Single technology appraisal: User guide for company evidence submission template

8 January 2015

# Instructions for companies

This is the user guide for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It explains what information NICE requires and the format in which it should be presented.

Information should be submitted in the [company evidence submission template](http://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance). Companies making evidence submissions to NICE should also refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/introduction), particularly section 5 (the reference case). The NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/introduction) gives further details of procedures relating to STA submissions.

The submission should be as brief and informative as possible. The main body of the submission must not exceed 250 pages, excluding the appendices and the pages covered by the template.

The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file. The submission must be a stand–alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested in the template, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee.

When making an evidence submission, companies must ensure that:

* All confidential information is highlighted and underlined in the electronic version sent to NICE.
* An executable electronic copy of the economic model is included in the version sent to NICE, with full access to the programming code. The content of the evidence submission and the content of the economic model should match.
* The checklist of confidential information (provided by NICE with the invitation to submit) is completed and submitted.

See section 3 of the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/the-appraisal-process) for information about all aspects of information handling.

To ensure that the appraisal process is as transparent as possible, NICE considers that evidence on which the Appraisal Committee’s decisions are based should be publicly available.

NICE requires the medical director of the company to sign a statement confirming that all clinical trial data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE, within the company’s or any of its associated companies’ possession, custody, or control in the UK, or elsewhere in the world, have been disclosed.

NICE considers that the definition of ‘all clinical trial data’ is not limited to conventional randomised controlled trials (RCTs), but is meant to include other types of interventional or observational clinical research methodologies, such as large simple trials, cohort studies, case control studies, or registry data. This definition is consistent with that used by the European Medicines Agency in its [policy on publication of clinical data on medicinal products for human use](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa).

NICE requires companies to consent to it being provided directly by European Economic Area regulatory authorities all clinical trial data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE. NICE will only ask regulatory authorities directly after having first approached the company for the information and the company is unable or unwilling to provide the information in a timely manner.

* + - 1. Executive summary

This section should summarise the main points of the submission. It should include the information requested under the headings given in the company evidence submission template. All information should be directly relevant to the final NICE scope, marketing authorisation (or CE mark for medical devices) and decision problem. It should be evidence‑based and clearly reference the relevant section of the submission.

* + - 1. The technology

When completing the template, refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/introduction) and the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/introduction).

In addition ensure that all information provided in the regulatory submission is available on request.

* 1. Description of the technology
     1. Give the brand name, UK approved name, the therapeutic class and a brief overview of the mechanism of action. For devices, provide details of any different versions of the same device.
  2. Marketing authorisation/CE marking and health technology assessment
     1. Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates (for example, date of application and/or expected date of approval from the Committee for Human Medicinal Products).
     2. Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company’s proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities.
     3. Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).
     4. Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
     5. Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals) and a (draft) technical manual for devices in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
     6. Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European public assessment report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation).
     7. If the technology has not been launched, supply the anticipated date of availability in the UK.
     8. State whether the technology has regulatory approval outside the UK. If so, please provide details.
     9. State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion.
  3. Administration and costs of the technology
     1. For pharmaceuticals, complete the table ‘Costs of the technology being appraised’ in the company evidence submission template, including details of the treatment regimen and method of administration. Indicate whether the acquisition cost is list price or includes a patient access scheme, and the anticipated care setting. Specify the sources of information and data used to complete the table, for example SmPC or trial data. For more information see section 5.5 of the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case).
     2. Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology. For more information see section 5 of the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/patient-access-schemes-and-flexible-pricing).
     3. For devices, provide the list price and average selling price in a table similar to the table presented in the template, ‘Costs of the technology being appraised’. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.
  4. Changes in service provision and management
     1. State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology. For more information see section 5.9 of the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case).
     2. Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/or secondary care, commissioned by NHS England specialised services and/or clinical commissioning groups), staff costs, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.
     3. Specify if the technology requires additional infrastructure in the NHS to be put in place.
     4. State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England.
     5. State whether there are any concomitant therapies specified in the marketing authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology.
  5. Innovation
     1. If you consider the technology to be innovative with potential to make a substantial impact on health‑related benefits that are unlikely to be included in the quality‑adjusted life year (QALY) calculation:
* state whether and how the technology is a ‘step‑change’ in the management of the condition
* provide a rationale to support innovation, identifying and presenting the data you have used.
  + - 1. Health condition and position of the technology in the treatment pathway

When completing the template, refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/introduction) and the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/introduction).

Provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Describe the effects of the disease or condition on patients, carers and society.

Present the clinical pathway of care that shows the context of the proposed use of the technology. This information may be presented in a diagram. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this point should be consistent with the guideline and any differences should be explained.

Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Please provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation also includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as a ‘life‑extending treatment at the end of life’ as described in section 6.2.10 of the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-appraisal-of-the-evidence-and-structured-decision-making).

Provide details of any relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.

Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies.

Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information about equality issues see NICE’s [equality scheme](http://www.nice.org.uk/About/Who-we-are/Policies-and-procedures/NICE-equality-scheme).

Provide an assessment of whether the use of this technology is likely to raise any equality issues. Please document if there are any potential issues that:

* could exclude from full consideration any people protected by the equality legislation who fall within the patient population for whom the technology is or will be licensed
* could lead to recommendations that have a different impact on people protected by the equality legislation compared with the wider population, for example by making it more difficult in practice for a specific group to access the technology
* could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please provide any evidence that would enable the Committee to identify and consider the impact of equality issues. State how the analysis has addressed these issues.

* + - 1. Clinical effectiveness

Section 4 provides detailed guidance on the level of information that should be included in the evidence submission template about the clinical effectiveness of the appraised technology.

Evidence on outcomes should be obtained from a systematic review, defined as systematically locating, including, appraising and synthesising the evidence to obtain a reliable and valid overview of the data.

When completing the template, also refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case) (section 5.2) and the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/the-appraisal-process) (section 3.2).

For further information on how to implement the approaches described in the NICE methods guide, see the technical support documents produced by the NICE Decision Support Unit[[1]](#footnote-1) about [evidence synthesis](http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series(2391675).htm):

* [Introduction to evidence synthesis for decision making](http://www.nicedsu.org.uk/TSD1%20Introduction.final.08.05.12.pdf) (technical support document 1).
* [A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials](http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf) (technical support document 2).
* [Heterogeneity: subgroups, meta-regression, bias and bias-adjustment](http://www.nicedsu.org.uk/TSD3%20Heterogeneity.final%20report.08.05.12.pdf) (technical support document 3).
* [Inconsistency in networks of evidence based on randomised controlled trials](http://www.nicedsu.org.uk/TSD4%20Inconsistency.final.15April2014.pdf) (technical support document 4).
* [Evidence synthesis in the baseline natural history model](http://www.nicedsu.org.uk/TSD5%20Baseline.final%20report.08.05.12.pdf) (technical support document 5).
* [Embedding evidence synthesis in probabilistic cost-effectiveness analysis: software choices](http://www.nicedsu.org.uk/TSD6%20Software.final.08.05.12.pdf) (technical support document 6).
* [Evidence synthesis of treatment efficacy in decision making: A reviewer’s checklist](http://www.nicedsu.org.uk/TSD7%20reviewer%20checklist.final.08.05.12.pdf) (technical support document 7).
  1. Identification and selection of relevant studies

To identify and select relevant studies, it is expected that a systematic literature search will be carried out in line with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case) sections 5.2.2 and 5.2.4.

In exceptional circumstances, however, such as when all published or unpublished clinical data are within the company’s possession, custody or control – a systematic literature search may not be necessary. If a systematic literature search is not included in the submission, the company must confirm that no other additional relevant studies have been done outside its organisation. NICE requires the medical director of the company to sign a statement confirming that all clinical trial data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE, within the company’s or any of its associated companies’ possession, custody, or control in the UK or elsewhere in the world, have been disclosed to NICE. NICE also requires companies to consent to it being provided directly by European Economic Area regulatory authorities all clinical trial data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE. This includes all data that have been submitted to the regulatory authorities by the company or any of its associated companies and that were relevant to the granting of a marketing authorisation, and for NICE to use those data in carrying out the technology appraisal. NICE will only ask regulatory authorities directly after having first approached the company for the information and the company is unable or unwilling to provide the information in a timely manner. See section 3.1 of the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/the-appraisal-process).

Provide the information specified in sections 4.1.1–4.1.6.

* + 1. Advise whether a search strategy was developed to identify relevant studies for the technology. If a search strategy was developed and a literature search carried out, provide details under the subheadings listed in this section. Key aspects of study selection can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) (University of York Centre for Reviews and Dissemination).

### Search strategy

* + 1. Describe the search strategies used to retrieve relevant clinical data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided so that the results may be reproduced. This includes a full list of all information sources and the full electronic search strategies for all databases, including any limits applied. The search strategies should be provided in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).

### Study selection

* + 1. Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process in a table. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.

### Table X Eligibility criteria used in the search strategy

|  |  |  |
| --- | --- | --- |
| **Clinical effectiveness** | **Inclusion criteria** | **Exclusion criteria** |
| **Population** |  |  |
| **Intervention** |  |  |
| **Comparators** |  |  |
| **Outcomes** |  |  |
| **Study design** |  |  |
| **Language restrictions** |  |  |

* + 1. A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta‑analyses, such as the PRISMA [flow diagram](http://www.prisma-statement.org/statement.htm). The total number of studies in the statement should equal the total number of studies listed in section 4.2.
    2. When data from a single study have been drawn from more than 1 source (for example, a poster and a published report) or when trials are linked (for example, an open‑label extension to a randomised controlled trial [RCT]), this should be clearly stated.
    3. Provide a complete reference list for excluded studies in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
  1. List of relevant randomised controlled trials

NICE prefers RCTs that directly compare the technology with 1 or more relevant comparators. The company must confirm that all relevant evidence globally within its possession, custody or control has been submitted in the evidence submission for the technology. Please refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9) sections 3.3.2–3.3.7, 5.2.1 and 5.2.3 for details on the types of evidence to be considered.

Provide the information specified in sections 4.2.1–4.2.2.

* + 1. In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, state this. A suggested table format is presented below.

### Table X List of relevant RCTs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trial number (acronym)** | **Population** | **Intervention** | **Comparator** | **Primary study reference** |
| **Trial 1** |  |  |  |  |
| **Trial 2** |  |  |  |  |
| **[Add more rows as needed]** |  |  |  |  |

* + 1. When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.
  1. Summary of methodology of the relevant randomised controlled trials

It is expected that all key aspects of methodology will be in the public domain; if a company wishes to submit aspects of the methodology in confidence, prior agreement must be obtained from NICE.

Provide the information specified in sections 4.3.1 and 4.3.2.

* + 1. Items 3 to 6b of the CONSORT [checklist](http://www.consort-statement.org/) should be provided for all RCTs listed:
* **Trial design** – brief description of trial design, including details of randomisation if applicable.
* **Eligibility criteria** – a comprehensive description of the eligibility criteria used to select the trial participants, including any definitions and any assessments used in recruitment.
* **Settings and locations where the data were collected** – describe the locations where the trial was carried out, including the country and, if applicable, the care setting (for example, primary care [GP or practice nurse], secondary care [inpatient, outpatient, day case]).
* **Trial drugs and concomitant medications** – provide details of trial drugs and comparator(s), with dosing information and titration schedules if appropriate. Provide an overview of concomitant medications permitted and disallowed during the trial.
* **Primary, secondary and tertiary outcomes** – all outcome measures listed in the trial protocol, whether primary, secondary or tertiary, should be identified and completely defined. The rationale for excluding data on any of the outcomes listed in the study protocol should be provided. When outcomes are assessed at several time points after randomisation, indicate the pre‑specified time point of primary interest. For many non‑pharmacological interventions it is helpful to specify who assessed outcomes (for example, if special skills are required to do so) and how many assessors there were. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant to the decision problem. This should include therapeutic outcomes, as well as patient–related outcomes such as assessment of health‑related quality of life (HRQL), and any arrangements to measure adherence. Data provided should be from pre‑specified outcomes rather than post‑hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).
  + 1. Provide a comparative summary of the methodology of the RCTs in a table. A suggested table format is presented below.

### Table X Comparative summary of trial methodology

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial number**  **(acronym)** | **Trial 1** | **Trial 2** | **[Add more columns as needed]** |
| **Location** |  |  |  |
| **Trial design** |  |  |  |
| **Eligibility criteria for participants** |  |  |  |
| **Settings and locations where the data were collected** |  |  |  |
| **Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)**  **Intervention(s) (n=[x]) and comparator(s) (n=[x])**  **Permitted and disallowed concomitant medication** |  |  |  |
| **Primary outcomes (including scoring methods and timings of assessments)** |  |  |  |
| **Secondary/tertiary outcomes (including scoring methods and timings of assessments)** |  |  |  |
| **Pre‑planned subgroups** |  |  |  |

* 1. Statistical analysis and definition of study groups in the relevant randomised controlled trials
     1. During completion of this section consider items 7a (sample size), 7b (interim analyses and stopping guidelines), 12a (statistical methods used to compare groups for primary and secondary outcomes) and 12b (methods for additional analyses, such as subgroup analyses and adjusted analyses) of the CONSORT [checklist](http://www.consort-statement.org/).
     2. For each trial listed, provide details of the trial population included in the primary analysis of the primary outcome and methods used to take account of missing data (for example, a description of the intention‑to‑treat analysis carried out, including censoring methods, or whether a per‑protocol analysis was carried out).
     3. For each trial, provide details of the statistical tests used in the primary analysis. Also provide details of the primary hypothesis or hypotheses under consideration, the power of the trial and a description of sample size calculation, including rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale. A suggested table format is presented below.

### Table X Summary of statistical analyses in the RCTs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trial number (acronym)** | **Hypothesis objective** | **Statistical analysis** | **Sample size, power calculation** | **Data management, patient withdrawals** |
| **Trial 1** |  |  |  |  |
| **Trial 2** |  |  |  |  |
| **[Add more rows as needed]** |  |  |  |  |

* 1. Participant flow in the relevant randomised controlled trials
     1. Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow‑up or withdrew from the RCT. Provide a CONSORT [diagram](http://www.consort-statement.org/) showing the flow of participants through each stage of each of the trials.
     2. In a table describe the characteristics of the participants at baseline for each of the trials. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between trial groups. A suggested table format is presented below.

### Table X Characteristics of participants in the studies across treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial number (acronym)**  **Baseline characteristic** | **Treatment group X** | **Treatment group Y** | **[Add more columns as needed]** |
| **Trial 1 (n=[x])** | (n=[x]) | (n=[x]) | (n=[x]) |
| **Age** |  |  |  |
| **Gender** |  |  |  |
| **[Add more rows as needed]** |  |  |  |
| **Trial 2 (n=[x])** | (n=[x]) | (n=[x]) | (n=[x]) |
| **Age** |  |  |  |
| **Gender** |  |  |  |
| **[Add more rows as needed]** |  |  |  |
| Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | |

* 1. Quality assessment of the relevant randomised controlled trials
     1. The validity of the results of an individual RCT will depend on the robustness of its overall design and execution, and its relevance to the decision problem. The quality of each RCT identified in section 4.2 should be appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part‑published studies. The quality assessment will be validated by the Evidence Review Group.

Provide the information specified in sections 4.6.2–4.6.4.

* + 1. Describe the methods used for assessing risk of bias and generalisability of individual RCTs (including whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
* The following are the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs, but the list is not exhaustive:
  + Was the randomisation method adequate?
  + Was the allocation adequately concealed?
  + Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?
  + Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?
  + Were there any unexpected imbalances in drop‑outs between groups? If so, were they explained or adjusted for?
  + Is there any evidence to suggest that the authors measured more outcomes than they reported?
  + Did the analysis include an intention‑to‑treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
* Consider how closely the RCT(s) reflects routine clinical practice in England.
* In addition to parallel group RCTs, there are other randomised designs (for example, randomised crossover trials and randomised cluster trials) in which further quality criteria may need to be considered when assessing bias. Key aspects of quality to be considered can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) (University of York Centre for Reviews and Dissemination).
  + 1. If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria. A suggested table format for the quality assessment results is presented below.

### Table X Quality assessment results for parallel group RCTs

|  |  |  |  |
| --- | --- | --- | --- |
| **Trial number (acronym)** | **Trial 1** | **Trial 2** | **[Add more columns as needed]** |
| Was randomisation carried out appropriately? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Was the concealment of treatment allocation adequate? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Were the groups similar at the outset of the study in terms of prognostic factors? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Were there any unexpected imbalances in drop‑outs between groups? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Did the analysis include an intention‑to‑treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | (yes/no/not clear/N/A) | (yes/no/not clear/N/A) |  |
| Adapted from [Systematic reviews: CRD’s guidance for undertaking reviews in health care](http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) (University of York Centre for Reviews and Dissemination) | | | |

* + 1. The complete quality assessment for each RCT should be included in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
  1. Clinical effectiveness results of the relevant randomised controlled trials
     1. Data from intention‑to‑treat analyses should be presented whenever possible and a definition of the included participants provided. If participants have been excluded from the analysis, the rationale for this should be given.
     2. The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.
     3. For each outcome, provide the following information from each study:
* The unit of measurement.
* The size of the effect; for dichotomous outcomes, the results ideally should be expressed both as relative risks (or odds ratios) and risk (or rate) differences. For time‑to‑event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
* A 95% confidence interval.
* The number of people in each group included in each analysis and whether the analysis was intention to treat. State the results in absolute numbers when feasible.
* When interim data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of the trial. Analytical adjustments should be described to cater for the interim nature of the data.
* Other relevant data that may help interpret the results may be included, such as adherence to medication or study protocol.
* Discuss and justify any clinically important differences in the results between the different arms of a trial and between trials.
* Specify whether unadjusted and adjusted analyses were performed, and whether the results were consistent.
  1. Subgroup analysis

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), sections 5.10.1–5.10.12.

* + 1. Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre‑planned or post‑hoc.
    2. Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.
    3. Provide details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.
    4. Provide a summary of the results for the subgroups, with full details provided in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
  1. Meta-analysis

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), sections 5.2.8–5.2.11. For further information on how to implement the approaches described in the guide, see the series of technical support documents produced by the NICE Decision Support Unit about [evidence synthesis](http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series(2391675).htm).

Provide the information specified in sections 4.9.1–4.9.3.

* + 1. If a qualitative overview is considered to be appropriate, summarise the overall results of the individual studies with reference to their critical appraisal.
    2. If a meta‑analysis has been performed, include the following in the results:
* The characteristics and possible limitations of the data (that is, population, intervention, setting, sample sizes and the validity of the evidence) should be fully reported for each study included in the analysis and a forest plot included.
* A statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to explain the heterogeneity.
* Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using either a fixed effects or random effects model as appropriate.
* Provide an adequate description of the methods of statistical combination and justify their choice.
* Carry out sensitivity analysis when appropriate.
* Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).
  + 1. If any of the relevant studies listed in section 4.2 are excluded from the meta‑analysis, the reasons for doing so should be explained. The impact that each excluded study has on the overall meta‑analysis should be explored.
  1. Indirect and mixed treatment comparisons

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), sections 5.2.12–5.2.18.

The principles of good practice for carrying out systematic reviews and meta‑analyses should be carefully followed for indirect and mixed treatment comparisons. In brief, a clear description of the methods of synthesis and the rationale for how RCTs of the technology and the comparators are identified, selected and excluded is needed.

For further information on how to implement the approaches described in the NICE methods guide, see the series of technical support documents produced by the NICE Decision Support Unit about [evidence synthesis](http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series(2391675).htm).

Provide the information specified in sections 4.10.1–4.10.19.

### Search strategy

* + 1. Provide details of the search strategies used to identify trials included in the indirect comparison and network meta‑analyses. As a guide, provide details of the following in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices):
* the eligibility criteria
* a list of all information sources
* full electronic search strategies for all databases
* a flow diagram providing details of the process for selecting studies; number of studies identified through searches, number of studies screened, number assessed for eligibility and the number included in the review with reasons for exclusion at each stage.

### Study selection

* + 1. Provide details of the treatments to be compared. This should include all treatments identified in the final NICE scope. If additional treatments have been included, the rationale should be provided. For example, additional treatments may be added in order to make a connected network.
    2. In a table, describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. Justification should be provided to ensure that the rationale for study selection is transparent. A suggested table format is provided below.

### Table X Criteria used in the trial selection process

|  |  |  |
| --- | --- | --- |
| **Clinical effectiveness** | **Inclusion criteria** | **Exclusion criteria** |
| **Population** |  |  |
| **Intervention** |  |  |
| **Comparators** |  |  |
| **Outcomes** |  |  |
| **Trial design** |  |  |
| **Language restrictions** |  |  |

* + 1. In a table provide a summary of the trials used to carry out the indirect comparison or mixed treatment comparison. A suggested table format is presented below. When there are more than 2 treatments in the comparator sets for synthesis, show a network diagram.

### Table X Summary of the trials used to carry out the indirect or mixed treatment comparison

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **References of trial** | **Intervention A** | **Intervention B** | **Intervention C** | **Intervention D** |
| **Trial 1** | Yes |  | Yes | Yes |
| **Trial 2** |  | Yes | Yes | Yes |
| **Trial 3** | Yes | Yes |  |  |
| **Trial 4** | Yes |  | Yes |  |
| **[Add more rows as needed]** | Etc. |  |  |  |

* + 1. If the table or network diagram provided in response to section 4.10.4 does not include all the trials that were identified in the search strategy, the rationale for exclusion should be provided.

### Methods and outcomes of included studies

* + 1. Provide the rationale for the choice of outcome measure chosen, along with the rationale for the choice of outcome scale selected.
    2. Discuss the populations in the included trials, especially if they are not the same as the populations specified in the NICE scope. If they are not the same:
* provide a rationale to justify including the study
* describe the assumptions made about the impact or lack of impact this may have on the relative treatment effect
* explain whether an adjustment has been made for these differences.
  + 1. Describe whether there are apparent or potential differences in patient populations between the trials. If this is the case, explain how this has been taken into account.
    2. In an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices), provide the following for each trial included in response to section 4.10.4:
* table(s) of the methods
* table(s) of the outcomes and the results
* table(s) of participants’ baseline characteristics.

### Risk of bias

* + 1. In an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices), provide a complete quality assessment of each trial included in response to section 4.10.4.
    2. Identify any risk of bias within the trials identified, and describe any adjustments made to the analysis.

### Methods of analysis and presentation of results

* + 1. Provide a clear description of the indirect or mixed treatment comparison methodology. If the company considers that an indirect treatment comparison or mixed treatment comparison is inappropriate, the rationale should be provided and alternative analyses explored (for example, naive indirect comparison or a narrative overview). Refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), sections 5.2.16–5.2.18.
    2. Supply any programming language in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices) (for example the WinBUGS code).
    3. For examples of how to present the results of the analysis, see the NICE Decision Support Unit [technical support documents 1-3](http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series%282391675%29.htm).
    4. Provide the results of the analysis.
    5. Provide the results of the statistical assessment of heterogeneity. The degree of heterogeneity, and the reasons for it, should be explored as fully as possible.
    6. Justify the choice of random or fixed effects model.
    7. If there is doubt about the relevance of particular trials, present separate sensitivity analyses in which these trials are excluded.
    8. Discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.
  1. Non-randomised and non-controlled evidence

RCTs directly comparing the technology being appraised with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non‑randomised and non‑controlled studies may be needed to supplement RCT data.

### List of relevant non-randomised and non-controlled evidence

Provide the information specified in sections 4.11.1 and 4.11.2.

* + 1. In a table present the list of non‑randomised and non‑controlled evidence (for example, experimental and observational data) considered relevant to the decision problem and justify including each study. A suggested table format is presented below.

### Table X List of relevant non-randomised and non-controlled evidence

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study number (acronym)** | **Objective** | **Population** | **Intervention** | **Comparator** | **Primary study reference** | **Justification for inclusion** |
| **Study 1** |  |  |  |  |  |  |
| **Study 2** |  |  |  |  |  |  |
| **[Add more rows as needed]** |  |  |  |  |  |  |

* + 1. If trials listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of data required, this should be stated.

### Summary of methodology of the relevant non-randomised and non-controlled evidence

It is expected that all key aspects of methodology will be in the public domain; if a company wishes to submit aspects of the methodology in confidence, prior agreement must be obtained from NICE.

* + 1. Provide a comparative summary of the methodology of the studies in a table.

### Statistical analysis of the non-randomised and non-controlled evidence

* + 1. For non‑randomised and non‑controlled evidence such as observational studies, the potential biases should be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline. Ideally these should be quantified and adjusted for.

### Participant flow in the studies

* + 1. In a table describe the characteristics of the participants at baseline for each of the studies. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between study groups. A suggested table format is presented below.

### Table X Characteristics of participants in the studies across treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| **Study number (acronym)**  **Baseline characteristic** | **Treatment group X** | **Treatment group Y** | **[Add more rows as needed]** |
| **Study 1 (n=[x])** | (n=[x]) | (n=[x]) | (n=[x]) |
| **Age** |  |  |  |
| **Gender** |  |  |  |
| **[Add more rows as needed]** |  |  |  |
| **Study 2 (n=[x])** | (n=[x]) | (n=[x]) | (n=[x]) |
| **Age** |  |  |  |
| **Gender** |  |  |  |
| **[Add more rows as needed]** |  |  |  |
| Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | |

### Quality assessment of the relevant non-randomised and non-controlled evidence

* + 1. The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study identified in section 4.11.1 should be quality appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part‑published studies. The quality assessment will be validated by the Evidence Review Group.

Provide the information specified in sections 4.11.7–4.11.9.

* + 1. Describe the methods used for assessing risk of bias of individual studies (including whether this was done at the study or outcome level) and how this information is to be used in any data synthesis. For the quality assessments of non‑randomised and non‑controlled evidence, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) (University of York Centre for Reviews and Dissemination). This includes information on a number of initiatives aimed at improving the quality of research reporting.
    2. If there is more than 1 non‑randomised or non‑controlled study, tabulate a summary of the responses applied to each of the quality assessment criteria.
    3. A complete quality assessment for each study should be included in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).

### Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

* + 1. Data from trial analyses should be presented whenever possible and a definition of the included participants provided. If participants have been excluded from the analysis, the rationale for this should be given.
    2. The information may be presented graphically to supplement text and tabulated data.
    3. For each outcome, provide the following information from each study:
* The unit of measurement.
* The size of the effect.
* A 95% confidence interval.
* The number of participants.
* When interim data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that study. Analytical adjustments should be described to cater for the interim nature of the data.
* Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication or study protocol.
* Include whether unadjusted and adjusted analyses were performed, and whether the results were consistent.
  1. Adverse reactions
     1. Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non‑comparative trials may sometimes be relevant. For example, post‑marketing surveillance data may demonstrate that the technology shows a relative lack of adverse reactions commonly associated with the comparator, or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.

Provide the information specified in sections 4.12.2–4.12.4.

* + 1. In a table, summarise adverse reactions reported in the studies listed in section 4.2. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.
    2. Provide details of any studies that report additional adverse reactions to those reported in section 4.2. Include the following.
* Details of the methodology used for the identification, selection and quality assessment of the studies. See instructions in sections 4.1, 4.2 and 4.6.
* Examples of search strategies for specific adverse reactions or generic adverse‑reaction terms. Key aspects of quality criteria for adverse reaction data can found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf) (University of York Centre for Reviews and Dissemination). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
* Details of the methodology of the studies. See instructions in sections 4.3–4.5 for the type of information required.
* Adverse reactions. In a table provide details of adverse reactions for each intervention group. For each group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.
  + 1. Provide a brief overview of the safety of the technology in relation to the decision problem.
  1. Interpretation of the clinical effectiveness and safety evidence

When concluding the clinical effectiveness and safety evidence, provide the information specified in sections 4.13.1 and 4.13.2.

* + 1. A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology.
    2. A discussion of the strengths and limitations of the clinical evidence base for the technology. This should include the following:
* A brief statement on the internal validity of the studies included in the clinical evidence base.
* A brief statement on the external validity of the studies included in the clinical evidence base. Include the relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice. Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Also provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as a ‘life‑extending treatment at the end of life’ as described in section 6.2.10 of the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-appraisal-of-the-evidence-and-structured-decision-making). Complete the table below and cross reference to where this information is found in the company submission.

### Table X End-of-life criteria

|  |  |
| --- | --- |
| **Criterion** | **Data available** |
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | [State mean and/or median life expectancy, and source of the data] |
| There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment | [State mean and/or median extension to life, and source of the data] |
| The treatment is licensed or otherwise indicated for small patient populations | [State the cumulative number of patients for all licensed indications in England and source of the data] |

* 1. Ongoing studies
     1. Provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.
        1. Cost effectiveness

Section 5 provides detailed guidance on the level of information that should be provided in the evidence submission template about the cost effectiveness of the appraised technology.

When completing the template, also refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/introduction) and the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/introduction).

* 1. Published cost-effectiveness studies

### Identification of studies

* + 1. Describe the strategies used to retrieve cost‑effectiveness studies relevant to decision‑making in England from published NICE technology appraisals, the published literature and from unpublished data held by the company. Justify the methods used with reference to the decision problem and the NICE reference case. Provide sufficient detail to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used. Provide the search strategy used in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).

### Description of identified studies

* + 1. Provide a brief overview of each cost‑effectiveness study only if it is relevant to decision‑making in England. Describe the aims, methods and results for each study. Each study’s results should be interpreted with reference to a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than 1 study is identified, please present the information in a table as suggested below.

### Table X Summary list of published cost-effectiveness studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Year** | **Summary of model** | **Patient population (average age in years)** | **QALYs (intervention, comparator)** | **Costs (currency) (intervention, comparator)** | **ICER (per QALY gained)** |
| Study 1 |  |  |  |  |  |  |
| Study 2 |  |  |  |  |  |  |
| [Add more rows as needed] |  |  |  |  |  |  |
| QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio | | | | | | |

* + 1. Provide a complete quality assessment for each relevant cost‑effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[[2]](#footnote-2) or Philips et al. (2004)[[3]](#footnote-3). Please provide these assessments in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
  1. De novo analysis

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5.2.

### Patient population

* + 1. State which patient groups are included in the economic evaluation and how they reflect the population defined in the scope and decision problem for the NICE technology appraisal, marketing authorisation/CE marking, and the population from the trials. If there are differences, please provide the rationale. Explain the implications of this for the relevance of the evidence base to the decision problem. For example, indicate if the population in the economic model is different from that described in the (draft) summary of product characteristics (SmPC) or information for use (IFU) and included in the trials.

### Model structure

* + 1. Describe the model structure and provide a diagram of the model submitted, including the following:
* Type of de novo analysis (for example, decision tree, Markov model, discrete event simulation model).
* Justification of the chosen structure in line with the clinical pathway of care described in [section 3.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/health-condition-and-position-of-the-technology-in-the-treatment-pathway).
* How the model structure and its health states capture the disease or condition for patients identified in [section 3.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/health-condition-and-position-of-the-technology-in-the-treatment-pathway).
* Where appropriate, state the cycle length and whether a half‑cycle correction has been applied.
  + 1. Complete the table below presenting the features of the de novo analysis. Compare and justify your chosen values with the methods specified by NICE in the reference case (see the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5, table 5.1).

### Table X Features of the de novo analysis

|  |  |  |
| --- | --- | --- |
| **Factor** | **Chosen values** | **Justification** |
| Time horizon |  |  |
| Were health effects measured in QALYs; if not, what was used? |  |  |
| Discount of 3.5% for utilities and costs |  |  |
| Perspective (NHS/PSS) |  |  |
| PSS, personal social services; QALYs, quality-adjusted life years | | |

### Intervention technology and comparators

* + 1. If the intervention and comparator(s) are not implemented in the model as per their marketing authorisations/CE marking, describe how and why there are differences. Make it clear whether the intervention and comparator(s) included in the model reflect the decision problem. If not, briefly describe how and why, cross‑referencing to the decision problem section in your submission.
    2. If a treatment continuation rule has been assumed for the intervention and comparator(s), provide the rationale for the continuation rule and where it is referenced (for example, [draft] SmPC, European public assessment report, comparator use, clinical practice, or clinical trial protocols). Please note that this refers to clinical continuation rules and not patient access schemes. If a treatment continuation rule is included in the model that is not stated in the (draft) SmPC or information for use (IFU), this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base‑case interventions and comparators. Consideration should be given to the following:
* the costs and health consequences of implementing the continuation rule (for example, any additional monitoring required)
* the robustness and plausibility of the end point on which the rule is based
* whether the ‘response’ criteria defined in the rule can be reasonably achieved
* the appropriateness and robustness of the time at which response is measured
* whether the rule can be incorporated into routine clinical practice
* whether the rule is likely to predict those people for whom the technology is particularly cost effective
* issues about withdrawal of treatment for people whose disease does not respond and other equity considerations.
  1. Clinical parameters and variables

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5.7.

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission ([section 4](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness)). Cross‑references to the clinical evidence section should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as justification for the approach. The answers should clearly specify the approach taken in the base case analysis.

Provide the information specified in sections 5.3.1–5.3.4.

* + 1. Describe how the clinical data were incorporated into the model, also commenting on the following factors:
* Whether intermediate outcome measures were linked to final outcomes (for example, if a change in a surrogate outcome was linked to a final clinical outcome). If so, explain how the relationship was estimated, what sources of evidence were used, and what other evidence there is to support it.
* Whether costs and clinical outcomes are extrapolated beyond the trial follow‑up period(s). If so, explain and justify the assumptions that underpin this extrapolation, particularly the assumption that was used about the longer‑term difference in effectiveness between the intervention and its comparator. For the extrapolation of clinical outcomes, present graphs of any curve fittings to patient‑level data or Kaplan–Meier plots and the methods and results of any internal and external validation exercises. The NICE Decision Support Unit[[4]](#footnote-4) has published [technical support document 14](http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf), which provides additional information on the implementation of methods and reporting standards for extrapolation with patient level data.
  + 1. Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here.
    2. If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has been included in the evaluation. If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.
    3. If clinical experts have assessed the applicability of the clinical parameters or approximated any of the clinical parameters, provide the following details :
* the criteria for selecting the experts
* the number of experts approached
* the number of experts who participated
* declaration of potential conflict(s) of interest from each expert whose opinion was sought
* the background information provided and its consistency with all the evidence provided in the submission
* the method used to collect the opinions
* the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self‑administered questionnaire?)
* the questions asked
* whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).
  1. Measurement and valuation of health effects

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5.3.

The NICE Decision Support Unit4 has published several technical support documents that provide additional information on measuring and valuing health benefits in economic evaluation:

* [An introduction to the measurement and valuation of health for NICE submissions](http://www.nicedsu.org.uk/TSD8%20Introduction%20to%20MVH_final.pdf) (technical support document 8).
* [The identification, review and synthesis of health state utility values from the literature](http://www.nicedsu.org.uk/TSD9%20HSUV%20values_FINAL.pdf) (technical support document 9).
* [The use of mapping methods to estimate health state utility values](http://www.nicedsu.org.uk/TSD%2010%20mapping%20FINAL.pdf) (technical support document 10).
* [Alternatives to EQ-5D for generating health state utility values](http://www.nicedsu.org.uk/TSD11%20Alternatives%20to%20EQ-5D_final.pdf) (technical support document 11).
* [The use of health state utility values in decision models](http://www.nicedsu.org.uk/TSD12%20Utilities%20in%20modelling%20FINAL.pdf) (technical support document 12).

### Health-related quality-of-life data from clinical trials

* + 1. If health‑related quality‑of‑life (HRQL) data were collected in the clinical trials identified in [section 4](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness), comment on whether the data are consistent with the reference case. Consider the following points, but note that this list is not exhaustive:
* method of elicitation
* method of valuation
* point when measurements were made
* consistency with reference case
* appropriateness for cost‑effectiveness analysis
* results with confidence intervals.

### Mapping

* + 1. If applicable, describe the mapping methods used to estimate health state utility values from the quality‑of‑life data collected in clinical trials. Please include the following information:
* which tool was mapped from and onto which other tool (for example, SF–36 to EQ–5D)
* details of the methodology used
* details of validation of the mapping technique
* if the mapping technique is published or has been used in other NICE technology appraisals for similar diseases or health conditions.

### Health-related quality-of-life studies

* + 1. Describe how systematic searches for relevant HRQL data were done. Consider published and unpublished studies, including any original research commissioned for the technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices).
    2. Tabulate the details of the studies in which HRQL was measured. Include the following, but note that this list is not exhaustive:
* population in which health effects were measured
* information on recruitment (for example, participants of a clinical trial, approximations from clinical experts, utility elicitation exercises including members of the general public or patients)
* interventions and comparators
* sample size
* response rates
* description of health states
* adverse reactions
* appropriateness of health states given the condition and treatment pathway
* method of elicitation
* method of valuation
* mapping
* uncertainty around values
* consistency with reference case
* appropriateness for cost‑effectiveness analysis
* results with confidence intervals
* appropriateness of the study for cost‑effectiveness analysis.
  + 1. Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

### Adverse reactions

* + 1. Describe how adverse reactions affect HRQL. The effect of adverse reactions on HRQL should be explored regardless of whether they are included in a cost‑effectiveness analysis in the base‑case analysis. Any exclusion of the effect of adverse reactions on HRQL in the cost‑effectiveness analysis should be fully justified.

### Health-related quality-of-life data used in cost-effectiveness analysis

* + 1. Define what a patient experiences in the health states in terms of HRQL in the cost‑effectiveness analysis. Explain how this relates to the aspects of the disease or condition that most affect patients’ quality of life.
    2. Clarify whether HRQL is assumed to be constant over time in the cost‑effectiveness analysis. If not, provide details of how HRQL changes over the course of the disease or condition.
    3. If appropriate, describe whether the baseline HRQL assumed in the cost‑effectiveness analysis is different from the utility values used for each of the health states. State whether quality‑of‑life events were taken from this baseline.
    4. If the health state utility values used in the cost‑effectiveness analysis have been adjusted, describe how and why they have been adjusted, including the methodologies used.
    5. Identify any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis and explain their exclusion.
    6. In a table, summarise the utility values chosen for the cost‑effectiveness analysis, referencing values obtained in sections 5.4.1–5.4.6. Justify the choice of utility values, giving consideration to the reference case. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed. See below for a suggested table format.

### Table X Summary of utility values for cost-effectiveness analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **State** | **Utility value: mean (standard error)** | **95% confidence interval** | **Reference in submission (section and page number)** | **Justification** |
| Health state 1 | HS1 |  |  |  |
| Health state 2 | HS2 |  |  |  |
| [Add more rows as needed] |  |  |  |  |
| Adverse reaction 1 | AR1 |  |  |  |
| Adverse reaction 2 | AR2 |  |  |  |
| HS, health state; AR, adverse reaction | | | | |

* + 1. If clinical experts assessed the applicability of the health state utility values available or approximated any of values, provide the details (see section 5.3.4).
  1. Cost and healthcare resource use identification, measurement and valuation

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5.5.

* + 1. All parameters used to estimate cost effectiveness should be presented clearly in a table with details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

### Resource identification, measurement and valuation studies

* + 1. Describe how relevant cost and healthcare resource use data for England were identified. Include the search strategy and inclusion criteria, and consider published and unpublished studies to demonstrate how relevant cost and healthcare resource use data for England were identified. The search strategy used should be provided in an [appendix](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/appendices). If the systematic search yields limited data for England, the search strategy may be extended to capture data from other countries. Please give the following details of included studies:
* country of study
* date of study
* applicability to clinical practice in England
* cost valuations used in the study
* costs for use in the economic analysis
* technology costs.
  + 1. When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment‑by‑results (PbR) tariffs are appropriate for costing the intervention being appraised. Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the PbR tariff. Provide the relevant Healthcare Resource Groups and PbR codes and justify their selection with reference to [section 2](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/the-technology).
    2. If clinical experts assessed the applicability of the cost and healthcare resource use values available, or approximated any of the values used in the cost‑effectiveness analysis, provide the details (see section 5.3.4).

### Intervention and comparators’ costs and resource use

* + 1. In a table, summarise the cost and associated healthcare resource use of each treatment. A suggested format for a table is provided below. Cross refer to other sections of the submission; for example, drugs costs should be cross‑referenced to section 2.3.1. Provide a rationale for the choice of values used in the cost‑effectiveness model discussed in section 5.2.2.

### Table X Unit costs associated with the technology in the economic model

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Items** | **Intervention (confidence interval)** | **Reference in submission** | **Comparator 1 (confidence interval)** | **Reference in submission** | **[Add more columns as needed]** |
| Technology cost |  |  |  |  |  |
| Mean cost of technology treatment |  |  |  |  |  |
| Administration cost |  |  |  |  |  |
| Monitoring cost |  |  |  |  |  |
| Tests |  |  |  |  |  |
| [Add more rows as needed] |  |  |  |  |  |
| Total |  |  |  |  |  |

### Health-state costs and resource use

* + 1. Summarise and tabulate the costs included in each health state. A suggested format for a table is provided below. Cross refer to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost‑effectiveness model. The health states should refer to the states in section 5.2.2.

### Table X List of health states and associated costs in the economic model

|  |  |  |  |
| --- | --- | --- | --- |
| **Health states** | **Items** | **Value** | **Reference in submission** |
| Health state 1 | Technology |  |  |
| Staff |  |  |
| Hospital costs |  |  |
| [Add more rows as needed] |  |  |
| Total |  |  |
| Health state 2 |  |  |  |
| [Add more rows as needed] |  |  |  |

### Adverse reaction unit costs and resource use

* + 1. Summarise and tabulate the costs for each adverse reaction listed in [section 4.12](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#adverse-reactions) and included in the de novo cost‑effectiveness analysis. These should include the costs of therapies identified in [section 2.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/the-technology#administration-and-costs-of-the-technology). A suggested format for a table is provided below. Cross refer to other sections of the submission for the resource costs.

### Table X List of adverse reactions and summary of costs in the economic model

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse reactions** | **Items** | **Value** | **Reference in submission** |
| Adverse reaction 1 | Technology |  |  |
| Staff |  |  |
| Hospital costs |  |  |
| [Add more rows as needed] |  |  |
| Total |  |  |
| Adverse reaction 2 | Technology |  |  |
| Staff |  |  |
| [Add more rows as needed] |  |  |  |

### Miscellaneous unit costs and resource use

* + 1. Describe and tabulate any additional costs and healthcare resource use that have not been covered elsewhere (for example, costs relating to subsequent lines of therapy received after disease progression, personal and social services costs). If none, please state.
  1. Summary of base case de novo analysis inputs and assumptions

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5.11.1.

### Summary of base case de novo analysis inputs

* + 1. Tabulate all variables included in the cost‑effectiveness analysis, detailing the values used, range (for example, confidence interval, standard error or distribution) and source. Cross refer to other parts of the submission. Complete the table below that summarises the variables applied in the economic model.
    2. For the base‑case de novo analysis the company should ensure that the cost‑effectiveness analysis reflects the NICE reference case as closely as possible. Describe the rationale if an input chosen in the base‑case de novo analysis:
* deviates from the NICE reference case or
* is taken from other sources (such as the published literature) rather than data from clinical trials of the technology (when available).

### Table X Summary of variables applied in the economic model

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Value (reference to appropriate table or figure in submission)** | **Measurement of uncertainty and distribution: CI (distribution)** | **Reference to section in submission** |
| [Age] | [A years] | [x to y (normal)] | [Patient characteristics section x] |
| [Overall survival] | [B months] | [x to y (Weibull)] | [Trial results section x] |
| [Add more rows as needed] |  |  |  |
| CI, confidence interval | | | |

### Assumptions

* + 1. Provide a list of all assumptions used in the de novo economic model and justify each assumption.
  1. Base-case results

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), sections 5.7.4 and 5.11.2–5.11.3.

* + 1. Provide the results of the analysis. In particular, results should include, but are not limited to, the following:
* the link between clinical‑ and cost‑effectiveness results
* costs, quality‑adjusted life years (QALYs) and incremental cost per QALY
* disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse reactions, and costs associated with follow‑up or subsequent treatment.

### Base-case incremental cost effectiveness analysis results

* + 1. When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost‑effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base‑case incremental cost‑effectiveness analysis with the patient access scheme.

### Table X Base-case results

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Technologies** | **Total costs (£)** | **Total LYG** | **Total QALYs** | **Incremental costs (£)** | **Incremental LYG** | **Incremental QALYs** | **ICER (£) versus baseline (QALYs)** | **ICER (£) incremental (QALYs)** |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | | |

### Clinical outcomes from the model

* + 1. For the outcomes highlighted in the decision problem (see [section 3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/health-condition-and-position-of-the-technology-in-the-treatment-pathway)), provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials, as suggested in the table below. Discuss reasons for any differences between the modelled results in the cost‑effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover).

### Table X Summary of model results compared with clinical data

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Clinical trial result** | **Model result** |
| Progression-free survival | C1 | R1 |
| Post-progression survival | C2 | R2 |
| Overall survival | C1+2 | R1+2 |
| Adverse reaction 1 | C3 | R3 |
| [Add more rows as needed] |  |  |

* + 1. Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator.
    2. Provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

### Disaggregated results of the base case incremental cost effectiveness analysis

* + 1. Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental cost effectiveness analysis by category of cost. The tables that should be completed summarising the disaggregated results (for example, QALY gain by health state, costs by health state, predicted resource use by category of cost) are presented below.

### Table X Summary of QALY gain by health state

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Health state** | **QALY intervention (X)** | **QALY comparator (Y)** | **Increment** | **Absolute increment** | **% absolute increment** |
| [Health state 1] | [XHS1] | [YHS1] | [XHS1 – YHS1] | [|XHS1 – YHS1|] | [|XHS1 – YHS1|/(Total absolute increment)] |
| [Health state 2] | [XHS2] | [YHS2] | [XHS2 – YHS2] | [|XHS2 – YHS2|] | [|XHS2 – YHS2|/(Total absolute increment)] |
| [Add more rows as needed] |  |  |  |  |  |
| Total | [XTotal] | [YTotal] | [XTotal – YTotall] | Total absolute increment | 100% |
| QALY, quality-adjusted life year; HS1, health state 1; HS2, health state 2  Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | | | |

### Table X Summary of costs by health state

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Health state** | **Cost intervention (X)** | **Cost comparator (Y)** | **Increment** | **Absolute increment** | **% absolute increment** |
| [Health state 1 (HS1)] | [XHS1] | [YHS1] | [XHS1 – YHS1] | [|XHS1 – YHS1|] | [|XHS1 – YHS1| / (Total absolute increment)] |
| [Health state 2] | [XHS2] | [YHS2] | [XHS2 – YHS2] | [|XHS2 – YHS2|] | [|XHS2 – YHS2| / (Total absolute increment)] |
| [Add more rows as needed] |  |  |  |  |  |
| Total | [XTotal] | [YTotal] | [XTotal – YTotal] | Total absolute increment | 100% |
| HS1, health state 1; HS2, health state 2  Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | | | |

### Table X Summary of predicted resource use by category of cost

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Item** | **Cost intervention (X)** | **Cost comparator (Y)** | **Increment** | **Absolute increment** | **% absolute increment** |
| [Technology cost] | [Xtech] | [Ytech] | [Xtech – Ytech] | [|Xtech – Ytech|] | [|Xtech – Ytech| / (Total absolute increment)] |
| [Mean total treatment cost] | [Xtreat] | [Ytreat] | [Xtreat – Ytreat] | [|Xtreat – Ytreat|] | [|Xtreat – Ytreat| / (Total absolute increment)] |
| [Administration cost] | [Xadmin] | [Yadmin] | [Xadmin – Yadmin] | [|Xadmin – Yadmin|] | [|Xadmin – Yadmin| / (Total absolute increment)] |
| [Monitoring cost] | [Xmon] | [Ymon] | [Xmon – Ymon] | [|Xmon – Ymon|] | [|Xmon – Ymon| / (Total absolute increment)] |
| [Tests] | [Xtests] | [Ytests] | [Xtests – Ytests] | [|Xtests – Ytests|] | [|Xtests – Ytests| / (Total absolute increment)] |
| [Add more rows as needed] |  |  |  |  |  |
| Total | [XTotal] | [YTotal] | [XTotal – YTotal] | Total absolute increment | 100% |
| Tech, technology; treat, treatment; admin, administration; mon, monitoring | | | | | |

* 1. Sensitivity analysis

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), sections 5.7 and 5.8.

### Probabilistic sensitivity analysis

* + 1. All inputs used in the analysis will be estimated with a degree of imprecision. As specified in the NICE guide to the methods of technology appraisal, probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared. In non‑linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes. The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions for probabilistic sensitivity analysis should not be arbitrarily chosen, but should represent the available evidence on the parameter of interest, and their use should be justified.

Provide the information specified in sections 5.8.2–5.8.4.

* + 1. The distributions and their sources for each parameter should be clearly stated if different from those presented in section 5.5, including the derivation and value of ‘priors’. If any parameters or variables were omitted from the probabilistic sensitivity analysis, please provide the rationale for the omission(s).
    2. Present the incremental cost effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals). Include scatter plots and cost‑effectiveness acceptability curves showing the probability that the treatment is cost effective if the incremental cost‑effectiveness ratio ICER is £20,000 to £30,000 per QALY gained. Describe how the probabilistic ICER(s) were calculated and provide the rationale.
    3. Describe and explain, if any, the variation between the incremental cost effectiveness analysis results estimated from the base‑case analysis (section 5.6) and the probabilistic sensitivity analysis.

### Deterministic sensitivity analysis

* + 1. Identify which variables were subject to deterministic sensitivity analysis, how they were varied, and the rationale behind this. If any parameters or variables listed in section 5.6.1 were omitted from sensitivity analysis, please provide the rationale.
    2. Present the results of deterministic sensitivity analysis. Consider the use of tornado diagrams.
    3. For technologies whose final price or acquisition cost has not been confirmed, sensitivity analysis should be done over a plausible range of prices. This may also include the price of a comparator that includes a confidential patient access scheme.

### Scenario analysis

* + 1. Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.
    2. Present the results of scenario analysis. Include details of structural sensitivity analysis.

### Summary of sensitivity analyses results

* + 1. Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost‑effectiveness results.
  1. Subgroup analysis

This section should be read with the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case), section 5.10.

When subgroups have been considered in the de novo cost‑effectiveness analysis, provide the information specified in sections 5.9.1–5.9.6.

* + 1. Types of subgroups that are not considered relevant are those based solely on the following factors:
* Individual utilities for health states and patient preference.
* Different treatment costs for individuals according to their social characteristics.
* Subgroups specified according to the costs of providing treatment in different locations in England (for example, when the costs of facilities available for providing the technology vary according to location).
  + 1. Please specify whether analysis of subgroups was carried out and how these subgroups were identified, referring to the scope and decision problem specified for the NICE technology appraisal. When specifying how subgroups were identified, confirm whether they were identified based on a prior expectation of different clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. Cross refer to the clinical effectiveness [section 4.7](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#clinical-effectiveness-results-of-the-relevant-randomised-controlled-trials).
    2. Clearly define the characteristics of patients in the subgroup.
    3. Describe how the statistical analysis was carried out.
    4. If subgroup analyses were done, please present the results in tables similar to those in section 5.7.
    5. Identify any obvious subgroups that were not considered and explain why. Please refer to the subgroups identified in the decision problem in [section 3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/health-condition-and-position-of-the-technology-in-the-treatment-pathway).
  1. Validation

### Validation of de novo cost-effectiveness analysis

* + 1. When describing the methods used to validate and quality assure the model, provide:
* the rationale for using the chosen methods
* references to the results produced and cross‑references to the evidence identified in the clinical evidence, measurement and valuation of health effects, and cost and healthcare resource sections.
  1. Interpretation and conclusions of economic evidence
     1. When interpreting and concluding your economic evidence, consider the following:
* Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?
* Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?
* How relevant (generalisable) is the analysis to clinical practice in England?
* What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?
* What further analyses could be carried out to enhance the robustness or completeness of the results?
  + - 1. Assessment of factors relevant to the NHS and other parties

When completing the template, refer to the NICE [guide to the methods of technology appraisal](http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/the-reference-case) section 5.12, and the NICE [guide to the processes of technology appraisal](http://publications.nice.org.uk/guide-to-the-processes-of-technology-appraisal-pmg19/introduction).

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness. This will allow subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

Provide the information specified in sections 6.2–6.10.

State how many people are eligible for treatment in England. Present results for the full marketing authorisation or CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Explain any assumptions that were made about current treatment options and uptake of technologies.

When relevant, explain any assumptions that were made about market share in England.

In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions).

State what unit costs were assumed and how they were calculated. If unit costs used in health economic modelling were not based on national reference costs or the payment‑by‑results tariff, explain how a cost for the activity was calculated.

If there were any estimates of resource savings, explain what they were and when they are likely to be made.

State the estimated annual budget impact on the NHS in England.

Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

Highlight the main limitations within the budget impact analysis.

* + - 1. References

Please use a recognised referencing style, such as Harvard or Vancouver. Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, Trial123/Jones et al.126 rather than One trial126).

* + - 1. Appendices

Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested in the template, but that is considered to be relevant to the submission. Any appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the template. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical‑effectiveness section with ‘see appendix X’. Clinical trial reports and protocols must be made available for relevant clinical studies; the remainder must be available on request. Submission appendices are not normally provided to the Appraisal Committee or published on the NICE website and therefore please send these as separate documents to the main submission. Examples of appendices submitted to NICE are as follows:

Appendix 1: European public assessment report, SmPC/IFU, scientific discussion or drafts ([section 2.2](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/the-technology#marketing-authorisationce-marking-and-health-technology-assessment))

Appendix 2: Search strategy for relevant studies ([section 4.1.2](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#identification-and-selection-of-relevant-studies))

Appendix 3: Quality assessment of randomised controlled trials (RCTs) ([section 4.6](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#quality-assessment-of-the-relevant-randomised-controlled-trials))

Appendix 4: Subgroup analysis ([section 4.8](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#subgroup-analysis))

Appendix 5: Search strategy for indirect and mixed treatment comparisons ([section 4.10.1](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#indirect-and-mixed-treatment-comparisons))

Appendix 6: Methods, results, outcomes and quality assessment of the relevant trials in the indirect or mixed treatment comparison ([section 4.10.9-10](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#indirect-and-mixed-treatment-comparisons))

Appendix 7: Programming language used in the analysis ([section 4.10.13](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#indirect-and-mixed-treatment-comparisons))

Appendix 8: Quality assessment of the relevant non‑randomised and non‑controlled evidence (see [section 4.11.6-9](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#non-randomised-and-non-controlled-evidence))

Appendix 9: Search strategy for adverse reactions ([section 4.12.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#adverse-reactions))

Appendix 10: Quality assessment of adverse reaction data ([section 4.12.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/clinical-effectiveness#adverse-reactions))

Appendix 11: Search strategy for cost‑effectiveness studies ([section 5.1.1](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/cost-effectiveness#published-cost-effectiveness-studies))

Appendix 12: Quality assessment of cost‑effectiveness studies ([section 5.1.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/cost-effectiveness#published-cost-effectiveness-studies))

Appendix 13: Search strategy for measurement and valuation of health effects ([section 5.4.3](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/cost-effectiveness#measurement-and-valuation-of-health-effects))

Appendix 14: Cost and healthcare resource identification, measurement and valuation ([section 5.5.2](http://publications.nice.org.uk/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pmg24/cost-effectiveness#cost-and-healthcare-resource-use-identification-measurement-and-valuation))

Appendix 15: Checklist of confidential information

# About this user guide

This is the user guide for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It explains what information NICE requires and the format in which it should be presented.

Nothing in this user guide shall restrict any disclosure of information by NICE that is required by law (including in particular but without limitation the Freedom of Information Act 2000).

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1. Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy. [↑](#footnote-ref-1)
2. Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313(7052): 275–83 [↑](#footnote-ref-2)
3. Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36. [↑](#footnote-ref-3)
4. Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy. [↑](#footnote-ref-4)