National Institute for Health and Care Excellence

Draft for Consultation

Attention deficit hyperactivity disorder: diagnosis and management (update)

NICE guideline: methods

NICE guideline CG72

Methods

September 2017

Draft for Consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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, where appropriate, their carer or guardian.

Local commissioners and 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.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1 Development of the guideline

1.1 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a guideline committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The guideline is made up of a collection of documents including this Methods report and a number of evidence reports covering each of the review questions included in the guideline. These can all be downloaded from NICE at www.nice.org.uk.

NICE also publishes a summary of the recommendation in this guideline, known as ‘the NICE guideline’.

NICE Pathways brings together all connected NICE guidance.

1.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline.

The remit for this guideline is:

to develop a clinical guideline on the diagnosis and management of attention deficit hyperactivity disorder (ADHD).

1.3 Who developed this guideline?

A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of guideline committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by Gillian Baird in accordance with guidance from NICE.

The group met approximately every 6 weeks during the development of the guideline. At the start of the guideline development process all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in the declaration of interest register for this guideline published on the NICE website.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information specialists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

1.3.1 What this guideline covers

This guideline updates and replaces the NICE guideline on attention deficit hyperactivity disorder. This update covers the areas of identification of risk factors, post-diagnostic advice, non-pharmacological and pharmacological management and intervention adherence for children, young people and adults with a diagnosis of ADHD (with or without any co-existing conditions).

For further details please refer to the scope for this guideline (published on the NICE website) and the review questions in section 2.1.

1.3.2 What this guideline does not cover

This update does not cover any other aspect from the previous guideline, nor managing co-existing conditions.

1.3.3 Relationships between the guideline and other NICE guidance

NICE technology appraisals to be updated by this guidance:

- Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. NICE technology appraisal guidance 98 (2006).

Related NICE guidelines:

- Antisocial behaviour and conduct disorders in children and young people: recognition and management. NICE guideline CG158 (2017).
- Controlled drugs: safe use and management. NICE guideline NG46 (2016).
- Mental health problems in people with learning difficulties. NICE guideline NG54 (2016).

- Mental health of adults in contact with the criminal justice system. NICE guideline NG66 (2016).
- Transition from children's to adults' services for young people using health or social care services. NICE guideline NG43 (2016).
- Patient experience in adult NHS services: improving the experience of care for people using adult NHS services. NICE guideline CG138 (2012).
- Hypertension in adults: diagnosis and management. NICE guideline CG127 (2011).
- Service user experience in adult mental health: improving the experience of care for people using adult NHS mental health services. NICE guideline CG136 (2011).
- Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE guideline CG76. (2009).

Related NICE guidance currently in development:

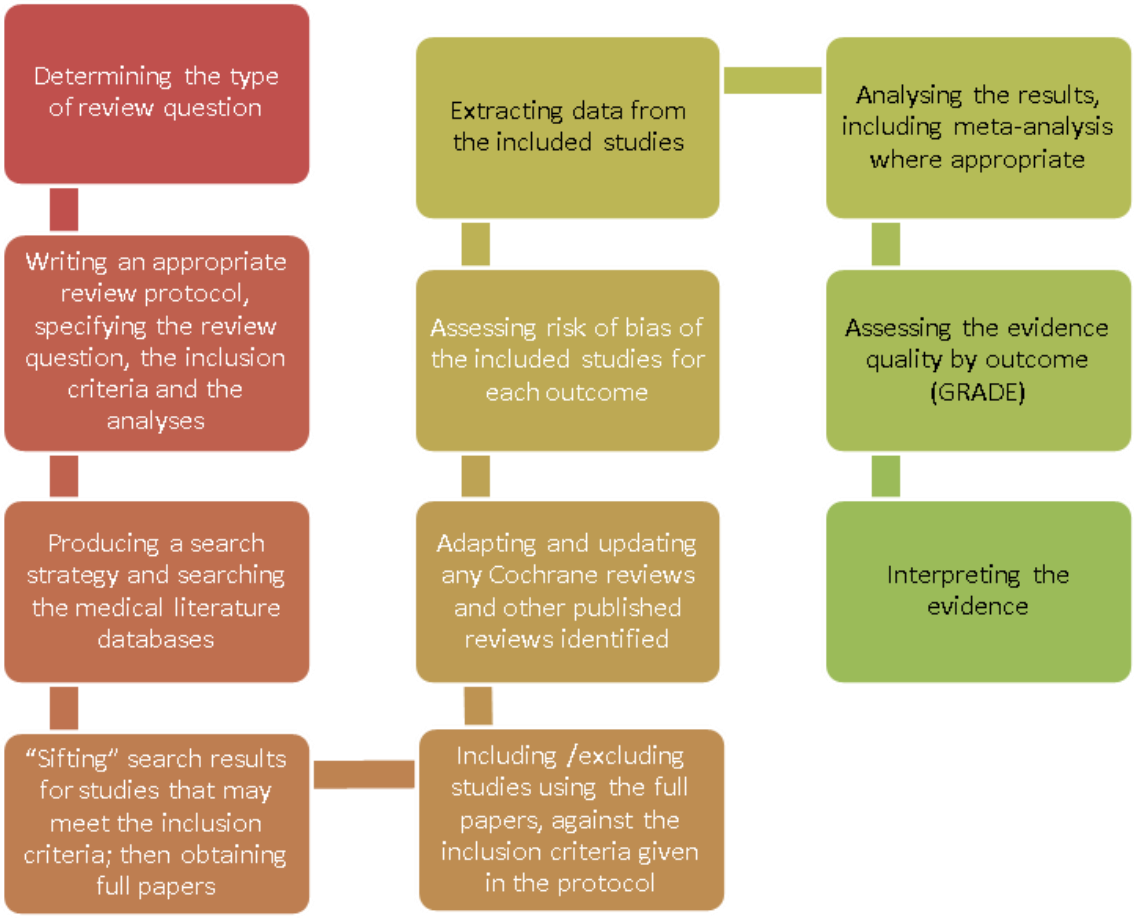
- Developmental follow-up of children and young people born preterm. NICE guideline. Publication expected August 2017.

2 Methods

This report sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in each of the evidence reviews for this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2014 version.[3]

Sections 2.1 to 2.3 describe the process used to identify and review clinical evidence (summarised in Figure 1), sections 2.2 and 2.4 describe the process used to identify and review the health economic evidence, and section 2.5 describes the process used to develop recommendations.

Figure 1: Step-by-step process of review of evidence in the guideline



2.1 Developing the review questions and outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews; and using a framework of population, setting and context for qualitative reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the guideline committee. The review questions were drafted by the NGC technical team and refined and

validated by the committee. The questions were based on the key clinical areas identified in the scope.

A total of 12 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Evidence report	Type of review	Review questions	Outcomes
[A]	Prognostic	Which groups of people are more likely than the general population to have ADHD or are more likely to have missed a diagnosis of ADHD?	Critical outcomes: • ADHD diagnoses • Missed ADHD diagnoses
[B]	Qualitative	What are the information and support needs of children, young people and adults with ADHD and their family and carers after diagnosis?	-
[C]	Intervention	What is the most clinically and cost-effective pharmacological treatment for children, young people and adults with ADHD? What is the most clinically and cost-effective sequence of pharmacological treatment for children, young people and adults with ADHD?	Critical outcomes: • Quality of life • ADHD symptoms • Responders by CGI Important outcomes: • Serious adverse events • Behavioural/functional measures • Emotional dysregulation • Academic outcomes • Substance use • Self-harm
[D]	Intervention	What are the adverse events associated with pharmacological treatment for people with ADHD?	Critical outcomes: • Total number of participants with an adverse event • All-cause mortality • Suicide or suicidal ideation • Cardiac mortality • Cardiac events • Substance misuse • Abnormal growth • Increase in seizures • Psychotic symptoms • Disturbed sleep • Liver damage • Increase in tics • Tremors • Congenital defects • Sexual dysfunction
[E]	Intervention	What is the most clinically and cost-effective non-pharmacological treatment, and combination of treatments, for people with ADHD?	Critical outcomes: • Quality of life • ADHD symptoms

Evidence report	Type of review	Review questions	Outcomes
			• Responders by CGI Important outcomes: • Serious adverse events • Behavioural/functional measures • Emotional dysregulation • Academic outcomes • Substance use • Self-harm
[E]	Qualitative	What do people with ADHD feel are the adverse impacts of non-pharmacological treatment for ADHD?	-
[F]	Intervention	What is the most clinically and cost-effective combination of pharmacological and non-pharmacological treatment for people with ADHD?	Critical outcomes: • Quality of life • ADHD symptoms • Responders by CGI Important outcomes: • Serious adverse events • Behavioural/functional measures • Emotional dysregulation • Academic outcomes • Substance use • Self-harm
[G]	Qualitative	What factors do people with ADHD believe affect their adherence to pharmacological or non-pharmacological treatment for ADHD?	-
[H]	Qualitative	What principles should clinicians follow when discussing decisions to start, adjust, or discontinue pharmacological treatment for people with ADHD?	-
[I]	Intervention	What are the clinical effects of withdrawing from pharmacological treatment for ADHD? What are the clinical effects of 'drug holidays' from pharmacological treatment for ADHD?	Critical outcomes: • Quality of life • ADHD symptoms • Responders by CGI Important outcomes: • Serious adverse events • Behavioural/functional measures • Emotional dysregulation • Academic outcomes • Substance use • Self-harm

2.2 Searching for evidence

1.1.1 Clinical and health economics literature searches

The full search 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 report.

Systematic literature searches were undertaken to identify all published clinical and health economics evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.[3] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed, where possible, searches were restricted to English Language. All searches were updated on 28 April 2017. Papers published or added to databases after this date were not considered. If new evidence falls outside of the timeframe for the guideline searches e.g. from stakeholder comments, the impact on the guideline will be considered, and any further action agreed between the developer and NICE staff with a quality assurance role.

Prior to running, searches were quality assured using different approaches. Medline search strategies were checked by a second information specialist before being run. Searches were cross-checked with reference lists of highly relevant papers, searches in other systematic reviews analysed, and committee members requested to highlight additional studies.

2.3 Identifying and analysing evidence of effectiveness

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in an appendix to each of the evidence reports).
- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.[3] Prognostic studies were critically appraised using NGC checklists. Qualitative studies were critically appraised using the GRADE CERQual approach for rating confidence in the body of evidence as a whole and using an NGC checklist for the methodological limitations section of the quality assessment.
- Extracted key information about interventional study methods and results using ‘Evibase’, NGC’s purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in an appendix to each of the evidence reports).
- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
  - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.
  - Data from non-randomised studies were presented as a range of values in GRADE profile tables or meta-analysed if appropriate.
  - Prognostic data were meta-analysed where appropriate and reported in GRADE profile tables.

  - Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables
  - Qualitative data were synthesised across studies and presented as summary statements with accompanying GRADE CERQual ratings for each review finding.
- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers and those for complex review questions (for example, prognostic reviews) were double-sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - correct methods were used to synthesise data
  - a sample of the risk of bias assessments.

2.3.1 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 another appendix to each of the evidence reports. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Children, young people and adults with ADHD, as diagnosed by ICD/DSM criteria

The key population exclusion criterion was:

- Children, young people and adults with some symptoms of ADHD but without a diagnosis or formal assessment, except in the context of comorbidity with other disorders including autism spectrum disorder

Conference abstracts were not automatically excluded from any review. The abstracts were initially assessed against the inclusion criteria for the review question and further processed when a full publication was not available for that review question. If the abstracts were included the authors were contacted for further information. No relevant conference abstracts were identified for this guideline. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

2.3.1.1 Saturation of qualitative studies

Data extraction in qualitative reviews is a thorough process and may require more time compared to intervention reviews. It is common practice to stop extracting data once saturation has been reached. This is the point when no new information emerges from studies that match the review protocol. The remaining identified studies are, however, not directly excluded from the review as they nevertheless fit the criteria defined in the review protocol. Any studies for which data were not extracted due to saturation having been reached, but that fit the inclusion criteria of the protocol, were listed in the table for studies 'identified but not included due to saturation' in an appendix to the qualitative evidence review.

2.3.2 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 most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. If non-randomised intervention studies were considered appropriate for inclusion (for example, where no randomised evidence was available for critical outcomes and the committee agreed that non-randomised studies would be relevant to potential recommendations) 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. Please refer to the review protocols in each evidence report for full details on the study design of studies selected for each review question.

For prognostic review questions, prospective and retrospective cohort studies were included. Case–control studies were not included.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

2.3.3 Methods of combining clinical studies

2.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[7] software to combine the data given in all studies for each of the outcomes of interest for the review question.

All analyses were stratified for age (under 5 years, 5 to 18 years and over 18 years), which meant that different studies with predominant age-groups in different age strata were not combined and analysed together. If studies population included participants from multiple age groups, the mean age of the study participants was used to assign the study to a single stratum. For some questions additional stratification was used, and this is documented in the individual review question protocols in each evidence report. When additional strata were used this led to substrata (for example, using 2 stratification criteria leads to 4 substrata, using 3 stratification criteria leads to 9 substrata) which were analysed separately.

2.3.3.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel–Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- improvement/response in terms of ADHD symptoms
- discontinuations
- serious adverse events.

The absolute risk difference was also calculated using GRADEpro[1] software, using the median event rate in the control arm of the pooled results.

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

Where sufficient information was provided, hazard ratios were calculated in preference for outcomes such as mortality where the time to the event occurring was important for decision-making.

Continuous outcomes

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

- heath-related quality of life (HRQoL)
- ADHD symptoms
- behavioural/functional measures
- emotional dysregulation.

Where the studies within a single meta-analysis had different scales of measurement, 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 Cochrane Review Manager (RevMan5)[7] software. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value was reported as 'p≤0.001', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

2.3.3.1.2 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.[7] If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[1] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported no absolute risk difference was calculated.

2.3.3.1.3 Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating substantial heterogeneity) as well as the distribution of confident intervals and estimates with regards to the MIDs. Where significant heterogeneity was present, predefined subgrouping of studies was carried out for as per the individual review protocols, this always included a subgrouping based on risk of bias estimates of the studies involved.

If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup. For example, instead of the single outcome of '*missed diagnosis'*, this was separated into 2 outcomes '*missed diagnosis in people aged under 65'* and '*missed diagnosis in people aged 65 and over'*. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding. If subgroup analysis resolved heterogeneity within some but not all of the derived subgroups, interpretation was discussed with the committee.

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, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

2.3.3.1.4 Complex analysis

Network meta-analysis (NMA) was considered for the comparison of interventional treatments, but was not pursued because of concerns over differences in trial populations, exact trial interventions (particularly for reviews involving non-pharmacological interventions) and insufficient data available for the relevant outcomes.

Trials varied widely in the previous treatment and treatment response of the population included. The committee included some criteria for exclusion to allow for meaningful meta-analysis (for example excluding trials in which the population was wholly selected based on response to a drug under investigation) but more stringent criteria, to select a truly homogenous population as would be ideal for a NMA, would have reduced the evidence based beyond the point at which a NMA would be useful.

Trial interventions also varied between studies limiting the applicability of an NMA. This issue was particularly relevant for reviews involving non-pharmacological interventions, interventions often were defined by study authors as one particular category but clearly from their description incorporated elements of various non-pharmacological strategies. However there was also heterogeneity across pharmacological interventions; dosing, titration strategy and the exact formulation all varied between studies.

The committee agreed that it was appropriate to prioritise continuous rather than dichotomous outcomes for assessing clinical benefit as mean values on continuous scales carried more information than arbitrary definition into responders or non-responders. A NMA of continuous outcomes is possible but where many different scales are used, with no one prioritised over any other – as is the case with ADHD symptom rating, it relies heavily on the use of standardised mean differences. Using standardised mean differences would then prevent the combination of parallel with crossover studies and final values with change scores, reducing the evidence base further.

Overall, the committee agreed that conducting NMAs for the intervention reviews of this guideline would introduce a greater reliance on questionable assumptions, limit the evidence base and not necessarily introduce a greater clarity to the conclusions of the reviews.

Where studies had used a crossover design, paired continuous data were extracted where possible, and forest plots were generated in RevMan5[7]with the generic inverse variance function. When a crossover study had categorical data and the number of subjects with an event in both interventions was known, the standard error (of the log of the risk ratio) was calculated using the simplified Mantel–Haenszel method for paired outcomes. Forest plots were also generated in RevMan5[7] with the generic inverse variance function. If paired continuous or categorical data were not available from the crossover studies, the separate group data were analysed in the same way as data from parallel groups, on the basis that this approach would overestimate the confidence intervals and thus artificially reduce study weighting resulting in a conservative effect. Where a meta-analysis included a mixture of studies using both paired and parallel group approaches, all data were entered into RevMan5[7] using the generic inverse variance function.

2.3.3.2 Data synthesis for prognostic factor reviews

Odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs), with their 95% CIs, for the effect of the prespecified prognostic factors were extracted from the studies. Studies were only

included if the confounders prespecified by the committee were either matched at baseline or were adjusted for in multivariate analysis.

Studies of lower risk of bias were preferred, taking into account the analysis and the study design. In particular, prospective cohort studies were preferred if they reported multivariable analyses that adjusted for key confounders identified by the committee at the protocol stage for that outcome.

2.3.3.3 Data synthesis for qualitative study reviews

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

2.3.4 Appraising the quality of evidence by outcomes

2.3.4.1 Intervention reviews

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

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

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

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely

Quality element	Description
	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 or other bias was only taken into consideration in the quality assessment if it was apparent.

4.2.3.4.1.1 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. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, 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 patients 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 of patients and healthcare professionals)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 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.

Limitation	Explanation
	• Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

The assessment of risk of bias differs for non-randomised intervention studies, as they are inherently at high risk of selection bias. For this reason, GRADE requires that non-randomised evidence is initially downgraded on the basis of study design, starting with a rating of −2. This accounts for selection bias and so non-randomised intervention studies are not downgraded any further on that domain. Non-randomised evidence was assessed against the remaining domains used for RCTs in Table 3, and downgraded further as appropriate.

2.3.4.1.2 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. A weighted average score was then calculated across all studies contributing to the outcome by taking into account 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.

2.3.4.1.3 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 tests for heterogeneity, as detailed below, are heuristic and reviewers took the I^2 and chi-squared results into account alongside other information including the relative positions of study confidence intervals and point estimates with regards to the MIDs.

When heterogeneity existed within an outcome (chi-squared $p<0.1$, or $I^2>50\%$), 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 prespecified subgroup analysis (that is, each subgroup had an $I^2<50\%$), the committee took this into account and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

2.3.4.1.4 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 2. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The 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. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are not amenable to patient-centred 'anchor' methods.

In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the GRADE default method, as follows:

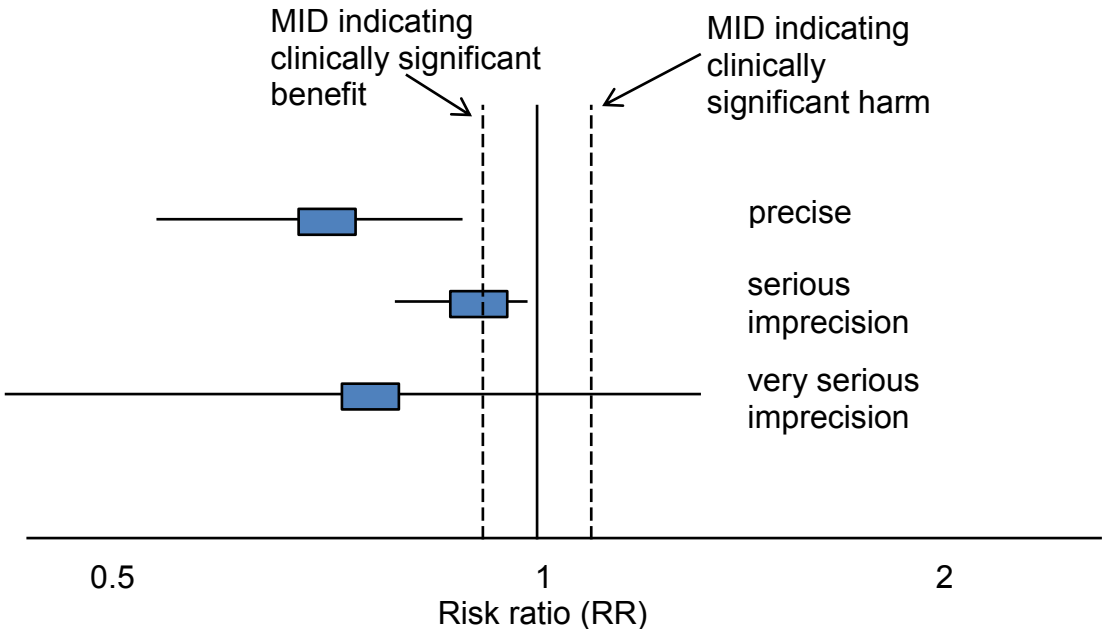
- For categorical outcomes the MIDs were taken to be ORs or RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the OR or RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically important harm, whilst the OR or RR of 1.25 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 OR or RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically important benefit, whilst the OR or RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically important 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.
- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the committee. If the committee decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was adopted for all outcomes except for ADHD symptoms. The committee agreed that for ADHD symptoms, a difference between groups that was >20% of the control group baseline score represented a minimally important difference. This MID was set based primarily on consensus but supported by the convention in ADHD research to use an improvement of >20% to define a person as responding to a treatment.

When risk difference was used (when some studies included in a meta-analysis had zero events in both arms), the absolute cut-offs for assessing importance (see below) were used as MIDs for imprecision.

Figure 2: 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)



2.3.4.1.5 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. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Non-randomised intervention studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Non-randomised intervention studies could, however, be upgraded if there was a large magnitude of effect or a dose-response gradient.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description

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

2.3.4.2 Prognostic reviews

The quality of evidence for prognostic studies was evaluated according to the criteria given in Table 5. This table was adapted from the Quality In Prognosis Studies tool (QUIPS).[2] 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.

Table 5: Description of quality elements for prospective studies

Domain	Considerations
Selection bias	Was there a lack of reported attempts made to achieve some group comparability between the risk factor and non-risk factor groups? (ignore if 2 or more risk factors considered)
	Was there a lack of consideration of any of the key confounders, or was this unclear?
	Was there a lack of consideration of non-key plausible confounders, or was this unclear?
	If the outcome is categorical: Were there <10 events per variable included in the multivariable analysis? If the outcome is continuous: Were there <10 people per variable included in the multivariable analysis?
	Was it very clear that one group was more likely to have had more outcomes occurring at baseline than another group?
Detection bias	Was there a lack of assessor blinding AND the outcome was not completely objective?
	Were the risk factors measured in a way that would systematically favour either group?
	Were the outcomes measured in a way that would systematically favour either group?
	If there were multiple raters, was there lack of adjustment for systematic inter-rater measurement errors, OR was inter-rater reliability unreported?
	Was there an excessively short follow up, such that there was not enough time for outcomes to occur?
Attrition bias	Was there >10% group differential attrition (for reasons related to outcome) and there was no appropriate imputation? (if one risk factor) or Was there >10% overall attrition(for reasons related to outcome) and there was no appropriate imputation? (if > 1 risk factor).

2.3.4.2.1 Inconsistency

Inconsistency was assessed as for intervention studies.

2.3.4.2.2 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. If the 95% CI were deemed subjectively to be very wide and cross the line of no effect, very serious imprecision was recorded. This decision required consensus between two reviewers.

2.3.4.2.3 Overall grading

Because prognostic reviews were not usually based on multiple outcomes per study, 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 for prospective cohort studies, 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.

2.3.4.3 Qualitative reviews

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

The CERQual Approach assesses the extent to which a review finding is a reasonable representation of the phenomenon of interest (the focus of the review question). Each review finding was assessed for each of the 4 quality elements listed and defined below in Table 6.

Table 6: Description of quality elements in GRADE-CERQual for qualitative studies

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

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

2.3.4.3.1 Methodological limitations

Each review finding had its methodological limitations assessed within each study first using the NGC checklist for assessing the risk of bias of qualitative studies. Based on the degree of methodological limitations studies were evaluated as having minor, moderate or severe limitations. The questions to be answered in the checklist below included:

- Was qualitative design an appropriate approach?
- Was the study approved by an ethics committee?
- Was the study clear in what it sought to do?
- Is the context clearly described?
- Is the role of the researcher clearly described?
- Are the research design and methods rigorous?
- Was the data collection rigorous?
- Was the data analysis rigorous?
- Are the data rich?
- Are the findings relevant to the aims of the study?
- Are the findings and conclusions convincing?

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

2.3.4.3.2 Coherence

Coherence is the extent to which the reviewer is able to identify a clear pattern across the studies included in the review, and if there is variation present (contrasting or disconfirming data) whether this variation is explained by the contributing study authors. If a review finding in 1 study does not support the main finding and there is no plausible explanation for this variation, then the confidence that the main finding reasonably reflects the phenomenon of interest is decreased. Each review finding was given a rating of minor, moderate or major concerns about coherence.

2.3.4.3.3 Relevance

Relevance is the extent to which the body of evidence from the included studies is applicable to the context (study population, phenomenon of interest, setting) specified in the protocol. As such, relevance is dependent on the individual review and discussed with the guideline committee. Relevance is categorised in 3 ways: partial relevance, indirect relevance and no concerns about relevance.

2.3.4.3.4 Adequacy

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

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

GRADE-CERQual is used to assess the body of evidence as a whole through a confidence rating representing the extent to which a review finding is a reasonable representation of the phenomenon of interest. The 4 components (methodological limitations, coherence, relevance and adequacy) are used in combination to form an overall judgement. GRADE-CERQual uses 4 levels of confidence: high, moderate, low and very low confidence. The significance of these overall ratings is explained in Table 7. Each review finding starts at a high level of confidence and is downgraded based on the concerns identified in any 1 or more of the 4 components. Quality assessment of qualitative reviews is a subjective judgement by the reviewer based on the concerns that have been noted. A detailed explanation of how such a judgement had been made was included in the narrative summary.

Table 7: Overall level of confidence for a review finding in GRADE-CERQual

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

2.3.5 Assessing clinical importance

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

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for most of the outcomes in the intervention reviews that if at least 100 more participants per 1000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this represented a clinical benefit or harm.

2.3.6 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each evidence report, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).

- A description of the overall quality of the evidence (GRADE overall quality).

2.4 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.[3]

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.

2.4.1 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.[3]
- 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.

2.4.1.1 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 2001 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. However, in this guideline, no economic studies were excluded on the basis that more applicable evidence was available.

For more details about the assessment of applicability and methodological quality see Table 8 below and the economic evaluation checklist (appendix H of the NICE guidelines manual[3]) 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.

2.4.1.2 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.[3] 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 8 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.[6]

Table 8: 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.
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).

Item	Description
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[3]

2.4.2 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 combination treatments as the highest priority area, and pharmacological and non-pharmacological treatments as medium priority areas for original health economic modelling.

Combination treatments were the highest priority because there is a large trade-off around whether the additional costs of two interventions together can be justified by the additional benefit.

Non-pharmacological treatments were a medium priority for modelling because this also has trade-offs around the costs and benefits of the possible non-pharmacological interventions available.

Finally pharmacological treatments were also a medium priority again because of the trade-offs around cost, benefits, and adverse events. Pharmacological treatments were later de-prioritised because of multiple economic evaluations identified in the area, and also because the clinical review identified many pairwise comparisons which were difficult to use without a network meta-analysis to combine them.

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.[3,5]
- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NGC.

Full methods and results of the cost-effectiveness analysis for the combination and non-pharmacological questions are described in a separate economic analysis report.

2.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.[4] 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 the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[4]

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.

2.4.4 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.

2.5 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–I).
- 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 analyses undertaken for the guideline (in separate economic analysis reports).

Recommendations were drafted 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. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. 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 clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations 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 2.5.1 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[3]).

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

2.5.1 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.

2.5.2 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.

2.5.3 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.

2.5.4 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.

2.5.5 Funding

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

3 Additional information

Integration with previous evidence

This guideline includes a number of entirely new reviews and others that cover areas that were assessed in the previous guideline (CG72) and in NICE's technology appraisal guidance on methylphenidate, atomoxetine and dexamfetamine for ADHD in children and adolescents (TA98). When the latter is true, the studies that were included and excluded from the previous guideline were checked against the protocols for this update and new searches were run and sifted from the date of the previous reviews.

Preferred assessor of ADHD symptoms

The guideline committee chose to include all possible assessors of ADHD symptoms scales including self (if person was 13 or older), parent (if child), teacher (if child) and investigator. The committee considered each of these outcomes to be critical to decision making. However in circumstances where different assessors gave differing assessments of efficacy, the committee in general prioritised assessors whose assessments were most likely to be free from bias. For children, in the majority of cases the committee considered teacher ratings to be the most free from bias and in adults this was more typically investigator ratings. The committee acknowledged that this approach is not without limitations (for example the likely degree of bias in a pharmaceutical company sponsored trial's investigator rating) but agreed that this was the most suitable approach overall.

4 Acronyms and abbreviations

Acronym or abbreviation	Description
AAQOL	Adult ADHD Quality of Life
ABC (-H)	Aberrant Behaviour Checklist (-Hyperactivity subscale)
ADD	Attention deficit disorder
ADHD	Attention deficit hyperactivity disorder
ADHD-RS (-P; -IV)	ADHD Rating Scale (-Parent; -Investigator rated)
AISRS	Adult ADHD Investigator Symptom Rating Scale
ASRS	Adult ADHD Self Report Scale
ASD	Autism spectrum disorder
BDI	Beck Depression Inventory
BRIEF (-A)	Behaviour Rating Inventory of Executive Function (-Adult version)
CAARS (-Inv)	Conners' Adult ADHD Rating Scale (-Investigator rated)
Conners' CBRS	Conners Comprehensive Behaviour Rating Scales
CBT	Cognitive behavioural therapy
CEA	Cost-effectiveness analysis
CGI (-ADHD;-S; -I)	Clinical Global Impression (-ADHD; -Severity; -Improvement)
CHIP-CE	Child Health and Illness Profile
CHQ	Child Health Questionnaire
CI	Confidence interval
CNS	Central nervous system
CPRS (-R; -S)	Conners' Parent Rating Scales (-Revised; -Short form)
CTRS (-R; -HI)	Conners' Teacher Rating Scales (-Revised; -Hyperactivity Index)
CUA	Cost-utility analysis
DBDRS	Disruptive Behaviour Disorders Rating Scale
DBT	Dialectical behaviour therapy
DSM-III (-R)	Diagnostic and Statistical Manual of Mental Disorders (3rd edition) (Revised)
DSM-IV (-TR)	Diagnostic and Statistical Manual of Mental Disorders (4th edition) (-Text Revision)
EEG	Electro-encephalography
FBB-ADHS	Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit- / Hyperaktivitätsstörungen, German scale using DSM-IV and ICD-10 diagnostic criteria for ADHD
FU	Follow-up, used to indicate when an outcome is reported at end of prolonged follow-up as opposed to directly after end of intervention
FV	Final values
GAF	Global Assessment of Functioning Scale
(C-) GAS	(Children's-) Global Assessment Scale/
GRADE	Grading of Recommendations: Assessment, Development, and Evaluation
HR	Hazard ratio
ICD-9	International Classification of Diseases (9th revision)
ICD-10	International Classification of Diseases (10th revision)
ICER	Incremental cost-effectiveness ratio

Acronym or abbreviation	Description
ID	Intellectual disability
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
MAOIs	Monoamine oxidase inhibitors
MPH	Methylphenidate
NGC	National Guideline Centre
NICE	National Institute for Health and Care Excellence
NSST	Non-specific supportive therapy
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
OROS	Osmotic release oral system
PT	Post-treatment
QALY	Quality-adjusted life year
QoL	Quality of life
RATE	Reasoning and Rehabilitation ADHD Training Evaluation
RR	Risk ratio
SDQ	Strengths and Difficulties Questionnaire
SNAP (-IV)	Swanson, Nolan and Pelham checklist (-Investigator Rated)
SNRI	Serotonin and noradrenaline reuptake inhibitor
SRQ	Social Relationships Questionnaire
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressants
WFIRS-P	Weiss Functional Impairment Rating Scale (-Parent-reported)
WFIRS-S	Weiss Functional Impairment Rating Scale (-Self-report)
WRAADS	Wender-Reimherr Adult Attention Deficit Disorder Scale

5 Glossary

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

5.1 Guideline-specific terms

Term	Definition
Attention deficit hyperactivity disorder (ADHD)	Characterised by symptoms across 2 domains: inattention, and hyperactivity or impulsivity. For the purposes of this guideline, the term ADHD will cover both attention deficit hyperactivity disorder and hyperkinetic disorder.
Cognitive behavioural therapy (CBT)	A type of psychotherapy in which negative patterns of thought about the self and the world are challenge in order to alter unwanted behaviour patterns or to treat mood disorders.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Dialectical behaviour therapy (DBT)	A type of cognitive behavioural therapy that has been adapted to help people who experience emotions very intensely. It places particular importance on people accepting who they are and on the relationship between the person and the therapist. See also cognitive behavioural therapy.
Discontinuation	A planned withdrawal from drug treatment.
Domain	Domain refers to an area that has specific characteristics, In ADHD this refers to the impact of the symptoms in a particular area, such as education or family relationships.
Drug holiday	An agreed period where the person does not use medication, usually for the management of side effects (for example children may have a break from stimulant medication in the school holidays if their growth is below expected). This includes short breaks, for example not taking medication at weekends, and longer breaks, for example school holidays. It is distinct from discontinuing a drug (see discontinuation)
Environmental modifications	Environmental modifications refers to changes that are made to the physical environment, for example at school changes to seating arrangements, lighting and exposure to noise.
First-line treatment	The treatment that a clinician offers the person first (as distinct from a legal licensing definition).
Neurofeedback	A form of biofeedback that uses the subject's brainwaves or other electrical activity of the nervous system to teach self-regulation of brain function.
Non-specific supportive therapy	Exact definitions vary from study to study. It is intended to act as a control group for non-pharmacological interventions.
Psychoeducation	The provision of education and information to those seeking or receiving mental health services.
Secure estate	A setting where people are incarcerated. This does not include people who are in halfway houses or who are on probation.
Treatment plan	A treatment plan is developed jointly with the clinician and the person with ADHD and their family. The treatment plan includes a description of the diagnosis, the impact of the diagnosis, any co-existing conditions, any agreed interventions including specific treatments , any liaison arrangements with the school and/or employment, arrangements for monitoring and contact with the treating team and follow up.

5.2 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.
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.
Anxiety	Anxiety is an umbrella term for anxiety disorders. This includes a number of specific conditions (for example hoarding) and not only generalised anxiety disorder.
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.

Term	Definition
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.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case the 95% CI would be 110 to 150.

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

Term	Definition
	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).
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	Explicit standards used to decide which studies should be excluded

Term	Definition
(literature review)	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.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
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

Term	Definition
	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.
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.
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.
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.
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

Term	Definition
	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	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has

Term	Definition
	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).
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.
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 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

Term	Definition
	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'.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true 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

Term	Definition
	be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model
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 include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

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