National Institute for Health and Care Excellence

Head injury: assessment and early management (update)

NICE guideline: methods

NICE guideline <number>

Methods

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Developed by NICE

Disclaimer

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

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

1 Development of the guideline

1.1 Remit

NICE received the remit for this guideline from NHS England.

The remit for this guideline is:

Head injury: assessment and early management (update)

This guideline will update the NICE guideline on head injury: assessment and early management (CG176).

“What this guideline covers” and “What this guideline does not cover”: please see the guideline scope.

1.2 What this guideline covers

Groups that will be covered

- All adults, young people and children (including babies under 1 year) who present with a suspected or confirmed head injury with or without other major trauma.

- All adults, young people and children (including babies under 1 year) with a suspected or confirmed head injury that may be overlooked, for example, because of very young age, intoxication or cognitive impairment.

- All adults, young people and children (including babies under 1 year) with traumatic brain injury sustained through indirect energy transfer such as shearing forces (that is, no history or findings suggesting direct injury to the head).

Specific consideration will be given to people with cognitive impairments (including learning disabilities and communication difficulties) and older adults with frailty.

Settings

Settings that will be covered

- Primary care, pre-hospital, emergency departments (or similar units), referral and transfer to a neuroscience centre, care of people already in hospital or those in residential care homes where NHS care is delivered, referral from and discharge to custodial settings.

Activities, services or aspects of care

Key areas that will be covered

1 Pre-hospital interventions.

□ Tranexamic acid.

□ Transport directly to a neuroscience centre past a closer non-specialist unit.

□ Direct access from the community to imaging (CT and MRI).

2 Assessment and management in the emergency department.

□ Selection of people with head injury for CT and MRI

□ Role of brain injury biomarkers (laboratory and point of care measurements).

□ Diagnosis of cervical spine injury in people with head injury, using CT and MRI, including timing of imaging.

□ Administering tranexamic acid.

3 Discharge and follow up, including follow up of people with normal scans for deterioration.

□ Observation of people on anticoagulation and antiplatelet therapy, people with post-concussion syndrome and people with asymptomatic small intracranial injuries after imaging.

□ Identification of hypopituitarism (timing and who to investigate).

The table below outlines all the areas that were included in the guideline.

Plans for each area in the current and updated guideline

Area of care	**NICE plans**
Pre-hospital assessment and advice, and referral to hospital	Review evidence: new area in the guideline for: • direct access from the community to imaging Retain other recommendations from existing guideline with editorial changes to clarify that: • pre-hospital assessment may include video assessment • community health services and NHS minor injury clinics including forensic medical officers. (no new evidence review will be conducted for these recommendations)

Immediate management at the scene and transport to hospital	Review evidence: new area in the guideline for: • tranexamic acid Review evidence: update existing recommendations as needed for: • transport from the scene directly to a neuroscience centre Retain other recommendations from existing guideline
Assessment in the emergency department	Review evidence: new area in the guideline for: • administering tranexamic acid Retain other recommendations from existing guideline
Investigating clinically important brain injuries	Review evidence: update existing recommendations as needed for: • selection of people with head injury for CT and MRI • role of brain injury biomarkers.
Investigating injuries to the cervical spine	Review evidence: update existing recommendations as needed for: • diagnosis of cervical spine injury in people with head injury, using CT and MRI, including timing of imaging
Information and support for families and carers	No evidence review: retain recommendations from existing guideline
Transfer from hospital to a neuroscience centre	No evidence review: retain recommendations from existing guideline

Admission and observation and Discharge and follow-up	Review evidence: new area in the guideline for: • observation of people on anticoagulation, including DOACs, and antiplatelet therapy • observation of people with post-concussion syndrome and people with asymptomatic small intracranial injuries after imaging • identifying hypopituitarism. Retain other recommendations from existing guideline with editorial changes to account for: • discharge and follow up for people discharged to custodial settings • follow up for people never admitted to hospital • follow up conducted via video. (no new evidence review will be conducted for these recommendations)

1.3 What this guideline does not cover

Groups that will not be covered

- Adults, young people and children (including babies under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.

Areas that will not be covered

1 Pre-hospital assessment, advice and referral to hospital (except for, direct access from the community to imaging, which will be an area for the update).

2 Immediate management at the scene and transport to hospital (except for tranexamic acid and transport directly to a neurosurgical centre, which will be areas for the update).

3 Involvement of the neurosurgical department.

4 Discharge and follow up (except for observation of people on anticoagulation, including DOACs, or antiplatelet therapy, people with post-concussion syndrome and people with asymptomatic small intracranial injuries after imaging, identifying hypopituitarism, which will be areas for the update).

5 Admission and observation

2 Methods

This guideline was developed using the methods described in the 2014 NICE guidelines manual[5] , updated 2020.

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. Sections 2.1.1 and 2.7 describe the process used to identify and review the health economic 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 technical team, refined and validated by the committee and signed off by NICE. A total of 18 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 (including test and treat)
- population, index tests, reference standard and target condition for reviews of diagnostic and prognostic test accuracy
- population, risk factors and outcomes for prognostic and diagnostic association reviews
- population and outcomes for single arm studies prognostic review

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.

1 **Table 1: Review questions**

Evidence report	Type of review	Review questions	Outcomes
A_Tranexamic acid	Intervention	What is the clinical and cost effectiveness of tranexamic acid (TXA) for managing suspected or confirmed isolated traumatic intracranial bleeding pre-hospital and in hospital?	• All-cause mortality at 30 days. • Mortality from head injury/TBI at 30 days. • Length of hospital stay • Surgical intervention • Objective measures of disability (including (Extended) Glasgow Outcome Scale, King's Outcome Scale for Childhood Head Injury and Cerebral Performance Category scale, Rivermead Post-Concussion Syndrome Questionnaire, Disability Rating Scale). • Serious adverse event • Post-concussion syndrome • Concussion/mild traumatic brain injury (TBI) • Quality of life (validated quality of life scores only).
B_Transfer to specialist care	Intervention	What is the clinical and cost effectiveness of pre-hospital strategies to convey people with head injury to a distant specialist neuroscience centre instead of a closer non-specialist unit?	• All-cause Mortality – at ≤30 days • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Length of stay in acute care (until discharged home or to rehabilitation) • Serious adverse event – i.e. deterioration of ABC at ≤30 days • Neurosurgery at ≤30 days • Other surgery at ≤30 days • Secondary transfer to specialist centre (for those initially transferred major trauma centre (MTC)) at ≤30 days
C_Direct access to imaging from the	Intervention	What is the clinical and cost effectiveness of providing direct access from the community to imaging?	• Mortality from head injury at ≤30 days.

Evidence report	Type of review	Review questions	Outcomes
community			• All-cause mortality at ≤30 days. • Objective measures of disability (including Glasgow Outcome Scale, King's Outcome Scale for Childhood Head Injury and Cerebral Performance Category scale, Rivermead Post-Concussion Syndrome Questionnaire). • Quality of life (validated quality of life scores only). • Length of hospital stay. • Serious adverse events • Referral to secondary care • Incidental findings (e.g. unruptured intracranial aneurysm)
D_Selecting people for CT or MRI	Diagnostic accuracy	What is the diagnostic accuracy of clinical decision rule/s for selecting adults, young people, children and babies with head injury for CT or MRI head scan?	• Diagnostic accuracy of clinical decision tool/triage tool for need for neurosurgical intervention • Diagnostic accuracy of clinical decision tool/triage tool for any acute intracranial abnormality
D_Selecting people for CT or MRI	Intervention (test and treat)	What is the clinical and cost effectiveness of clinical decision rules for selecting adults, young people, children and babies with head injury for CT or MRI head scan?	• All-cause Mortality – at ≤30 days • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Length of stay in acute care (until discharged home or to rehabilitation) • Serious adverse event at – ≤30 days
E_Selecting sub-groups for CT or MRI	Diagnostic association review	2.1(b) What are the indications for selecting adults, children and infants with head injury for CT or MRI head scan in a sub-group including - people on anticoagulant or antiplatelet therapy, including those	• Any traumatic intracranial abnormality detected by CT or MR imaging or autopsy -Any intracranial abnormality that causes death, neurosurgical intervention or neuro critical care.

Evidence report	Type of review	Review questions	Outcomes
		with no history of amnesia or loss of consciousness -- people with liver or coagulopathy disorders - people with pre-injury cognitive impairment sustaining injury through low level falls - people sustaining recurrent head injuries through sport - people presenting more than 24 hours after injury?	
F_Biomarkers and MRI forpost-concussion syndrome	Prognostic accuracy	What is the prognostic accuracy of brain injury biomarkers and/or MRI for predicting post-concussion syndrome?	• Prognostic accuracy of MRI for predicting post-concussion syndrome • Prognostic accuracy of biomarkers for predicting post-concussion syndrome • Prognostic accuracy of biomarkers and MRI for predicting post-concussion syndrome
F_Biomarkers and MRI for post-concussion syndrome	Intervention (test and treat)	What is the clinical and cost effectiveness of biomarkers and/or MRI when each is followed by the appropriate treatment for post-concussion syndrome to improve patient outcomes?	• Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Time to return to education/work/usual activities • Duration of post-concussion syndrome (to analyse 2 weeks to <3 months and 3 months and longer than 3 months separately)
G_Biomarkers for post-injury complications	Diagnostic accuracy	What is the diagnostic accuracy of brain injury biomarkers for predicting acute post-brain injury complications?	• diagnostic accuracy of biomarkers for predicting acute post-brain injury complications
G_Biomarkers for post-injury complications	Intervention (test and treat)	What is the clinical and cost effectiveness of biomarkers when followed by the appropriate treatment for acute post-brain injury complications to improve patient outcomes?	• Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or

Evidence report	Type of review	Review questions	Outcomes
			extended GOS - at 3 months or more • Time to return to education/work/usual activities • Duration of post-injury complications
H_Imaging of the cervical spine	Diagnostic accuracy	What is the diagnostic accuracy of CT, MRI and X-ray of the cervical spine for initial imaging in people with head injury?	• Diagnostic accuracy CT, MRI and X-ray of the cervical spine for any significant cervical spine injury (fracture/bony injury, soft tissue/ligament damage, spinal cord injuries, vascular injuries)
H_Imaging of the cervical spine	Intervention (test and treat)	What is the clinical and cost effectiveness of CT, MRI and X-ray of the cervical spine for initial imaging in people with head injury?	• Mortality at 3 months • Quality of life - 3 months or more • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Length of hospital stay • Unscheduled re-admission (28 days or longer) • Neurological deterioration
I_-Admission and observation of people on anti-coagulants or anti-platelets	Intervention	How long should people with head injury who are on anticoagulant or antiplatelet therapy be observed in hospital after normal brain imaging or no indication for early imaging?	• Rate of delayed intracranial bleeding (30 days) • time after injury when bleeding was detected • Time to diagnosis of intracranial injury on CT/MRI/clinical follow-up or autopsy • Re-admission as a result of delayed diagnosis of intracranial injury (30 days) • Serious adverse events within 2 weeks • TBI related mortality (30 days) • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more

Evidence report	Type of review	Review questions	Outcomes
J_Admission and observation of people with concussion	Intervention	Should people with concussion symptoms be admitted or discharged from hospital after normal brain imaging or no indication for early imaging?	• Time to diagnosis of intracranial injury on CT/MRI/clinical follow-up or autopsy • Quality of life (at least 3 months) • Re-admission as a result of delayed diagnosis of intracranial injury within 4 weeks • TBI related mortality • Objectively applied score of disability e.g. Glasgow Outcome Score (GOS) or extended GOS - at 3 months or more • Return to work/study/usual activities • Post-concussion outcomes: ongoing cognitive difficulties , RPQ measure of post-concussion symptoms • Mental health measures e.g. SDQ, Birrleson Depression and Anxiety scales, patient health questionnaire (PHQ), generalised anxiety disorder (GAD)
K_Indications for admission in people with small intracranial injuries	Prognostic	What are the indications for hospital admission in people with small intracranial injuries?	• Clinical deterioration Which includes: • Death or neurosurgery within 30 days of injury • Need for critical care admission • Reduction in GCS (drop of of 2 or more) • Seizures • Unplanned hospital re-admission at 30 days
L_Rate of clinical deterioration in people with isolated	Prognostic	What is the rate of clinical deterioration in people with isolated skull fracture?	• Clinical deterioration which includes: -Death within 30 days of injury -Neurosurgery within 30 days of injury

Evidence report	Type of review	Review questions	Outcomes
skull fracture			-Need for critical care admission (within 30 days) -Reduction in GCS (drop of 2 or more) (within 30 days) -Unplanned hospital re-admission at 30 days -delayed intracranial injury identified on repeated neuroimaging (within 30 days) -seizure, meningitis within 30 days of injury -diagnosis of suspected abusive head trauma within 3 months of injury
M_Who to investigate for hypopituitarism	Diagnostic association review	Which patients should be investigated for hypopituitarism after head injury?	• Diagnosis of hypopituitarism: -Clinical or biochemical diagnosis of hypopituitarism -Post-mortem diagnosis of hypopituitarism
N_ When to investigate for hypopituitarism	Intervention	When should people with head injury be investigated for hypopituitarism?	• Mortality • Quality of life (all validated quality of life scores). • Need for treatment of hypopituitarism (growth rate for children will be covered here) • Time to treatment of hypopituitarism • Return to work/return to school

2.1.1 Stratification

Stratification is applied where the committee are confident the intervention will work differently in the groups and separate recommendations are required, therefore they should be reviewed separately. In this guideline all analyses were stratified for age (adults (aged ≥16 years), children (aged ≥1 to <16 years), infants (aged <1 year)), which meant that different studies with predominant age-groups in different age strata were not combined and analysed together. Where applicable analyses were also stratified for severity of TBI based on GCS (mild GCS 13-15, moderate 9-12, severe GCS 3-8). Where studies reported a mix of populations across strata (for both age and severity of TBI), a threshold of [60%] was agreed with the committee as a cut off for what would be acceptable to constitute a predominant group.

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 published clinical and health economic evidence relevant to the review questions. These were run according to the parameters as stipulated within the NICE guideline's manual, https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission.

Databases were searched using relevant medical subject headings, free-text terms and where appropriate study-type filters. Studies published in languages other than English were not reviewed, and where possible, searches were restricted to English language. Searches were updated on 22 June 2022. Papers published or added to databases after this date were not considered. Where new evidence was identified, for example in consultation comments received from stakeholders, the impact on the guideline was considered, and the action agreed between the technical team and NICE staff with a quality assurance role.

Searches were quality assured using different approaches prior to being run. Medline search strategies were peer reviewed by a second information specialist using a QA process based on the PRESS checklist [4]. Key (seed) papers if provided, were checked if retrieved by the search.

Searching for unpublished literature was not undertaken. NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the committee for pharmaceutical interventions may be different from that considered by the MHRA and European Medicines Agency for the purposes of licensing and safety regulation.

Additional studies were added to the evidence base these consisted of references included in relevant systematic reviews, and those highlighted by committee members.

During the scoping stage, a search was conducted for guidelines and systematic reviews in Medline and Embase (OVID)

2.3 Reviewing 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.[6] 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 EPPI reviewer version 5. Summary evidence tables were produced from data entered into EPPI Reviewer, 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 evidence profiles.
    - Data from non-randomised studies were meta-analysed where appropriate and reported in GRADE evidence profiles.
    - Prognostic data were meta-analysed where appropriate and reported in adapted GRADE evidence profiles.
    - Diagnostic data were meta-analysed where appropriate or presented as a range of values in GRADE evidence profiles.
    - Single arm studies were meta-analysed using R code (metafor) and reported in adapted GRADE evidence profiles.
- 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.

Conference abstracts were not generally considered for inclusion. If abstracts were included the authors were contacted for further information. 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 controlled trials, non-randomised intervention studies, other observational studies (including diagnostic or prognostic studies) and case series (single arm 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, cross-sectional studies and prospective and retrospective cohort studies were included. For prognostic review questions, prospective and retrospective cohort studies were included. Case–control studies were not included.

For single arm review question, case series and prospective and retrospective cohort studies were included.

2.4 Methods of combining evidence

2.4.1 Data synthesis for intervention reviews

Meta-analyses were conducted using Cochrane Review Manager (RevMan5)[12] 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[2] 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 as they 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.

Where the studies within a single meta-analysis had different scales of measurement for the same outcomes, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was ‘normalised’ to the standard deviation value pooled between the intervention and comparator groups in that same study.

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 RevMan5[12].

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.[12] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[2] 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 if the person had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were pre-specified by the committee (upper threshold at 90% and the lower threshold at 60% for both sensitivity and specificity) including whether or not data could be pooled across a range of thresholds. 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 usually varies across 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.[12] 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.[13] 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.[10]) The pooled median sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For analyses with fewer than 3 studies included, the results of the study with the lower sensitivity value was reported when there were 2 studies, or reported individually for a single study.

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[12] 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.

A second analysis was conducted by restricting the set of studies to those with the same clinically relevant threshold as agreed by the committee, to ensure the data were comparable. They were presented as forest plots and ROC curves and heterogeneity was investigated.

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
- 0.81–0.90: good
- 0.91–1.00: excellent or perfect test.

Heterogeneity or inconsistency amongst studies was visually inspected.

2.4.3 Data synthesis for prognostic reviews

Separate review protocols were produced for prognostic RCTs and prognostic accuracy.

2.4.3.1 Prognostic RCTs

Prognostic RCTs (sometimes referred to as test and treat trials) are a randomised comparison of 2 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).

2.4.3.2 Prognostic accuracy studies

For prognostic test accuracy studies, a positive result on the index test was found if the person had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were pre-specified by the committee (0.95 and 0.75, respectively, which were the thresholds used for specificity and 0.9 and 0.7, respectively, which were the thresholds used for sensitivity) including whether or not data could be pooled across a range of thresholds. The threshold of a test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice this usually varies across 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.[12] 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.

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.[13] 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.[10]) The pooled median sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For analyses with fewer than 3 studies included, the results of the study with the lower sensitivity value was reported when there were 2 studies, or reported individually for a single study.

If appropriate, to allow comparison between tests, summary ROC curves were generated for each test from the pairs of sensitivity and specificity calculated from the 2by 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[12] and ROC curves were fitted using the Moses-Littenberg approach. In order to compare tests, 2 or more tests were plotted on the same graph. The performance of the different 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.

A second analysis was conducted by restricting the set of studies to those with the same clinically relevant threshold as agreed by the committee, to ensure the data were comparable. They were presented as forest plots and ROC curves and heterogeneity was investigated.

Area under the ROC curve (AUC) data for each study were also plotted on a graph, for each test. The AUC describes the overall diagnostic/prognostic 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
- 0.81–0.90: good
- 0.91–1.00: excellent or perfect test.

Heterogeneity or inconsistency amongst studies was visually inspected.

2.4.4 Data synthesis for prognostic risk factor reviews

Adjusted odds ratios, risk ratios, or hazard ratios, with their 95% CIs, for the effect of the pre-specified prognostic factors were extracted from the studies. Studies were only included if the confounders pre-specified by the committee were either matched at baseline or were adjusted for in multivariate analysis. Prospective cohort studies reporting multivariable analyses that adjusted for key confounders identified by the committee at the protocol stage for that outcome were the preferred study design.

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

2.4.5 Data synthesis for single arm studies reviews

Meta-analyses were conducted using R software (metafor) and were used to calculate estimate values (SE) or predictive values (CI) depending on the type of data set. Estimate values were used for data sets without zero events and predictive values were used when there were zero events in the data set. Proportion of people with events/predicted proportion of people with events for that population was also reported based on the estimate and predictive values. Fixed or random effects models were considered for the analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology or population was identified by the reviewer in advance of data analysis.

- The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%.

If there was significant heterogeneity as defined above, results were pooled using random effects.

Standard analysis

In studies where event rates do not equal 0 or 1, the standard meta-analysis function (.rma) within the metafor package was used.

Variation in analysis

In an analysis containing studies where event rates equate to either 0 or 1, problems could occur when synthesising the data using the code for event rates which do not equal 0 or 1, due to these studies having a standard error of 0. In such situations, a transformation was performed prior to the synthesis, and an appropriate back transformation post-synthesis to get an estimate of the synthesised values. Freeman-Tukey double arcsine transformation[1] was incorporated to stabilise the variation of studies using the escalc function within R, with the inverse transformation post-synthesis made using the predict function.

2.5 Appraising the quality of evidence by outcomes

2.5.1 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[2]) 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%

Quality element	Description
	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. Publication bias was considered with the committee. If there was reason to suspect it was present, it was explored with funnel plots. Funnel plots were constructed using RevMan5 software to assess against potential publication bias for outcomes containing more than 5 studies. This was taken into consideration when assessing the quality of the evidence.

2.5.1.1 Risk of bias

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 non-randomised studies or ROBIS for systematic reviews). For each study, if there was no risk of bias in any domain, the risk of bias was given a rating of 0; 'no serious risk of bias'. 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.
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

Limitation	Explanation
	• 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, due to the possibility of confounding and the greater risk of selection bias. The assessment of risk of bias therefore requires a different checklist (ROBINS-I) and 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 non-randomised 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 deviation from the intended intervention(s). Assessment of bias in this domain

Bias	Explanation
	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.

2.5.1.2 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.

2.5.1.3 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 for that forest plot (providing at least 2 studies 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.

2.5.1.4 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 modified GRADE ‘default’ values, as follows:

- For dichotomous outcomes the MIDs were taken to be RRs of 0.8* and 1.25. 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.

  - In cases where there are zero events in one arm of a single study, or some or all of the studies in one arm of a meta-analysis, the same process is followed as for dichotomous outcomes. However, if there are no events in either arm in a meta-analysis (or in a single unpooled study) the sample size is used to determine imprecision using the following rule of thumb:
    - No imprecision: sample size ≥350
    - Serious imprecision: sample size ≥70 but <350
    - Very serious imprecision: sample size <70.
  - When there was more than one study in an analysis and zero events occurred in both groups for some but not all of the studies across both arms, the optimum information size was used to determine imprecision using the following guide:
    - No imprecision: >90% power
    - Serious imprecision: 80-90% power
    - Very serious imprecision: <80% power.
- Time to event data, there aren't established default values for HRs so the same values as dichotomous outcomes are applied here (0.8 and 1.25) 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. As these vary for each outcome per review, details of the values used are reported in the footnotes of the relevant GRADE summary table.

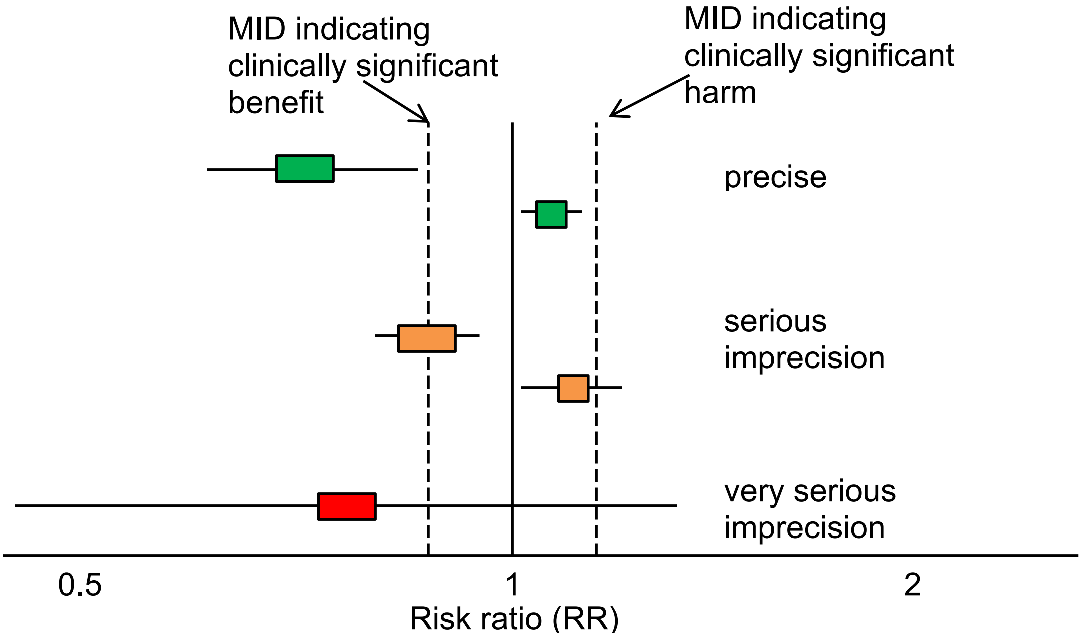
*NB GRADE report the default values as 0.75 and 1.25. These are consensus values. This guideline follows NICE process to use modified values of 0.8 and 1.25 as they are symmetrical on a relative risk scale.

For this guideline, the following MIDs for continuous outcomes were found in the literature and adopted for use:

Table 5: Published or pre-agreed MIDs

Outcome measure	MID	Source
EQ-5D	0.03	Consensus pragmatic MID used in some previous NICE guidelines
SF36	Physical component summary: 2 Mental component summary: 3	User's manual for the SF-36v2 Health Survey, Third Edition[3]

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)



2.5.1.5 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. RCTs start 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 6. The reasons for downgrading in each case are specified in the footnotes of the GRADE tables.

Table 6: 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
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

2.5.2 Diagnostic reviews

2.5.2.1 Diagnostic RCTs

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

2.5.2.2 Diagnostic test accuracy

2.5.2.2.1 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[6]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see **Table 7**):

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

Table 7 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 interpreted without knowledge of the	Did all patients receive a reference standard?
	Did the study avoid			Did all patients receive the same reference standard?

Domain	Patient selection	Index test	Reference standard	Flow and timing
	inappropriate exclusions?		results of the index test?	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?	

2.5.2.2.2 *Inconsistency*

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by visual inspection of the primary outcome measures (sensitivity and specificity) using the point estimates and 95% CIs of the individual studies on the forest plots or the summary value if a diagnostic meta-analysis had been conducted. The evidence was downgraded by 1 increment if there was no overlap of 95% confidence intervals or by 2 increments if there was wide variability. Where only a single study reports an outcome, inconsistency is rated as ‘not detected’.

2.5.2.2.3 *Imprecision*

The judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point 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. The decision thresholds set by the committee (upper threshold at 90% and the lower threshold at 60% for both sensitivity and specificity) were used to determine whether imprecision is not serious, serious or very serious depending on whether confidence intervals cross zero, one or two thresholds.

2.5.2.2.4 *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 GRADE evidence profile.

2.5.3 Prognostic reviews

2.5.3.1 Prognostic RCTs

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

2.5.3.2 Prognostic test accuracy

2.5.3.2.1 Risk of bias

The risk of bias for prognostic studies was evaluated according to the QUIPS checklist, which was used without the confounding section of the checklist as although this is relevant for prognostic reviews reporting odds ratios, this is less relevant to studies reporting accuracy measures such as sensitivity and specificity. The main criteria are given in **Table 9**.

Table 8: 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.

2.5.3.2.2 Inconsistency

Inconsistency was assessed as for intervention studies.

2.5.3.2.3 Imprecision

The judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point from the prognostic accuracy meta-analysis, if a meta-analysis was conducted. Where a 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. The decision thresholds set by the committee (0.95 and 0.75, respectively, which were the thresholds used for specificity and 0.9 and 0.7, respectively, which were the thresholds used for sensitivity) were used to determine whether imprecision is not serious, serious or very serious depending on whether confidence intervals cross zero, one or two thresholds

2.5.3.2.4 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 GRADE evidence profile.

2.5.4 Prognostic risk factor reviews

An adapted GRADE evidence profile was used for quality assessment per outcome. If data were meta-analysed, the quality for pooled studies was presented. If the data were not pooled, then a quality rating was presented for each study.

2.5.4.1.1 Risk of bias

The risk of bias for prognostic studies was evaluated according to the QUIPS checklist, the main criteria are given in **Table 9**.

Table 9: 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.

2.5.4.1.2 Inconsistency

Inconsistency was assessed as for intervention studies.

2.5.4.1.3 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.

2.5.4.1.4 Overall grading

Quality rating started at high for prospective studies and each major limitation brought the rating down by 1 increment to a minimum grade rating of very low, as explained for interventional reviews. For prognostic reviews prospective cohort studies with a multivariate analysis are regarded as the gold standard because RCTs are usually an inappropriate design to answer the question for these types of review. Furthermore, if the study is looking at more than 1 prognostic factor of interest then randomisation would be inappropriate as it can only be applied to 1 of the prognostic factors.

2.5.5 Single arm studies review

2.5.5.1.1 Risk of bias

Risk of bias for case series (single arm studies) were evaluated by study using the Institute of Health Economics (IHE) checklist for case series. (see appendix H in the NICE guidelines manual 2014[5]). The main criteria are given in Table 9.

- **Table 10: Description of risk of bias criteria for case series**

Risk of bias	Aim of section
Study objective	To assess if hypothesis/aim/objective of the study is clearly stated
Study design	To assess if study is conducted prospectively, cases collected in more than one centre and patients are recruited consecutively
Study population	To assess if characteristics of the patients included in the study described, eligibility criteria are clearly stated, if patients enter the study at a similar point in the disease
Intervention and co-intervention	To assess if interventions and co-interventions are clearly described
Outcome measure	To assess if relevant outcome measures are established a priori, outcome assessors are blinded to the intervention that patients received, relevant outcomes were measured using appropriate objective/subjective methods, relevant outcome measures were made before and after the intervention.
Statistical analysis	To assess if statistical tests used to assess the relevant outcomes are appropriate.
Results and conclusions	To assess if follow-up long is enough for important events and outcomes to occur, losses to follow-up reported, provided estimates of random variability in the data analysis of relevant outcomes, adverse events are reported and conclusions of the study are supported by results.
Competing interests and sources of support	To assess if competing interests and sources of support for the study are reported.

Checklist questions on interventions and co-interventions were not relevant for our review. Studies were also assessed if they had adjusted for key confounders as stated in the protocol.

2.5.5.2 Indirectness

Indirectness refers to the extent to which the populations 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. 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.

2.5.5.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Significant between study heterogeneity in methodology or population was identified by the reviewer in advance of data analysis. Statistical heterogeneity was assessed for each meta-analysis estimate by an I-squared (I^2) inconsistency statistic. The presence of significant statistical heterogeneity in the meta-analysis was defined as I2≥50%. If there was significant heterogeneity as defined above, results were pooled using random effects model.

2.5.5.4 Imprecision

Imprecision was assessed based on the width of the CI for the estimate of the proportion, or equivalently the standard error.

2.5.5.5 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. Studies start 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 6. The reasons for downgrading in each case are specified in the footnotes of the GRADE tables.

Table 11: 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
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

2.6 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[2] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio. In single arm studies predicted proportion of people who had the outcome/events for that population were used to assess clinical importance.

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 dichotomous 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 mortality any reduction represented a clinical benefit. For adverse events 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 outcomes such as mortality any reduction or increase was considered to be clinically important.

Established MIDs found in the literature and were agreed to be used for SF-36 (Physical and Mental) and EQ-5D.

The published values used for imprecision and clinical importance are provided in **Table 5**.

For continuous outcomes where the GRADE default MID has been used, the values for each outcome are provided in the footnotes of the relevant GRADE tables. For single arm studies review the assessment of clinically important results was based on the point estimate of predicted proportion of events for each outcome. Thresholds for clinically important results were decided by the committee on a case by-case basis.

Table 12: MIDs

Outcome measure	MID	Source
SF 36- Physical	2	SF36v2 Health Survey Users manual[3]
SF 36- Mental	3	SF36v2 Health Survey Users manual[3]
EQ5D	0.03	as used previously in NICE guidelines based on consensus.

2.7 Identifying and analysing evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their ‘cost effectiveness’) rather than the total implementation cost. However, the committee will also need to be increasingly confident in the cost effectiveness of a recommendation as the cost of implementation increases.

Therefore, the committee may require more robust evidence on the effectiveness and cost effectiveness of any recommendations that are expected to have a substantial impact on resources; any uncertainties must be offset by a compelling argument in favour of the recommendation. The cost impact or savings potential of a recommendation should not be the sole reason for the committee's decision.[5]

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

2.7.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual.[5]
- Extracted key information about the studies' methods and results into health economic evidence tables (which can be found in appendices to the relevant evidence reports).
- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant evidence report for each review question) – see below for details.

2.7.2 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2006 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant evidence report.

For more details about the assessment of applicability and methodological quality see **Table 13** below and the economic evaluation checklist (appendix H of the NICE guidelines manual[5]) and the health economics review protocol, which can be found in each of the evidence reports.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

2.7.3 NICE health economic evidence profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each evidence review report. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[5] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See **Table 13** for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[11]

Table 13: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:(a) Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness. Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:(a) Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost effectiveness. Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.

Item	Description
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in appendix H of the NICE guidelines manual[5]

2.7.4 Undertaking new health economic analysis

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 selected areas. Priority areas for new analysis were agreed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified the following as the highest priority areas for original health economic modelling:

- Tranexamic acid (TXA) vs No TXA for people with moderate or severe traumatic brain injury in the pre-hospital setting
    - For the pre-hospital setting, there was a large randomised controlled trial setting but no published economic evaluation. As this is not established practice, it was important to explicitly evaluate the trade-off between costs and benefits.
- Computed tomography (CT) of the head vs No CT of the head for people with minor head injury on anticoagulants.
    - A published economic evaluation suggested that CT was not cost effective. However, this study had some limitations. The published model was reconstructed, and additional sensitivity analyses were conducted.
- Admission for observation vs no admission for people with an isolated skull fracture on CT and no other indication for admission.
    - The clinical evidence showed that adverse events in this population are very rare. However, given that admission is common, it was important to explicitly evaluate the trade-off between costs and benefits.

For all other questions either the existing economic evaluations were assessed to be sufficient or the clinical evidence was insufficient to build an economic model (in which case, the committee recommended further research).

The following general principles were adhered to in developing the cost-effectiveness analyses:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[5, 8]

- 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.

Full methods and results of the cost-effectiveness analysis are described in a separate economic analysis report.

2.7.5 Cost-effectiveness criteria

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[5, 7, 9] 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.[5]

When QALYs 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.

2.7.6 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.

2.8 Developing recommendations

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

- Summaries of clinical and health economic evidence and quality (as presented in evidence reports [A–N]).
- 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).

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 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 also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 2.8.1 below).

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.
- Consistency with NICE’s standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the NICE guidelines manual[6]).

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

2.8.1 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.

2.8.2 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.

2.8.3 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.

2.9 General terms

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

Term	Definition
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)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. 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.

Term	Definition
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 positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.

Term	Definition
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-

Term	Definition
	nothing alternative then Option A is said to have extended 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.
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 evidence 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 evidence profile.
Harms	Adverse effects of an intervention.
Hazard Ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
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.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) − Incremental cost.

Term	Definition
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.
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)

Term	Definition
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
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.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
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 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	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
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.

Term	Definition
	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, or more extreme 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.
Polypharmacy	The use or prescription of multiple medications.
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.

Term	Definition
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 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.

Term	Definition
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 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.

Term	Definition
	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
Stratification	When a different estimate effect is thought to underlie two or more groups based on the PICO characteristics. The groups are therefore kept separate from the outset and are not combined in a meta-analysis, for example; children and adults. Specified a priori in the protocol.
Sub-groups	Planned statistical investigations if heterogeneity is found in the meta-analysis. Specified a priori in the protocol.
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.
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

Term	Definition
	include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

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