

Final

# Acute Kidney Injury (update)

NICE guideline: methods

*NICE guideline NG148*

*Methods*

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*Final*

*Developed by NICE*



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# 1 Development of the guideline

## 1.1 Remit

NICE received the remit for this guideline from NHS England.

To see what the guideline covers and what this guideline does not cover, please see the guideline scope.

## 2 Methods

This guideline was developed using the methods described in the NICE guidelines manual as outlined in Table 1 below.

**Table 1 Versions of the NICE guidelines manual followed during guideline development and guideline validation**

Stage	2018 update	2020 update	2022 update
Scoping			X
Development			X
Validation			X

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 2.2 and 2.4 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 National Guideline Centre technical team and refined and validated by the committee and signed off by NICE. A total of two review questions were developed in this guideline and outlined in Table 2.

The review questions were based on the following frameworks:

- population, exposure and outcomes for prognostic reviews

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

**Table 2: Review questions**

Evidence report	Type of review	Review questions	Outcomes
1.1	Prognostic risk assessment tools	What is the prognostic accuracy of risk assessment tools/questionnaires to predict the occurrence of AKI following the administration of iodine-based contrast media?	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> <li>• Dialysis</li> <li>• Mortality (AUC, sensitivity, specificity, PPV, NPV, and OR and RR for dialysis and mortality)</li> </ul>
1.2	Prognostic risk factor	What is the prognostic accuracy of eGFR for iodine-based contrast media-associated AKI?	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> <li>• Dialysis</li> <li>• Mortality (adjusted OR and RR)</li> </ul>

#### 2.1.1.1 Stratification

Stratification is applied where the committee are confident the risk will be different in the groups and separate recommendations are required, therefore they should be reviewed separately. In this guideline all analyses were stratified for age (intravenous and intra-arterial

contrast administration), which meant that different studies with predominant administration routes in different strata were not combined and analysed together. Where studies reported a mix of populations across strata, a threshold of [80%] 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 by a senior information specialist to identify all published clinical and health economic evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the 2014 NICE guidelines manual.

Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed, and where possible, searches were restricted to English language. Searches were run on 09/02/2024 (clinical) and 19/02/2024 (economic). If new evidence falls outside of the timeframe for the guideline searches, for example from stakeholder comments, the impact on the guideline will be considered, and any further action agreed between the developer and NICE staff with a quality assurance role.

Searches were quality assured using different approaches prior to being run. Medline search strategies were peer reviewed by a second senior information specialist using a process adapted from the [2015 PRESS Guideline Statement](#). All translated search strategies were peer reviewed to ensure their accuracy. Key (seed) papers were checked if retrieved.

Searching for unpublished literature was not undertaken.

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

## 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 (NICE, 2024). The checklist used is included in the individual review protocols in each of the evidence reports.
- Key information was extracted about study methods and results into EPPI reviewer version 5. Summary evidence tables were produced from data entered into EPPI Reviewer, including critical appraisal ratings (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:
  - Prognostic data were meta-analysed where appropriate and reported in adapted GRADE profile tables.
- A minimum of 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.
- All of the evidence reviews were quality assured by a senior systematic reviewer. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - a sample of the risk of bias assessments
  - correct methods were used to synthesise data.Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).

### **2.3.1 Types of studies and inclusion and exclusion criteria**

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

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 published in English language were excluded.

#### **2.3.1.1 Type of studies**

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

For prognostic risk prediction tool review questions, prospective cohort studies were included. Studies had to include validated risk prediction tools that were either developed in a separate cohort within the study or had previously been developed in an earlier paper. For prognostic risk factor review questions, prospective and retrospective cohort studies were included. Case–control studies were not included.

Systematic reviews and meta-analyses conducted to the same methodological standards as the NICE reviews were included within the evidence reviews in preference to primary studies, where they were available and applicable to the review questions and updated or added to where appropriate to the guideline review question. Individual patient data (IPD) meta-analyses were preferentially included if meeting the protocol and methodological criteria.

## **2.4 Methods of combining evidence**

### **2.4.1 Data synthesis for intervention reviews**

Meta-analyses were conducted using Cochrane Review Manager (RevMan, 2014) software



### 2.4.1.1 Analysis of different types of data

### 2.4.2 Data synthesis for prognostic risk factor reviews

Adjusted odds ratios or risk 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.

### 2.4.3 Data synthesis for risk prediction tools

Evidence for risk prediction rules or risk prediction tools were presented for discrimination and calibration. Data were analysed according to the principles of data synthesis for diagnostic accuracy studies.

Coupled forest plots of the agreed primary paired outcome measures for decision making (sensitivity and specificity) with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5. 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. Positive and negative predictive values were extracted if reported, but not included on forest plots due to the inability to calculate 2 by 2 tables with these statistics.

Meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Predictive 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 (Lunn, 2000) 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). 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 median when there were 2 studies or reported individually for a single study.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots.

If available, area under the ROC curve (AUC) data for each study were also plotted on a graph, for each risk tool. The AUC describes the overall predictive accuracy across the full range of thresholds. The following criteria were used for evaluating AUCs:

- $\leq 0.50$ : 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.

Calibration was assessed using calibration plots and the Hosmer-Lemeshow (H-L) test. No calibration plots were reported in the identified evidence. The H-E test is a goodness of fit test for logistic regression, with the outputs indicating if the observed event rate matches the predicted event rate. For this review, a p-value of >0.05 was deemed to be indicative of a risk prediction tool that accurately predicted the observed event rate. Note that in this test, a p-value typically deemed to be significant in scientific research (<0.05) is undesirable as this indicates a significant difference between the predicted and observed events.

## 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 (Malmivaara, 2015), 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 3.

**Table 3: Description of quality elements in GRADE for intervention studies**

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

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

## 2.5.2 Prognostic reviews

An adapted GRADE 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.

### 2.5.2.1.1 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 4: 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.

### 2.5.2.1.2 Inconsistency

Where multiple studies reported the same threshold, inconsistency was assessed by a visual assessment of the point estimates and their corresponding 95% CIs. Where 95% CIs overlapped there was deemed to be no inconsistency. When 95% CIs did not overlap, downgrading for inconsistency was applied, with either 1 or 2 increments depending on the magnitude of the difference between estimates.

### 2.5.2.1.3 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.

### 2.5.2.1.4 Overall grading

Quality rating was assigned by study. However, if there was more than 1 outcome involved in a study, then the quality rating of the evidence statements for each outcome was adjusted accordingly. For example, if one outcome was based on an invalidated measurement method, but another outcome in the same study was not, the second outcome would be graded 1 grade higher than the first outcome.

Quality rating started at high, and each major limitation brought the rating down by 1 increment to a minimum grade rating of very low. 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.

### **2.5.3 Risk prediction tools**

#### **2.5.3.1.1 Risk of bias**

Risk of bias and applicability of evidence for prognostic risk data were evaluated by study using the Prediction study Risk of Bias Assessment Tool (PROBAST) checklist. Risk of bias and applicability in risk prediction studies in PROBAST consists of 4 domains:

- patient selection
- predictors
- outcome
- analysis.

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.

#### **2.5.3.1.2 Inconsistency**

Inconsistency for discrimination outcomes was assessed by inspection of the primary outcome measures (sensitivity and specificity) using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (prediction based on chance alone) and the threshold set by the committee (the threshold above which it would be acceptable to recommend a rule/model). The evidence was downgraded by 1 increment if the CI varied across 2, and by 2 increments if the individual studies varied across 3 areas. Where only a single study reports an outcome, inconsistency is rated as 'not detected'.

#### **2.5.3.1.3 Imprecision**

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. For discrimination outcomes, the judgement of precision was based on visual inspection of the confidence region around the primary paired outcome measures for decision-making (sensitivity and specificity) from the 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 were used to determine whether imprecision is not serious, serious or very serious depending on whether confidence intervals cross zero, one or two thresholds.

#### **2.5.3.1.4 Overall grading**

Quality rating started at High, and each major limitation brought the rating down by 1 increment to a minimum grade 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 inappropriate for these types of review for ethical or pragmatic reasons. Furthermore, if the study is looking at more than 1 risk factor of interest then randomisation would be inappropriate as it can only be applied to 1 of the risk factors. This was presented in a modified GRADE profile.

## 2.6 Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a potential clinical utility of both risk prediction tools and eGFR thresholds.

## 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 (NICE, 2024)

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

A literature search was carried out for both review questions (i.e. risk prediction tools and eGFR evidence) to identify relevant published economic studies. In total, 244 records were retrieved from database. After title and abstract screening, no relevant studies were found for this review question.

#### 2.7.1.1 Inclusion and exclusion criteria

No relevant health economic studies were found from the economic literature review.

#### 2.7.1.2 NICE health economic evidence profiles

Not applicable as no economic evidence was identified for both review questions.

### 2.7.2 Undertaking new health economic analysis

No original economic model was developed for this review question. Given that the resource impact was unlikely significant, a decision for not doing economic modelling was made before the start of development.

### 2.7.3 Cost-effectiveness criteria

Not applicable.

### 2.7.4 In the absence of health economic evidence

Since no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement by considering expected

differences in resource use between options alongside the results of the review of clinical effectiveness evidence.

## 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 report A).
- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables can be found in appendices of the evidence report.
- 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).

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.

### **2.8.4 Disclaimer**

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

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

### **2.8.5 Funding**

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

- 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.
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.
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').
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.  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.



Term	Definition
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.
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.
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

Term	Definition
	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.
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).

Term	Definition
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended 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.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Term	Definition
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.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
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: $TN/(TN+FN)$
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

Term	Definition
	threshold is £20,000 per QALY gained, then the NMB for an intervention is calculated as: $(£20,000 \times \text{mean QALYs}) - \text{mean cost}$ . 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.
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. 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.
Polypharmacy	The use or prescription of multiple medications.

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



Term	Definition
	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.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	<p>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).</p> <p>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.</p>
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	<p>Selection bias occurs if:</p> <ol style="list-style-type: none"> <li>The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or</li> <li>There are differences between groups of participants in a study in terms of how likely they are to get better.</li> </ol>
Sensitivity	<p>How well a test detects the thing it is testing for.</p> <p>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').</p> <p>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.</p> <p>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').</p> <p>Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high</p>

Term	Definition
	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	<p>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.</p> <p>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.</p> <p>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.</p> <p>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.</p> <p>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).</p>
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	<p>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.</p> <p>See related term 'Sensitivity'.</p> <p>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.</p>
Stakeholder	<p>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:</p> <ul style="list-style-type: none"> <li>• manufacturers of drugs or equipment</li> <li>• national patient and carer organisations</li> <li>• NHS organisations</li> <li>• organisations representing healthcare professionals.</li> </ul>
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.
Univariate	Analysis which separately explores each variable in a data set.



Term	Definition
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

## References

NICE (2024) Developing NICE guidelines: the manual.

RevMan (2014) Review Manager (RevMan).

Lunn T, Best, and Spiegelhalter. (2000) WinBUGS \– A Bayesian modelling framework: Concepts, structure, and extensibility *Statistics and Computing* 10 (4): 325-337.

Malmivaara (2015) Methodological considerations of the GRADE method *Annals of Medicine* 47 (1): 1-5.