

## Chronic heart failure

### NICE guideline: methods

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*Methods*

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# 1 Development of the guideline

## 1.1 Remit

The remit to partially update clinical guideline NG106 – Chronic heart failure in adults: diagnosis and management came from an Exceptional Surveillance Review.

Members of NICE’s cardiovascular disease committee, and other topic experts, have highlighted that the recommendations on pharmacological treatment of chronic heart failure with reduced ejection fraction may be out of date. Clinical practice regarding when to start pharmacological treatments for chronic heart failure with reduced ejection fraction is changing. Details are set out in the [surveillance review decision](#).

The committee identified that there is also a move towards considering treatments for chronic heart failure with mildly reduced ejection fraction and new evidence has been identified on mineralocorticoid receptor antagonists (MRAs) for chronic heart failure with preserved ejection fraction.

This update is needed to assess the full range of first-line treatments for chronic heart failure with reduced and mildly reduced ejection fraction, and MRAs for chronic heart failure with preserved ejection fraction.

In addition, many people with heart failure lack iron in their blood, which is linked to more severe symptoms, for example reduced exercise capacity and an increased risk of hospitalisation or mortality. The committee identified new evidence for the use of intravenous iron in adults with chronic heart failure and iron deficiency. Therefore, this will also be reviewed as part of this update.

## 1.2 What this update covers

The methods outlined in this document relate to the following sections of the guideline:

- Treating heart failure with reduced ejection fraction
- Treating heart failure with mildly reduced ejection fraction
- Treating heart failure with preserved ejection fraction
- Managing all types of heart failure:
  - Iron status

## 1.3 What this update does not cover

This guideline update does not include the following sections:

- Team working in the management of heart failure
- Diagnosing heart failure
- Giving information to people with heart failure
- Treating heart failure with reduced ejection fraction in people with chronic kidney disease
- Managing all types of heart failure:
  - Pharmacological treatment
  - Vaccinations

- 1                   ○ Contraception and pregnancy
- 2                   ○ Depression
- 3                   ○ Lifestyle advice
- 4                   ● Monitoring treatment for all types of heart failure
- 5                   ● Interventional procedures
- 6                   ● Cardiac rehabilitation
- 7                   ● Palliative care

8                   The wording of some recommendations in these sections have been amended for  
9                   consistency with sections covered by the guideline update.

10                  The evidence for these sections relates to the methods from previous versions of the  
11                  guideline. Please see chapter 4 of the [NG106 full guideline document](#).

12  
13  
14

## 2 Methods

This guideline was developed using the methods described in the 2014 [NICE guidelines manual](#), updated May 2024.

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

Sections 2.1 to 2.3 describe the process used to identify and review evidence. Sections 2.1.1 and 2.7 describe the process used to identify and review the health economic evidence.

### 2.1 Developing the review questions and outcomes

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

The review questions were based on the following framework:

- population, intervention, comparator and outcome (PICO) for reviews of interventions

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

**Table 1: Review questions**

Evidence report	Type of review	Review questions	Outcomes
A1	Intervention	<p>Is it clinically- and cost-effective to use a combination of some of the following first-line pharmacological interventions in adults with chronic heart failure with reduced left ventricular ejection fraction:</p> <ul style="list-style-type: none"> <li>• angiotensin converting enzyme inhibitor</li> <li>• angiotensin-receptor blocker</li> <li>• angiotensin receptor neprilysin inhibitor</li> <li>• beta blocker</li> <li>• mineralocorticoid receptor antagonist</li> <li>• sodium glucose cotransporter 2 inhibitor?</li> </ul>	<ul style="list-style-type: none"> <li>• All-cause mortality (time-to-event)</li> <li>• Cardiovascular mortality (time-to-event)</li> <li>• Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value)</li> <li>• Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported) <ul style="list-style-type: none"> <li>○ all cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study, but</li> </ul> </li> </ul>

Evidence report	Type of review	Review questions	Outcomes
			<p>this will be downgraded for outcome indirectness</p> <p>Adverse events (recorded as the number of people with at least one event, not the total number of events):</p> <ul style="list-style-type: none"> <li>• Withdrawal due to drug-related adverse events (dichotomous)</li> <li>• Acute kidney injury – serum creatinine rise of <math>\geq 50\%</math> over <math>\leq 7</math> days (dichotomous)</li> <li>• Hyponatraemia – serum sodium concentration <math>&lt; 135</math> mmol/L (dichotomous)</li> <li>• Hyperkalaemia – serum potassium concentration <math>\geq 5.5</math> mmol/L (dichotomous)</li> <li>• Falls (dichotomous)</li> </ul>
A2	Intervention	<p>Is it clinically- and cost-effective to use any of the following first-line pharmacological interventions, alone or in combination, in adults with chronic heart failure with mildly reduced left ventricular ejection fraction:</p> <ul style="list-style-type: none"> <li>• angiotensin converting enzyme inhibitor</li> <li>• angiotensin-receptor blocker</li> <li>• angiotensin receptor neprilysin inhibitor</li> <li>• beta blocker</li> <li>• mineralocorticoid receptor antagonist?</li> </ul>	<ul style="list-style-type: none"> <li>• All-cause mortality (time-to-event)</li> <li>• Cardiovascular mortality (time-to-event)</li> <li>• Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value)</li> <li>• Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported) <ul style="list-style-type: none"> <li>○ all cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study, but this will be downgraded for outcome indirectness</li> </ul> </li> </ul> <p>Adverse events (recorded as the number of people with at least one event, not the total number of events)</p> <ul style="list-style-type: none"> <li>• Withdrawal due to drug-related adverse events (dichotomous)</li> <li>• AKI – serum creatinine rise of <math>\geq 50\%</math> over <math>\leq 7</math> days (dichotomous)</li> </ul>

Evidence report	Type of review	Review questions	Outcomes
			<ul style="list-style-type: none"> <li>• Hyponatraemia – serum sodium concentration &lt; 135 mmol/L (dichotomous)</li> <li>• Hyperkalaemia – serum potassium concentration ≥ 5.5 mmol/L (dichotomous)</li> <li>• Falls (dichotomous)</li> </ul>
A3	Intervention	What is the clinical and cost effectiveness of intravenous iron supplementation in adults with chronic heart failure and iron deficiency?	<ul style="list-style-type: none"> <li>• All-cause mortality (time-to-event)</li> <li>• Cardiovascular mortality (time-to-event)</li> <li>• Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value)</li> <li>• Unplanned hospitalisation or visits (all-cause) (time-to-event; including repeat events when reported)</li> <li>• Unplanned hospitalisation or visits (heart-failure-related) unplanned hospitalisation or visits (time-to-event; including repeat events when reported)</li> <li>• Improvement in exercise tolerance – 6-minute walk test or peak VO<sub>2</sub> (continuous; change from baseline) <ul style="list-style-type: none"> <li>○ Both measures will be extracted where available; if neither is reported, other measures of exercise tolerance/functional capacity will be accepted.</li> </ul> </li> <li>• Haemoglobin in anaemic patients (continuous; change from baseline)</li> </ul> <p>Adverse events (recorded as the number of people with at least one event, not the total number of events)</p> <ul style="list-style-type: none"> <li>• Withdrawal due to drug-related adverse events (dichotomous)</li> <li>• Hypophosphataemia (dichotomous)</li> </ul>

Evidence report	Type of review	Review questions	Outcomes
			<ul style="list-style-type: none"> <li>• Extravasation (dichotomous)</li> <li>• Anaphylaxis/hypersensitivity (dichotomous)</li> <li>• Hospitalisation for infection (dichotomous)               <ul style="list-style-type: none"> <li>○ Sepsis, hospitalisation for pneumonia and infections categorised as serious adverse events will be included in this outcome.</li> </ul> </li> <li>• Atrial fibrillation (dichotomous)</li> </ul>
A4	Intervention	What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists (eplerenone, finerenone, and spironolactone) in people with chronic heart failure with preserved ejection fraction?	<ul style="list-style-type: none"> <li>• All-cause mortality (time-to-event)</li> <li>• Cardiovascular mortality (time-to-event)</li> <li>• Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value))</li> <li>• Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported)               <ul style="list-style-type: none"> <li>○ All cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study, but this will be downgraded for outcome indirectness</li> </ul> </li> </ul> <p>Adverse events (recorded as the number of people with at least one event, not the total number of events)</p> <ul style="list-style-type: none"> <li>• Withdrawal due to drug-related adverse events (dichotomous)</li> <li>• AKI – serum creatinine rise of <math>\geq 50\%</math> over <math>\leq 7</math> days (dichotomous)</li> <li>• Hyponatraemia – serum sodium concentration <math>&lt; 135</math> mmol/L (dichotomous)</li> <li>• Hyperkalaemia – serum potassium concentration <math>\geq 5.5</math> mmol/L (dichotomous)</li> <li>• Falls (dichotomous)</li> </ul>

Evidence report	Type of review	Review questions	Outcomes
			<ul style="list-style-type: none"> <li>Gynaecomastia (dichotomous)</li> </ul>

### 1 2.1.1 Stratification

2 For the review on chronic heart failure with reduced ejection fraction, stratified  
3 analyses were carried out for the presence or absence of type 2 diabetes when  
4 included studies investigated SGLT2 inhibitors as the randomised intervention  
5 (regardless of heterogeneity). This was done to determine if there are subgroup  
6 differences between those with and without type 2 diabetes for outcomes relevant to  
7 this review protocol.

8 For the review on intravenous iron therapy, stratified analyses for iron saturation  
9 (TSAT <20% vs TSAT ≥20%) were explored as a secondary analysis. This was done  
10 regardless of the presence of heterogeneity.

## 11 2.2 Searching for evidence

### 12 2.2.1 Clinical and health economics literature searches

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

16 Systematic literature searches were undertaken to identify published clinical and  
17 health economic evidence relevant to the review questions. These were run  
18 according to the parameters as stipulated within the NICE guideline's manual,  
19 [https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-  
20 searching-and-evidence-submission](https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission).

21 Databases were searched using relevant medical subject headings, free-text terms  
22 and where appropriate study-type filters. Studies published in languages other than  
23 English were not reviewed, and where possible, searches were restricted to English  
24 language. Searches were updated in January 2025. Papers published or added to  
25 databases after this were not considered. Where new evidence was identified, for  
26 example in consultation comments received from stakeholders, the impact on the  
27 guideline was considered, and the action agreed between the technical team and  
28 NICE staff with a quality assurance role. For review A3, one randomised controlled  
29 trial published after the search cut-off was identified by committee members as  
30 meeting the protocol. It was agreed to include this trial in the evidence review  
31 because there was uncertainty in the estimates, which may be reduced by increasing  
32 the number of participants analysed.

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

37 Searching for unpublished literature was not undertaken. NICE do not have access to  
38 drug manufacturers' unpublished clinical trial results, so the clinical evidence  
39 considered by the committee for pharmaceutical interventions may be different from

1 that considered by the MHRA and European Medicines Agency for the purposes of  
2 licensing and safety regulation.

3 Searches for evidence reviews on pharmacological treatment of CHF with reduced  
4 and mildly reduced ejection fractions were conducted with a start date of 01/10/2002  
5 to identify newly published evidence since CG5. For evidence reviews on intravenous  
6 iron therapy and MRA therapy for CHF with preserved ejection fraction, searches  
7 were conducted with a start date of 01/12/2017 to identify newly published evidence  
8 since NG106 (2018). Evidence used in NG106 was also added to the evidence base,  
9 along with any references identified from relevant systematic reviews, and those  
10 highlighted for consideration by committee members.

## 11 **2.3 Reviewing evidence**

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

- 13 • Potentially relevant studies were identified from the search results by reviewing  
14 titles and abstracts. The full papers were then obtained.
  - 15 • Full papers were evaluated against the pre-specified inclusion and exclusion  
16 criteria set out in the protocol to identify studies that addressed the review  
17 question. The review protocols are included in an appendix to each of the  
18 evidence reports.
  - 19 • Relevant studies were critically appraised using the preferred study design  
20 checklist as specified in the NICE guidelines manual (updated January 2024). The  
21 checklist used is included in the individual review protocols in each of the  
22 evidence reports.
  - 23 • Key information was extracted about interventional study methods and results into  
24 EPPI reviewer version 5. Summary evidence tables were produced from data  
25 entered into EPPI Reviewer, including critical appraisal ratings.
  - 26 • Summaries of the evidence were generated by outcome. All studies in the  
27 evidence reviews were randomised controlled trials. Randomised data were meta-  
28 analysed where appropriate and reported in GRADE evidence profiles.
  - 29 • A minimum of 10% of the abstracts were reviewed by two reviewers, with any  
30 disagreements resolved by discussion or, if necessary, a third independent  
31 reviewer.
  - 32 • All of the evidence reviews were quality assured by a senior technical analyst.  
33 This included checking:
    - 34 ○ papers were included or excluded appropriately
    - 35 ○ a sample of the data extractions
    - 36 ○ a sample of the risk of bias assessments
    - 37 ○ correct methods were used to synthesise data.
- 38 Discrepancies were identified and resolved through discussion (with a third  
39 analyst where necessary).

### 40 **2.3.1 Types of studies and inclusion and exclusion criteria**

41 The inclusion and exclusion of studies was based on the criteria defined in the review  
42 protocols, which can be found in an appendix to each of the evidence reports.  
43 Excluded studies (with the reasons for their exclusion) are listed in an appendix to

1 each of the evidence reports. The committee was consulted about any uncertainty  
2 regarding inclusion or exclusion.

3 Conference abstracts were not generally considered for inclusion. Literature reviews,  
4 posters, letters, editorials, comment articles, unpublished studies and studies not in  
5 published in English language were excluded.

#### 6 **2.3.1.1 Type of studies**

7 All evidence reviews were intervention reviews, so randomised controlled trials  
8 (RCTs) were included because they are considered the most robust type of study  
9 design that can produce an unbiased estimate of the intervention effects. Refer to the  
10 review protocols in each evidence report for full details on the study design of studies  
11 that were appropriate for each review question.

12 Systematic reviews and meta-analyses of RCTs, including those using individual  
13 patient data, conducted to the same methodological standards as the NICE reviews  
14 were eligible for inclusion within the evidence reviews in preference to primary  
15 studies.

## 16 **2.4 Methods of combining evidence**

### 17 **2.4.1 Data synthesis for intervention reviews**

18 Meta-analyses were conducted using Cochrane Review Manager web version  
19 8.21.0.

#### 20 **2.4.1.1 Analysis of different types of data**

##### 21 ***Time to event data***

22 In line with review protocols, time-to-event outcomes were preferred for mortality and  
23 hospitalisation outcomes because time to the event occurring was important for  
24 decision making. Where sufficient information was provided, hazard ratios were  
25 reported. However, both hazard ratios and risk ratios were presented, as most  
26 studies reported data to calculate the risk ratio rather than hazard ratio. The  
27 committee prioritised the hazard ratios for decision making where available, but if  
28 there were differences in effect estimates between the two measures, potential  
29 reasons for this were considered in the interpretation of the evidence.

##### 30 ***Dichotomous outcomes***

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

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

38 Where there were studies in a meta-analysis with zero events in both arms, and less  
39 than 1% event rate overall in the analysis, the risk difference was calculated and

1 reported instead. In instances where there was meta-analysis including one or more  
2 small studies with zero events in both arms in addition to other larger studies, if the  
3 event rate for the whole analysis was >1%, risk ratios were used. This is because:  
4 the overall event rates were not low for these outcomes, but the zero event studies  
5 were too small to detect them; the contribution of the zero event studies was small  
6 (typically <2%) so very little data was omitted from the analyses; and risk ratios are  
7 easier to interpret for the committee, providing more useful data to inform  
8 recommendations.

### 9 **Rate data**

10 For hospitalisations, the occurrence of repeat events was important for decision  
11 making. Therefore, when reported, total hospitalisation rates (incidence rates) and  
12 participant years of follow-up were also extracted, and rate ratios were calculated.

### 13 **Continuous outcomes**

14 Continuous outcomes were analysed using an inverse variance method for pooling  
15 weighted mean differences. Change from baseline or final values were both included  
16 and combined in analyses, but change values were preferred. If possible, change  
17 from baseline scores were calculated from baseline and final values reported in the  
18 studies. The variance of the change score was imputed using the baseline and final  
19 standard deviation values, assuming a correlation between baseline and endpoint of  
20 0.75.

21 The means and standard deviations of continuous outcomes are required for meta-  
22 analysis. However, in cases where standard deviations were not reported, the  
23 standard error was calculated if the p values or 95% confidence intervals (95% CI)  
24 were reported, and meta-analysis was undertaken with the mean and standard error  
25 using the generic inverse variance method in Cochrane Review Manager web  
26 version 8.21.0.

27 The health-related quality of life measure, Kansas City Cardiomyopathy  
28 Questionnaire, can be reported as overall summary score (OSS), clinical summary  
29 score (CSS) or total summary score (TSS). OSS and CSS were preferred over TSS.  
30 TSS was only used if neither OSS or CSS was available from a given study.

### 31 **Generic inverse variance**

32 If a study reported only the summary statistic and 95% CI, the generic-inverse  
33 variance method was used to enter data into Cochrane Review Manager web version  
34 8.21.0. If the control event rate was reported this was used to generate the absolute  
35 risk difference in GRADEpro. If multivariate analysis was used to derive the summary  
36 statistic but no adjusted control event rate was reported no absolute risk difference  
37 was calculated.

## 39 **2.5 Appraising the quality of evidence by outcomes**

### 40 **2.5.1 Intervention reviews**

41 The evidence for outcomes from the included RCTs were evaluated and presented  
42 using the 'Grading of Recommendations Assessment, Development and Evaluation

(GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>). The software (GRADEpro) 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 1.

**Table 1: Description of quality elements in GRADE for intervention studies**

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

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication bias was considered with the guideline committee, and if suspected was tested for when there were more than 10 studies for that outcome. This deviation from the threshold of 5 studies specified in the review protocols was implemented to align with updated methods. None of the evidence reviews included  $\geq 10$  studies for a single outcome, so it was not possible to explore publication bias using funnel plots.

### 2.5.1.1 Risk of bias

The main domains of bias for RCTs are listed in Table 2. Each outcome had its risk of bias assessed within each study first using the appropriate checklist for the study design (Cochrane RoB 2 for RCTs or PRISMA IPD for individual participant data meta-analyses). For each study, if there was no risk of bias in any domain, the risk of bias was given a rating of 'low risk of bias'. An overall judgment of 'some concerns' was made if some concerns were present in at least one domain, and no domain was

1 judged to be at high risk of bias. An overall judgment of ‘high risk of bias’ was made if  
 2 high risk of bias was present in at least one domain or there were ‘some concerns’ in  
 3 multiple domains in a way that substantially lowers confidence in the result. An  
 4 overall rating of not serious, serious or very serious was applied in GRADEpro across  
 5 all studies combined in a meta-analysis by taking into account the weighting of  
 6 studies according to study precision.

7 **Table 2: Principle domains of bias in randomised controlled trials**

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling participants are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: <ul style="list-style-type: none"> <li>• knowledge of that participant’s likely prognostic characteristics, and</li> <li>• a desire for one group to do better than the other.</li> </ul>
Performance and detection bias (lack of blinding)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which the participants are allocated. Knowledge of the group can influence: <ul style="list-style-type: none"> <li>• the experience of the placebo effect</li> <li>• performance in outcome measures</li> <li>• the level of care and attention received, and</li> <li>• the methods of measurement or analysis</li> </ul> all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of at least 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: <ul style="list-style-type: none"> <li>• Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules.</li> <li>• Use of unvalidated patient-reported outcome measures.</li> <li>• Lack of washout periods to avoid carry-over effects in crossover trials.</li> <li>• Recruitment bias in cluster-randomised trials.</li> </ul>

### 8 2.5.1.2 Indirectness

9 Indirectness refers to the extent to which the populations, interventions, comparisons  
 10 and outcome measures are dissimilar to those defined in the inclusion criteria for the  
 11 reviews. Indirectness is important when these differences are expected to contribute  
 12 to a difference in effect size, or may affect the balance of harms and benefits  
 13 considered for an intervention.

14 As time-to-event outcomes were preferred for all mortality and hospitalisation  
 15 outcomes, when these outcomes were reported dichotomously, they were  
 16 downgraded for outcome indirectness.

1 Any studies using drugs not licensed for CHF as the intervention or comparison were  
2 downgraded for intervention indirectness. Similarly, studies that included populations  
3 that deviated significantly from the relevant protocol definition of CHF (including the  
4 specific LVEF required) were downgraded for population indirectness.

5 As for the risk of bias, each outcome had its indirectness assessed within each study  
6 first. For each study, if there were no sources of indirectness, indirectness was given  
7 a rating of 'directly applicable'. If there was indirectness in just 1 source (for example  
8 in terms of population), indirectness was given a rating of 'partially applicable', but if  
9 there was indirectness in 2 or more sources (for example, in terms of population and  
10 treatment) the indirectness was given an 'indirectly applicable' rating. An overall  
11 rating of not serious, serious, or very serious was applied GRADEpro across all  
12 studies by taking into account the weighting of studies according to study precision.

### 13 2.5.1.3 Inconsistency

14  
15 Inconsistency refers to an unexplained heterogeneity of results for an outcome  
16 across different studies. When estimates of the treatment effect across studies differ  
17 widely, this suggests true differences in the underlying treatment effect, which may  
18 be due to differences in populations, settings or doses. Statistical heterogeneity was  
19 assessed for each meta-analysis estimate by an I-squared ( $I^2$ ) inconsistency statistic.

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

25 In the review on pharmacological treatment for CHF with reduced ejection fraction,  
26 ethnicity was a pre-specified subgroup. However, this was not adequately reported in  
27 included papers so geographical location (Europe/Japan) was used as a proxy for  
28 ethnicity to explore sources of heterogeneity.

29 When heterogeneity existed within an outcome ( $I^2 > 40\%$ ), but no plausible  
30 explanation could be found, the quality of evidence for that outcome was  
31 downgraded. Inconsistency for that outcome was given a 'serious' rating if the  $I^2$  was  
32 40–60%, and a 'very serious' rating if the  $I^2$  was over 60%.

33 If inconsistency could be explained based on pre-specified subgroup analysis (that is,  
34 each subgroup had an  $I^2 < 40\%$ ) then each of the derived subgroups were presented  
35 separately for that forest plot and GRADE profile (providing at least 2 studies  
36 remained in each subgroup). The committee took this into account and considered  
37 whether to make separate recommendations based on the variation in effect across  
38 subgroups within the same outcome. In such a situation the quality of evidence was  
39 not downgraded.

40 If all predefined strategies of subgrouping were unable to explain statistical  
41 heterogeneity, then a random effects (DerSimonian and Laird) model was considered  
42 for the entire group of studies in the meta-analysis. A random-effects model assumes  
43 a distribution of populations, rather than a single population. This leads to a widening  
44 of the confidence interval around the overall estimate.

45 However, if heterogeneity was  $> 80\%$  or studies reported opposite directions of effect,  
46 the validity of pooling the data was discussed with the committee and if agreed, no

1 meta-analysis was performed, with study estimates being reported separately. The  
2 individual study results were downgraded by one level for inconsistency to reflect the  
3 heterogeneous findings within the evidence base.

#### 4 2.5.1.4 Imprecision

5 The criteria applied for imprecision were based on the 95% CIs for the pooled  
6 estimate of effect, and the minimal important differences (MID) for the outcome. The  
7 MIDs are the threshold for appreciable benefits and harms, separated by a zone  
8 either side of the line of no effect where there is assumed to be no clinically important  
9 effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the  
10 MID lines, imprecision was regarded as serious in the GRADEpro rating. This was  
11 because the overall result, as represented by the span of the confidence interval,  
12 was consistent with 2 interpretations as defined by the MID (for example, both no  
13 clinically important effect and clinical benefit were possible interpretations). If both  
14 MID lines were crossed by either or both ends of the 95% CI then imprecision was  
15 regarded as very serious. This was because the overall result was consistent with all  
16 3 interpretations defined by the MID (no clinically important effect, clinical benefit and  
17 clinical harm). This is illustrated in Figure 1.

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

27 In the absence of values identified in the literature, the alternative approach to  
28 deciding on MID levels is to use the modified GRADE 'default' values, as follows:

- 29 • For dichotomous outcomes the MIDs were taken to be RRs of 0.8\* and 1.25. For  
30 'positive' outcomes such as 'patient satisfaction', the RR of 0.8 is taken as the line  
31 denoting the boundary between no clinically important effect and a clinically  
32 important harm, whilst the RR of 1.25 is taken as the line denoting the boundary  
33 between no clinically important effect and a clinically important benefit. For  
34 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.8 is  
35 taken as the line denoting the boundary between no clinically important effect and  
36 a clinically important benefit, whilst the RR of 1.25 is taken as the line denoting the  
37 boundary between no clinically important effect and a clinically important harm.  
38 There aren't established default values for ORs and the same values (0.8 and  
39 1.25) are applied here but are acknowledged as arbitrary thresholds agreed by the  
40 committee.
- 41 ○ In cases where there are zero events in one arm of a single study, or some or  
42 all of the studies in one arm of a meta-analysis, the same process is followed  
43 as for dichotomous outcomes. However, if there are no events in either arm in  
44 a meta-analysis (or in a single unpooled study) the sample size is used to  
45 determine imprecision using the following rule of thumb:
  - 46 – No imprecision: sample size  $\geq 350$
  - 47 – Serious imprecision: sample size  $\geq 70$  but  $< 350$
  - 48 – Very serious imprecision: sample size  $< 70$ .

- 1           ○ When there was more than one study in an analysis and zero events occurred  
2           in both groups for some but not all of the studies across both arms, the  
3           optimum information size was used to determine imprecision using the  
4           following guide:
- 5           – No imprecision: >90% power
  - 6           – Serious imprecision: 80-90% power
  - 7           – Very serious imprecision: <80% power.
- 8           ● For time to event and rate data, there are no established default values for HR  
9           and rate ratios so the same values as dichotomous outcomes have been applied  
10          here (0.8 and 1.25) but are acknowledged as arbitrary thresholds agreed by the  
11          committee.
  - 12          ● For continuous outcome variables the MID was taken as half the median baseline  
13          standard deviation of that variable, across all studies in the meta-analysis. Hence  
14          the MID denoting the minimum clinically important benefit was positive for a  
15          ‘positive’ outcome (for example, a quality of life measure where a higher score  
16          denotes better health), and negative for a ‘negative’ outcome (for example, a  
17          visual analogue scale [VAS] pain score). Clinically important harms will be the  
18          converse of these. If baseline values are unavailable, then half the median  
19          comparator group standard deviation of that variable will be taken as the MID. As  
20          these vary for each outcome per review, details of the values used are reported in  
21          the footnotes of the relevant GRADE summary table.

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

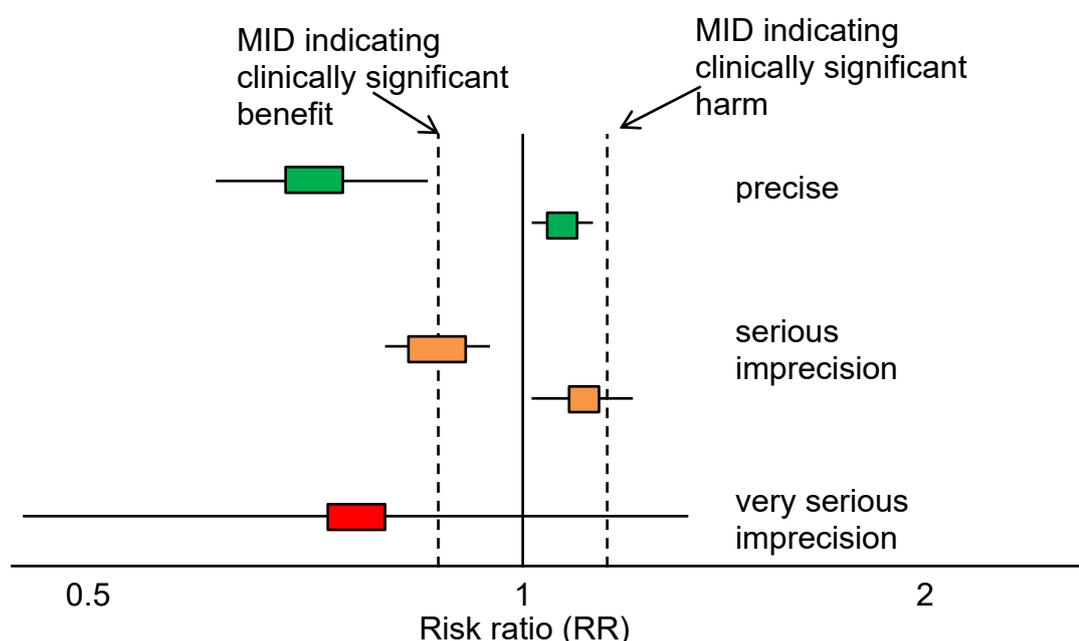
24          **Table 3: Published or pre-agreed MIDs**

Outcome measure	MID	Source
EQ-5D	±0.03	Consensus pragmatic MID used in some previous NICE guidelines
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Overall summary score: ±5 Clinical summary score: ±5	Butler J, Khan MS, Mori C, Filippatos GS, Ponikowski P, Comin-Colet J, Roubert B, Spertus JA, Anker SD. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. <i>Eur J Heart Fail.</i> 2020 Jun;22(6):999-1005. doi: 10.1002/ejhf.1810. Epub 2020 Apr 2. PMID: 32239794.
Minnesota Living with Heart Failure questionnaire	±5	Rector TS, Tschumperlin LK, Spencer HK et al (1995) Use of the living with heart failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. <i>Journal of Cardiac Failure</i> 1(3), 201-206.
SF36	Physical component summary: ±2 Mental component summary: ±3 Physical functioning: ±3 Role-physical: ±3 Bodily pain: ±3	User's manual for the SF-36v2 Health Survey, Third Edition <sup>3</sup>

Outcome measure	MID	Source
	General health: $\pm 2$ Vitality: $\pm 2$ Social functioning: $\pm 3$ Role-emotional: $\pm 4$ Mental health: $\pm 3$	

1

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



### 2 2.5.1.5 Overall grading of the certainty of clinical evidence

3 Once an outcome had been appraised for the main quality elements, as above, an  
 4 overall certainty grade was calculated for that outcome from the ratings from each of  
 5 the main elements were summed to give a score that could be anything from high to  
 6 very low. The evidence for each outcome started at High, and the overall confidence  
 7 in the evidence remained High if there were no reasons for downgrading, or became  
 8 Moderate, Low or Very Low according to the number of independent reasons for  
 9 downgrading. The significance of these overall ratings is explained in Table 4. The  
 10 reasons for downgrading in each case are specified in the footnotes of the GRADE  
 11 tables.

12 **Table 4: Overall certainty of outcome evidence in GRADE**

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

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

## 2.6 Assessing clinical importance

The committee assessed the evidence by outcome to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions.

To support this, binary outcomes for mortality and hospitalisation outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio. These absolute values were easier to interpret by the Committee. 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 a number of factors when determining a minimally important difference for clinical importance for each outcome including the baseline rate of the outcome and the impact of the event on the person with the condition. For mortality any reduction represented a clinical benefit. For hospitalisation outcomes, at least 25 fewer events per 1000 was interpreted as a clinically important benefit. For adverse events, 40 more events per 1000 represented a clinically important harm.

For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this represented a clinical benefit or harm.

Established MIDs found in the literature and were agreed to be used for two disease-specific health-related quality of life scores (Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure questionnaires).

The published values used for imprecision and clinical importance are provided in **Table 33**. For continuous outcomes where the GRADE default MID has been used, the values for each outcome are provided in the footnotes of the relevant GRADE tables.

Time-to-event outcomes were preferred for all-cause mortality, cardiovascular mortality and hospitalisation outcomes, and in most cases it was not possible to calculate absolute risk differences due to insufficient data being available. For example, the proportion of patients that are event-free in the control group or the median time event-free in the control group were often not reported.

## 2.7 Identifying and analysing evidence of cost effectiveness

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

1 Therefore, the committee may require more robust evidence on the effectiveness and  
2 cost effectiveness of any recommendations that are expected to have a substantial  
3 impact on resources; any uncertainties must be offset by a compelling argument in  
4 favour of the recommendation. The cost impact or savings potential of a  
5 recommendation should not be the sole reason for the committee's decision  
6 ([PMG20](#)).

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

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

## 11 **2.7.1 Literature review**

12 The health economists:

- 13 • Identified potentially relevant studies for each review question from the health  
14 economic search results by reviewing titles and abstracts. Full papers were then  
15 obtained.
- 16 • Reviewed full papers against prespecified inclusion and exclusion criteria to  
17 identify relevant studies (see below for details).
- 18 • Critically appraised relevant studies using economic evaluations checklists as  
19 specified in the NICE guidelines manual. ([PMG20](#))
- 20 • Extracted key information about the studies' methods and results into health  
21 economic evidence tables (which can be found in appendices to the relevant  
22 evidence reports).
- 23 • Generated summaries of the evidence in NICE health economic evidence profile  
24 tables (included in the relevant evidence report for each review question) – see  
25 below for details.

### 26 **2.7.1.1 Inclusion and exclusion criteria**

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

32 Studies that only reported cost per hospital (not per patient), or only reported average  
33 cost effectiveness without disaggregated costs and effects were excluded. Literature  
34 reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies  
35 and studies not in English were excluded. Studies published before 2010 and studies  
36 from non-OECD countries or the USA were also excluded, on the basis that the  
37 applicability of such studies to the present UK NHS context is likely to be too low for  
38 them to be helpful for decision-making.

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

1 For more details about the assessment of applicability and methodological quality  
 2 see **Table 5** below and the economic evaluation checklist (appendix H of the NICE  
 3 guidelines manual, [PMG20](#)) and the health economics review protocol, which can be  
 4 found in each of the evidence reports.

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

### 9 2.7.1.2 NICE health economic evidence profiles

10 NICE health economic evidence profile tables were used to summarise cost and  
 11 cost-effectiveness estimates for the included health economic studies in each  
 12 evidence review report. The health economic evidence profile shows an assessment  
 13 of applicability and methodological quality for each economic study, with footnotes  
 14 indicating the reasons for the assessment. These assessments were made by the  
 15 health economist using the economic evaluation checklist from the NICE guidelines  
 16 manual ([PMG20](#)). It also shows the incremental costs, incremental effects (for  
 17 example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness  
 18 ratio (ICER) for the base case analysis in the study, as well as information about the  
 19 assessment of uncertainty in the analysis. See **Table 5** for more details.

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

22 **Table 5: 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: <sup>(a)</sup> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness.</li> <li>• 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.</li> </ul>
Limitations	An assessment of methodological quality of the study: <sup>(a)</sup> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost effectiveness.</li> <li>• 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.</li> </ul>
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.

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

(a) *Applicability and limitations were assessed using the economic evaluation checklist in appendix H of the NICE guidelines manual (PMG20)*

### 2.7.2 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 the following as the highest priority areas for original health economic modelling:

- Early use of medicines for HF<sub>r</sub>EF
  - There were not any includable published health economic evaluations that looked at earlier use of medicines in this population. Some of these medicines were not available in generic form and so could lead to a significant cost impact.
- ARNI vs ARB for HF<sub>m</sub>rEF
  - There were not any includable published health economic evaluations in this population. ARNI was the only medicine included in the review that was not available in generic form.

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. [PMG36](#), [PMG20](#)
- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist.

Full methods and results of the cost-effectiveness analysis for Medicines for HF<sub>r</sub>EF are described in a separate economic analysis report. For ARNI vs ARB, the

1 methods and results are contained within the Evidence Review report on Medicines  
2 for Heart Failure with mildly-reduced ejection fraction (HFmrEF).

### 3 **2.7.3 Cost-effectiveness criteria**

4 NICE sets out the principles that committees should consider when judging whether  
5 an intervention offers good value for money.

- 6 • [NICE Charter](#)
- 7 • [NICE Principles](#)
- 8 • Developing NICE Guidelines [PMG20](#)

9 In general, an intervention was considered to be cost effective (given that the  
10 estimate was considered plausible) if either of the following criteria applied:

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

16 If the committee recommended an intervention that was estimated to cost more than  
17 £20,000 per QALY gained, or did not recommend one that was estimated to cost less  
18 than £20,000 per QALY gained, the reasons for this decision are discussed explicitly  
19 in 'The committee's discussion of the evidence' section of the relevant evidence  
20 report, with reference to issues regarding the plausibility of the estimate or to factors  
21 set out in NICE methods manuals. [PMG20](#)

### 22 **2.7.4 In the absence of health economic evidence**

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

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

## 32 **2.8 Developing recommendations**

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

- 35 • Summaries of clinical and health economic evidence and quality (as presented in  
36 evidence reports A1–A4).
- 37 • Evidence tables of the clinical and health economic evidence reviewed from the  
38 literature. All evidence tables can be found in appendices to the relevant evidence  
39 reports.
- 40 • Forest plots (in appendices to the relevant evidence reports).

- 1 • A description of the methods and results of the cost-effectiveness analysis  
2 undertaken for the guideline (in a separate economic analysis report).

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

21 When clinical and health economic evidence was of poor quality, conflicting or  
22 absent, the committee decided on whether a recommendation could be made based  
23 on its expert opinion. The considerations for making consensus-based  
24 recommendations include the balance between potential harms and benefits, the  
25 economic costs compared to the economic benefits, current practices,  
26 recommendations made in other relevant guidelines, patient preferences and equality  
27 issues. The consensus recommendations were agreed through discussions in the  
28 committee. The committee also considered whether the uncertainty was sufficient to  
29 justify delaying making a recommendation to await further research, taking into  
30 account the potential harm of failing to make a clear recommendation (see  
31 section 2.8.1 below).

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

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

- 46 • The actions health professionals need to take.  
47 • The information readers need to know.  
48 • The strength of the recommendation (for example the word 'offer' was used for  
49 strong recommendations and 'consider' for weaker recommendations).

- 1 • The involvement of patients (and their carers if needed) in decisions on treatment  
2 and care.
- 3 • Consistency with NICE’s standard advice on recommendations about drugs,  
4 waiting times and ineffective interventions (see section 9.2 in the NICE guidelines  
5 manual<sup>4</sup>).

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

### 8 **2.8.1 Research recommendations**

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

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

### 16 **2.8.2 Validation process**

17 This guidance is subject to a 4-week public consultation and feedback as part of the  
18 quality assurance and peer review of the document. All comments received from  
19 registered stakeholders are responded to in turn and posted on the NICE website.

### 20 **2.8.3 Updating the guideline**

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

## 24 **2.9 General terms**

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.

Term	Definition
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.  A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
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).
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.

Term	Definition
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
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

Term	Definition
	duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
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.
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

Term	Definition
	trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
GRADE, GRADE evidence profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE evidence profile.
Harms	Adverse effects of an intervention.
Hazard Ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.

Term	Definition
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
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.

Term	Definition
	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.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	<p>The p value is a statistical measure that indicates whether or not an effect is statistically significant.</p> <p>For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these, or more extreme results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant.</p> <p>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.</p>
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Prevalence	See Pre-test probability.

Term	Definition
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.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Rate ratio	The ratio of the rate of an event occurring among those exposed to certain conditions compared with the rate for those who are not exposed to the same conditions.
RCT	See 'Randomised controlled trial'.
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.

Term	Definition
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	<p>The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke).</p> <p>If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.</p>
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	<p>Selection bias occurs if:</p> <ol style="list-style-type: none"> <li>The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or</li> <li>There are differences between groups of participants in a study in terms of how likely they are to get better.</li> </ol>
Sensitivity analysis	<p>A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.</p> <p>One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.</p> <p>Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated.</p> <p>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.</p> <p>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).</p>
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ( $p < 0.05$ ).
Stakeholder	<p>An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be:</p> <ul style="list-style-type: none"> <li>manufacturers of drugs or equipment</li> <li>national patient and carer organisations</li> <li>NHS organisations</li> <li>organisations representing healthcare professionals.</li> </ul>
State transition model	See Markov model
Stratification	When a different estimate effect is thought to underlie two or more groups based on the PICO characteristics. The groups are therefore kept separate from the outset and are not combined in a meta-

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

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