National Institute for Health and Care Excellence

Guideline version (Consultation)

Subarachnoid haemorrhage

[R] Evidence review on long-term medication for managing the consequences of SAH

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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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

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ISBN
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Contents

1 Long-term medication for managing the consequences

Evidence review underpinning recommendations 1.4.11 to 1.4.13 in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of long-term medicines such as antiepileptic medicines for managing the consequences of subarachnoid haemorrhage?

1.2 Introduction

People who have had an aneurysmal subarachnoid haemorrhage may experience various troublesome and painful symptoms during follow-up, with a significant negative impact on quality of life. Headache is common after subarachnoid haemorrhage and in current practice treatment options range from simple analgesia to more complex and specialist interventions.

People who sustain significant brain injury from subarachnoid haemorrhage are at risk of seizures, which are generally managed with standard antiepileptic medications.

This review assessed evidence for the clinical and cost-effectiveness of medicines to manage headache and epilepsy 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.

Intervention(s)	• Antiepileptic medicines
	• Medicines to control headache:
	  ○ Beta-blockers
	  ○ Simple analgesia
	  - Acetaminophen
	  - NSAIDs
	  ○ Neuropathic nerve stabilisers
	  ○ Tricyclic antidepressants (TCA)
	  ○ Topiramate

Comparison(s)	Comparators: • To each other (within and between class comparison) • To no treatment/placebo
Outcomes	Primary outcomes • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Secondary outcomes • Return to daily activity e.g driving

	• Need for retreatment • Headache (frequency/severity) • Number of seizures • Complications of medication (any)
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

No relevant clinical studies comparing long-term medications were identified. See also the study selection flow chart in Appendix C:

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

No clinical evidence was included.

1.4.4 Quality assessment of clinical studies included in the evidence review

No studies were included.

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:.

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee agreed that the main focus of this review was to determine the safety and efficacy of long-term medication to manage the consequences of aSAH. The committee considered critical outcomes for decision making to be mortality, health and social related quality of life, and degree of disability or dependence in daily activities (e.g. Modified Rankin scale and patient reported outcome measures). The committee also considered return to daily activity, need for re-treatment, headache, number of seizures and complications to be important outcomes to guide decision making.

1.6.1.2 The quality of the evidence

No clinical evidence was identified.

The committee agreed that headache in people who have had SAH should be managed in line with the NICE guideline on headaches in the over 12s and the committee made a recommendation to cross-refer to this guideline. The consensus of the committee was that following the recommendations within this guideline was accepted practice and there was no requirement to make any research recommendations for this area.

1.6.1.3 Benefits and harms

Headache

The committee acknowledged that headache is a common symptom in people who have had a SAH and generally has a benign course, but in a small proportion headache may be due to chronic hydrocephalus and these people may have additional symptoms or signs of raised intracranial pressure.

The committee acknowledged the potential for anxiety amongst survivors of SAH who experience headache, reflecting their concerns that headache may indicate complications in their treatment or occurrence of new aneurysmal bleeding. The committee noted these are common concerns raised by people after SAH, which may be associated with morbidity, multiple presentations to healthcare professionals and unnecessary investigations.

There committee discussed the lack of evidence on the efficacy of specific long-term medicines to relieve headache after SAH. The committee agreed that in their experience long term management of headache in people who have had aneurysmal subarachnoid

haemorrhage would be the same as in the general population. The committee noted that in current practice most people with SAH who experience recurrent headache can be managed with reassurance and simple analgesics for pain relief.

The committee agreed healthcare professionals should be aware that headache in people who have had a subarachnoid haemorrhage is common and generally benign, but in some people may indicate chronic hydrocephalus. The committee agreed a consensus recommendation to support this message.

Seizures

Seizures can occur in people who have had a subarachnoid haemorrhage and survivors of SAH are considered to be at increased risk of seizures and epilepsy. The committee noted that there was no evidence on the efficacy of long-term antiepileptic medication to prevent or relieve seizures as a consequence of subarachnoid haemorrhage. The committee agreed that in their experience long term management of seizures in people who have had SAH would be the same as in the general population. The committee noted that current practice is to offer anticonvulsants to prevent recurrent seizures. The committee agreed that seizures after SAH should be treated in line with NICE guidance for the diagnosis and management of epilepsies and so decided to cross refer to this guideline. The consensus of the committee was that following the recommendations within this guideline was accepted practice and there was no requirement to make any research recommendations for this area.

1.6.2 Cost effectiveness and resource use

No published economic literature was identified for the management of headaches or seizures as a consequence of subarachnoid haemorrhage. The committee considered that these consequences should be managed in the same way as those who have not had a previous subarachnoid haemorrhage and so cross-referred to the NICE guidelines on headache and epilepsies where economic considerations will have been taken into account when making recommendations.

These recommendations are not expected to change current practice and result in a substantial impact on NHS resources.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 2: Review protocol: Long-term medicines to manage the consequences of SAH**

ID	Field	Content
0.	PROSPERO registration number	CRD42019153690
1.	Review title	What is the clinical and cost effectiveness of long-term medicines such as antiepileptic medicines for managing the consequences of subarachnoid haemorrhage?
2.	Review question	What is the clinical and cost effectiveness of long-term medicines such as antiepileptic medicines for managing the consequences of subarachnoid haemorrhage?
3.	Objective	To determine which long-term medication to manage the consequences of subarachnoid haemorrhage is the most clinically and cost-effective.
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 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	• Antiepileptic medicines

		• Medicines to control headache: ○ Beta-blockers ○ Simple analgesia - Acetaminophen - NSAIDs ○ Neuropathic nerve stabilisers ○ Tricyclic antidepressants (TCA) ○ Topiramate
8.	Comparator/Reference standard/Confounding factors	Comparators: • To each other (within and between class comparison) • To no treatment/placebo
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 aims to address the long-term management of people with aSAH following discharge.
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
13.	Secondary outcomes (important outcomes)	• Return to daily activity e.g driving • Need for retreatment • Headache (frequency/severity) • Number of seizures • Complications of medication (any) Outcomes will be grouped at <30 days, 30days-6 months, 6-12 months, and at yearly time-points thereafter.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The

		full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
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. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-

<table>
<tr><td></td><td></td><td colspan="3">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">Strata:
• n/a
Subgroups (if heterogeneity):
• Primary treatment of haemorrhage:
○ clipping
○ coiling
○ conservative management
• Grade of SAH
○ Good grade
○ Poor 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><td></td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre</td></tr>
</table>

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

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

1

2 **Table 3: 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.[64] **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 long-term medicines such as antiepileptic medicines for managing the consequences of subarachnoid haemorrhage?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[64]

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

B.18 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 4: 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
Embase (OVID)	1974 – 24 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.	exp case control study/
40.	case control*.ti,ab.
41.	Cross-sectional studies/
42.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
43.	or/29-42
44.	Meta-Analysis/
45.	exp Meta-Analysis as Topic/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(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.
52.	cochrane.jw.
53.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
54.	or/44-52
55.	randomized controlled trial.pt.
56.	controlled clinical trial.pt.

57.	randomi#ed.ti,ab.
58.	placebo.ab.
59.	randomly.ti,ab.
60.	Clinical Trials as topic.sh.
61.	trial.ti.
62.	or/55-61
63.	(anticonvuls* or anti-convuls* or anti epileptic* or antiepileptic* or AED*).ti,ab.
64.	(phenobarbit* or carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).ti,ab.
65.	(seizure* adj3 (prevent* or prophyla* or manag* or treatment* or control*)).ti,ab.
66.	exp Anticonvulsants/
67.	(nsaid* or ((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory))).ti,ab.
68.	(cox adj2 inhibitor*).ti,ab.
69.	coxibs.ti,ab.
70.	((cyclooxygenase or cyclo oxygenase) adj2 inhibitor*).ti,ab.
71.	(prostaglandin* adj2 (synthase* or synthesis or cyclooxygenase or cyclo oxygenase)).ti,ab.
72.	(ibuprofen or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or dichlofenal or aceclofenac or indometacin or indomethacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or etodolac or rofecoxib).ti,ab.
73.	exp Anti-Inflammatory Agents, Non-Steroidal/
74.	exp Prostaglandin-Endoperoxide Synthases/
75.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol).ti,ab.
76.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
77.	exp Adrenergic beta-Antagonists/
78.	((pain* or headache*) adj3 (manage* or managing or control* or treat* or relief*)).ti,ab.
79.	(acetaminophen or paracetamol).ti,ab.
80.	analges*.ti,ab.
81.	exp Analgesics/
82.	exp analgesia/
83.	exp Antidepressive Agents/
84.	(antidepress* or anti-depress*).ti,ab.
85.	serotonin norepinephrine reuptake inhibitor*.ti,ab.
86.	selective serotonin reuptake inhibitor*.ti,ab.
87.	(SSRI* or SNRI*).ti,ab.
88.	(amiltriptyline or doxepin or nortriptyline or imipramine or clomipramime or desipramine).ti,ab.
89.	(Duloxetine or milnacipran on venlafaxine or levomilnacipran or sertraline).ti,ab.
90.	or/63-89
91.	28 and 90 and (43 or 54 or 62)

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.	exp case control study/
42.	case control*.ti,ab.

43.	cross-sectional study/
44.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
45.	or/27-33,36-44
46.	random*.ti,ab.
47.	factorial*.ti,ab.
48.	(crossover* or cross over*).ti,ab.
49.	((doubl* or singl*) adj blind*).ti,ab.
50.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
51.	crossover procedure/
52.	single blind procedure/
53.	randomized controlled trial/
54.	double blind procedure/
55.	or/46-54
56.	systematic review/
57.	meta-analysis/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(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.
64.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
65.	cochrane.jw.
66.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
67.	or/56-65
68.	(anticonvuls* or anti-convuls* or anti epileptic* or antiepileptic* or AED*).ti,ab.
69.	(phenobarbit* or carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).ti,ab.
70.	(seizure* adj3 (prevent* or prophyla* or manag* or treatment* or control*)).ti,ab.
71.	exp anticonvulsive agent/
72.	(nsaid* or ((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory))).ti,ab.
73.	(cox adj2 inhibitor*).ti,ab.
74.	coxibs.ti,ab.
75.	((cyclooxygenase or cyclo oxygenase) adj2 inhibitor*).ti,ab.
76.	(prostaglandin* adj2 (synthase* or synthesis or cyclooxygenase or cyclo oxygenase)).ti,ab.
77.	(ibuprofen or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or dichlofenal or aceclofenac or indometacin or indomethacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or etodolac or rofecoxib).ti,ab.
78.	exp topiramate/

79.	nonsteroid antiinflammatory agent/
80.	prostaglandin synthase/
81.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol).ti,ab.
82.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
83.	beta adrenergic receptor blocking agent/
84.	((pain* or headache*) adj3 (manage* or managing or control* or treat* or relief*)).ti,ab.
85.	(acetaminophen or paracetamol).ti,ab.
86.	analges*.ti,ab.
87.	analgesic agent/
88.	analgesia/
89.	antidepressant agent/
90.	(antidepress* or anti-depress*).ti,ab.
91.	serotonin norepinephrine reuptake inhibitor*.ti,ab.
92.	selective serotonin reuptake inhibitor*.ti,ab.
93.	(SSRI* or SNRI*).ti,ab.
94.	(amiltriptyline or doxepin or nortriptyline or imipramine or clomipramime or desipramine).ti,ab.
95.	(Duloxetine or milnacipran on venlafaxine or levomilnacipran or sertraline).ti,ab.
96.	or/68-95
97.	26 and 96 and (55 or 67 or 45)

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.	(anticonvuls* or anti-convuls* or anti epileptic* or antiepileptic* or AED*):ti,ab
#8.	((phenobarbit* OR carbamazepine OR clobazam OR clonazepam OR ethosuximide OR gabapentin OR lacosamide OR lamotrigine OR levetiracetam OR oxcarbazepine OR phenytoin OR pregabalin OR rufinamide OR topiramate OR valproate OR vigabatrin OR zonisamide):ti,ab)
#9.	(seizure* near/3 (prevent* or prophyla* or manag* or treatment* or control*)):ti,ab
#10.	MeSH descriptor: [Anticonvulsants] explode all trees
#11.	(nsaid* or ((non-steroid* or nonsteroid*) near/1 (antiinflammatory or anti-inflammatory))):ti,ab
#12.	(cox near/2 inhibitor*):ti,ab
#13.	coxibs:ti,ab
#14.	((cyclooxygenase or cyclo oxygenase) near/2 inhibitor*):ti,ab
#15.	(prostaglandin* near/2 (synthase* or synthesis or cyclooxygenase or cyclo oxygenase)):ti,ab
#16.	(ibuprofen or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or dichlofenal or aceclofenac or indometacin or indomethacin or mefenamic acid or meloxicam or nabumetone or

	phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or etodolac or rofecoxib):ti,ab
#17.	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#18.	MeSH descriptor: [Prostaglandin-Endoperoxide Synthases] explode all trees
#19.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol):ti,ab
#20.	((beta or b) near/3 (block* or antagonist*)):ti,ab
#21.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#22.	((pain* or headache*) near/3 (manage* or managing or control* or treat* or relief*)):ti,ab
#23.	(acetaminophen or paracetamol):ti,ab
#24.	analges*:ti,ab
#25.	MeSH descriptor: [Analgesics] explode all trees
#26.	MeSH descriptor: [Analgesia] explode all trees
#27.	MeSH descriptor: [Antidepressive Agents] explode all trees
#28.	(antidepress* or anti-depress*):ti,ab
#29.	serotonin norepinephrine reuptake inhibitor*:ti,ab
#30.	selective serotonin reuptake inhibitor*:ti,ab
#31.	(SSRI* or SNRI*):ti,ab
#32.	(amiltriptyline or doxepin or nortriptyline or imipramine or clomipramime or desipramine):ti,ab
#33.	(Duloxetine or milnacipran on venlafaxine or levomilnacipran or sertraline):ti,ab
#34.	(or #7-#33)
#35.	#6 and #34

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 5: 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

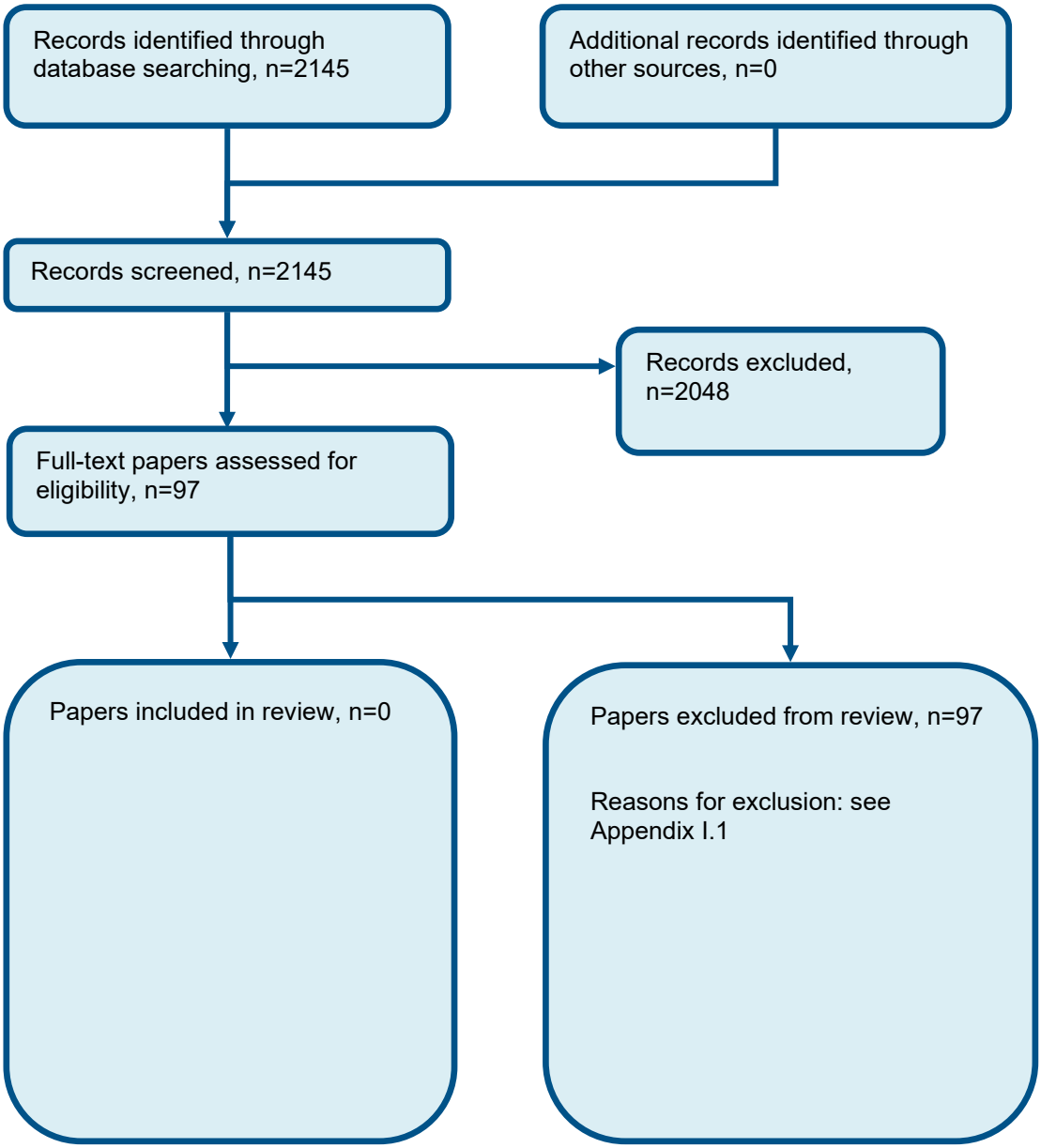
1 NHS EED and HTA (CRD) search terms

#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)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of long term medication consequences



Appendix D: Clinical evidence tables

No studies were included.

Appendix E: Forest plots

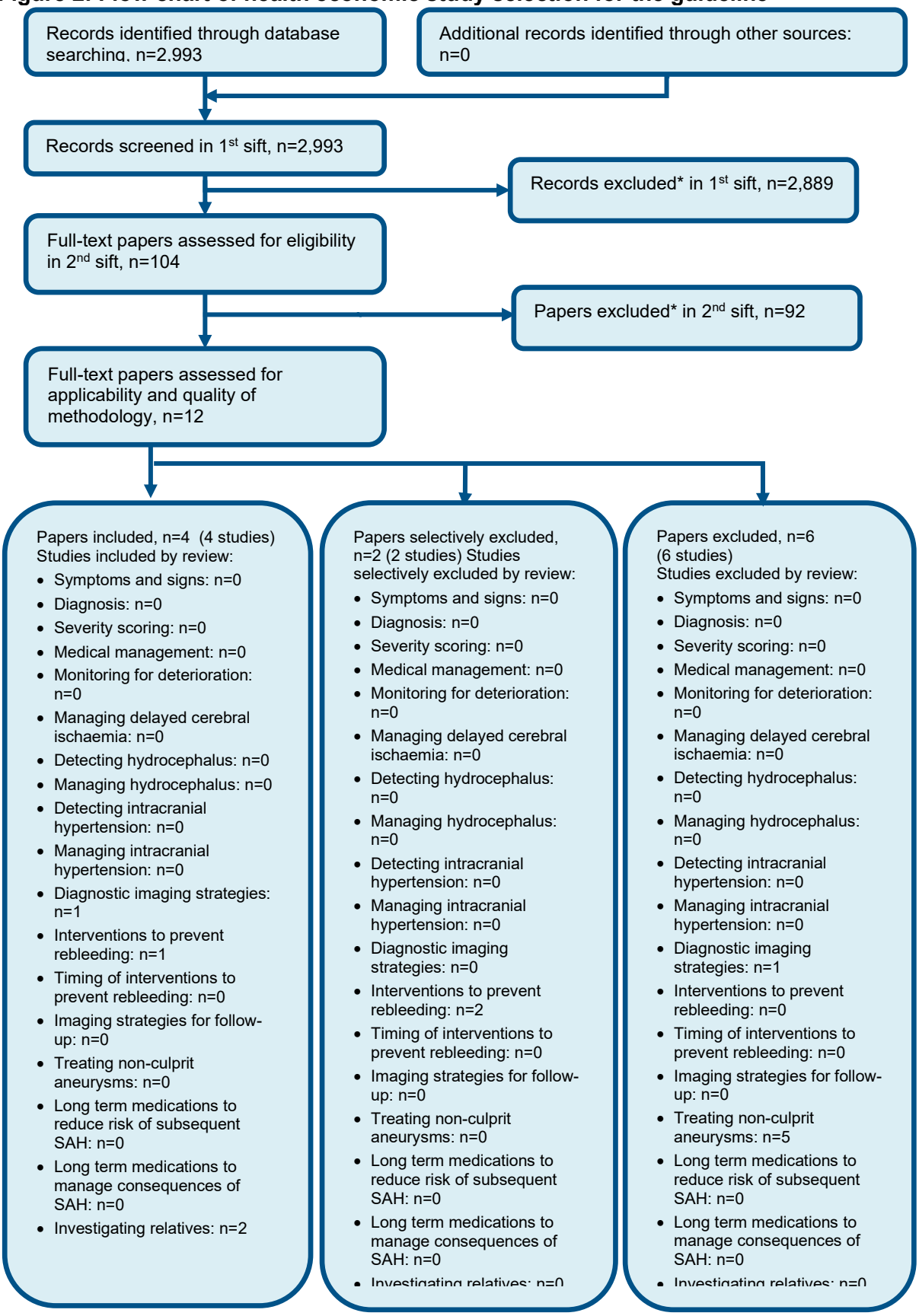
No studies were included.

Appendix F: GRADE tables

No studies were included.

Appendix G: Health economic evidence selection

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



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

1

Appendix H: Health economic evidence tables

None.

1 Appendix I: Excluded studies

I.1 2 Excluded clinical studies

3 **Table 6: Studies excluded from the clinical review**

Study	Exclusion reason
Allen 2018[1]	Inappropriate study design – no comparison group
Arena 2017[2]	Inappropriate study design – telephone interview post intervention
Baker 1995[3]	Inappropriate comparison – between antiepileptic medications
Basurto 2013[4]	Systematic review – references checked
Battey 2012[5]	Inappropriate intervention – short term use of medication only
Bidzinski 1992[6]	Inappropriate intervention – no antiepileptic medication given
Boyanpally 2018[7]	Citation only
Branco 2017[8]	Inappropriate study design – literature review
Buczacki 2004[9]	Inappropriate study design – risk factors for late epilepsy
Butzkueven 2000[10]	Inappropriate comparison – delayed seizure compared to no seizure
Byrne 2003[11]	Inappropriate study design – no comparison group
Chalouhi 2016[12]	Inappropriate study design – no comparison group
Choi 2009[13]	Inappropriate intervention – short term use of medication only
Chumnanvej 2007[14]	Inappropriate intervention – short term use of medication only
Claassen 2003[15]	Inappropriate study design – no comparison group
De Marchis 2016[16]	Inappropriate comparison – seizure as a risk factor
Dennis 2002[17]	Inappropriate comparison – status epilepticus compared to non status epilepticus
Dewan 2015[18]	Inappropriate study design – survey / questionnaire
Dhakal 2015[19]	Inappropriate study design
Dmytriw 2019[20]	Inappropriate intervention – short term use of medication only
Dorhout Mees 2010[21]	Incorrect comparison – magnesium sulphate
Elwood 2016[22]	Systematic review – references checked
Enomoto 2010[23]	Inappropriate study design – medication administration manual
Feng 2017[24]	Systematic review – references checked
Fung 2015[25]	Inappropriate comparison – seizure as a risk factor
Gilmore 2010[26]	Inappropriate study design – literature review
Gross 2014[27]	Incorrect population – majority of patients non SAH
Hamann 1993[28]	Inappropriate comparison – beta blocker comparison
Hart 1981[29]	Inappropriate comparison – different aneurysm sites
Hasan 1993[30]	Inappropriate comparison – patients with epileptic seizures compared to without seizures
Hasan 2011[31]	Inappropriate study design – cohort study
Hayashi 1999[32]	Inappropriate population – ruptured and unruptured aneurysms
Heros 2007[33]	Inappropriate study design – literature review
Hertle 2016[34]	Inappropriate study design – non-interventional study
Hop 2000[35]	Inappropriate intervention – short term use of medication only
Hudson 2019[36]	Literature review - references checked

Study	Exclusion reason
Human 2018[37]	Inappropriate intervention – short term use of medication only
Huttunen 2015[38]	Inappropriate comparison – all patients received same intervention
Huttunen 2017[39]	Inappropriate comparison – all patients received same intervention
Juvela 1995[40]	Inappropriate comparison – unadjusted for age
Karamchandani 2011[41]	Citation only
Karamchandani 2014[42]	Inappropriate study design – retrospective record review only
Keranen 1985[43]	Inappropriate study design – survey
Kuijlen 1996[44]	Systematic review – references checked
Lanzino 2011[45]	Systematic review – references checked
Lewis 2009[46]	Citation only
Lin 2008[48]	Inappropriate study design – no intervention
Lin 2003[47]	Inappropriate comparison – seizure as a risk factor
Liu 2017[49]	Inappropriate population – angioneurotic headache
Mahmoud 2017[50]	Systematic review – references checked
Marigold 2013[51]	Systematic review – references checked
McQuaid 2006[52]	Systematic review – references checked
Messe 2009[53]	Citation only
Messe 2009[54]	Inappropriate population – patients with SAH excluded
Milligan 2008[55]	Inappropriate study design – no adjustment for age
Mink 2011[56]	Inappropriate comparison – comparison between antiepileptic medication
Mocjiduki 2014[57]	Inappropriate population – patients with traumatic brain injury
Muroi 2014[58]	Inappropriate study design – no comparison group
Murphy-Human 2011[60]	Inappropriate intervention – short term use of medication only
Murphy-Human 2012[59]	Citation only
Naidech 2005[62]	Inappropriate intervention – short term use of medication only
Naidech 2009[61]	Inappropriate intervention – short term use of medication only
Nassiri 2016[63]	Inappropriate intervention – short term use of medication only
Neil Dwyer 1983[65]	Inappropriate study design – unclear methodology
Neil-Dwyer 1982[67]	Citation only
Neil-Dwyer 1985[66]	Inappropriate study design – unclear methodology
Neshige 2015[68]	Inappropriate comparison – patients with seizure compared to patients without seizure
North 1980[69]	Inappropriate population – supratentorial procedure
Panczykowski 2016[70]	Inappropriate study design – retrospective review
Perry 2008[71]	Inappropriate population – amyloidosis
Rahmanian 2019[72]	Inappropriate intervention – short term use of medication only
Ramos 2018[73]	Inappropriate study design – literature review
Raper 2011[74]	Inappropriate population – mixes ruptured and unruptured aneurysms
Raper 2013[75]	Systematic review – references checked
Ratilal 2013[76]	Systematic review – references checked
Reddig 2011[77]	Inappropriate study design – no adjustment for age
Rhoney 2000[78]	Inappropriate intervention – short term use of medication only
Riordan 2010[79]	Inappropriate study design – literature review

Study	Exclusion reason
Rosengart 2007[80]	Systematic review – references checked
Rowe 2014[81]	Systematic review – references checked
Rush 2016[82]	Inappropriate comparison – seizure as a risk factor
Shah 2009[83]	Inappropriate study design – no comparison group
Shaw 1990[84]	Inappropriate population – protocol exclusions
Spencer 2011[85]	Inappropriate population – protocol exclusions
Spoelhof 2018[86]	Citation only
Sundaram 1986[87]	Inappropriate study design – non comparative
Swope 2014[88]	Inappropriate comparison – retrospective data review
Szaflarski 2007[89]	Inappropriate population – protocol exclusions
Taylor 2011[90]	Inappropriate study design – no adjustment for age
Ukkola 1990[91]	Inappropriate study design – case series
Walter 1981[92]	Citation only
Yeh 1993[93]	Inappropriate population – protocol exclusions
Yerram 2018[94]	Inappropriate study design – literature review
Zafar 2012[95]	Systematic review – references checked
Zanaty 2019[96]	Inappropriate review population - patients harbouring aneurysms (not explicitly SAH)
Zandieh 2016[97]	Inappropriate intervention – short term use of medication only
Zeiler 2016[98]	Inappropriate study design – survey and audit

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 7: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	