

Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template

Process and methods

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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 and highly specialised technologies evaluations 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](#). Companies making evidence submissions to NICE should also refer to [NICE's health technology evaluation guidance development manual](#), which gives further details of procedures and methods relating to single technology appraisal and highly specialised technologies evaluation submissions.

The submission should be as brief and informative as possible. The main body of the submission must not be longer than 150 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. Some of the information we request should be submitted as appendices to the main submission (when this is the case, it is clearly marked). The information in these appendices is required by the external assessment group (EAG) to fully critique the submission. The appendices are not normally presented to the evaluation committee, but will be available to them on request.

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 5.3 and 5.4 of [NICE's health technology evaluation guidance development](#)

[manual](#) for information about all aspects of information handling.

To ensure that the evaluation process is as transparent as possible, NICE considers that evidence on which the evaluation 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 evaluation as issued by the Department of Health and Social Care 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](#).

NICE requires companies to consent to European Economic Area regulatory authorities directly providing NICE with all clinical trial data necessary to address the remit and scope of the technology evaluation as issued by the Department of Health and Social Care 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 evaluation. 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.

All information that should be provided in an appendix is outlined in the [user guide for company evidence submission appendices](#)

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

Please choose the most appropriate option(s) from those provided in the submission template about whether the submission covers all or only part of the technology's marketing authorisation for this indication.

Specify the decision problem that the submission addresses. Present the decision problem in the table in section 1.1 of the template, making reference to the final NICE scope.

1.2 Description of technology being evaluated

Provide details of the technology being evaluated using the table in section 1.2 of the template.

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Provide a brief overview of the disease or condition for which the technology is indicated.

1.3.2 Present the clinical pathway of care that shows the context of the proposed use of the technology. This information should be summarised in a diagram if possible. 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.

1.4 Equality considerations

1.4.1 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](#).

1.4.2 Provide an assessment of whether the use of this technology is likely to raise any equality issues. Please document 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.

1.4.3 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.

2 Clinical effectiveness

Section 2 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 [NICE's health technology evaluation guidance development manual \(section 3\)](#).

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](#) about evidence synthesis:

- Introduction to evidence synthesis for decision making (technical support document 1).
- A general linear modelling framework for pairwise and network meta-analysis of randomised controlled trials (technical support document 2).
- Heterogeneity: subgroups, meta-regression, bias and bias-adjustment (technical support document 3).
- Inconsistency in networks of evidence based on randomised controlled trials (technical support document 4).
- Evidence synthesis in the baseline natural history model (technical support document 5).
- Embedding evidence synthesis in probabilistic cost-effectiveness analysis: software choices (technical support document 6).
- Evidence synthesis of treatment efficacy in decision making: A reviewer's checklist (technical support document 7).

- Methods for population-adjusted indirect comparisons in submissions to NICE (technical support document 18).

Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy.

2.1 Identification and selection of relevant studies

This section provides guidance on identifying and selecting relevant studies that provide evidence for:

- the technology being evaluated
- comparator technologies, when an indirect or mixed treatment comparison is carried out.

This information should be submitted as **appendix D** to the main submission. See the [user guide for company evidence submission appendices](#).

2.2 List of relevant clinical effectiveness evidence

NICE prefers RCTs that directly compare the technology with 1 or more relevant comparators. 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. In addition, data from trials that compare the technology with non-relevant comparators may be needed to enable the technology and the comparators to be linked in an indirect or mixed treatment comparison. Please provide details of the RCTs and non-randomised and non-controlled trials identified in the systematic literature review as providing evidence for the technology being appraised. A suggested table format for each source of evidence is below. Indicate whether the trial was used to support the application for marketing authorisation. Indicate if the trial was used to inform the economic model, and give a justification if it was not. Provide details on additional and supporting evidence, including expert elicitation, expert opinion, real-world evidence or natural history data used to support any severity assumptions. Additional and supporting evidence may be presented as a written description.

Table [X] Clinical effectiveness evidence

Study	[Clinical trial name or primary author surname (year published)]
Study design	
Population	
Intervention(s)	
Comparator(s)	
Indicate if study supports application for marketing authorisation	Yes No
Indicate if study used in the economic model	Yes No
Rationale if study not used in model	
Reported outcomes specified in the decision problem	[Please mark in bold the outcomes that are incorporated into the model]
All other reported outcomes	[Please mark in bold the outcomes that are incorporated into the model]

2.2.1 Sections 2.2 to 2.6 of the submission should include only the trials that were included in the economic model. If you wish to include additional studies in sections 2.2 to 2.6, which were not included in the economic model but are relevant to your submission (for example, natural history data to support severity assumptions), please provide your rationale below, using the following format:

[Study name] was not used to populate the economic model but is included in sections 2.2 to 2.6. The results of this study support [include details of why they are relevant]. This study was not included in the economic model because [add rationale].

2.3 Summary of methodology of the relevant clinical effectiveness 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.

2.3.1 Items 3 to 6b of the [CONSORT checklist](#) should be provided for all RCTs identified in section 2.2 as relevant to your submission.

- **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.
- **Outcomes used in the economic model or specified in the scope, including primary outcome.** This should always include the primary outcome even if it is not used in the economic model. Please state if the outcomes were pre-specified or post-hoc analyses.

2.3.2 Provide a comparative summary of the methodology of the trials 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)			
Other outcomes used in the economic model/specified in the scope			
Pre-planned subgroups			

2.3.3 In a table describe the characteristics of the participants at baseline for each of the trials in your submission. Provide details of baseline demographics, including age, sex and relevant variables describing disease severity and duration and 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)	Treatment group X	Treatment group Y	[Add more columns as needed]
Baseline characteristic			
Trial 1 (n=[x])	(n=[x])	(n=[x])	(n=[x])
Age			

Trial number (acronym) Baseline characteristic	Treatment group X	Treatment group Y	[Add more columns as needed]
Sex			
[Add more rows as needed]			
Trial 2 (n=[x])	(n=[x])	(n=[x])	(n=[x])
Age			
Sex			
[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.

- 2.3.4 Clearly describe the methods used for expert elicitation or expert opinion, including the identification and selection of experts, and the reporting of results including the consensus of opinions or data aggregation. Follow existing reporting guidelines when possible.
- 2.3.5 See section 3.3.14 of [NICE's health technology guidance development manual](#) for additional guidance on the design, conduct and reporting of non-randomised and real-world studies.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

- 2.4.1 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](#).

- 2.4.2 For each study identified in 2.2 as relevant to your submission, provide details of the study 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).
- 2.4.3 For each study, 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 the rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale. A suggested table format is presented below.
- 2.4.4 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.

Table [X] Summary of statistical analyses

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

Participant flow in the relevant randomised controlled trials

See **appendix D** to the main submission in the [user guide for company evidence submission appendices](#) for details of additional information that should be provided.

2.5 Critical appraisal of the relevant clinical

effectiveness evidence

In **appendix D**, provide the complete quality assessment for each trial. See the [user guide for company evidence submission appendices](#) for details.

- 2.5.1 The validity of the results of an individual RCT or non-randomised or non-controlled study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. The quality of each source of evidence identified as relevant to your submission in section 2.2 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.
- 2.5.2 Describe the methods used for assessing risk of bias and generalisability of individual trials (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?
 - Also consider whether the authors of the study publication declared any conflicts of interest.
- 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](#) (University of York Centre for Reviews and Dissemination).

- 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 (University of York Centre for Reviews and Dissemination). This includes information on a number of initiatives aimed at improving the quality of research reporting. Include consideration of the following:
 - Was the cohort recruited in an acceptable way?
 - Was the exposure accurately measured to minimise bias?
 - Was the outcome accurately measured to minimise bias?
 - Have the authors identified all important confounding factors?
 - Have the authors taken account of the confounding factors in the design or analysis, or both?
 - Was the follow up of patients complete?
 - How precise (for example, in terms of confidence intervals and p values) are the results?

2.5.3 Consider how closely the studies reflect routine clinical practice in England.

2.5.4 If there is more than 1 study, tabulate a summary of the responses applied to each of the quality assessment criteria. Suggested table formats for the quality assessment results are:

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)	

Trial number (acronym)	Trial 1	Trial 2	[Add more columns as needed]
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 (University of York Centre for Reviews and Dissemination).

Table [X] Quality assessment results for non-randomised and non-controlled studies

Study name	Study 1 yes/no/ not clear/ N/A)	Study 2	[Add more columns as needed]
Was the cohort recruited in an acceptable way?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	
Was the exposure accurately measured to minimise bias?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	
Was the outcome accurately measured to minimise bias?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	
Have the authors identified all important confounding factors?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	
Have the authors taken account of the confounding factors in the design and/or analysis?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	
Was the follow-up of patients complete?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	
How precise (for example, in terms of confidence interval and p values) are the results?	(yes/no/ not clear/ N/A)	(yes/no/ not clear/ N/A)	

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study

2.6 Clinical effectiveness results of the relevant trials

- 2.6.1 Present results for all outcomes that inform the economic model or are specified in the scope from the trials identified as relevant to your submission (including real-world studies when applicable). The primary outcome of the studies must be reported. 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.
- 2.6.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.
- 2.6.3 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.

2.7 Subgroup analysis

This section should be read with [NICE's health technology evaluation guidance development manual section 4.9](#).

- 2.7.1 Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre-planned or post-hoc.
- 2.7.2 Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.
- 2.7.3 Provide details of the statistical tests used in the primary analysis of the subgroups, including any tests for interaction.

Provide a summary of the results for the subgroups in **appendix E**. See the [user guide for company evidence submission appendices](#) for details.

2.8 Meta-analysis

This section should be read with the [NICE's health technology evaluation guidance development manual, sections 3.4.8 to 3.4.10](#). For further information on how to implement the approaches described in the manual, see the series of [technical support documents produced by the NICE Decision Support Unit](#) about evidence synthesis. See also [technical support document 20](#).

- 2.8.1 If a meta-analysis cannot be conducted and instead a qualitative overview is considered to be appropriate, summarise the overall results of the individual studies with reference to their critical appraisal.
- 2.8.2 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).

2.8.3 If any of the relevant studies listed in section 2.1 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.

2.9 Indirect and mixed treatment comparisons

2.9.1 In a table provide a summary of the trials used to carry out the indirect comparison or mixed treatment comparison. There is a suggested table format below. When there are more than 2 treatments in the comparator sets for synthesis, include 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

References of trial	Intervention A	Intervention B	Intervention C	Intervention D
Trial 3	Yes	Yes		
Trial 4	Yes		Yes	
[Add more rows as needed]				

2.9.2 If the table or network diagram provided does not include all the trials that were identified in the search strategy, the rationale for exclusion should be provided.

Full details of the methodology for the indirect comparison or mixed treatment comparison should be presented in **appendix D**. See the [user guide for company evidence submission appendices](#) for details.

2.9.3 Provide the results of the analysis. For examples of how to present the results, see the [NICE Decision Support Unit technical support documents 1 to 3](#).

2.9.4 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.

2.9.5 If there is doubt about the relevance of particular trials, present separate sensitivity analyses in which these trials are excluded.

2.9.6 Discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

2.10 Adverse reactions

2.10.1 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.

- 2.10.2 In a table, summarise the adverse reactions reported in the studies identified in section 2.2, as relevant to your submission. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the adverse reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

In **appendix F**, provide details of any studies that report additional adverse reactions to those reported by the studies identified in section 2.2. See the [user guide for company evidence submission appendices](#) for details.

- 2.10.3 Provide a brief overview of the safety of the technology in relation to the decision problem.

2.11 Ongoing studies

- 2.11.1 Provide details of all completed and ongoing studies that should provide additional evidence in the next 12 months for the indication being appraised.

2.12 Interpretation of clinical effectiveness and safety evidence

When making conclusions about the clinical effectiveness and safety evidence, provide the information specified below.

- 2.12.1 A statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology.
- 2.12.2 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.

3 Cost effectiveness

Section 3 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 [NICE's health technology evaluation guidance development manual](#).

3.1 Published cost-effectiveness studies

In **appendix G**, provide details of the identified studies. See the [user guide for company evidence submission appendices](#) for details.

In the main submission, summarise the published cost-effectiveness studies using a table similar to the one 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]						

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

3.2 Economic analysis

Summarise how the cost-effectiveness studies identified in appendix G inform the economic analysis.

If a de novo model economic model is included in the submission, please justify why this is necessary.

Patient population

3.2.1 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 evaluation, marketing authorisation or 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

3.2.2 Describe the model structure and provide a diagram of the model submitted, including the following:

- Type of 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 1.3.
- How the model structure and its health states capture the disease or condition for patients identified in section 1.3.
- Where appropriate, state the cycle length and whether a half-cycle correction has been applied.

3.2.3 Complete the table below presenting the features of the analysis. If there have been NICE technology evaluations in the same disease area, please

summarise the main inputs to the economic models accepted by evaluation committees. If the model in this evaluation uses different inputs, give a rationale.

- 3.2.4 Compare and justify your chosen values with the methods specified by NICE in the reference case (see [NICE's health technology evaluation guidance development manual](#), section 4.2, table 4.1).

Table [X] Features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	TAXXX	TAXXX	Chosen values	Justification
Time horizon				
Treatment waning effect?				
Source of utilities				
Source of costs				

Intervention technology and comparators

- 3.2.5 If the intervention and comparator(s) are not implemented in the model as per their marketing authorisations or 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.
- 3.2.6 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, UK 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 or commercial arrangements. If a treatment continuation rule is included in the model that is not stated in the (draft) SmPC or 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.

3.3 Clinical parameters and variables

This section should be read with [NICE's health technology evaluation guidance development manual](#), section 4.6.

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 2). 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.

3.3.1 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 has published technical support document 14](#), which provides additional information on the implementation of methods and reporting standards for extrapolation with patient level data, and [technical support document 21](#), which provides information on flexible methods for survival analysis.

Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy.

- 3.3.2 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.
- 3.3.3 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.
- 3.3.4 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).

3.4 Measurement and valuation of health effects

This section should be read with the [NICE's health technology evaluation guidance development manual](#), section 4.3.

The [NICE Decision Support Unit](#) 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 (technical support document 8).
- The identification, review and synthesis of health state utility values from the literature (technical support document 9).
- The use of mapping methods to estimate health state utility values (technical support document 10).
- Alternatives to EQ-5D for generating health state utility values (technical support document 11).
- The use of health state utility values in decision models (technical support document 12).

Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy.

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

A hierarchy of preferred health-related quality-of-life methods is presented in [NICE's health technology evaluation guidance development manual](#) figure 4.1. Use this figure for guidance when the EQ-5D is not available or not appropriate.

3.4.1 If health-related quality-of-life data were collected in the clinical trials identified in section 2, 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

3.4.2 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 evaluations for similar diseases or health conditions.

Health-related quality-of-life studies

In **appendix H** describe how systematic searches for relevant health-related quality-of-life data were done. See the [user guide for company evidence submission appendices](#) for details.

- 3.4.3 Present the results (including confidence intervals) of the studies identified in the literature review. Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials. Comment on the appropriateness of the study for the cost-effectiveness analysis.

Adverse reactions

- 3.4.4 Describe how adverse reactions affect health-related quality of life. The effect of adverse reactions on health-related quality of life 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 health-related quality of life in the cost-effectiveness analysis should be fully justified.

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

- 3.4.5 Define what a patient experiences in the health states in terms of health-related quality of life in the cost-effectiveness analysis. Explain how this relates to the aspects of the disease or condition that most affect patients' quality of life.
- 3.4.6 Clarify whether health-related quality of life is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how it changes over the course of the disease or condition.
- 3.4.7 If appropriate, describe whether the baseline health-related quality of life 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.

- 3.4.8 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.
- 3.4.9 Identify any health effects found in the literature or clinical trials that were excluded from the cost-effectiveness analysis and explain their exclusion.
- 3.4.10 In a table, summarise the utility values chosen for the cost-effectiveness analysis, referencing values obtained in sections 3.4.1 to 3.4.4. 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	Health state 1			
Health state 2	Health state 2			
[Add more rows as needed]				
Adverse reaction 1	Adverse reaction 1			
Adverse reaction 2	Adverse reaction 2			

- 3.4.11 If clinical experts assessed the applicability of the health state utility values available or approximated any of values, provide the details (see [section 3.3.4](#)).

3.5 Cost and healthcare resource use identification, measurement and valuation

This section should be read with [NICE's health technology evaluation guidance development manual](#), section 4.4.

- 3.5.1 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

- In **appendix I** describe how relevant cost and healthcare resource use data for England were identified.
- In **appendix K** provide the relevant details for each treatment, including the intervention, comparator and subsequent treatments used in the model, including concomitant treatments.

See the [user guide for company evidence submission appendices](#) for details.

- 3.5.2 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.
- 3.5.3 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 3.3.4](#)).

Intervention and comparators' costs and resource use

- 3.5.4 In a table, summarise the cost and associated healthcare resource use of

each treatment. A suggested format for a table is provided below. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in [section 3.1](#).

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 unit costs and resource use

3.5.5 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 3.2](#).

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

3.5.6 Summarise and tabulate the costs for each adverse reaction listed in [section 2.10](#) and included in the cost-effectiveness analysis. 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		

Adverse reactions	Items	Value	Reference in submission
	Staff		
[Add more rows as needed]			

Miscellaneous unit costs and resource use

3.5.7 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.

3.6 Severity

This section should be read with [NICE's health technology evaluation guidance development manual](#) section 6.2.12 to 6.2.22.

3.6.1 When relevant, outline whether this technology meets the criteria for a severity weight. Provide details about the calculation of quality-adjusted life year (QALY) shortfall, including source of population EQ-5D data and survival data. Present supporting evidence and validation of model outcomes. Complete the tables below and, when relevant, cross reference to where this information is found in the company submission.

3.6.2 The data used to estimate both absolute and proportional QALY shortfall should focus on the specific population for which the technology will be used and be based on established clinical practice in the NHS. Calculation of absolute and proportional shortfall should include an estimate of the total QALYs for the general population with the same age and sex distribution as those with the condition. The data used to estimate both absolute and proportional QALY shortfall should focus on the specific population for which the new technology will be used and be based on established clinical practice in the NHS.

Table [X] Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution		[Patient characteristics section x]
Starting age		[Trial results section x]

Table [X] Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
TAXXX			
[Add more rows as needed]			

Table [X] Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Health state 1	Health state 1	
Health state 2	Health state 2	
[Add more rows as needed]		

Table [X] Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
	Comparator A	

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
[Add more rows as needed]	Comparator B	

3.7 Uncertainty

If relevant, include a statement on how the nature of this condition or technology impacts the ability to generate high-quality evidence.

3.8 Managed access proposal

This section should be read with [NICE's health technology evaluation guidance development manual](#) sections 5.5.20 to 5.5.29.

A managed access proposal may be made for any technology that is eligible for the Cancer Drugs Fund or the Innovative Medicines Fund. The committee can consider a recommendation with managed access for eligible technologies when:

- the technology has the plausible potential to be cost effective at the currently agreed price, but the evidence is currently too uncertain, and
- new evidence that could sufficiently support the case for recommendation is expected from ongoing or planned clinical trials, or could be collected from patients having the medicine in clinical practice, and
- the data could feasibly be collected within a reasonable timeframe (up to a maximum of 5 years) without undue burden.

A managed access proposal should include the following:

3.8.1 Specify whether you consider the technology to be eligible for one of the managed access funds. Cancer drugs are eligible for the Cancer Drugs Fund. Medicines that have the potential to address an unmet need and provide clinically significant benefits to patients are eligible for the Innovative Medicines Fund. When detailing the unmet need and clinically

significant benefits cross refer to other parts of the submission, including the severity section and the incremental QALYs gained within the base-case increment cost-effectiveness analysis results.

- 3.8.2 List the key uncertainties that you consider could prevent the committee from making a recommendation from routine use, and the outcome data and data source that could be collected to sufficiently support the case for recommendation after a period of managed access. Where there are multiple sources identified, mark in bold the data source you consider would be the primary source to address the evidential uncertainty. A suggested table format is provided below.

Table X List of uncertainties and the data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
[Add more rows as needed]		

- 3.8.3 When a primary source of data is not currently included within the NICE economic model, for example a yet to be published clinical study or data collected in clinical practice, describe how the data would be analysed and, if applicable, how it would be incorporated into the economic model at the end of managed access.

- 3.8.4 Provide an overview of all the clinical studies or registries listed within the suitability for managed access section. A suggested format for clinical trial data sources and data collected through the Systemic Anti-Cancer Therapy (SACT) dataset is provided below.

Table X Overview of data source

Study	[Clinical trial name or primary author surname (year published)]
Study design	
Population	
Intervention(s)	

Comparator(s)	
Outcomes	Mark in bold the outcomes listed as a primary source within the 'suitability for managed access' section
Indicate if study used in the NICE economic model	
Trial start date	Month Year
Data cut submitted to NICE	complete as 'Not applicable' for trial data not presented within the NICE submission
Anticipated data cut after a period of managed access	Month Year

Table X Overview of data source

Registry	Systemic Anti-Cancer Therapy (SACT)
Type of registry	Mandated dataset as part of the Health and Social Care Information Standards
Population	All patients who use systemic-anti cancer therapies across all NHS England trusts
Relevant data items collected	Mark in bold the outcomes listed as a primary source within the 'suitability for managed access' section
Data analysis	The company will not have access to the NHS Digital patient data, but will receive de-personalised summary data
Governance	All necessary governance arrangements through SACT, and other datasets brought together by NHS Digital, have been established with NHS Trusts and NHSE&I.
Indicate if registry previously used within a NICE managed access	Yes

3.8.5 For registries other than the SACT dataset please include whether you have approached the registry to explore collecting, analysing and sharing the data in your managed access proposal and whether there are any considerations around information governance and data sharing that may

need to be addressed.

3.8.6 Specify the anticipated timeframe of data collection required to provide meaningful data. Please justify why you consider this timeframe is as short as necessary to address the identified uncertainties.

3.8.7 Describe any additional considerations that may impact the feasibility of data collection within managed access. These may include:

- any additional burden that you have identified that a managed access may cause patients, clinicians, or the NHS.
- potential barriers to agreeing or implementing a managed access
- any ethical, equality, or patient safety concerns with the proposed data collection and analysis.
- actions you have taken to improve the feasibility of a managed access.

3.8.8 You must submit a separate commercial access proposal as part of the managed access proposal. The process for submitting a patient access scheme or commercial access agreement is outlined in [NICE's health technology evaluation guidance development manual](#) section 5.8.

3.9 Summary of base-case analysis inputs and assumptions

This section should be read with [NICE's health technology evaluation guidance development manual](#) section 4.10.1.

Summary of base-case analysis inputs

3.9.1 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.

3.9.2 For the base-case 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 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: confidence interval (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]			

Assumptions

3.9.3 Provide a list of all assumptions used in the economic model and justify each assumption, particularly any assumptions that do not align with the reference case.

3.10 Base-case results

This section should be read with [NICE's health technology evaluation guidance development manual](#) sections 4.6.4 and 4.10.6 to 4.10.7.

3.10.1 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, QALYs and incremental cost per QALY
- when appropriate, expected net health benefits, using values placed on a QALY gain of £20,000 and £30,000
- 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

3.10.2 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 or commercial arrangement with NHS England, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme or commercial arrangement.

Table [X] Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

In **appendix J** please provide the clinical outcomes and disaggregated results from the model. See the [user guide for company evidence submission appendices](#) for details.

3.11 Exploring uncertainty

This section should be read with [NICE's health technology evaluation guidance development manual](#) sections 4.6 and 4.7.

3.11.1 Present an overall assessment of uncertainty, including the relative effect of different types of uncertainty on cost-effectiveness estimates, and an assessment of whether the uncertainties that can be included in the analyses have been adequately captured. Highlight the presence of uncertainties that are unlikely to be reduced by further evidence or expert input.

Probabilistic sensitivity analysis

3.11.2 All inputs used in the analysis will be estimated with a degree of imprecision. As specified in NICE's health technology evaluation guidance development manual, 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.

3.11.3 Consider evidence about the extent of correlation between individual parameters and reflect this in the probabilistic analysis. When considering relationships between ordered parameters, consider approaches that neither artificially restrict distributions nor impose an

unsupported assumption of perfect correlation. Clearly present assumptions made about the correlations.

Provide the information specified below:

- 3.11.4 The distributions and their sources for each parameter should be clearly stated if different from those presented in [section 3.5](#), 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).
- 3.11.5 Present the incremental cost-effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals). Appropriate ways of presentation include confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves should include a representation and explanation of the cost-effectiveness acceptability frontier. Present results exploring uncertainty in a table, identifying parameters that have a substantial effect on the modelling results. As well as details of the expected mean results (costs, outcomes and ICERs), also present the probability that the treatment is cost effective if the ICER is £20,000 to £30,000 per QALY gained. Describe how the probabilistic ICER(s) were calculated and provide the rationale.
- 3.11.6 Describe and explain, if any, the variation between the incremental cost-effectiveness analysis results estimated from the base-case analysis ([section 3.10](#)) and the probabilistic sensitivity analysis.

Deterministic sensitivity analysis

- 3.11.7 If relevant, identify which variables were subject to deterministic sensitivity analysis, how they were varied, and the rationale behind this. Only report analyses when there is genuine uncertainty about a parameter, giving a rationale for why this is the case.
- 3.11.8 For example, there may be uncertainty about the extrapolation of outcomes or costs beyond the time horizon of a trial.

- Do not deviate from the reference case. For example, there should not be sensitivity analysis around the discount rate for costs and outcomes.
- Ensure that values are clinically plausible and not extreme. For example, do not present analyses assuming no treatment effect for comparators.

- 3.11.9 If relevant, present the results of deterministic sensitivity analysis, focusing on the key drivers of the model. Consider the use of tornado diagrams. Deterministic threshold analysis may be helpful if there are influential but highly uncertain parameters.
- 3.11.10 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 or commercial arrangement.

Scenario analysis

- 3.11.11 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.
- 3.11.12 Describe the methods and tabulate the incremental cost-effectiveness results of the scenario analyses done. Include details of structural sensitivity analysis.
- 3.11.13 Include the impact on the estimates of QALY shortfall when appropriate.

3.12 Subgroup analysis

This section should be read with [NICE's health technology evaluation guidance development manual](#) section 4.9.

When subgroups have been considered in the cost-effectiveness analysis, provide the information specified in sections 3.12.1 to 3.12.6.

- 3.12.1 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).

3.12.2 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 evaluation. 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 2.6](#).

3.12.3 Clearly define the characteristics of patients in the subgroup.

3.12.4 Describe how the statistical analysis was carried out.

3.12.5 If subgroup analyses were done, please present the results in tables similar to those used in [section 2.7](#).

3.12.6 Identify any obvious subgroups that were not considered and explain why. Please refer to the subgroups identified in the decision problem in [section 1](#).

3.13 Benefits not captured in the QALY calculation

3.13.1 If you consider that there are potential health benefits of the technology that have been inadequately captured and may therefore misrepresent the health utility gained, identify and present the data and provide a rationale for your decision.

3.14 Validation

Validation of cost-effectiveness analysis

3.14.1 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.

3.15 Interpretation and conclusions of economic evidence

3.15.1 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?

4 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, 'Trial ¹²³/Jones et al. ¹²⁶' rather than 'One trial¹²⁶').

Please also provide references as a separate RIS file.

5 Appendices

Clinical trial reports and protocols must be made available for relevant clinical studies; the remainder must be available on request. The information that NICE requests in appendices is needed by the EAG to fully critique the submission. The appendices are not normally provided to the evaluation committee or published on the NICE website; please send these as separate documents to the main submission.

Appendices should start at C, because document A is the submission summary and document B is the main submission.

All information that should be provided in an appendix is outlined in the [user guide for company evidence submission appendices](#)

Appendix C: Summary of product characteristics or information for use, UK public assessment report, scientific discussion or drafts

Appendix D: Identification, selection and synthesis of clinical evidence (see [sections 2.1, 2.4, 2.5 and 2.9](#))

Appendix E: Subgroup analysis (see [section 2.7](#))

Appendix F: Adverse reactions (see [section 2.10](#))

Appendix G: Published cost-effectiveness studies (see [section 3.1](#))

Appendix H: Health-related quality-of-life studies (see [section 3.4.3](#))

Appendix I: Cost and healthcare resource identification, measurement and valuation (see [section 3.5](#))

Appendix J: Clinical outcomes and disaggregated results from the model (see [sections 3.7.1–3.7.2](#))

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Any additional appendices should start at appendix M.

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