National Institute for Health and Care Excellence

Final

# Subarachnoid haemorrhage

## [T] Evidence review for investigating relatives of people with aneurysmal subarachnoid haemorrhage

*NICE guideline NG228*

*Methods, evidence and recommendations*

*November 2022*

*Final*

*National Institute for Health and Care Excellence*

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ISBN: 978-1-4731-4815-4

# Contents

# 1 Detecting intracranial arterial aneurysms in first-degree relatives

Evidence review underpinning recommendation 1.4.15 and research recommendations in the NICE guideline.

## 1.1 Review question: What is the clinical and cost effectiveness of investigations to detect intracranial arterial aneurysms in relatives of adults who have had a subarachnoid haemorrhage?

## 1.2 Introduction

The reported prevalence of intracranial aneurysms varies between studies but is estimated to range from 2% to 5% in the general population. The chance of detecting an aneurysm on screening is reported to be around 10% in people with 2 first-degree relatives who have had subarachnoid haemorrhage. People with a family history are also at higher risk of subarachnoid haemorrhage than the general population.

Current practice varies, but some relatives of adults who have had a subarachnoid haemorrhage are offered investigation and those found to have an aneurysm at risk of rupture may be considered for intervention.

This review assessed evidence of clinical and cost-effectiveness of investigations to detect intracranial arterial aneurysms in relatives of adults who have had a subarachnoid haemorrhage.

## 1.3 PICO table

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

**Table 1: PICO characteristics of review question**

| | | |
|---|---|---|
| **Population** | First degree relatives of adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm. | |
| **Intervention(s)** | Assessment of first degree relatives of people with aSAH<br>• Assessment with CTA or MRA | |
| **Comparison(s)** | To no routine assessment | |
| **Outcomes** | Critical outcomes:<br>• Mortality<br>• Health and social-related quality of life (any validated measure)<br>• Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)<br>• Subarachnoid haemorrhage | Important outcomes:<br>• Presence of cerebral aneurysm<br>• Elective treatment |
| **Study design** | • Randomised controlled trials (RCTs), systematic reviews of RCTs.<br>• 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 assessment of first-degree relatives of people with SAH to no routine assessment 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 studies were included.

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

No studies were included.

# 1.5 Economic evidence

## 1.5.1 Included studies

Two health economic studies with the relevant comparison were included in this review.[24,3] These are summarised in the health economic evidence profile below (Table 2) and the health economic evidence tables in Appendix H:.

## 1.5.2 Excluded studies

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

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

### 1.5.3 Summary of studies included in the economic evidence review

**Table 2: Health economic evidence profile: Screening strategies compared to no screening**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Hopmans 2016[24] [Netherlands] | Partially applicable[(a)] | Potentially serious limitations[(b)] | • Probabilistic Markov model based on estimated incidence of aneurysm and rupture risk throughout lifetime.<br>• Cost-utility analysis (QALYs)<br>• Population: People with one affected first degree relative with aneurysmal subarachnoid haemorrhage.<br>• Comparators:<br>○ No screening<br>○ Multiple different screening strategies - every 5, 10 or 15 years between age bands 20-60, 20-70, 30-60, 30-70, 40-60,40-70<br>○ One time screening strategies at age 30,35,40, 45, 50, 55<br>Time horizon: Lifetime | For full incremental analysis of all 25 strategies please see the full evidence table in Appendix H. | | All screening strategies cost effective when compared to no screening.<br>The most cost effective strategy is screening every 5 years aged 30 to 70 with an ICER of £16,409 per QALY gained. | Probability strategies cost effective (£20/£30K threshold): NR<br><br>No further sensitivity analyses undertaken. |
| Bor 2010[3] [Netherlands] | Partially applicable[(c)] | Potentially serious limitations[(d)] | • Probabilistic Markov model based on estimated incidence of aneurysm and rupture risk throughout lifetime. | For full incremental analysis of the most efficient 10 strategies please see the full evidence table in Appendix H.[(e)] | | All screening strategies cost effective when compared to no screening. | ANCOVA analysis suggested that utility of individuals who were not offered screening and did |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | • Cost-utility analysis (QALYs)<br>• Population: People with two or more first degree relatives with aneurysmal subarachnoid haemorrhage.<br>• Comparators:<br>○ No screening<br>○ Multiple different screening strategies with different age and screening intervals<br>• Time horizon: Lifetime | | | The most cost effective strategy is screening every 2 years aged 20 to 80 with an ICER of £15,714 per QALY gained. | not experience SAH and utility of individuals having a negative screening most influenced health effectiveness. |

*Abbreviations: ANCOVA = Analysis of covariance; ICER= incremental cost-effectiveness ratio; NR= Not reported; QALY= quality-adjusted life years; RCT= randomised controlled trial*

*(a) Dutch resource use data (mix 1997-2003, 1996-97) and unit costs (2012) may not reflect current NHS context. Costs and health effects were discounted at a non-reference case rate (4%, 1.5% respectively). Non-NICE reference case utility measure used to estimate some utility values to calculate QALYs.*

*(b) Risk of aneurysm development and rupture were estimated from non-comparative cohort studies and assumptions made to estimate risk over time. Uncertainty not explored through sensitivity analysis.*

*(c) Dutch resource use data (mix 1997-2003, 1996-97) and unit costs (2007) may not reflect current NHS context. Costs and health effects were discounted at a non-reference case rate (1.5%). Unclear how estimates of utility values to calculate QALYs were determined.*

*(d) Treatment effects estimated primarily from non-comparative cohort studies and assumptions about aneurysm development and rupture risk over time.*

*(e) Due to the large volume of strategies in this study, the full incremental analysis in Appendix H does not include the interventions that were subject to dominance or extended dominance.*

### 1.5.4 Unit costs

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

**Table 3: UK costs of screening**

| Description | Unit cost |
|---|---|
| Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over [NHS Reference cost code: RD01A] | £121 |
| Neurosurgery consultant led outpatient follow up appointment [NHS Reference cost code: WF01B,150] | £228 |

*Source: NHS Reference Cost 2018/19*[50]

## 1.6 Evidence statements

### 1.6.1 Clinical evidence statements

No relevant published evidence was identified.

### 1.6.2 Health economic evidence statements

- One cost–utility analysis found that different screening strategies (that varied by age range and frequency of screening) were cost effective compared to no screening in people with one affected first degree relative with aneurysmal subarachnoid haemorrhage. When all the screening strategies compared in the model are considered, screening every 5 years between the age of 30 and 70 was the most cost-effective intervention (ICER: £16,409 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–utility analysis found that different screening strategies (that varied by age range and frequency of screening) were cost effective compared to no screening in people with two or more first degree relatives with aneurysmal subarachnoid haemorrhage. When all the screening strategies compared in the model are considered, screening every 2 years between the ages of 20 and 80 was the most cost-effective intervention (ICER: £15,714 per QALY gained). This analysis was assessed as partially applicable with very serious limitations.

## 1.7 The committee's discussion of the evidence

### 1.7.1 Interpreting the evidence

#### 1.7.1.1 The outcomes that matter most

The critical outcomes were mortality; health and social-related quality of life; degree of disability and subarachnoid haemorrhage. These outcomes were selected to understand the impact of screening and potential treatment on a relative's health and quality of life. The important outcomes were presence of cerebral aneurysm and elective treatment.

#### 1.7.1.2 The quality of the evidence

No relevant published clinical evidence was identified.

#### 1.7.1.3 Benefits and harms

The committee acknowledged that the main objective of investigating relatives of adults who have had a subarachnoid haemorrhage is detection of intracranial arterial aneurysms, some of which may be considered to require treatment. Despite the potential risks, treatment to secure an aneurysm could prevent death or other adverse consequences of subarachnoid haemorrhage.

The committee discussed that any benefits of investigation of relatives must be balanced against the risks and costs of investigation, including possible psychological burden of people knowing that they have an aneurysm. Investigation may also reveal an aneurysm that is not suitable for treatment, or the absence of aneurysms but the potential for development of new aneurysms. In some patients such findings may lead to increased anxiety and a fear of symptoms associated with subarachnoid haemorrhage, such as headache, potentially increasing unnecessary primary care or emergency department attendances.

The committee noted that routine screening of relatives for intracranial arterial aneurysms is currently not supported within NHS practice and any change in practice would have a significant resource impact including additional investigations and interventions requiring hospital consultations. The committee also agreed that the optimal timing and frequency of investigations to detect and monitor intracranial aneurysms in relatives is unknown. Nevertheless, the committee acknowledged that there is significant variation in national practice and a small number of relatives of people with a SAH currently undergo MR angiography to look for aneurysms. The committee noted that investigation would only be recommended for people thought to have a significant risk of having a brain aneurysm that could rupture at some point in the future, and the committee discussed this would apply to people with two or more first-degree relatives who have had subarachnoid haemorrhage as these individuals are at substantially increased risk of SAH. The committee acknowledged this reflected the guidance on brain aneurysm provided by the NHS and in their experience reflected practice at many UK neurosurgical centres. The committee also agreed that the risk of SAH is recognised to be greater in individuals with 2 first degree relatives with aSAH than those with 1 first degree relative with a SAH.

The committee noted the lack of evidence to support investigation, and decided to make a consensus recommendation to explain to patients (and if appropriate their family members) the uncertainties surrounding the risks and benefits of investigation for intracranial aneurysms in relatives of people with a SAH. The committee also acknowledged that in their experience some people do not want to be investigated for a potential aneurysm. The committee noted information about the rationale for and timing of investigations for brain aneurysms is available via the NHS website, and agreed this resource should be highlighted within the recommendations. The committee added that the relatives' own risk of developing an intracranial aneurysm should be taken into account when considering investigation, taking into account risk factors such as smoking, high blood pressure, and autosomal dominant polycystic kidney disease. The committee concluded that further research was needed.

### 1.7.2 Cost effectiveness and resource use

Two published economic evaluations were included in this review. Both studies assessed multiple different screening strategies in first degree relatives of people with subarachnoid haemorrhage from a Dutch perspective. One paper assessed screening strategies in people with 1 first degree relative, and showed that all screening strategies were cost effective compared to no screening; the most cost effective strategy was to screen every 5 years between the ages of 30 and 70. This paper was assessed as partially applicable with potentially serious limitations. One paper assessed screening strategies in people with 2 or more first degree relatives with aSAH, which also suggested that all screening strategies were cost effective compared to no screening; the most cost effective strategy was to screen

every 2 years between the ages of 20 and 80. This study was assessed as partially applicable with very serious limitations.

The committee were concerned that this evidence is not reflective of NHS practice or the NICE reference case. It was noted that any aneurysms identified on screening in England are typically only treated if they measure at least 7mm in diameter, whereas in the models the threshold for treatment was 5mm. Furthermore, the committee were concerned that there are likely to be some additional costs of monitoring aneurysms that have been identified but are too small to require treatment.

The committee considered the evidence used in the model to simulate the incidence of de novo aneurysms, aneurysm growth, rupture risk, and outcomes of aneurysm treatment and concluded the data used for the model were reasonable estimates. However, the committee could not make recommendations with potentially large resource impact without the support of comparative clinical evidence.

The committee noted that screening could sometimes be more detrimental (compared to no screening), and lead to additional costs for the NHS due to increased patient concerns and worries incurred as a result of screening. The committee acknowledged routine investigations for aneurysms in first-degree relatives could lead to an increase in visits to GPs and emergency departments when the NHS does not currently support routine investigation.

Overall, this recommendation is not expected to have a substantial resource impact as it is reflective of current practice in England.

### 1.7.3 Other factors the committee took into account

The committee discussed that requests for monitoring people with relatives who have had a subarachnoid haemorrhage is increasing and this is an important concern for patients and their families. Given the lack of evidence, the committee considered this to be an important area for further research and so by consensus made a research recommendation for the clinical and cost effectiveness of investigations to detect intracranial arterial aneurysms in first-degree relatives of people who have had a SAH (see Appendix J).

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81. Wermer MJ, Rinkel GJ, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. Stroke. 2003; 34(12):2788-2791

82. White PM. How to manage the patient with a family history of aneurysmal subarachnoid haemorrhage. Practical Neurology. 2004; 4(2):88-103

83. Woo D, Khoury J, Haverbusch MM, Sekar P, Flaherty ML, Kleindorfer DO et al. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. Neurology. 2009; 72(1):69-72

84. Zuurbier C, Mensing L, Wermer M, Juvela S, Lindgren A, Jaaskelainen J et al. Comparison of rupture risk between familial and sporadic intracranial aneurysms: an individual patient data meta-analysis. European Journal of Neurology. 2019; 26(Suppl 1):282

85. Zuurbier CCM, Mensing LA, Wermer MJH, Juvela S, Lindgren AE, Jaaskelainen JE et al. Comparison of rupture risk between familial and sporadic intracranial aneurysms: an individual patient data meta-analysis. European Stroke Journal. 2019; 4(Suppl 1):75-76

# Appendices

# Appendix A: Review protocols

**Table 4: Review protocol: Detecting aneurysms in relatives of people with SAH**

| Field | Content |
|---|---|
| PROSPERO registration number | CRD42019160102 |
| Review title | What is the clinical and cost effectiveness of investigations to detect intracranial arterial aneurysms in relatives of adults who have had a subarachnoid haemorrhage? |
| Review question | What is the clinical and cost effectiveness of investigations to detect intracranial arterial aneurysms in relatives of adults who have had a subarachnoid haemorrhage? |
| Objective | To determine if investigations to detect intracranial arterial aneurysms in relatives of people with SAH is clinically and cost-effective. |
| Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br><br>Searches will be restricted by:<br>• English language only<br><br>The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review. |
| Condition or domain being studied | Aneurysmal subarachnoid haemorrhage |
| Population | Inclusion: First degree relatives of adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm.<br>Exclusion:<br>• Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation.<br>• Children and young people aged 15 years and younger. |
| Intervention/Exposure/Test | • Assessment of first degree relatives of people with aSAH<br>• Assessment with CTA or MRA<br>• Diagnostic accuracy of CTA and MRA has been shown to be high. DSA is invasive and so should not be used as a screening intervention on relatives who may not have aneurysms. |
| Comparator/Reference standard/Confounding factors | Comparators:<br>• To no routine assessment |
| Types of study to be included | Randomised controlled trials (RCTs), systematic reviews of RCTs.<br>If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies. |
| Other exclusion criteria | Exclusions: |

| Field | Content |
|---|---|
| | • Non-English language studies<br>• Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. |
| Context | n/a |
| Primary outcomes (critical outcomes) | • Mortality<br>• Health and social-related quality of life (any validated measure)<br>• Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)<br>• Subarachnoid haemorrhage<br><br>Outcomes will be captured at or after the point of imaging follow-up. Outcomes will therefore be grouped at <1 year, 1-2 years and >2-5 years. |
| Secondary outcomes (important outcomes) | • Presence of cerebral aneurysm<br>• Elective treatment<br><br>Outcomes will be captured at or after the point of imaging follow-up. Outcomes will therefore be grouped at <1 year, 1-2 years and >2-5 years. |
| 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.<br>• EviBASE will be used for data extraction.<br>• If not an intervention review, add: A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). |
| Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>Randomised Controlled Trial: Cochrane RoB (2.0)<br>Non randomised study, including cohort studies: Cochrane ROBINS-I<br><br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br>• papers were included /excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br>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. |
| Strategy for data synthesis | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).<br>GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta- |

| Field | Content | |
|---|---|---|
| | 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.<br>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/<br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.<br>Subgroups will be investigated separately if meta-analysed results show heterogeneity.<br>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-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. | |
| Analysis of sub-groups | Strata:<br>• n/a<br>Subgroups for heterogeneity:<br>• Extent of familial history:<br>• single first degree relative<br>• multiple first-degree relatives<br>• Smoking status<br>• Smoker<br>• Non-smoker<br>• Blood pressure<br>• Hypertensive (>140/90)<br>• Non-hypertensive (<140/90)<br>• Polycystic kidney<br>○ Yes<br>○ No<br>• Genetic causes present (identifiable connective tissue disorders e.g. Marfans, Ehlers-Danlos)<br>○ Yes<br>○ No | |
| Type and method of review | ☒ | Intervention |
| | ☒ | Diagnostic |
| | ☐ | Prognostic |
| | ☐ | Qualitative |
| | ☐ | Epidemiologic |
| | ☐ | Service Delivery |
| | ☐ | Other (please specify) |
| Language | English | |
| Country | England | |
| Anticipated or actual start date | | |

| Field | Content | | |
|---|---|---|---|
| Anticipated completion date | 3 February 2021 | | |
| Stage of review at time of this submission | Review stage | Started | Completed |
| | Preliminary searches | ☑ | ☑ |
| | Piloting of the study selection process | ☑ | ☑ |
| | Formal screening of search results against eligibility criteria | ☑ | ☑ |
| | Data extraction | ☑ | ☑ |
| | Risk of bias (quality) assessment | ☑ | ☑ |
| | Data analysis | ☑ | ☑ |
| Named contact | 5a. Named contact<br>National Guideline Centre<br>5b Named contact e-mail<br>SAH@nice.org.uk<br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | | |
| Review team members | From the National Guideline Centre:<br>• Ms Gill Ritchie<br>• Mr Ben Mayer<br>• Mr Audrius Stonkus<br>• Mr Vimal Bedia<br>• Ms Emma Cowles<br>• Ms Jill Cobb<br>• Ms Elizabeth Pearton<br>• Ms Amelia Unsworth | | |
| Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. | | |
| 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. | | |
| 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. | | |
| Other registration details | | | |
| Reference/URL for published protocol | | | |

| Field | Content | |
|---|---|---|
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts<br>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. | |
| Keywords | | |
| Details of existing review of same topic by same authors | None | |
| Current review status | ☒ | Ongoing |
| | ☐ | Completed but not published |
| | ☐ | Completed and published |
| | ☐ | Completed, published and being updated |
| | ☐ | Discontinued |
| Additional information | | |
| Details of final publication | www.nice.org.uk | |

**Table 5: 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.<br>• 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).<br>• 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.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• 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.<br>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.[49]<br><br>Inclusion and exclusion criteria<br>• 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.<br>• 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 investigations to detect intracranial arterial aneurysms in relatives of adults who have had a subarachnoid haemorrhage?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[49]

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 6: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 26 June 2020 | Exclusions |
| Embase (OVID) | 1974 – 26 June 2020 | Exclusions |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2020 Issue 6 of 12<br>CENTRAL to 2020 Issue 6 of 12 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp Subarachnoid Hemorrhage/ |
| 2. | ((subarachnoid* or arachnoid* or cerebral or intracerebral or intra-cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab. |
| 3. | (SAH or aSAH).ti,ab. |
| 4. | Intracranial Aneurysm/ |
| 5. | ((subarachnoid* or arachnoid* or cerebral or intracerebral or intra-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. | Magnetic Resonance.ti,ab. |
| 30. | (MRA or MRAs or MRI or MRIs or NMR or NMRs).ti,ab. |
| 31. | Magnetic Resonance Angiography/ or Magnetic Resonance Imaging/ |
| 32. | (tomograph* or CTA or CTAs or CAT).ti,ab. |
| 33. | tomography, x-ray computed/ or computed tomography angiography/ |
| 34. | diagnostic imaging/ or tomography/ |
| 35. | (angiogra* or arteriogra*).ti,ab. |
| 36. | cerebral angiography/ |
| 37. | Mass screening/ |
| 38. | screen*.ti,ab. |
| 39. | (scan* or image* or imaging).ti,ab. |
| 40. | risk assess*.ti,ab. |
| 41. | Risk assessment/ |
| 42. | or/29-41 |
| 43. | (family or families or familial or parent* or sibling*).ti,ab. |
| 44. | (first degree adj2 (relative* or relation*)).ti,ab. |
| 45. | (hereditary or heredity or heritability or inherit*).ti,ab. |
| 46. | ((genetic or gene or genes) adj2 (predispos* or factor* or influenc* or risk* or determin* or prognos* or test or tests or defect* or fault* or mutation or mutate* or mutant)).ti,ab. |
| 47. | genetic predisposition to disease/ |
| 48. | family health/ |
| 49. | Heredity/ |
| 50. | Family/ |
| 51. | or/43-50 |
| 52. | 28 and 42 and 51 |

**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. | Magnetic Resonance.ti,ab. |
| 28. | (MRA or MRAs or MRI or MRIs or NMR or NMRs).ti,ab. |
| 29. | nuclear magnetic resonance imaging/ or magnetic resonance angiography/ |
| 30. | (tomograph* or CTA or CTAs or CAT).ti,ab. |
| 31. | computer assisted tomography/ or computed tomographic angiography/ |
| 32. | brain angiography/ |
| 33. | mass screening/ |
| 34. | screening test/ |
| 35. | screen*.ti,ab. |
| 36. | (angiogra* or arteriogra*).ti,ab. |
| 37. | (scan* or image* or imaging).ti,ab. |
| 38. | diagnostic imaging/ |
| 39. | risk assess*.ti,ab. |
| 40. | risk assessment/ |
| 41. | or/27-40 |
| 42. | (family or families or familial or parent* or sibling*).ti,ab. |
| 43. | (first degree adj2 (relative* or relation*)).ti,ab. |
| 44. | (hereditary or heritability or heredity or inherit*).ti,ab. |
| 45. | ((genetic or gene or genes) adj2 (predispos* or factor* or influenc* or risk* or determin* or prognos* or test or tests or defect* or fault* or mutation or mutate* or mutant)).ti,ab. |
| 46. | genetic predisposition/ |
| 47. | family health/ |
| 48. | heredity/ |
| 49. | familial disease/ or "genetic and familial disorders"/ |
| 50. | family/ |
| 51. | family assessment/ |
| 52. | or/42-51 |
| 53. | 26 and 41 and 52 |

**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] this term only |
| #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. | Magnetic Resonance:ti,ab |
| #8. | (MRA or MRAs or MRI or MRIs or NMR or NMRs):ti,ab |
| #9. | MeSH descriptor: [Magnetic Resonance Angiography] this term only |
| #10. | MeSH descriptor: [Magnetic Resonance Imaging] this term only |
| #11. | (tomograph* or CTA or CTAs or CAT):ti,ab |
| #12. | MeSH descriptor: [Tomography, X-Ray Computed] this term only |
| #13. | MeSH descriptor: [Computed Tomography Angiography] this term only |
| #14. | MeSH descriptor: [Diagnostic Imaging] this term only |
| #15. | MeSH descriptor: [Tomography] this term only |
| #16. | (angiogra* or arteriogra*):ti,ab |
| #17. | MeSH descriptor: [Cerebral Angiography] this term only |
| #18. | MeSH descriptor: [Mass Screening] this term only |
| #19. | screen*:ti,ab |
| #20. | (scan* or image* or imaging):ti,ab |
| #21. | risk assess*:ti,ab |
| #22. | MeSH descriptor: [Risk Assessment] this term only |
| #23. | (or #7-#22) |
| #24. | (family or families or familial or parent* or sibling*):ti,ab |
| #25. | (first degree next/2 (relative* or relation*)):ti,ab |
| #26. | (hereditary or heredity or heritability or inherit*):ti,ab |
| #27. | ((genetic or gene or genes) next/2 (predispos* or factor* or influenc* or risk* or determin* or prognos* or test or tests or defect* or fault* or mutation or mutate* or mutant)):ti,ab |
| #28. | MeSH descriptor: [Genetic Predisposition to Disease] this term only |
| #29. | MeSH descriptor: [Family Health] this term only |
| #30. | MeSH descriptor: [Heredity] this term only |
| #31. | MeSH descriptor: [Family] this term only |
| #32. | (or #24-#31) |
| #33. | #6 and #23 and #32 |

## 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 7: Database date parameters and filters used**

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

**Medline (Ovid) search terms**

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

| | |
|---|---|
| 33. | Economics, Pharmaceutical/ |
| 34. | exp "Fees and Charges"/ |
| 35. | exp Budgets/ |
| 36. | budget*.ti,ab. |
| 37. | cost*.ti. |
| 38. | (economic* or pharmaco?economic*).ti. |
| 39. | (price* or pricing*).ti,ab. |
| 40. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 41. | (financ* or fee or fees).ti,ab. |
| 42. | (value adj2 (money or monetary)).ti,ab. |
| 43. | or/27-42 |
| 44. | 26 and 43 |

**Embase (Ovid) search terms**

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

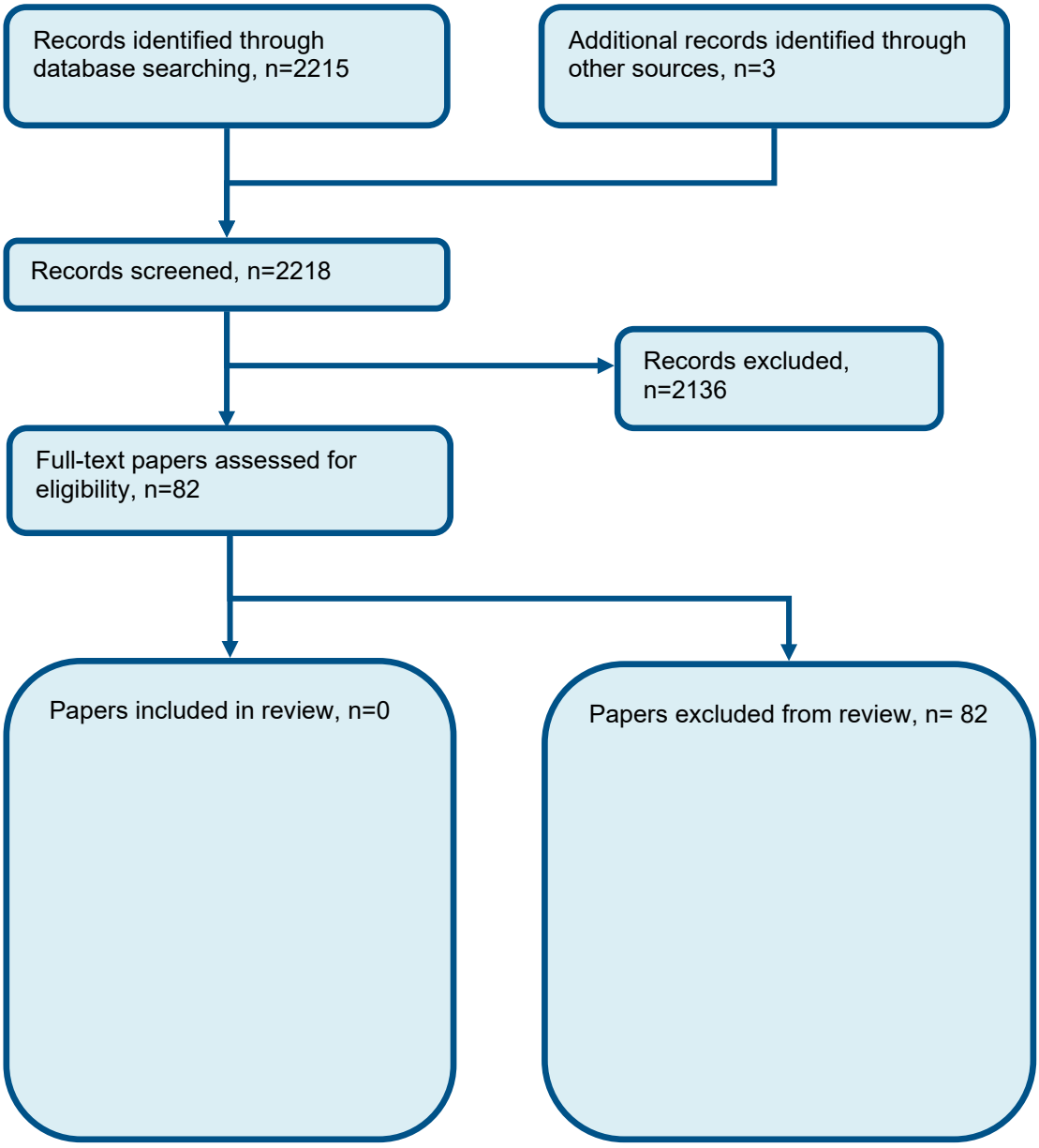
| | |
|---|---|
| 29. | budget/ |
| 30. | funding/ |
| 31. | budget*.ti,ab. |
| 32. | cost*.ti. |
| 33. | (economic* or pharmaco?economic*).ti. |
| 34. | (price* or pricing*).ti,ab. |
| 35. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 36. | (financ* or fee or fees).ti,ab. |
| 37. | (value adj2 (money or monetary)).ti,ab. |
| 38. | or/25-37 |
| 39. | 24 and 38 |

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

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

# Appendix C: Clinical evidence selection

**Figure 1: Flow chart of clinical study selection for the review of detecting aneurysms in relatives of people with SAH**



# Appendix D: Clinical evidence tables

No studies were included.

# Appendix E: Forest plots

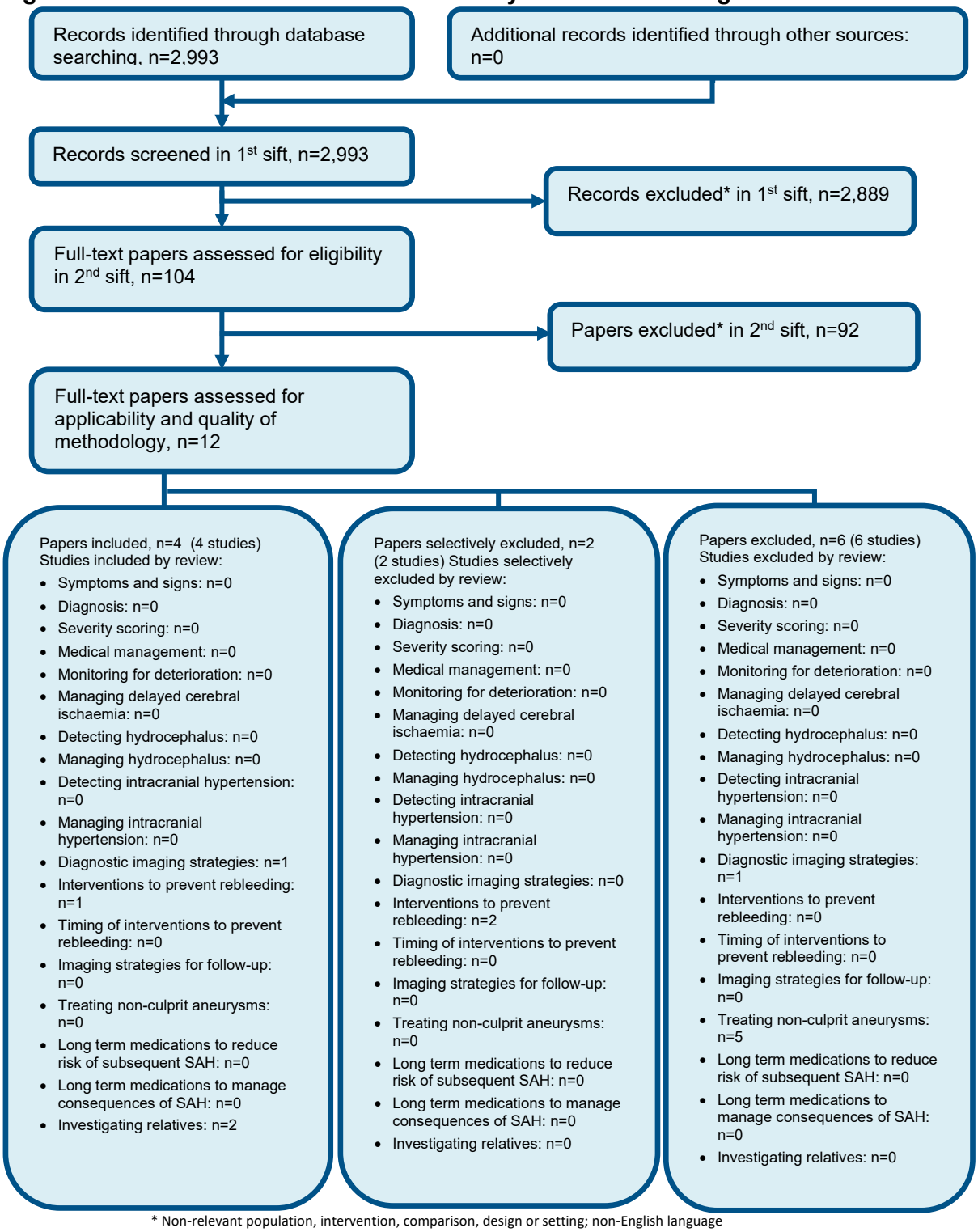
No studies were included.

# 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

# Appendix H: Health economic evidence tables

| Study | Hopmans 2016 | | |
|---|---|---|---|
| **Study details** | **Population & Interventions** | **Costs** | **Health outcomes** | **Cost effectiveness** |

**Economic analysis:** CUA (health outcome: QALYs)

**Study design:** Probabilistic decision analytic model

**Approach to analysis:** Markov model with health states: healthy no aneurysm, healthy with aneurysm, healthy with known small aneurysm, disabled, dead. 1 year cycles. Incidence of aneurysm and rupture risk constant throughout lifetime. Detected aneurysms >5mm treated with either clipping or coiling.

**Perspective:** Dutch healthcare provider

**Time horizon:** Lifetime

**Treatment effect duration:** n/a

**Discounting:** Costs: 4%; Outcomes: 1.5%

**Population:** People with one affected first degree relative with aneurysmal subarachnoid haemorrhage.

**Cohort settings:**
Start age: 15
Male: NR

**Interventions:**

1. No screening
2. Screening every 5 years, age 20 to 60
3. Screening every 10 years, age 20 to 60
4. Screening every 15 years, age 20 to 60
5. Screening every 5 years, age 20 to 70
6. Screening every 10 years, age 20 to 70
7. Screening every 15 years, age 20 to 70
8. Screening every 5 years, age 30 to 60
9. Screening every 10 years, age 30 to 60
10. Screening every 15 years, age 30 to 60
11. Screening every 5 years, age 30 to 70

Full incremental analysis[(a)(b)]

| Intv | Cost | QALY | Incr cost | Incr QALY | ICER |
|---|---|---|---|---|---|
| 1 | £0 | 0 | Baseline | | |
| 25 | £76 | 0.01 | £76 | 0.01 | £7,600 |
| 23 | £109 | 0.011 | Dominated by 24 | | |
| 24 | £90 | 0.011 | £14 | 0.001 | Extendedly dominated |
| 22 | £126 | 0.013 | £50 | 0.003 | Extendedly dominated |
| 20 | £184 | 0.014 | Dominated by 21 | | |
| 21 | £147 | 0.016 | £71 | 0.006 | Extendedly dominated |
| 16 | £215 | 0.027 | £139 | 0.017 | £8,176 |
| 19 | £253 | 0.028 | £38 | 0.001 | Extendedly dominated |
| 15 | £279 | 0.03 | £64 | 0.003 | Extendedly dominated |
| 10 | £361 | 0.035 | Dominated by 18 | | |
| 18 | £318 | 0.035 | £103 | 0.008 | £12,875 |
| 13 | £369 | 0.036 | £51 | 0.001 | Extendedly dominated |
| 14 | £430 | 0.038 | £112 | 0.003 | Extendedly dominated |
| 4 | £509 | 0.043 | Dominated by 9 | | |
| 9 | £460 | 0.044 | £142 | 0.009 | £15,778 |

12. Screening every 10 years, age 30 to 70
13. Screening every 15 years, age 30 to 70
14. Screening every 5 years, age 40 to 60
15. Screening every 10 years, age 40 to 60
16. Screening every 15 years, age 40 to 60
17. Screening every 5 years, age 40 to 70
18. Screening every 10 years, age 40 to 70
19. Screening every 15 years, age 40 to 70
20. Screening once at age 30
21. Screening once at age 35
22. Screening once at age 40
23. Screening once at age 45
24. Screening once at age 50
25. Screening once at age 55

| | | | | | |
|---|---|---|---|---|---|
| 12 | £498 | 0.044 | Dominated by 9 | | |
| 17 | £505 | 0.045 | £45 | 0.001 | Extendedly dominated |
| 7 | £558 | 0.048 | £98 | 0.004 | Extendedly dominated |
| 3 | £707 | 0.056 | £247 | 0.012 | Extendedly dominated |
| 6 | £746 | 0.06 | £286 | 0.016 | Extendedly dominated |
| 8 | £746 | 0.06 | £286 | 0.016 | Extendedly dominated |
| 11 | £821 | 0.066 | £361 | 0.022 | £16,409 |
| 2 | £1,197 | 0.076 | £376 | 0.01 | Extendedly dominated |
| 5 | £1,272 | 0.084 | £451 | 0.018 | £25,056 |

| | | | | | |
|---|---|---|---|---|---|
| | | | **Currency & cost year:** 2012 Euros (presented here as 2012 UK pounds[c]) **Cost components incorporated:** Costs of screening - MRA and outpatient consultation with a neurologist and specialised nurse. Costs of UIA treatment - hospitalisation, follow-up in outpatient clinic and imaging. Cost associated with being disabled (in nursing home). | | Each individual screening strategy compared to no screening is cost effective at £20,000 per QALY gained. The most cost effective screening strategy when compared to each other is 11 (screening every 5 years, age 30 to 70). **Analysis of uncertainty:** No further sensitivity analyses undertaken. |
| **Data sources** | | | | | |
| **Health outcomes:** Calibrated the probability of unruptured intracranial aneurysm developing and rupture risk to ensure unruptured intracranial aneurysm prevalence and aSAH incidence as estimated in the model were similar to reported literature from Danish and Swedish cohort studies (Bor 2008 & Bromberg 1995) of 4.0% in first degree relatives and 20.7/100,000 per year in first degree relatives respectively. Mortality for other causes based on age-specific mortality rates in the general Dutch-population. **Quality-of-life weights:** Converted SF-36 scores to utilities using the method as described by Nichol 2001 or used available EQ5D scores. Assumed that the effect of screening on utility lasted one year and that utility changed each time screening was performed. **Cost sources:** Costs were derived from the Dutch manual for costing 2012, local data of Utrecht University Medical Centre and literature (Halkes 2006 & Roos 2002). | | | | | |

| Comments |
| --- |
| **Source of funding:** Grant of the Netherlands Organisation for Scientific Research (NWO). **Limitations:** Dutch resource use data (mix 1997-2003, 1996-97) and unit costs (2012) may not reflect current NHS context. Costs and health effects were discounted at a non-reference case rate (4%, 1.5% respectively). Non-NICE reference case utility measure used to estimate some utility values to calculate QALYs. Risk of aneurysm development and rupture were estimated from non-comparative cohort studies and assumptions made to estimate risk over time. Uncertainty not explored through sensitivity analysis. **Other:** None. |
| **Overall applicability:**[(d)] Partially applicable **Overall quality:**[(e)] Potentially serious limitations |

*Abbreviations: CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; n/a= not applicable; QALYs= quality-adjusted life year; SF-36=36-Item Short Form Health Survey*

*(a) Intervention number in order of least to most effective*

*(b) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.*

*(c) Converted using 2012 purchasing power parities[52]*

*(d) Directly applicable / Partially applicable / Not applicable*

*(e) Minor limitations / Potentially serious limitations / Very serious limitations*

<table>
<tr><th>Study</th><th colspan="4">Bor 2010</th></tr>
<tr><th>Study details</th><th>Population & Interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)<br><br>Study design: Decision analytic model<br>Approach to analysis:<br>Markov model with health states: healthy without aneurysm, healthy with aneurysm, healthy with known small aneurysm, disabled, and dead. 1 year cycles. Incidence of aneurysm and rupture risk constant throughout lifetime. If aneurysm suspected on MRA then DSA was undertaken to identify false positives. Detected aneurysms treated with either clipping or coiling unless too small (<3-5mm). 63%-67% considered too small for treatment.<br><br>Perspective: Dutch healthcare provider<br>Time horizon: Lifetime<br>Treatment effect duration: n/a<br>Discounting: Costs: 1.5%; Outcomes: 1.5%</td>
<td>Population: People with two or more first degree relatives with aneurysmal subarachnoid haemorrhage.<br><br>Cohort settings:<br>Start age: 15<br>Male: NR<br><br>Interventions:<br>1. No screening<br>2. Screening every 10 years, age 20 to 60<br>3. Screening every 15 years, age 20 to 60<br>4. Screening every 15 years, age 20 to 70<br>5. Screening every 2 years, age 20 to 80<br>6. Screening every 3 years, age 20 to 80<br>7. Screening every 5 years, age 20 to 80<br>8. Screening every 7 years, age 20 to 80<br>9. Screening every 10 years, age 20 to 80<br>10. Screening every 15 years, age 40 to 60</td>
<td>Full incremental analysis[a][b]<br><table><tr><th>Intv</th><th>Cost</th><th>QALY</th><th>Incr cost</th><th>Incr QALY</th><th>ICER</th></tr><tr><td>1</td><td>£0</td><td>0</td><td colspan="3">Baseline</td></tr><tr><td>10</td><td>£69</td><td>0.060</td><td>£69</td><td>0.060</td><td>£1,150</td></tr><tr><td>3</td><td>£143</td><td>0.120</td><td>£74</td><td>0.060</td><td>£1,233</td></tr><tr><td>4</td><td>£268</td><td>0.150</td><td>£125</td><td>0.030</td><td>£4,167</td></tr><tr><td>2</td><td>£370</td><td>0.170</td><td>£102</td><td>0.020</td><td>£5,100</td></tr><tr><td>9</td><td>£639</td><td>0.210</td><td>£269</td><td>0.040</td><td>£6,725</td></tr><tr><td>8</td><td>£955</td><td>0.250</td><td>£316</td><td>0.040</td><td>£7,900</td></tr><tr><td>7</td><td>£1,374</td><td>0.280</td><td>£419</td><td>0.030</td><td>£13,967</td></tr><tr><td>6</td><td>£2,257</td><td>0.340</td><td>£883</td><td>0.060</td><td>£14,717</td></tr><tr><td>5</td><td>£3,357</td><td>0.410</td><td>£1,100</td><td>0.070</td><td>£15,714</td></tr></table>
Currency & cost year:<br>2007 Euros (presented here as 2007 UK pounds[b])<br>Cost components incorporated:<br>Costs of screening - MRA and outpatient consultation with a neurologist and specialised nurse.<br>Costs of UIA treatment - hospitalisation, follow-up in outpatient clinic and imaging.<br>Cost associated with being disabled (in nursing home).<br>Complications from recoiling not included.</td>
<td></td>
<td>All screening strategies cost effective when compared to no screening.<br><br>Multiple other strategies (37 in total) were included in the analysis. Those reported are those that are most efficient (dominated or extendedly dominated strategies not reported here).<br><br>The most cost effective screening strategy when compared to each other is 5 (screening every 2 years, age 20 to 80).</td>
</tr>
</table>

| | | | | |
|---|---|---|---|---|
| | | | | **Analysis of uncertainty:** To identify which input variables influence model outcomes the most an ANCOVA analysis was undertaken. Only suitable for models that are highly linear – in this model this only applied to the health effects. This analysis suggested that utility of individuals who were not offered screening and did not experience SAH and utility of individuals having a negative screening most influenced health effectiveness. |

**Data sources**

**Health outcomes:** Due to limited evidence decided to use a probability of aneurysm development of 0.3%-0.7% per annum, and a probability of aneurysm rupture of 1.0 – 2.0% per annum. Small aneurysms were assigned a rupture rate of 0.5%-1.0% per annum, and an enlargement (>1mm) of 2.2%-4.9%. Small aneurysms were imaged every 2 years until they either enlarged or ruptured. Enlarged small aneurysms changed the next cycle to rupture rate of 1.0%-2.0%, and were always treated following the next imaging moment. With these probabilities approximately 27% of the study population would develop 1 or more aneurysms during their lifetime, and approximately 10% of the study population would develop SAH during their lifetime in the natural history (no screening) scenario. **Quality-of-life weights:** Not reported. **Cost sources:** College voor zorgverzekeringen kostenhandleiding 2004 (Dutch Health Care Insurance Board), Halkes 2006, Roos 2002.

**Comments**

**Source of funding:** Grant of the Netherlands Organisation for Scientific Research (NWO). **Limitations:** Dutch resource use data (mix 1997-2003, 1996-97) and unit costs (2007) may not reflect current NHS context. Costs and health effects were discounted at a non-reference case rate (1.5%). Unclear how estimates of utility values to calculate QALYs were determined. Risk of aneurysm development and rupture were estimated from non-comparative cohort studies and assumptions made to estimate risk over time. **Other:** None.

**Overall applicability:**[c] Partially applicable **Overall quality:**[d] Very serious limitations

*Abbreviations: CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; n/a= not applicable; QALYs= quality-adjusted life year; SF-36=36-Item Short Form Health Survey*

*(a) Converted using 2007 purchasing power parities[52]*

*(b) Intervention number in order of least to most effective*

*(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies*

*by comparing each to the next most effective option. Due to the large volume of strategies, interventions that were subject to dominance or extended dominance were not reported here.*

*(d) Directly applicable / Partially applicable / Not applicable*

*(e) Minor limitations / Potentially serious limitations / Very serious limitations*

# Appendix I: Excluded studies

## I.1 Excluded clinical studies

**Table 8: Studies excluded from the clinical review**

| Reference | Reason for exclusion |
|---|---|
| Bhat 2011[1] | Incorrect intervention – no assessments to detect SAH in families |
| Bhat 2012[2] | Incorrect intervention – no assessments to detect SAH in families |
| Bor 2010[3] | Incorrect study design – economics Markov model |
| Bor 2008[4] | Incorrect intervention – no assessments to detect SAH in families |
| Bor 2014[5] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Bossuyt 2005[6] | No relevant outcomes identified |
| Broderick 2009[7] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Broderick 2005[8] | Incorrect study design – study protocol only |
| Bromberg 1995[9] | Incorrect intervention – no assessments to detect SAH in families |
| Bromberg 1995[10] | Incorrect intervention – no assessments to detect SAH in families |
| Brown 1999[11] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Brown 2014[12] | Incorrect study design – review / editorial (references checked) |
| Chalouhi 2011[13] | Incorrect study design – Systematic review (references checked) |
| Chan 2016[14] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Coppola 1973[15] | No relevant outcomes identified |
| Crawley 1999[16] | Incorrect study design – modelling of potential investigation results |
| Dippel 1992[17] | Incorrect study design – economics paper |
| Edelsohn 1972[18] | No relevant outcomes identified |
| Flahault 2016[19] | Incorrect study design – opinions based on e-questionnaire |
| Flahault 2018[20] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Fox 1980[21] | No relevant outcomes identified |
| Greebe 1997[22] | Incorrect intervention – no assessments to detect SAH in families |
| Hashimoto 1977[23] | No relevant outcomes identified |
| Huston 1996[25] | Incorrect intervention – investigation and follow up of intracranial haemorrhage for people with ADPKD |
| Jacoby 2006[26] | Incorrect study design – review / editorial (references checked) |
| Jain 1974[27] | No relevant outcomes identified |

| Reference | Reason for exclusion |
|---|---|
| Kasuya 2000[28] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Kelly 2014[29] | Incorrect study design – Systematic review (references checked) |
| Kim 2003[31] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Kim 2005[30] | Incorrect study design – retrospective investigation of SAH in families (no screening) |
| Kojima 1998[32] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Koshy 2010[33] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Kubota 2001[34] | Incorrect intervention – prevalence of risk factors for SAH |
| Leblanc 1997[35] | Incorrect study design – Literature review (references checked) |
| Leblanc 1995[36] | Incorrect study design – mixed methodology of screening (DSA/MRA); no comparison group for people with familial risk of SAH |
| Lee 2008[37] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Lin 2005[38] | Incorrect study design – abstracts / case reports only |
| Lindgaard 2003[39] | Incorrect study design – retrospective investigation of SAH in families (no screening) |
| Lorenzo-Betancor 2018[40] | Incorrect intervention – gene mutation search study |
| Lozano 1987[41] | No relevant outcomes identified |
| Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group 1999[42] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Mensing 2017[43] | Incorrect study design – abstract only |
| Mensing 2017[44] | Incorrect study design – citation only |
| Mensing 2019[45] | Incorrect study design – does not match protocol. Investigation of incidence of unruptured intracranial aneurysms compared to sporadic incidence of unruptured intracranial aneurysms (both groups have screening). |
| Mensing 2016[46] | Incorrect intervention - comparison of shape between familial and sporadic |
| Miller 2012[47] | Incorrect study design – incidence of SAH with specific risk factors; no comparison of familial screening compared to no screening |
| Nagae 1972[48] | No relevant outcomes identified |
| Okamoto 2003[51] | Incorrect intervention – no assessments to detect SAH in families; data gained through questionnaire |
| Pei Shan 1995[53] | Incorrect intervention – no assessments to detect SAH in families |
| Phillips 1963[54] | No relevant outcomes identified |
| Raaymakers 1999[55] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Raaymakers 1998[56] | Incorrect study design – no comparison group for people with familial risk of SAH |

| Reference | Reason for exclusion |
|---|---|
| Raaymakers 2000[57] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Rinkel 2005[58] | Incorrect study design – review / editorial (references checked) |
| Rinkel 1998[59] | Incorrect study design – Systematic review on incidence of ICA rupture |
| Roberts 1999[60] | Incorrect intervention – no assessments to detect SAH in families; data gained through questionnaire |
| Ronkainen 1997[61] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Ronkainen 1994[62] | Incorrect study design – no comparison group for people with familial risk of SAH; unclear cohorts of familial SAH |
| Ronkainen 1995[63] | Incorrect study design – special features of familial intracranial aneurysms |
| Ronkainen 1998[64] | Incorrect intervention – incidence of familial SAH via autopsy |
| Ronkainen 1999[65] | Incorrect study design – comparison between familial and sporadic SAH screening; no correct comparison group for people with familial risk of SAH |
| Ronkainen 1995[66] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Ronkainen 1998[67] | Incorrect study design – Systematic review (references checked) |
| Ruigrok 2004[68] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Sakai 1974[69] | No relevant outcomes identified |
| Schievink 1994[70] | Incorrect study design – no comparison group for people with familial risk of SAH |
| Sundquist 2007[71] | Incorrect intervention – no assessments to detect SAH in families |
| Takao 2008[72] | Incorrect study design – Economical Markov model |
| Teasdale 2005[73] | Incorrect study design – no comparison group for people with familial risk of SAH |
| ter Berg 1986[74] | Incorrect intervention – no assessments to detect SAH in families |
| ter Berg 1988[75] | Incorrect intervention – screening for familial intracranial aneurysms via DSA (exclusion criteria) |
| ter Berg 1992[76] | Incorrect study design – Literature review (references checked) |
| Toglia 1972[77] | No relevant outcomes identified |
| van der Voet 2004[78] | Incorrect study design – investigating genetic causes of familial SAH |
| Verdure 2015[79] | Incorrect study design – investigating genetic causes of familial SAH |
| Vlak 2013[80] | Incorrect study design – investigating risk factors for aneurysm rupture |
| Wermer 2003[81] | Incorrect study design – no comparison group for people with familial risk of SAH |
| White 2004[82] | Incorrect study design – Literature review (references checked) |
| Woo 2009[83] | Incorrect intervention – no assessments to detect SAH in families |

| Reference | Reason for exclusion |
|---|---|
| Zuurbier 2019[84] | Incorrect study design – citation only |
| Zuurbier 2019[85] | Incorrect study design – abstract only |

## 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 9: Studies excluded from the health economic review**

| Reference | Reason for exclusion |
|---|---|
| None. | |

# Appendix J: Research recommendations

## J.1 Investigations for relatives

**Research question: What is the clinical and cost effectiveness of investigations to detect intracranial arterial aneurysms in first-degree relatives of people who have had an aneurysmal subarachnoid haemorrhage?**

**Why this is important:**

The reported prevalence of intracranial aneurysms varies between studies but is estimated to range from 2% to 5% in the general population. The chance of detecting an aneurysm on screening of people with 2 first-degree relatives who have had subarachnoid haemorrhage is reported to be around 10%. People with a family history of subarachnoid haemorrhage are also at higher personal risk of subarachnoid haemorrhage than the general population. Current practice varies, but some relatives of adults who have had a subarachnoid haemorrhage are offered investigation and those found to have an aneurysm at risk of rupture may be considered for intervention.

**Criteria for selecting priority research recommendations:**

| | |
|---|---|
| **PICO question** | Population: First degree relatives of adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm.<br><br>Intervention(s):<br>• Assessment of first-degree relatives of people with aSAH with CTA or MRA.<br><br>Comparison:<br>• To no routine assessment.<br><br>Outcome(s):<br>• Mortality<br>• Health and social-related quality of life (any validated measure)<br>• Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures)<br>• Subarachnoid haemorrhage |

| | |
|---|---|
| | • Presence of cerebral aneurysm |
| **Importance to patients or the population** | The risk of SAH is recognised to be increased in people with first-degree relatives. Assessment of relatives for intracranial aneurysms may allow for detection of intracranial arterial aneurysms, some of which may be considered to require treatment. Despite the potential risks, treatment to secure an aneurysm could prevent death or other adverse consequences of subarachnoid haemorrhage. |
| **Relevance to NICE guidance** | Current guidance is provided based on committee consensus. It is recommended that information regarding assessment of relatives and the potential risks of SAH in relatives be explained to people (and their families if appropriate) who have had an aneurysmal subarachnoid haemorrhage and are concerned about possible aneurysms in their relatives. |
| **Relevance to the NHS** | Routine screening of relatives for intracranial arterial aneurysms is currently not supported within NHS practice and any change in practice would have a significant resource impact including additional investigations and interventions requiring hospital consultations. |
| **National priorities** | This question is not relevant to a national priority area |
| **Current evidence base** | No clinical evidence was identified on the effectiveness of investigations to detect intracranial arterial aneurysms in first-degree relatives of people who have had an aneurysmal subarachnoid haemorrhage. Two cost-effectiveness studies were identified, however the committee did not consider these fully applicable to the NHS. |
| **Equality** | No equality issues |
| **Study design** | New research should be carried out using a prospective randomised controlled trial study design. |
| **Timeframe** | New research should be conducted over 5-15 years to allow for sufficient data collection and follow-up of participants. |
| **Feasibility** | The research is considered to be feasible. |
| **Other comments** | Prospective study could include a subgroup analysis by no. of relatives and frequency of investigation:<br><br>• No. of first degree relatives:<br>  ○ Assessment of people with 1 first degree relative with SAH compared to assessment of people with >1 first degree relative<br>• Frequency of assessment:<br>  ○ Assessment every 2 years compared to assessment every 5 years. |
| **Importance** | • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates. |