid hemorrhage patients undergoing aggressive management of intracranial hypertension. Intensive Care Medicine. 2006; 32(8):1143-1150

10. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012; 43(6):1711-1737

11. de Rooij NK, Rinkel GJE, Dankbaar JW, Frijns CJM. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. Stroke. 2013; 44(1):43-54

12. Deb S, Gogos AJ, Drummond KJ, Teddy PJ. The role of transcranial Doppler ultrasound monitoring in patients with aneurysmal subarachnoid haemorrhage. Journal of Clinical Neuroscience. 2012; 19(7):950-955

13. Eide PK, Sorteberg A, Meling TR, Sorteberg W. The effect of baseline pressure errors on an intracranial pressure-derived index: results of a prospective observational study. Biomedical Engineering Online. 2014; 13:99

14. Ekelund A, Saveland H, Romner B, Brandt L. Is transcranial Doppler sonography useful in detecting late cerebral ischaemia after aneurysmal subarachnoid haemorrhage? British Journal of Neurosurgery. 1996; 10(1):19-25

15. Fontanella M, Valfre W, Benech F, Carlino C, Garbossa D, Ferrio M et al. Vasospasm after SAH due to aneurysm rupture of the anterior circle of Willis: value of TCD monitoring. Neurological Research. 2008; 30(3):256-261

16. Ghani AR, John JT, Idris Z, Ghazali MM, Murshid NL, Musa KI. Functional outcome at 6 months in surgical treatment of spontaneous supratentorial intracerebral haemorrhage. The Malaysian Journal of Medical Science. 2008; 15(4):48-55

17. Han SJ, Rutledge WC, Englot DJ, Winkler EA, Browne JL, Pflugrath L et al. The Presto 1000: a novel automated transcranial Doppler ultrasound system. Journal of Clinical Neuroscience. 2015; 22(11):1771-1775

18. Hanggi D, Eicker S, Beseoglu K, Behr J, Turowski B, Steiger HJ. A multimodal concept in patients after severe aneurysmal subarachnoid hemorrhage: results of a controlled single centre prospective randomized multimodal phase I/II trial on cerebral vasospasm. Central European Neurosurgery. 2009; 70(2):61-67

19. Hanggi D, Liersch J, Turowski B, Yong M, Steiger HJ. The effect of lumboventricular lavage and simultaneous low-frequency head-motion therapy after severe subarachnoid hemorrhage: results of a single center prospective Phase II trial. Journal of Neurosurgery. 2008; 108(6):1192-1199

20. Hanggi D, Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Monitoring and detection of vasospasm II: EEG and invasive monitoring. Neurocritical Care. 2011; 15(2):318-323

21. Hanley DF, Naff NJ, Harris DM. Intraventricular hemorrhage: presentation and management options. Seminars in Cerebrovascular Diseases and Stroke. 2005; 5(3):209-216

22. Helbok R, Olson DM, Le Roux PD, Vespa P, Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations. Neurocritical Care. 2014; 21(Suppl 2):S85-94

23. Hollingworth M, Jamjoom AAB, Bulters D, Patel HC. How is vasospasm screening using transcranial doppler associated with delayed cerebral ischemia and outcomes in aneurysmal subarachnoid hemorrhage? Acta Neurochirurgica. 2019; 161(2):385-392

24. Hwang SH, Park YS, Kwon JT, Nam TK, Hwang SN, Kang H. Significance of C-Reactive protein and transcranial doppler in cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Journal of Korean Neurosurgical Society. 2013; 54(4):289-295

25. Karnchanapandh K. Effect of increased ICP and decreased CPP on DND and outcome in ASAH. Acta Neurochirurgica - Supplement. 2012; 114:339-342

26. Karnchanapandh K. Effect of increased intracranial pressure on cerebral vasospasm in SAH. Acta Neurochirurgica - Supplement. 2008; 102:307-310

27. Kiphuth IC, Huttner HB, Breuer L, Engelhorn T, Schwab S, Kohrmann M. Vasospasm in intracerebral hemorrhage with ventricular involvement: a prospective pilot transcranial Doppler sonography study. Cerebrovascular Diseases. 2011; 32(5):420-425

28. Klimo Jr P, Kestle JRW, Macdonald JD, Schmidt RH. Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. Journal of Neurosurgery. 2004; 100(2):215-224

29. Kramer DR, Winer JL, Pease BA, Amar AP, Mack WJ. Cerebral vasospasm in traumatic brain injury. Neurology Research International. 2013; 2013:415813

30. Kumar G, Albright KC, Donnelly JP, Shapshak AH, Harrigan MR. Trends in transcranial doppler monitoring in aneurysmal subarachnoid hemorrhage: a 10-year analysis of the nationwide inpatient sample. Journal of Stroke and Cerebrovascular Diseases. 2017; 26(4):851-857

31. Kumar G, Shahripour RB, Harrigan MR. Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Journal of Neurosurgery. 2016; 124(5):1257-1264

32. Lang EW, Chesnut RM. Intracranial pressure and cerebral perfusion pressure in severe head injury. New Horizons. 1995; 3(3):400-409

33. Laumer R, Steinmeier R, Gonner F, Vogtmann T, Priem R, Fahlbusch R et al. Cerebral hemodynamics in subarachnoid hemorrhage evaluated by transcranial Doppler sonography. Part 1. Reliability of flow velocities in clinical management. Neurosurgery. 1993; 33(1):1-9

34. Lysakowski C, Walder B, Costanza MC, Tramer MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: a systematic review. Stroke. 2001; 32(10):2292-2298

35. Mack WJ, King RG, Ducruet AF, Kreiter K, Mocco J, Maghoub A et al. Intracranial pressure following aneurysmal subarachnoid hemorrhage: monitoring practices and outcome data. Neurosurgical Focus. 2003; 14(4):e3

36. Mascia L, Fedorko L, terBrugge K, Filippini C, Pizzio M, Ranieri VM et al. The accuracy of transcranial Doppler to detect vasospasm in patients with aneurysmal subarachnoid hemorrhage. Intensive Care Medicine. 2003; 29(7):1088-1094

37. McGirt MJ, Blessing RP, Goldstein LB. Transcranial Doppler monitoring and clinical decision-making after subarachnoid hemorrhage. Journal of Stroke and Cerebrovascular Diseases. 2003; 12(2):88-92

38. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

39. Neulen A, Prokesch E, Stein M, Konig J, Giese A. Image-guided transcranial Doppler sonography for monitoring of vasospasm after subarachnoid hemorrhage. Clinical Neurology and Neurosurgery. 2016; 145:14-18

40. NHS England and NHS Improvement. National cost collection for the NHS 2018-19. 2019. Available from: https://improvement.nhs.uk/resources/national-cost-collection/ Last accessed: 01/04/2020.

41. Oertel MF, Scharbrodt W, Wachter D, Stein M, Schmidinger A, Boker DK. Arteriovenous differences of oxygen and transcranial Doppler sonography in the management of aneurysmatic subarachnoid hemorrhage. Journal of Clinical Neuroscience. 2008; 15(6):630-636

42. Proust F, Callonec F, Clavier E, Lestrat JP, Hannequin D, Thiebot J et al. Usefulness of transcranial color-coded sonography in the diagnosis of cerebral vasospasm. Stroke. 1999; 30(5):1091-1098

43. Proust F, Debono B, Gerardin E, Hannequin D, Derrey S, Langlois O et al. Angiographic cerebral vasospasm and delayed ischemic deficit on anterior part of the circle of Willis. Usefulness of transcranial doppler. Neuro-Chirurgie. 2002; 48(6):489-499

44. Ramanan R, Joseph M. Utility of transcranial doppler in estimating cerebral perfusion pressure in traumatic brain injury: a prospective observational trial. Indian Journal of Neurotrauma. 2017; 14(2-3):152-155

45. Rigamonti A, Ackery A, Baker AJ. Transcranial Doppler monitoring in subarachnoid hemorrhage: a critical tool in critical care. Canadian Journal of Anaesthesia. 2008; 55(2):112-123

46. Rynkowski CB, de Oliveira Manoel AL, Dos Reis MM, Puppo C, Worm PV, Zambonin D et al. Early transcranial doppler evaluation of cerebral autoregulation independently predicts functional outcome after aneurysmal subarachnoid hemorrhage. Neurocritical Care. 2019; 31:253-263

47. Sadahiro H, Shirao S, Yoneda H, Ishihara H, Oku T, Inamura A et al. Decreased flow velocity with transcranial color-coded duplex sonography correlates with delayed cerebral ischemia due to peripheral vasospasm of the middle cerebral artery. Journal of Stroke and Cerebrovascular Diseases. 2016; 25(10):2352-2359

48. Samagh N, Bhagat H, Jangra K. Monitoring cerebral vasospasm: how much can we rely on transcranial doppler. Journal of Anaesthesiology Clinical Pharmacology. 2019; 35(1):12-18

49. Simm RF, de Aguiar PH, de Oliveira Lima M, Paiva BL. Transcranial Doppler as a routine in the treatment of vasospasm following subarachanoid hemorrhage (SAH). Acta Neurochirurgica - Supplement. 2013; 115:75-76

50. Soehle M, Chatfield DA, Czosnyka M, Kirkpatrick PJ. Predictive value of initial clinical status, intracranial pressure and transcranial doppler pulsatility after subarachnoid haemorrhage. Acta Neurochirurgica. 2007; 149(6):575-583

51. Steiger HJ, Aaslid R, Stooss R, Seiler RW. Transcranial doppler monitoring in head injury: relations between type of injury, flow velocities, vasoreactivity, and outcome. Neurosurgery. 1994; 34(1):79-85; discussion 85-76

52. Steiner LA, Balestreri M, Johnston AJ, Coles JP, Chatfield DA, Pickard JD et al. Effects of moderate hyperventilation on cerebrovascular pressure-reactivity after head injury. Acta Neurochirurgica. 2005; 95(Suppl.):17-20

53. Suarez JI, Qureshi AI, Yahia AB, Parekh PD, Tamargo RJ, Williams MA et al. Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: evaluation of transcranial Doppler ultrasound and cerebral angiography as related to compromised vascular distribution. Critical Care Medicine. 2002; 30(6):1348-1355

54. Suzuki J, Yoshimoto T, Hori S. Continuous ventricular drainage to lessen surgical risk in ruptured intracranial aneurysm. Surgical Neurology. 1974; 2(2):87-90

55. Swiat M, Weigele J, Hurst RW, Kasner SE, Pawlak M, Arkuszewski M et al. Middle cerebral artery vasospasm: transcranial color-coded duplex sonography versus conventional nonimaging transcranial Doppler sonography. Critical Care Medicine. 2009; 37(3):963-968

56. Torbey MT, Hauser TK, Bhardwaj A, Williams MA, Ulatowski JA, Mirski MA et al. Effect of age on cerebral blood flow velocity and incidence of vasospasm after aneurysmal subarachnoid hemorrhage. Stroke. 2001; 32(9):2005-2011

57. Valentin A, Lang T, Karnik R, Ammerer HP, Ploder J, Slany J. Intracranial pressure monitoring and case mix-adjusted mortality in intracranial hemorrhage. Critical Care Medicine. 2003; 31(5):1539-1542

58. Vergouwen MDI. Vasospasm versus delayed cerebral ischemia as an outcome event in clinical trials and observational studies. Neurocritical Care. 2011; 15:308

59. Wachter D, Hans F, Kreitschmann-Andermahr I, Rohde V. Lower incidence of transcranial Doppler and symptomatic vasospasm after aneurysmal subarachnoid hemorrhage and aneurysm clipping in the elderly patient? Neurosurgery. 2011; 69(2):261-266; discussion 266-267

60. Westermaier T, Pham M, Stetter C, Willner N, Solymosi L, Ernestus RI et al. Value of transcranial Doppler, perfusion-CT and neurological evaluation to forecast secondary ischemia after aneurysmal SAH. Neurocritical Care. 2014; 20(3):406-412

61. Wozniak MA, Sloan MA, Rothman MI, Burch CM, Rigamonti D, Permutt T et al. Detection of vasospasm by transcranial Doppler sonography. The challenges of the anterior and posterior cerebral arteries. Journal of Neuroimaging. 1996; 6(2):87-93

Appendices

Appendix A: Review protocols

Table 5: Review protocol: Monitoring for raised intracranial pressure and vasospasm

ID	Field	Content
0.	PROSPERO registration number	CRD42019153670
1.	Review title	What is the clinical and cost effectiveness of interventions to monitor for intracranial hypertension or vasospasm in adults with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?
2.	Review question	What is the clinical and cost effectiveness of interventions to monitor for intracranial hypertension or vasospasm in adults with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?
3.	Objective	To determine which intervention to screen patients following subarachnoid haemorrhage is the most clinically and cost-effective. The review will address and inform the detection of people with aSAH who deteriorate and may go on to experience delayed cerebral ischemia (DCI).
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 studies 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 e will be published in the final review.
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm. 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	• Transcranial Doppler
		• Direct pressure monitoring
		  ○ Bolt
		  ○ Drain

8.	Comparator/Reference standard/Confounding factors	Comparators: • To no routine screening • To each other (across class and within class comparison)
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 • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Review will capture the efficacy of routine monitoring for people with aSAH, specifically to address those who may go on to experience further complication such as DCI.
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Stroke • DCI • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to daily activity • Length of hospital stay • Complications of investigation • Need for retreatment 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.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • 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.

<table>
<tr><td></td><td></td><td colspan="3">• Heterogeneity between the studies in effect measures will be assessed using the I² statistic and visually inspected. An I² value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Subgroups (if heterogeneity):
• Location of care/monitoring
○ Level 1 (postoperative recovery on a surgical ward with access to a critical care outreach team)
○ Level 2 (high dependency unit, post-anaesthesia care unit)
○ Level 3 (intensive care unit)
• Primary treatment of haemorrhage:
○ clipping,
○ coiling,
○ conservative management
• Grade of SAH
○ Good grade
○ Poor grade
• Frequency of monitoring
○ <6 hour intervals
○ 6 hour intervals
○ daily</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="3">23.</td><td rowspan="3">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>
</table>

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

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords		
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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Table 6: Health economic review protocol

Review question	All questions where health economic evidence applicable
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[38] **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.

1

Appendix B: Literature search strategies

This literature search strategy was used for the following review;

- What is the clinical and cost effectiveness of interventions to monitor for intracranial hypertension or vasospasm in adults with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[38]

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

B.1 Clinical search literature search strategy

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

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 26 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational 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.	Epidemiologic studies/
30.	Observational study/
31.	exp Cohort studies/
32.	(cohort adj (study or studies or analys* or data)).ti,ab.
33.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
34.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
35.	Controlled Before-After Studies/
36.	Historically Controlled Study/
37.	Interrupted Time Series Analysis/
38.	(before adj2 after adj2 (study or studies or data)).ti,ab.
39.	or/29-38
40.	exp case control study/
41.	case control*.ti,ab.
42.	or/40-41
43.	39 or 42
44.	Cross-sectional studies/
45.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
46.	or/44-45
47.	39 or 46
48.	39 or 42 or 46
49.	Meta-Analysis/
50.	exp Meta-Analysis as Topic/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(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.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-57
60.	randomized controlled trial.pt.
61.	controlled clinical trial.pt.
62.	randomi#ed.ti,ab.
63.	placebo.ab.
64.	randomly.ti,ab.
65.	Clinical Trials as topic.sh.
66.	trial.ti.
67.	or/60-66
68.	28 and (48 or 59 or 67)
69.	exp Ultrasonography, Doppler/
70.	Spinal Puncture/
71.	intracranial pressure/
72.	(intracranial adj2 monitor*).ti,ab,kw.
73.	((ICP or non invasive or noninvasive or invasive) adj2 monitor*).ti,ab,hw.
74.	((intraventricular or intraparenchymal or extraventricular) adj3 (catheter* or bolt* or drain* or device* or microsensor*)).ti,ab,kw.
75.	((spinal or lumbar) adj1 (puncture* or tap*)).ti,ab.
76.	(transcranial adj (doppler or ultrasound* or ultrason*)).ti,ab,kw.
77.	(doppler ultrasound* or doppler ultrason*).ti,ab.
78.	or/69-76
79.	68 and 78

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.	Clinical study/
28.	Observational study/
29.	family study/
30.	longitudinal study/
31.	retrospective study/
32.	prospective study/
33.	cohort analysis/
34.	follow-up/
35.	cohort*.ti,ab.
36.	34 and 35
37.	(cohort adj (study or studies or analys* or data)).ti,ab.
38.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
39.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
40.	(before adj2 after adj2 (study or studies or data)).ti,ab.
41.	or/27-33,36-40
42.	exp case control study/
43.	case control*.ti,ab.
44.	or/42-43
45.	41 or 44
46.	cross-sectional study/
47.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
48.	or/46-47
49.	41 or 48
50.	41 or 44 or 48
51.	random*.ti,ab.
52.	factorial*.ti,ab.
53.	(crossover* or cross over*).ti,ab.
54.	((doubl* or singl*) adj blind*).ti,ab.
55.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
56.	crossover procedure/
57.	single blind procedure/

58.	randomized controlled trial/
59.	double blind procedure/
60.	or/51-59
61.	systematic review/
62.	meta-analysis/
63.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
64.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
65.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
66.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
67.	(search* adj4 literature).ab.
68.	(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.
69.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
70.	cochrane.jw.
71.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
72.	or/61-70
73.	26 and (50 or 60 or 72)
74.	exp Doppler flowmetry/
75.	lumbar puncture/
76.	intracranial pressure/
77.	(intracranial adj2 monitor*).ti,ab,kw.
78.	((ICP or non invasive or noninvasive or invasive) adj2 monitor*).ti,ab,hw.
79.	((intraventricular or intraparenchymal or extraventricular) adj3 (catheter* or bolt* or drain* or device* or microsensor*)).ti,ab,kw.
80.	((spinal or lumbar) adj1 (puncture* or tap*)).ti,ab.
81.	(transcranial adj (doppler or ultrasound* or ultrason*)).ti,ab,kw.
82.	(doppler ultrasound* or doppler ultrason*).ti,ab.
83.	or/74-82
84.	73 and 83

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

#1.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#3.	(SAH or aSAH):ti,ab
#4.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Ultrasonography, Doppler] explode all trees
#8.	MeSH descriptor: [Spinal Puncture] explode all trees
#9.	MeSH descriptor: [Intracranial Pressure] explode all trees
#10.	(intracranial near/2 monitor*):ti,ab
#11.	((ICP or non invasive or noninvasive or invasive) near/2 monitor*):ti,ab

#12.	((intraventricular or intraparenchymal or extraventricular) near/3 (catheter* or bolt* or drain* or device* or microsensor*)):ti,ab
#13.	((spinal or lumbar) near/1 (puncture* or tap*)):ti,ab
#14.	((transcranial next Doppler*) or (transcranial next ultrasound*) or (transcranial next ultrason*)).ti,ab
#15.	(transcranial next (doppler or ultrasound* or ultrason*)):ti,ab
#16.	(or #7-#15)
#17.	#6 and #16

B.2 Health Economics literature search strategy

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

Table 8: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.

15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/

11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

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

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

#13.	(((ruptur* or weak* or brain or trauma*) adj3 (aneurysm* or hematoma* or haematoma*)))
#14.	#12 OR #13
#15.	(#5 or #8 or #11 or #14)

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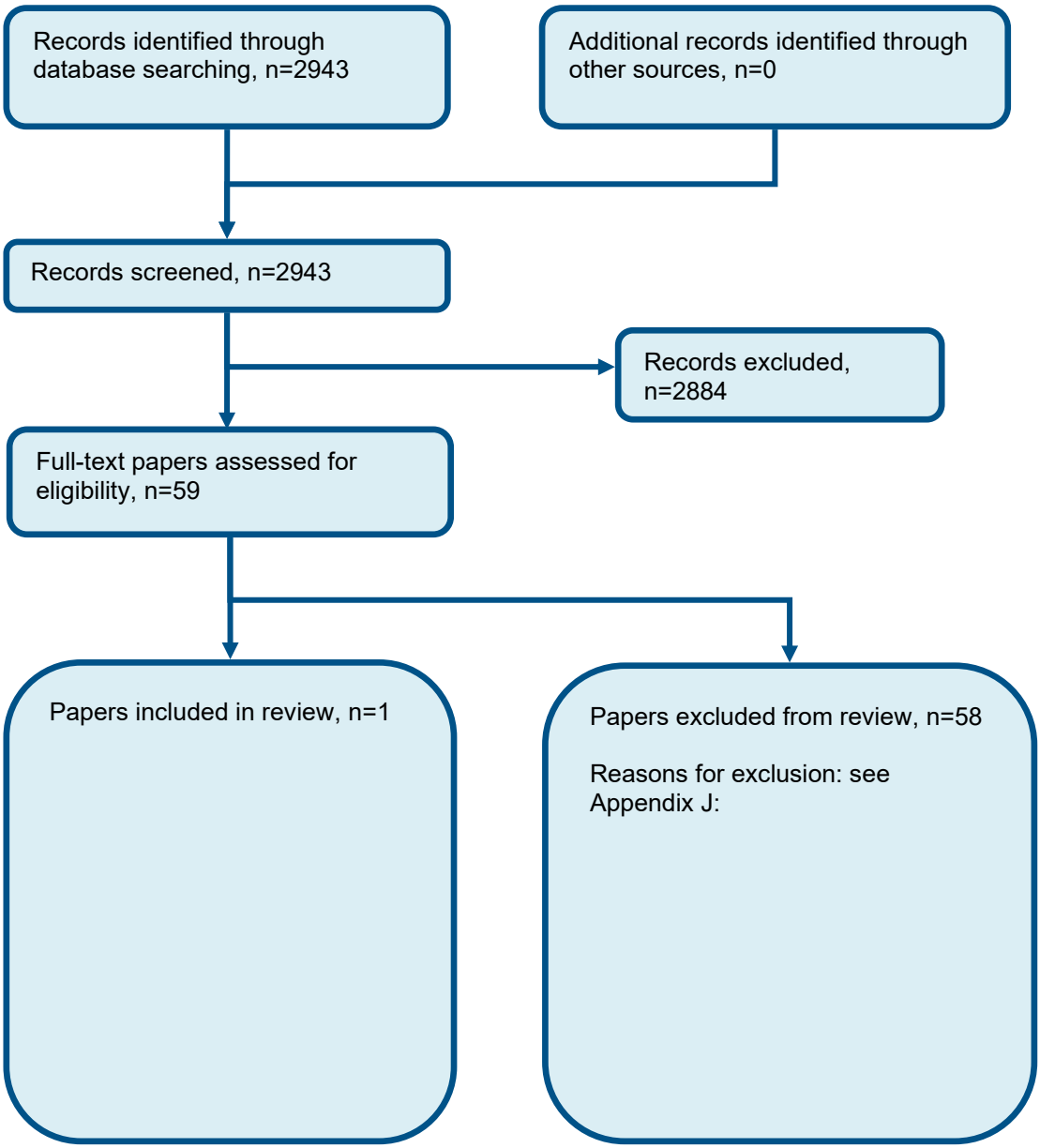
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of screening for raised intracranial pressure and vasospasm



Appendix D: Clinical evidence tables

Study	Hollingworth 2019[23]
Study type	Retrospective cohort study
Number of studies (number of participants)	(n=2082)
Countries and setting	Conducted in Irish Republic, United Kingdom; Setting: Neurosurgical centres across UK and Ireland
Line of therapy	Not applicable
Duration of study	Intervention + follow up: not specified
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aSAH patients treated by surgical clip or coil embolization within 3 days of ictus, >16 of age, who survived into the DCI period (>3 days) with known outcomes, age and WFNS grade were included in the final analysis.
Exclusion criteria	<16 years of age, aneurysm secured beyond 3 days, unknown diagnosis of delayed cerebral ischemia, unknown in hospital outcomes or unknown WFNS grade
Recruitment/selection of patients	Prospectively recorded registry of consecutive SAH patients admitted to major neurosurgical centres across the UK and Ireland.
Age, gender and ethnicity	Age - Mean (SD): Non screening centres: 54.63 (12.45); screening centres: 54.91 (12.71). Gender (M:F): 734/1336. Ethnicity: NA
Further population details	1. Frequency of monitoring: Not stated / Unclear 2. Location of care/monitoring: Not stated / Unclear 3. Patient grade: Not stated / Unclear (WFNS 1: 985; WFNS 2: 419; WFNS 3: 136; WFNS 4: 263; WFNS 5: 225). 4. Primary treatment of haemorrhage: Not stated / Unclear (Neurosurgical or endovascular).
Extra comments	Model A: adjusted for age and WFNS Model B: adjusted for age, WFNS, comorbid hypertension, smoking, ischemic heart disease, CSF diversion and re-bleed.
Indirectness of population	Serious indirectness: results from registry data from centres

Interventions	(n=963) Intervention 1: Transcranial Doppler - Transcranial Doppler. centres which routinely screen for vasospasm with transcranial doppler . Duration NS. Concurrent medication/care: NS (n=1065) Intervention 2: No treatment - No routine screening . Centres with no routine screening . Duration NS. Concurrent medication/care: NS
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANNIAL DOPPLER versus NO ROUTINE SCREENING

Protocol outcome 1: Mortality
- Actual outcome: GOS 1 (death) at post intervention; Group 1: 76/963, Group 2: 72/1065; Comments: p value 0.475
Risk of bias: All domain – Very high, Selection – Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high

Protocol outcome 2: Degree of disability
- Actual outcome: GOS 2 at post intervention; Group 1: 24/963, Group 2: 9/1065; Comments: p value 0.003
Risk of bias: All domain – Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high
- Actual outcome: GOS 3 at post intervention; Group 1: 215/963, Group 2: 137/1065; Comments: p value 0.001
Risk of bias: All domain – Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high
- Actual outcome: GOS 4 at post intervention; Group 1: 160/963, Group 2: 197/1065; Comments: p value 0.315
Risk of bias: All domain – Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high
- Actual outcome: GOS 5 at post intervention; Group 1: 488/963, Group 2: 650/1065; Comments: p value 0.001
Risk of bias: All domain – Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high
- Actual outcome: GOS 4 or 5 ; adjusted OR; Model B: 0.56 OR (0.42 - 0.82) p value <0.001);
Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high

Protocol outcome 3: DCI
- Actual outcome: DCI ; Group 1: 220/963, Group 2: 239/1065; Comments: p value 0.828
Risk of bias: All domain – Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high - Actual outcome: DCI ; OR; Model B: 0.90 adjusted OR (0.72 - 1.12) p value 0.347); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0; Confounding - high Protocol outcome 5: Length of hospital stay - Actual outcome: length of stay in hospital at admission to discharge; Group 1: mean 21.98 days (SD 19.78); n=963, Group 2: mean 20.8 days (SD 17.31); n=1065; Comments: p value 0.266 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: 0; Group 2 Number missing: 0; Confounding - high	
Protocol outcomes not reported by the study	Stroke ; Quality of life ; Cerebral infarction ; Return to daily activity (e.g. work) ; Complications of intervention ; Need for re-treatment

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1 Appendix E: Forest plots

E.12 Screening vs no screening

Figure 2: DCI (adjusted)

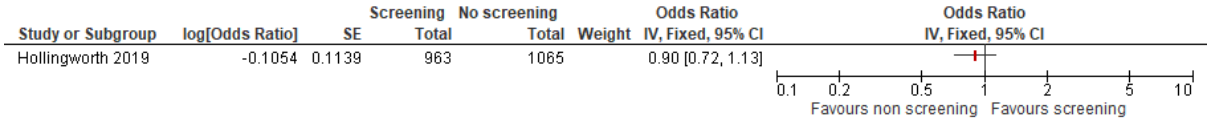

Figure 3: GOS 4 or 5 (adjusted)

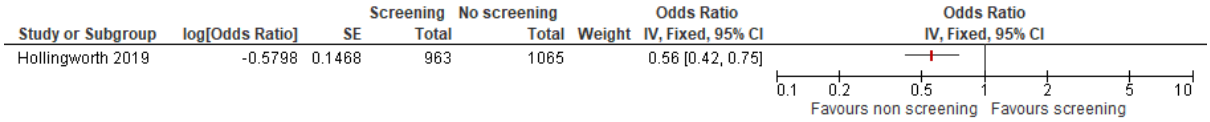

Figure 4: Length of stay (unadjusted)

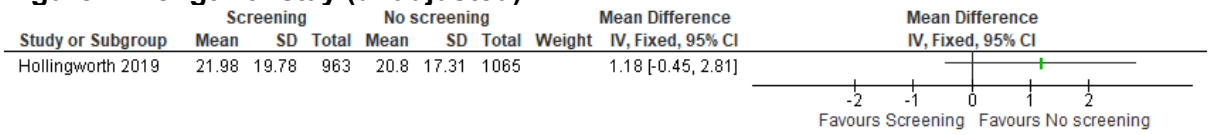

Figure 5: Rebleed (unadjusted)

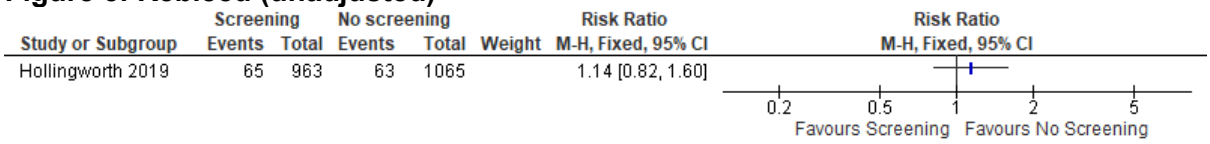

Figure 6: Delayed Cerebral Ischemia (unadjusted)

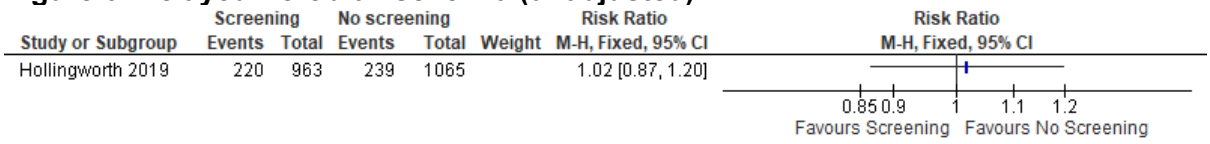

Figure 7: GOS 1 (unadjusted)

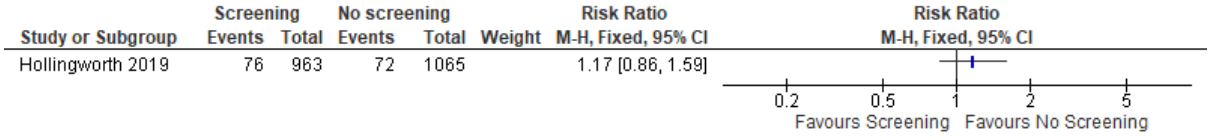

Figure 8: GOS 2 (unadjusted)

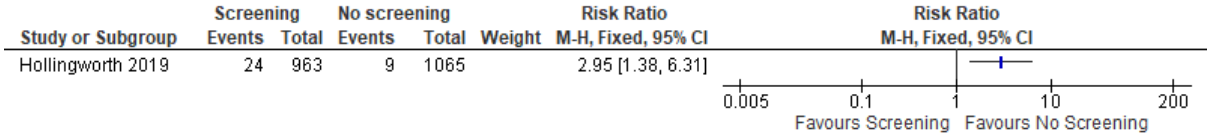

Figure 9: GOS 3 (unadjusted)

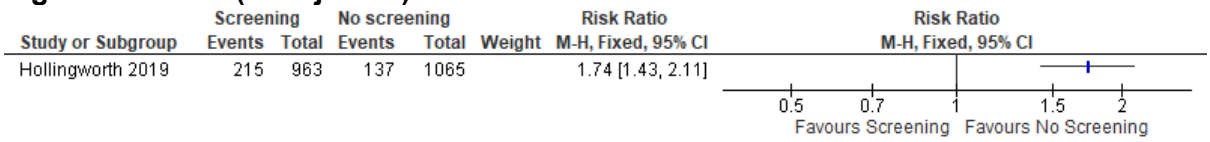

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Figure 10: GOS 4 (unadjusted)

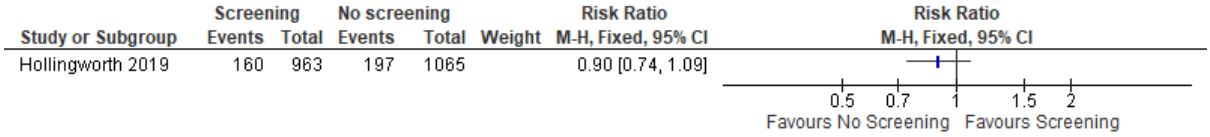
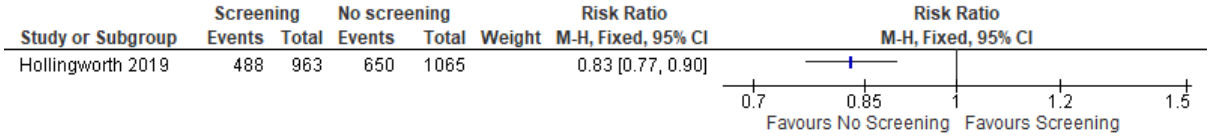


Figure 11: GOS 5 (unadjusted)



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Appendix F: Minimal Important Difference for continuous outcomes

Table 9: Minimal important differences: Screening versus no screening

Outcomes	Minimally important difference (MID)
Length of hospital stay (days)	8.65

1

Appendix G: GRADE tables

Table 10: Clinical evidence profile: Screening vs No screening

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening	No Screening	Relative (95% CI)	Absolute		
DCI (adjusted)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	Serious[2]	none	-	-	Adjusted OR 0.9 (0.72 to 1.13)	-[3]	⊕OOO VERY LOW	CRITICAL
GOS 4 or 5 (adjusted)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Adjusted OR 0.56 (0.42 to 0.75)	-[3]	⊕⊕OO LOW	CRITICAL
Length of stay (Better indicated by lower values) (unadjusted)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	963	1065	-	MD 1.18 higher (0.45 lower to 2.81 higher)	⊕⊕OO LOW	IMPORTANT
Rebleed (unadjusted)												

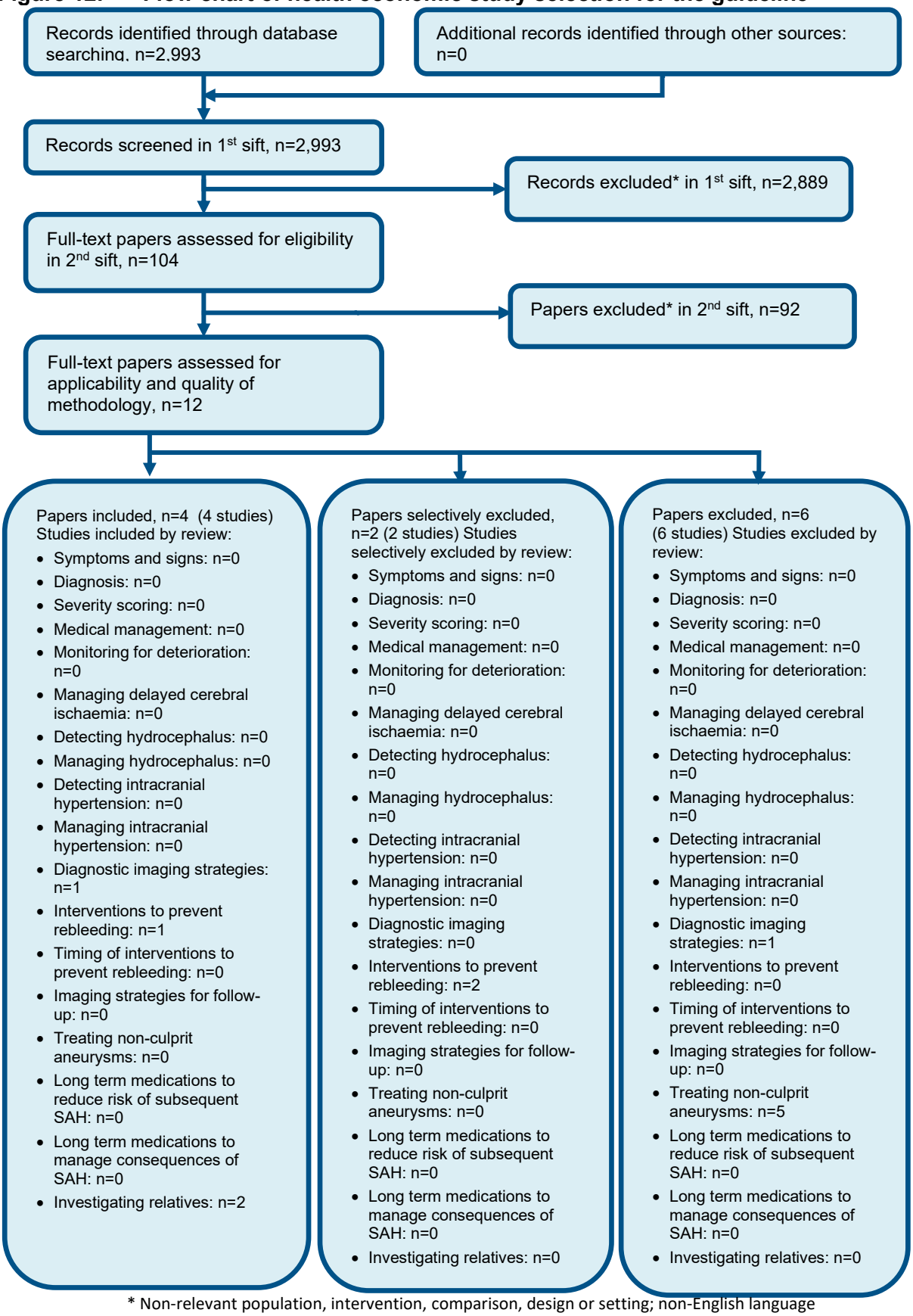
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Serious[2]	none	65/963 (6.7%)	5.9%	RR 1.14 (0.82 to 1.6)	8 more per 1000 (from 11 fewer to 35 more)	⊕OOO VERY LOW	IMPORTANT
Delayed Cerebral Ischemia (unadjusted)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	220/963 (22.8%)	22.4%	RR 1.02 (0.87 to 1.2)	4 more per 1000 (from 29 fewer to 45 more)	⊕⊕OO LOW	CRITICAL
GOS 1 (unadjusted)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Serious[2]	none	76/963 (7.9%)	6.8%	RR 1.17 (0.86 to 1.59)	12 more per 1000 (from 10 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
GOS 2 (unadjusted)												
1	observational studies	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/963 (2.5%)	0.9%	RR 2.95 (1.38 to 6.31)	18 more per 1000 (from 3 more to 48 more)	⊕⊕OO LOW	CRITICAL
GOS 3 (unadjusted)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	215/963 (22.3%)	12.9%	RR 1.74 (1.43 to 2.11)	95 more per 1000 (from 55 more to 143 more)	⊕⊕OO LOW	CRITICAL
GOS 4 (unadjusted)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	Serious[2]	none	160/963 (16.6%)	18.5%	RR 0.9 (0.74 to 1.09)	19 fewer per 1000 (from 48 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL

GOS 5 (unadjusted)												
1	observational studies[1]	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	488/963 (50.7%)	61%	RR 0.83 (0.77 to 0.9)	104 fewer per 1000 (from 61 fewer to 140 fewer)	⊕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
[3] Risk difference was not estimable due to insufficient data for calculation from the study

Appendix H: Health economic evidence selection

Figure 12: Flow chart of health economic study selection for the guideline



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

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Appendix I: Health economic evidence tables

None.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 11: Studies excluded from the clinical review

Reference	Reason for exclusion
Al-Mufti 2018[1]	Inappropriate study design – literature review (references checked)
Amato 2011[2]	Inappropriate comparison – similar intervention in both groups
Aminmansour 2009[3]	Inappropriate population – head injury
Aydin 2015[4]	Inappropriate study design – no comparison group
Bailey 2019[5]	Inappropriate study design – no comparison group
Bian 2012[6]	Inappropriate comparison - No relevant outcomes
Biersteker 2012[7]	Inappropriate population – mixed population
Can 2008[8]	Incorrect study design – no comparison group
Chieregato 2006[9]	Inappropriate comparison - No relevant outcomes
Connolly 2012[10]	Inappropriate study design – literature review (references checked)
de Rooij 2013[11]	Inappropriate comparison – predictors of DCI
Deb 2012[12]	Inappropriate study design – no comparison group
Eide 2014[13]	Inappropriate comparison - No relevant outcomes
Ekelund 1996[14]	Inappropriate study design – no comparison group
Fontanella 2008[15]	Inappropriate study design – no comparison group
Ghani 2008[16]	Inappropriate population – supratentorial ICH
Han 2015[17]	Inappropriate comparison - No relevant outcomes
Hanggi 2009[18]	Inappropriate intervention – active treatment compared to no treatment
Hanggi 2008[19]	Inappropriate intervention – active treatment compared to no treatment
Hanggi 2011[20]	Inappropriate study design – systematic review (references checked)
Hanley 2005[21]	Inappropriate study design – literature review (references checked)
Helbok 2014[22]	Inappropriate study design – literature review (references checked)
Hwang 2013[24]	Inappropriate comparison - No relevant outcomes
Karnchanapandh 2008[26]	Inappropriate study design – no comparison group / multiple interventions
Karnchanapandh 2012[25]	Inappropriate study design – no comparison group
Kiphuth 2011[27]	Inappropriate population – SAH not included
Klimo Jr 2004[28]	Inappropriate intervention – no active monitoring
Kramer 2013[29]	Inappropriate study design – literature review (references checked)
Kumar 2017[30]	Inappropriate study design – survey on frequency of TCD usage
Kumar 2016[31]	Inappropriate study design – systematic review (references checked)
Lang 1995[32]	Inappropriate study design – literature review (references checked)
Laumer 1993[33]	Inappropriate comparison - No relevant outcomes
Lysakowski 2001[34]	Inappropriate study design – systematic review (references checked)
Mack 2003[35]	Inappropriate comparison – EVD drain compared to ICP monitor

Reference	Reason for exclusion
Mascia 2003[36]	Inappropriate study design – accuracy of TCD
McGirt 2003[37]	Inappropriate study design – validation study
Neulen 2016[39]	Inappropriate study design – no comparison group
Oertel 2008[41]	Inappropriate study design – no comparison group
Proust 1999[42]	Inappropriate study design – accuracy of TCD
Proust 2002[43]	Inappropriate study design – no comparison group
Ramanan 2017[44]	Inappropriate study design – no comparison group
Rigamonti 2008[45]	Inappropriate study design – review / editorial (references checked)
Rynkowski 2019[46]	Inappropriate study design – no comparison group
Sadahiro 2016[47]	Inappropriate comparison - No relevant outcomes
Samagh 2019[48]	Inappropriate study design – review / editorial (references checked)
Simm 2013[49]	Inappropriate study design – no comparison group
Soehle 2007[50]	Inappropriate study design – no comparison group
Steiger 1994[51]	Inappropriate population – Traumatic brain injury & no relevant outcomes
Steiner 2005[52]	Inappropriate population – Traumatic brain injury & no relevant outcomes
Suarez 2002[53]	Inappropriate study design – no compa4rison group
Suzuki 1974[54]	Inappropriate study design – no comparison group, multiple interventions and no relevant outcomes
Swiat 2009[55]	Inappropriate study design – no comparison group & no relevant outcomes
Torbey 2001[56]	Inappropriate comparison – TCD changes according to age
Valentin 2003[57]	Inappropriate population/ outcome - No relevant outcomes & mixed population
Vergouwen 2011[58]	Paper not available
Wachter 2011[59]	Inappropriate comparison – TCD changes according to age
Westermaier 2014[60]	Inappropriate study design – accuracy of TCD
Wozniak 1996[61]	Inappropriate study design – accuracy of TCD

J.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 12: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	