National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

NICE guideline: methods

NICE guideline NG228

Methods

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1 Development of the guideline

1.1 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the National Guideline Centre to produce the guideline.

The remit for this guideline is on subarachnoid haemorrhage caused by a ruptured aneurysm.

1.2 What this guideline covers

This guideline covers the diagnosis and management of aneurysmal subarachnoid haemorrhage (a SAH) in adults (16 and older) with a suspected or confirmed subarachnoid haemorrhage caused by a suspected or confirmed ruptured aneurysm and adult relatives (16 and older) of people who have had a subarachnoid haemorrhage.

1.3 What this guideline does not cover

This guideline does not cover adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation.

1.4 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

2 Methods

This guideline was developed using the methods described in the 2014 NICE guidelines manual, updated 2018[3].

Declarations of interest were recorded according to the NICE conflicts of interest policy.

Sections 2.1 to 2.3 describe the process used to identify and review evidence.

2.1 Developing the review questions and outcomes

The review questions developed for this guideline were based on the key areas and draft review questions identified in the guideline scope. They were drafted by the National Guideline Centre technical team and refined and validated by the committee and signed off by NICE. A total of 21 review questions were developed in this guideline and outlined in Table 1.

The review questions were based on the following frameworks:

- population, intervention, comparator and outcome (PICO) for reviews of interventions
- population, index tests, reference standard and target condition for reviews of diagnostic test accuracy
- population, exposure and outcomes for prognostic reviews
- population, setting and context for qualitative reviews.

This use of a framework informed a more detailed protocol that guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the guideline committee. Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Evidence report	Type of review	Review questions	Outcomes
1	Diagnostic	What symptoms and signs indicate subarachnoid haemorrhage?	• Diagnostic accuracy data ○ Sensitivity, specificity, PPV, NPV • Association data Adjusted RR or.
2	Diagnostic	What is the diagnostic accuracy of investigations in adults with suspected subarachnoid haemorrhage?	Statistical measure to detecting aSAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) Receiver Operating Characteristic (ROC) curve or area under curve
3	i) Diagnostic	a) What is the diagnostic accuracy of different diagnostic timing strategies in adults with suspected subarachnoid haemorrhage?	Statistical measure to detecting aSAH: • Sensitivity • Specificity

Evidence report	Type of review	Review questions	Outcomes
		b) What is the diagnostic accuracy of different diagnostic location strategies in adults with suspected subarachnoid haemorrhage? What is the diagnostic accuracy of different diagnostic sequencing strategies in adults with suspected subarachnoid haemorrhage?	• Positive Predictive Value (PPV) • Negative Predictive Value (NPV) Receiver Operating Characteristic (ROC) curve or area under curve
	ii) Intervention	What is the clinical and cost effectiveness of different diagnostic strategies in adults with suspected subarachnoid haemorrhage, including the timing, location and sequencing of investigations?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Length of hospital stay Complications (any)
4	Prognostic (risk prediction)	What is the prognostic utility of severity scoring systems in adults with suspected or confirmed subarachnoid haemorrhage?	Markers of poor outcome: • Mortality • Functional status ○ Modified Rankin Scale (MRS) ○ Glasgow Outcome Score (GOS) ○ Oxford Handicap Score (OHS) • Rebleed subarachnoid haemorrhage Measured by: • Accuracy data ○ SN, SP, PPV, NPV • Association data Adjusted RR or OR
5	Intervention	What is the clinical and cost effectiveness of medical management strategies for adults with confirmed subarachnoid haemorrhage?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities (any validated

Evidence report	Type of review	Review questions	Outcomes
			measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Change in grade of aSAH • Rebleed of index aneurysm Important outcomes: • Return to usual daily activity i.e. work • Rate of major complications: DCI, hydrocephalus, intracranial hypertension Length of hospital stay
6	Intervention	What is the clinical and cost effectiveness of interventions to monitor for intracranial hypertension or vasospasm in adults with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Stroke • DCI • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to daily activity • Length of hospital stay • Complications of investigation Need for retreatment
7	Intervention	What is the clinical and cost effectiveness of options for managing delayed cerebral ischaemia?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to usual daily activity e.g. work • Cerebral infarction

Evidence report	Type of review	Review questions	Outcomes
			• Intracranial bleed • Cardiopulmonary complications Length of stay in hospital
8	Diagnostic	What is the diagnostic accuracy of investigations for detecting hydrocephalus for the person with aSAH and signs of neurological deterioration?	Statistical measure to detecting hydrocephalus: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) Receiver Operating Characteristic (ROC) curve or area under curve
9	Intervention	What is the clinical and cost effectiveness of options for managing hydrocephalus?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Risk of subsequent subarachnoid haemorrhage • Return to work (driving) • Complications of procedure (including infection, Intracranial haemorrhage, epilepsy, cerebral infarction) Repeat procedure
10	Diagnostic	What is the diagnostic accuracy of investigations for detecting intracranial hypertension for the deteriorating or unconscious person?	Statistical measure to detecting intracranial hypertension: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) Receiver Operating Characteristic (ROC) curve or area under curve
11	Intervention	What is the clinical and cost effectiveness of options for managing intracranial hypertension?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure)

Evidence report	Type of review	Review questions	Outcomes
			• Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work, driving) Complications of intervention (any)
12	Diagnostic	What is the accuracy of different imaging strategies to detect a culprit aneurysm in adults with confirmed subarachnoid haemorrhage?	Statistical measure to detecting aSAH: • Sensitivity • Specificity • Positive Predictive Value (PPV) • Negative Predictive Value (NPV) Receiver Operating Characteristic (ROC) curve or area under curve)
13	Intervention	What is the clinical and cost effectiveness of neurosurgical compared to endovascular interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to daily activity • Length of hospital stay • Complications of intervention (any) Need for retreatment
14	Intervention	What is the optimal timing of interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated

Evidence report	Type of review	Review questions	Outcomes
			measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Rebleed from culprit aneurysm Important outcomes: • Subsequent subarachnoid haemorrhage • Return to usual daily activity (e.g. work) • Length of post-intervention hospital stay Complications (any)
15	Incidence	What is the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?	• A confirmed subsequent aSAH (confirmed by CT/LP +/- angiography) Measured by a weighted pooled incidence
16	Intervention	What is the clinical and cost effectiveness of different imaging strategies for follow-up of adults with confirmed aneurysmal subarachnoid haemorrhage?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated score) • Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) • Complications of investigation (e.g. stroke, vascular injury) Important outcomes: • Subsequent subarachnoid haemorrhage • Return to daily activity (e.g. work) • Need for retreatment Length of hospital stay (if rehospitalised)
17	Intervention	What is the clinical and cost effectiveness of different options for managing non-culprit aneurysms in adults with a confirmed aneurysmal subarachnoid haemorrhage?	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)

Evidence report	Type of review	Review questions	Outcomes
			• Subsequent subarachnoid haemorrhage • Complications of treatment allocation Important outcomes: Return to daily activity
18	Intervention	What is the clinical and cost effectiveness of long-term medicines, such as antihypertensive or blood thinning medicines, for reducing the risk of subsequent subarachnoid haemorrhage in adults with confirmed subarachnoid haemorrhage?	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) • Subsequent subarachnoid haemorrhage Important outcomes: • Number achieving target BP • Return to daily activity (e.g. driving) • Need for retreatment Complications of intervention (such as headache, dizziness, nausea and vomiting, tiredness)
19	Intervention	What is the clinical and cost effectiveness of long-term medicines such as antiepileptic medicines for managing the consequences of subarachnoid haemorrhage?	Critical outcomes: • Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) Important outcomes: • Return to daily activity e.g. driving • Need for retreatment • Headache (frequency/severity) • Number of seizures Complications of medication (any)

Evidence report	Type of review	Review questions	Outcomes
20	Qualitative	What patient information (including lifestyle advice) should be given to adults who have had an aneurysmal subarachnoid haemorrhage?	Themes will be derived from the evidence identified for this review and not pre-specified. Quantitative data such as incidence rate or frequencies of reported information preference will be extracted and presented alongside the themes identified from qualitative analysis.
21	Intervention	What is the clinical and cost effectiveness of investigations to detect intracranial arterial aneurysms in relatives of adults who have had a subarachnoid haemorrhage?	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) • Subarachnoid haemorrhage Important outcomes: • Presence of cerebral aneurysm Elective treatment

2.1.1.1 Stratification

Stratification is applied where the committee are confident the intervention will work differently in particular groups and separate recommendations are required, therefore the data for these groups should be reviewed separately. Stratification was applied for two reviews in this guideline:

For review of medical management:

- Stratified by timing of medical management – pre and post-surgical/endovascular intervention

For review of managing hydrocephalus:

- Stratified by type of hydrocephalus – acute hydrocephalus (within acute admission / within 30 days of ictus) and chronic hydrocephalus (post discharge / after 30 days from ictus)

2.2 Searching for evidence

2.2.1 Clinical and health economics literature searches

The full strategy including population terms, intervention terms, study types applied, the databases searched and the years covered can be found in Appendix B of the evidence review.

Systematic literature searches were undertaken to identify all published clinical and health economic evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual.[3] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed, and where possible, searches were restricted to English language. All searches were updated on 24 June 2020. If new evidence falls outside of the timeframe for the guideline searches, e.g. from stakeholder comments, the impact on the guideline will be considered, and any further action agreed between the developer and NICE staff with a quality assurance role.

Prior to running, searches were quality assured using different approaches. Checking key papers were retrieved and Medline search strategies were peer reviewed by a second information specialist using a QA process based on the PRESS checklist.[2] Additional studies were added by checking reference lists of relevant systematic reviews, and those highlighted by committee members.

During the scoping stage, a search was conducted for guidelines and reports on the websites including:

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- NHS Evidence Search (www.evidence.nhs.uk).
- ECRI Institute (ECRI) (http://www.ecri.org/)
- TRIP (www.tripdatabase.com)

Searching for unpublished literature was not undertaken

2.3 Reviewing research evidence

The evidence for each review question was reviewed using the following process:

- Potentially relevant studies were identified from the search results by reviewing titles and abstracts. The full papers were then obtained.
- Full papers were evaluated against the pre-specified inclusion and exclusion criteria set out in the protocol to identify studies that addressed the review question. The review protocols are included in an appendix to each of the evidence reports.
- Relevant studies were critically appraised using the preferred study design checklist as specified in the NICE guidelines manual.[3] The checklist used is included in the individual review protocols in each of the evidence reports.
- Key information was extracted about interventional study methods and results into ‘EviBase’, NGC’s purpose-built software. Summary evidence tables were produced from data entered into EviBase, including critical appraisal ratings. Key information about non-interventional study methods and results were manually extracted into standard Word evidence tables (evidence tables are included in an appendix to each of the evidence reports).
- Summaries of the evidence were generated by outcome. Outcome data were combined, analysed and reported according to study design:
    - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.
    - Data from non-randomised studies were meta-analysed where appropriate and reported in GRADE profile tables.

  - Prognostic data were meta-analysed where appropriate and reported in adapted GRADE profile tables.
  - Diagnostic data were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables.
  - Qualitative data were synthesised across studies using thematic analysis and presented as summary statements in GRADE CERQual tables.
- A minimum of 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.
- All of the evidence reviews were quality assured by a senior systematic reviewer. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - a sample of the risk of bias assessments
  - correct methods were used to synthesise data.

  Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).

2.3.1 Types of studies and inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in an appendix to each of the evidence reports. Excluded studies (with the reasons for their exclusion) are listed in an appendix to each of the evidence reports. The committee was consulted about any uncertainty regarding inclusion or exclusion.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in published in English language were excluded.

2.3.1.1 Type of studies

Randomised trials and other observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For intervention reviews, randomised controlled trials (RCTs) were included where identified as because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. Non-randomised intervention studies were considered appropriate for inclusion if there was insufficient randomised evidence for the committee to make a decision. In this case the committee stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Refer to the review protocols in each evidence report for full details on the study design of studies that were appropriate for each review question.

For diagnostic review questions, diagnostic RCTs (test and treat reviews), cross-sectional studies and retrospective studies were included. For prognostic review questions, prospective and retrospective cohort studies were included. Case–control studies were not included.

Published systematic reviews and meta-analyses conducted to the same methodological standards as the NICE reviews were included within the evidence reviews in preference to primary studies, where they were available and applicable to the review questions and updated or added to where appropriate to the guideline review question.

2.3.1.1.1 Qualitative studies

In the qualitative reviews, studies using focus groups, or structured or semi-structured interviews were considered for inclusion. Survey data or other types of questionnaires were included if they addressed the topic of information provision and support needs. Due to the known lack in depth of qualitative data in this area, descriptive quantitative data was considered to supplement the qualitative information identified.

2.4 Methods of combining evidence

2.4.1 Data synthesis for intervention reviews

Meta-analyses were conducted using Cochrane Review Manager (RevMan5)[8] software.

2.4.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel–Haenszel) techniques were used to calculate risk ratios (relative risk, RR) for the binary outcomes. The absolute risk difference was also calculated using GRADEpro[1] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events. Where there are zero events in both arms, the risk difference was calculated and reported instead.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals (95% CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5[8] software.

Generic inverse variance

If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5.[8] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[1] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported no absolute risk difference was calculated.

2.4.2 Data synthesis for diagnostic reviews

Two separate review protocols were produced to reflect the 2 different diagnostic study designs.

2.4.2.1 Diagnostic RCTs

Diagnostic RCTs (sometimes referred to as test and treat trials) are a randomised comparison of 2 diagnostic tests, with study outcomes being clinically important consequences of the diagnosis (patient-related outcome measures similar to those in

intervention trials, such as mortality). Patients are randomised to receive test A or test B, followed by identical therapeutic interventions based on the results of the test (so someone with a positive result would receive the same treatment regardless of whether they were diagnosed by test A or test B). Downstream patient outcomes are then compared between the 2 groups. As treatment is the same in both arms of the trial, any differences in patient outcomes will reflect the accuracy of the tests in correctly establishing who does and does not have the condition. Data were synthesised using the same methods for intervention reviews (see section 2.4.1.1 above).

2.4.2.2 Diagnostic accuracy studies

For diagnostic test accuracy studies, a positive result on the index test was found either through a binary identification of the target condition, or if the patient had values of the measured quantity above or below a threshold value, such as the intracranial pressure deemed to signal intracranial hypertension. Diagnostic outcome data were reported separately for each threshold reported. Diagnostic test accuracy measures used in the analysis were: area under the receiver operating characteristics (ROC) curve (AUC), and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice this varies amongst studies. If a test has a high sensitivity then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives).

Coupled forest plots of the agreed primary paired outcome measure for decision making (sensitivity and specificity) with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5.[8] In order to do this, 2 by 2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Diagnostic meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random-effects approach in WinBUGS software.[9] The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. The bivariate method uses logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity and specificity and confidence regions were plotted (using methods outlined by Novielli 2010.[7]) The pooled median sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For scores with fewer than 3 studies, sensitivity and the paired specificity were reported on a per-study basis.

If appropriate, to allow comparison between tests, summary ROC curves were generated for each diagnostic test from the pairs of sensitivity and specificity calculated from the 2 by 2 tables, selecting 1 threshold per study. A ROC plot shows true positive rate (sensitivity) as a function of false positive rate (1 minus specificity). Data were entered into RevMan5[8] and ROC curves were fitted using the Moses-Littenberg approach. In order to compare diagnostic tests, 2 or more tests were plotted on the same graph. The performance of the different diagnostic tests was then assessed by examining the summary ROC curves visually: the test that had a curve lying closest to the upper left corner (100% sensitivity and 100% specificity) was interpreted as the best test.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots and pooled diagnostic meta-analysis plots.

Area under the ROC curve (AUC) data for each study were also plotted on a graph, for each diagnostic test. The AUC describes the overall diagnostic accuracy across the full range of thresholds. The following criteria were used for evaluating AUCs:

- ≤0.50: worse than chance
- 0.50–0.60: very poor
- 0.61–0.70: poor
- 0.71–0.80: moderate
- 0.81–0.92: good
- 0.91–1.00: excellent or perfect test.

Heterogeneity or inconsistency amongst studies was visually inspected.

2.4.3 Data synthesis for incidence reviews

The incidence rate of the outcome under review (subsequent SAH) was recorded for populations with exposure to the factor under review (previous SAH). Data on the sum of SAH events relative to the total number of participants under investigation was used to assess pooled incidence rate per 100 people and per 100,000 people. This value was used to estimate the incidence rate of SAH using Byar's method to calculate the 95% CI for the observed number of events.

2.4.4 Data synthesis of risk prediction reviews

Adjusted odds ratios, risk ratios, or hazard ratios, with their 95% CIs, for the prognostic accuracy of pre-specified risk tools were extracted from the studies. Prospective cohort studies reporting outcome data correlated to the risk prediction tool thresholds identified by the committee at the protocol stage were the preferred study design.

Data were not combined in meta-analyses for risk prediction studies unless they were agreed to be similarly homogenous to pool and adjusted for the same confounders.

2.4.5 Data synthesis for qualitative reviews

The main findings for each included paper were identified and thematic analysis methods were used to synthesise this information into broad overarching themes which were summarised into the main review findings. The evidence was presented in the form of a narrative summary detailing the evidence from the relevant papers and how this informed the overall review finding plus a statement on the level of confidence for that review finding. Considerable limitations and issues around relevance were listed. A summary evidence table with the succinct summary statements for each review finding was produced including the associated quality assessment. Appraising the quality of evidence by outcomes

2.4.6 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[1]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below.

2.4.6.1 Risk of bias

Risk of bias were evaluated using the Risk of Bias checklist. The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each study first using the appropriate checklist for the study design (Cochrane RoB 2 for RCTs, or ROBINS-I for nonrandomised studies). For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. An overall rating is calculated across all studies by taking into account the weighting of studies according to study precision. For example if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 3: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling participants are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.

Limitation	Explanation
Performance and detection bias (lack of blinding)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which the participants are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of at least 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

The assessment of risk of bias differs for non-randomised intervention studies, as they are inherently at higher risk of bias due to the possibility of confounding and the greater risk of selection bias. The assessment of risk of bias therefore involves consideration of more domains and varies by study type. Table 4 shows the domains considered for most types of non-randomised studies.

Table 4: Principle domains of bias in nonrandomised studies

Bias	Explanation
Pre-intervention	
Confounding bias	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline. ROBINS-I can also address time-varying confounding, which occurs when post-baseline prognostic factors affect the intervention received after baseline.
Selection bias	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events, is related to both intervention and outcome, there will be an association between interventions and outcome even if the effect of interest is truly null. This type of bias is distinct from confounding. A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention.
At intervention	
Information bias	Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome.
Post-intervention	
Confounding bias	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a

Bias	Explanation
	deviation from the intended intervention(s). Assessment of bias in this domain will depend on the effect of interest (either the effect of assignment to intervention or the effect of adhering to intervention).
Selection bias	Bias that arises when later follow-up is missing for individuals initially included and followed (e.g. differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.
Information bias	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.
Reporting bias	Selective reporting of results from among multiple measurements of the outcome, analyses or subgroups in a way that depends on the findings.

2.4.6.2 Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. An overall rating is calculated across all studies by taking into account the weighting of studies according to study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

2.4.6.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. Statistical heterogeneity was assessed for each meta-analysis estimate by an I-squared (I^2) inconsistency statistic.

Heterogeneity or inconsistency amongst studies was also visually inspected. Where statistical heterogeneity as defined above was present or there was clear visual heterogeneity not captured in the I^2 value predefined subgrouping of studies was carried out according to the protocol. See the review protocols for the subgrouping strategy.

When heterogeneity existed within an outcome (I^2>50%), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an I^2<50%) then each of the derived subgroups were presented separately (providing at least 1 study remained in each subgroup). The committee took this into account and considered whether to make separate recommendations based on the variation in effect across subgroups within the same outcome. In such a situation the quality of evidence was not downgraded.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval around the overall estimate. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were not pooled and were described narratively.

2.4.6.4 Imprecision

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 1.

The value / position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health.

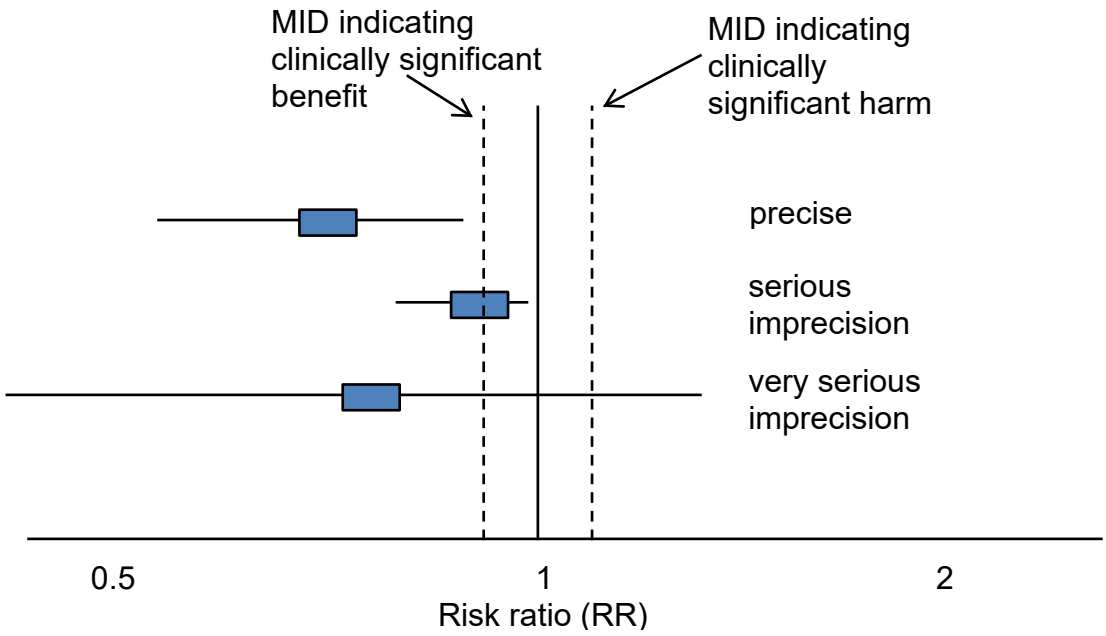
In the absence of values identified in the literature, the alternative approach to deciding on MID levels is to use the standard values used by the NGC, as follows:

- For dichotomous outcomes the committee agreed that MIDs for RRs of 0.8 and 1.25 would be reflective of clinically important thresholds. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.8 is taken as the line denoting the boundary between no clinically important effect and a clinically important harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically important benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.8 is taken as the line denoting the boundary between no clinically important effect and a clinically important benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically important harm. There aren't established default values for ORs and the same values (0.8 and 1.25) are applied here but are acknowledged as arbitrary thresholds agreed by the committee.
- For mortality any change was considered to be clinically important and the imprecision was assessed on the basis of the whether the confidence intervals crossed the line of no effect, that is whether the result was consistent with both benefit and harm.
- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically important benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically important harms will be the converse of these. If baseline values are

unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was adopted.

Figure 1: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (Note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)



If an outcome containing data from a single study reporting zero events in both arms was included, imprecision was measured by sample size: No imprecision - sample size >350, serious imprecision – sample size >70 to ≤350, very serious imprecision - sample size ≤70.

2.4.6.5 Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. Outcome quality started at High, the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case are specified in the footnotes of the GRADE tables.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Level	Description
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

2.4.7 Diagnostic reviews

2.4.7.1 Diagnostic RCTs

Appraising the quality of evidence from diagnostic RCTs follows the same process as section 2.5.1 for intervention reviews.

2.4.7.2 Diagnostic test accuracy

2.4.7.2.1 Risk of bias

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see appendix H in the NICE guidelines manual 2014[3]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Table 5):

- patient selection
- index test
- reference standard
- flow and timing.

Table 5: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions.

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2×2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/ unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case–control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results	Did all patients receive a reference standard?

Domain	Patient selection	Index test	Reference standard	Flow and timing
	Did the study avoid inappropriate exclusions?		interpreted without knowledge of the results of the index test?	Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias; (high/low/ unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/ unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

2.4.7.2.2 Inconsistency

Inconsistency refers to any unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by inspection of the diagnostic accuracy outcome measures using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which it would be acceptable to recommend a test). The committee set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the CI varied across 2 areas (for example, 50–90% and 90–100%) and by 2 increments if the CI varied across 3 areas. Where only a single study reported an outcome, inconsistency was rated as 'not serious'.

2.4.7.2.3 Imprecision

The judgement of precision was based on visual inspection of the confidence region around the diagnostic accuracy summary statistic from the diagnostic meta-analysis if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. After considering the likely downstream implications of diagnostic test accuracy measures on patient-important outcomes, the committee decided that a sensitivity and a specificity of 0.9/90% corresponded to a threshold for recommending a diagnostic test. The committee also agreed that thresholds of 0.6/60% for sensitivity and specificity corresponded to the point below which a test would have no clinical use. The committee agreed that 90% and 60% were also suitable thresholds to determine the clinical importance of PPV, NPV and AUC outcomes. The decision thresholds set by the committee were used to determine whether imprecision is not serious, serious or very serious depending on whether confidence intervals cross zero, one or two thresholds. The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate crossed one threshold, and downgraded by 2 increments when the range covered two thresholds.

2.4.7.2.4 Overall grading

Quality rating started at high for prospective and retrospective cross-sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment to a minimum grade of very low, as explained for intervention reviews. This was presented in a modified GRADE profile.

2.4.8 Prognostic (risk scores) reviews

The outcomes from evidence for the included risk prediction studies were assessed against the same principles of quality listed for intervention reviews. These were considered against criteria specifically for risk prediction evidence reviews (outlined below).

2.4.8.1.1 Risk of bias

The risk of bias for prognostic studies was evaluated according to the QUIPS checklist, the main criteria are given in Table 6.

Table 6: Description of risk of bias criteria for prognostic studies

Risk of bias	Aim of section
Study participation	To judge selection bias (likelihood that relationship between the prognostic factor and outcome is different for participants and eligible non-participants)
Study attrition	To judge the risk of attrition bias (likelihood that relationship between prognostic factor and outcome are different for completing and non-completing participants).
Prognostic factor measurement	To judge the risk of measurement bias related to how the prognostic factor was measured (differential measurement of prognostic factor related to the baseline level of outcome).
Outcome measurement	To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of prognostic factor).
Study confounding	To judge the risk of bias due to confounding (i.e. the effect of the prognostic factor is distorted by another factor that is related to the prognostic factor and outcome).
Statistical Analysis and Reporting	To judge the risk of bias related to the statistical analysis and presentation of results.

2.4.8.1.2 Inconsistency

Inconsistency was assessed as for intervention studies.

2.4.8.1.3 Imprecision

In meta-analysed outcomes, or for non-pooled outcomes, the position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded.

2.4.8.1.4 Overall grading

Quality rating started at High for included studies, and each major limitation brought the rating down by 1 increment to a minimum grade of Very Low, as explained for interventional reviews.

2.4.9 Incidence studies

The outcomes from evidence for the incidence studies were assessed against the same principles of quality listed for intervention reviews. These were considered against criteria specifically for incidence/prevalence evidence reviews (outlined below).

2.4.9.1.1 Risk of bias

Risk of bias and applicability was assessed for each study using The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for studies reporting prevalence data (Table 7). Bias occurs if systematic flaws or limitations in the design, conduct or analysis of a primary study distort the results.

Table 7: Summary of JBI Critical Appraisal Checklist for studies reporting prevalence.

Risk of bias questions
1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

2.4.9.1.2 Inconsistency

Inconsistency was assessed by visual inspection of a plotted summary of incidence rate of subsequent SAH, and for overlap of confidence intervals where possible.

2.4.9.1.3 Imprecision

Imprecision was assessed by visual inspection of the position of the 95% CIs for each study in relation to the incidence plots. Variance of a 1% incidence rate (1 per 100 or 100 per 100,000) within the confidence region was considered by the committee to be a high risk of imprecision and a variance of 2% incidence rate (2 per 100 or 200 per 100,000) was considered to be very high imprecision. The committee considered a 1% outcome risk to be clinically significant and so deemed this an appropriate threshold to measure outcome imprecision. A weighted average of imprecision across all studies contributing evidence for each analysis was taken.

2.4.9.1.4 Overall grading

The quality rating of pooled incidence risks was assessed by a weighted review of the risk of bias associated with the included studies within that analysis.

2.4.10 Qualitative reviews

Review findings from the included qualitative studies were evaluated and presented using the ‘Confidence in the Evidence from Reviews of Qualitative Research’ (CERQual) Approach developed by the GRADE-CERQual Project Group, a subgroup of the GRADE Working Group.

The CERQual Approach assesses the extent to which a review finding is a reasonable representation of the phenomenon of interest (the focus of the review question). Each review finding was assessed for each of the 4 quality elements listed and defined below in Table 8.

Table 8: Description of quality elements in GRADE-CERQual for qualitative studies

Quality element	Description
Methodological limitations	The extent of problems in the design or conduct of the included studies that could decrease the confidence that the review finding is a reasonable representation of the phenomenon of interest. Assessed at the study level using the CASP checklist.
Coherence	The extent to how clear and cogent the fit is between the data from the primary studies and the review finding.
Relevance	The extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol.
Adequacy	The degree of the confidence that the review finding is being supported by sufficient data. This is an overall determination of the richness (depth of analysis) and quantity of the evidence supporting a review finding or theme.

Details of how the 4 quality elements (methodological limitations, coherence, relevance and adequacy) were appraised for each review finding are given below.

2.4.10.1 Methodological limitations

Each review finding had its methodological limitations assessed within each study first using the CASP checklist. Based on the degree of methodological limitations, studies were evaluated as having minor, moderate or severe limitations. A summary of the domains and questions covered is given below.

Table 9: Description of limitations assessed in the CASP checklist for qualitative studies

Domain	Aspects considered
Are the results valid?	• Was there a clear statement of the aims of the research? • Is qualitative methodology appropriate? • Was the research design appropriate to address the aims of the research? • Was the recruitment strategy appropriate to the aims of the research? • Was the data collected in a way that addressed the research issue? • Has the relationship between researcher and participants been adequately considered?
What are the results?	Have ethical issues been taken into consideration? Was the data analysis sufficiently rigorous? Is there a clear statement of findings?
Will the results help locally?	How valuable is the research?

The overall assessment of the methodological limitations of the evidence was based on the limitations of the primary studies contributing to the review finding. The relative contribution of each study to the overall review finding and of the type of methodological limitation(s) were taken into account when giving an overall rating of concerns for this component.

2.4.10.2 Relevance

Relevance is the extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol. As such, relevance is dependent on the individual review and discussed with the guideline committee.

2.4.10.3 Coherence

Coherence is the extent to which the reviewer is able to identify a clear pattern across the studies included in the review, and if there is variation present (contrasting or disconfirming data) whether this variation is explained by the contributing study authors. For example, if a review finding in 1 study does not support the main finding and there is no plausible explanation for this variation, or if there is ambiguity in the descriptions in the primary data, then the confidence that the main finding reasonably reflects the phenomenon of interest is decreased.

2.4.10.4 Adequacy

The judgement of adequacy is based on the confidence of the finding being supported by sufficient data. This is an overall determination of the richness and quantity of the evidence supporting a review finding or theme. Rich data provide sufficient detail to gain an understanding of the theme or review finding, whereas thin data do not provide enough detail for an adequate understanding. Quantity of data is the second pillar of the assessment of adequacy. For review findings that are only supported by 1 study or data from only a small number of participants, the confidence that the review finding reasonably represents the phenomenon of interest might be decreased because there is less confidence that studies undertaken in other settings or participants would have reported similar findings. As with richness of data, quantity of data is review dependent. Based on the overall judgement of adequacy, a rating of no concerns, minor concerns, or substantial concerns about adequacy was given.

2.4.10.5 Quantitative data

Descriptive quantitative data such as incidence rate or frequencies of information preference from survey questionnaires will be synthesised, quality assessed, and considered alongside qualitative evidence.

Risk of bias for quantitative data was assessed depending on the design of the study:

- Randomised Controlled Trial: Cochrane RoB (2.0)
- Non randomised study, including cohort studies: Cochrane ROBINS-I
- Case control study: CASP case control checklist
- Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool
- Cross sectional study: JBI checklist for cross sectional study
- Case series: Institute of Health Economics (IHE) checklist for case series

2.4.10.6 Overall judgement of the level of confidence for a review finding

GRADE-CERQual is used to assess the body of evidence as a whole through a confidence rating representing the extent to which a review finding is a reasonable representation of the phenomenon of interest. For each of the above components, level of concern is categorised as either;

- no or very minor concerns
- minor concerns
- moderate concerns, or
- serious concerns.

The concerns from the 4 components (methodological limitations, coherence, relevance and adequacy) are used in combination to form an overall judgement of confidence in the finding. GRADE-CERQual uses 4 levels of confidence: high, moderate, low and very low confidence.

The significance of these overall ratings is explained in Table 10. Each review finding starts at a high level of confidence and is downgraded based on the concerns identified in any 1 or more of the 4 components. Quality assessment of qualitative reviews is a subjective judgement by the reviewer based on the concerns that have been noted. An explanation of how such a judgement had been made for each component is included in the footnotes of the GRADE CERQual summary of evidence tables.

Table 10: Overall level of confidence for a review finding in GRADE-CERQual

Level	Description
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate confidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest.
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

The overall quality rating of quantitative data was assessed by a weighted review of the risk of bias associated with the included studies within that analysis.

2.5 Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[1] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for most of the outcomes in the intervention reviews that if at least 100 more participants per 1000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For the critical outcome of mortality a reduction of 10 per 1000 (1%) represented a clinical benefit. For severe degrees of disability (e.g. vegetative state), 50 events or more per 1000 (5%) represented clinical harm.

For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this represented a clinical benefit or harm. For continuous outcomes where the NGC standard MIDs or published MIDs have been used, the values for each outcome are provided in tables as an appendix in the relevant evidence review.

Any cases of serious uncertainty around the effect estimate were also taken into account when considering the clinical importance of outcome measures.

2.6 Health economic modelling

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was undertaken by the health economist in a selected area. The priority area for new analysis was agreed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified diagnostic accuracy and diagnostic strategies as the highest priority area for original health economic modelling. The committee noted that in most institutions, the current first-line diagnostic test for people with a suspected SAH is non-contrast CT brain scan. If the CT scan is negative then a lumbar puncture is the most common second line test, although there is some variation in practice. The committee were concerned about the use of lumbar puncture due to the invasiveness and the cost to the NHS.

The following general principles were adhered to in developing the threshold analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[3, 6]
- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the National Guideline Centre.

Full methods and results of the threshold analysis of the diagnostic pathway for subarachnoid haemorrhage are described in the health economic analysis section of the evidence report.

2.6.1 Cost-effectiveness criteria

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[3-5] In general, an intervention was considered to be cost effective (given that the estimate was considered plausible) if either of the following criteria applied:

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in 'The committee's discussion of the evidence' section of the relevant evidence report, with reference to issues regarding the plausibility of the estimate or to factors set out in NICE methods manuals.[3]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

2.6.2 In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

2.7 Developing recommendations

Over the course of the guideline development process, the committee was presented with:

- Evidence review protocols
- Summaries of clinical and health economic evidence and quality (as presented in evidence reports A-T).
- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables can be found in appendices to the relevant evidence reports.
- Forest plots (in appendices to the relevant evidence reports).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (in a separate economic analysis report).
- Excluded studies lists

Decisions on whether a recommendation could be made, and if so in which direction, were made on the basis of the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. The net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes alongside the magnitude of the effect (or clinical importance), quality of evidence (including the uncertainty) and amount of evidence available. When this was done informally, the committee took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions. When the clinical harms were judged by the committee to outweigh any clinical benefits, they considered making a recommendation not to offer an intervention. This was dependant on whether the intervention had any reasonable prospect of providing cost-effective benefits to people using services and whether stopping the intervention was likely to cause harm for people already receiving it.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee decided on whether a recommendation could be made based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the committee.

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Ensuring equality standards are met.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the NICE guidelines manual[3]).

The main considerations specific to each recommendation are outlined in 'The committee's discussion of the evidence' section within each evidence report.

2.7.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

2.7.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

2.7.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

2.7.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

2.7.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

3 Acronyms and abbreviations

Acronym or abbreviation	Description
ACA	Anterior cerebral artery
ADC	Apparent adhesion coefficient
AED	Anti-epileptic drug
aSAH	Aneurysmal subarachnoid haemorrhage
AUC	Area under curve
AVM	Arterio-venous malformation
BRAT	Barrow Ruptured Aneurysm Trial
BP	Blood pressure
CARAT	Cerebral Aneurysm Re-rupture After Treatment
CDU	Clinical decisions unit
CEA	Cost effectiveness analysis
CI	Confidence interval
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT (scan)	Computed tomography
CTA	CT angiography
CUA	Cost utility analysis
DCI	Delayed cerebral ischaemia
DSA	Digital subtraction angiography
DWI	Diffusion weight imaging
ED	Emergency department
EVD	External ventricular drain
EVT	Endovascular treatment
FN	False negative
FP	False positive
GCS	Glasgow Coma scale
GOS	Glasgow Outcome scale
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRE	Gradient echo sequences
HH	Hunt & Hess grade
HR	Hazard Ratio
ICA	Intracranial aneurysm
ICA	Internal carotid artery
ICD	International classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial hypertension
ICH	Intracranial haemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
IHD	Ischemic heart disease
ISAT	International Subarachnoid Haemorrhage Trial

Acronym or abbreviation	Description
ISUIA	International Study of Unruptured Intracranial Aneurysms
IV	Intra-venous (administration)
LOC	Loss of consciousness
LP	Lumbar puncture
MCA	Middle cerebral artery
MMSE	Mini mental state examination
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale score
NGC	National Guideline Centre
NICE	National Institute of Health and Care Excellence
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drug
OECD	Organization for Economic Cooperation and Development
ONSAD	Optic nerve sheath diameter
OR	Odds ratio
PAASH	Prognosis on Admission of Aneurysmal Subarachnoid Haemorrhage Scale
PCA	Posterior cerebral artery
PCR	Polymerase chain reaction
PED	Pipeline embolization device
PICO	Population; Intervention / Index test; Comparison; Outcome
PO	Par oral (oral administration)
PPV	Positive predictive value
QALY	Quality-adjusted life years
RBC	Red blood cells
RCT	Randomized controlled trial
ROB	Risk of bias
ROC	Receiver operating curve
RR	Research recommendation
RR	Risk ratio
SAH	Subarachnoid haemorrhage
SD	Standard deviation
TCA	Tricyclic antidepressant
TCD	Transcranial Doppler
TN	True negative
TP	True positive
TXA	Tranexamic Acid
UIA	Unruptured Intracranial Aneurysm
UK NEQAS	United Kingdom National External Quality Assurance Service
US	Ultrasound
VAS	Visual analogue scale
VPS	Ventriculoperitoneal shunt
WBC	White blood cells

Acronym or abbreviation	Description
WFNS	World Federation of Neurosurgical Societies grade
mWFNS	Modified World Federation of Neurological Societies Grade
rWFNS	World Federation of Neurological Societies grade (post resuscitation)

4 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

4.1 Guideline-specific terms

Term	Definition
Aneurysm (see also 'non-culprit aneurysm')	Enlargement of an artery caused by a weakness in the arterial wall that creates a bulge.
Aneurysmal subarachnoid haemorrhage	A bleed from a ruptured aneurysm into the fluid-filled subarachnoid space around the brain and spinal cord.
Angiography	Radiography of blood vessels, usually carried out after introduction of a radiopaque substance
Cerebral perfusion pressure (CPP)	The blood pressure within the brain calculated as the difference between mean arterial blood pressure and the intracranial pressure. It is calculated, as opposed to being measured directly.
Computed tomography	A form of tomography in which a computer controls the motion of the X-ray source and detectors, processes the data, and produces the image
Delayed cerebral ischaemia	The development of new focal neurological signs and/or deterioration in the level of consciousness lasting for more than 1 hour, which cannot be attributed to other causes by means of clinical assessment or imaging.
Hydrocephalus	A build-up of fluid in the brain.
Ictus	An attack or seizure of sudden onset especially of stroke.
Intracranial hypertension	Build-up of pressure of the fluid surrounding the brain.
Lumbar puncture	A procedure of taking cerebrospinal fluid (CSF) from the spine in the lower back through a hollow needle for examination, usually done for diagnostic purposes.
Non-culprit aneurysm (see also 'aneurysm')	Unruptured aneurysm(s), not the index aneurysm responsible for the presentation.
Opioids	A group of pain-relieving drugs that work by interacting with opioid receptors in your cells. Opioids can be made from the poppy plant e.g. morphine, or synthetic e.g. fentanyl.
Poor grade	Poor grade aSAH may mean a high WFNS grade, high Hunt & Hess grade or high Fisher score.
Subarachnoid haemorrhage	A bleed into the fluid-filled subarachnoid space around the brain and spinal cord.
'Thunderclap' headache	Sudden onset of severe headache with instantly peaking pain (typically peaking within 60 seconds).
Vasopressor	A group of drugs that cause vasoconstriction (narrowing of blood vessels) and raise systemic blood pressure. In people with aSAH vasopressors are used to raise systemic blood pressure and maintain or increase cerebral blood flow.
Vasospasm	Arterial spasm which leads to narrowing of the arteries and restricted blood flow.

4.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.

Term	Definition
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition.

Term	Definition
	For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with.

Term	Definition
	For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost–benefit analysis (CBA)	Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being

Term	Definition
	positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended

Term	Definition
	dominance over Option B. Option A is therefore cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
First degree relative	A person's father, mother, sister or brother.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.

Term	Definition
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN)
Non-randomised intervention study	A quantitative study investigating the effectiveness of an intervention that does not use randomisation to allocate patients (or units) to treatment groups. Non-randomised studies include observational studies, where allocation to groups occurs through usual treatment decisions or people's preferences. Non-randomised studies can also be experimental, where the investigator has some degree of control over the allocation of treatments. Non-randomised intervention studies can use a number of different study designs, and include cohort studies, case–control studies, controlled before-and-after studies, interrupted-time-series studies and quasi-randomised controlled trials.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one

Term	Definition
	characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.

Term	Definition
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP)
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often

Term	Definition
	measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true

Term	Definition
	positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model

Term	Definition
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Threshold analysis	See sensitivity analysis
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

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