NICE National Institute for Health and Care Excellence

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

NICE process and methods
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Contents

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 single technology appraisal company evidence submission template. Companies making evidence submissions to NICE should also refer to the NICE health technology evaluations 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 standalone 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 evaluations 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 has 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 this 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 section 5.

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. Include details of any subsequent treatments that are used in current clinical practice and how these are expected to change if the new technology was to be introduced. 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 action plan.

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 section 3 of NICE's health technology evaluations manual.

For further information on how to implement the approaches described in the NICE methods guide, see the following 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 B.

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. See the following suggested table format for each source of evidence. 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 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. See the following suggested table format.

Table [X] Comparative summary of trial methodology

Trial number	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)			
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. Include separate tables for the full trial population

and if different, the population included in the decision problem and any subgroups. 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. See the following suggested table format.

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]
Trial 1 (n=[x])	(n=[x])	(n=[x])	(n=[x])
Age			
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 evaluations 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 at the end of this section.

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 B for details of additional information that should be provided.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

In appendix B, please provide the complete quality assessment for each trial.

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 dropouts 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 several 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 as follows.

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 dropouts 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)	

Trial number (acronym)	Trial 1	Trial 2	[Add more columns as needed]
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	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

studies

2.6.1 Present results for all outcomes that inform the economic model or are specified in the scope from the studies 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. If the decision problem is for a narrower population than in the trial, the same information should also be presented for the population in the decision problem as well as any subgroups.

2.6.2 If you are presenting pooled results for multiple parallel trials, also present the results for each individual trial.

2.6.3 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

2.6.4 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 Subsequent treatments used in the relevant studies

2.7.1 Present information on the subsequent treatments received in the trials identified as relevant to your submission. This should include the number and percentage of people receiving each treatment by arm and by line of treatment if multiple subsequent lines of treatment are applicable. Indicate where subsequent treatments are used in combination when reporting this data. A suggested table for reporting this data is provided at the end of this section.

2.7.2 Include information on both drug and non-drug subsequent treatments (for example, stem cell transplants, surgery and radiotherapy).

2.7.3 Provide details of the subsequent treatment data collected in the trial protocol, such as how many lines of treatment were considered and whether subsequent treatment data was collected by individual drug or by class.

2.7.4 Report the mean time spent on each subsequent treatment including a measure of uncertainty such as the 95% confidence interval. Report time to next treatment and PFS2 data where these have been collected with associated Kaplan–Meier plots.

Table [X] Summary of the subsequent lines of treatment used in [trial A]

	Arm A (N=): N (%) treated (N=)	Mean time on treatment (95% CI) (N=) in Arm A	Arm B (N=): N (%) treated (N=)	Mean time on treatment (95% CI) (N=) in Arm B
2L subsequent treatment 1				
2L subsequent treatment 2				
2L subsequent treatment 3				

	Arm A (N=): N (%) treated (N=)	Mean time on treatment (95% CI) (N=) in Arm A	Arm B (N=): N (%) treated (N=)	Mean time on treatment (95% CI) (N=) in Arm B
[Add more rows as needed]				
3L subsequent treatment 4				
3L subsequent treatment 5				
3L subsequent treatment 6				
[Add more rows as needed]				

2.8 Subgroup analysis

This section should be read with NICE's health technology evaluations manual section 4.9.

2.8.1 Provide details of any subgroup analyses carried out. Specify the rationale and whether they were pre-planned or post-hoc.

2.8.2 Clearly specify the characteristics of the participants in the subgroups and explain the appropriateness of the analysis to the decision problem.

2.8.3 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 C.

2.9 Meta-analysis

This section should be read with the NICE's health technology evaluations 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.

2.9.1 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.

2.9.2 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).

2.9.3 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.

2.10 Indirect and mixed treatment comparisons

2.10.1 In a table provide a summary of the trials used to carry out the indirect comparison or mixed treatment comparison. The following is a suggested table format. 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

References of trial	Intervention A	Intervention B	Intervention C	Intervention D
Trial 2		Yes	Yes	Yes
Trial 3	Yes	Yes		
Trial 4	Yes		Yes	
[Add more rows as needed]				

2.10.2 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 B.

2.10.3 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.

2.10.4 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.

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

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

2.11 Adverse reactions

2.11.1 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.

2.11.2 In a table, summarise the adverse reactions reported in the studies identified in

section 2.2, as relevant to your submission, including those for the full trial population and the population in the decision problem, if different. 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 D, provide details of any studies that report additional adverse reactions to those reported by the studies identified in section 2.2.

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

2.12 Ongoing studies

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

2.13 Interpretation of clinical effectiveness and safety evidence

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

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

2.13.2 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 evaluations manual.

3.1 Published cost-effectiveness studies

In appendix E, provide details of the identified studies.

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

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

3.2 Economic analysis

Summarise how the cost-effectiveness studies identified in appendix E 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 after 3.2.4 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 evaluations manual,

section 4.2, table 4.1).

Table [X] Features of the economic analysis

Factor	Previous evaluation, TAXXX	Previous evaluation, TAXXX	Current evaluation, chosen values	Current evaluation, 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 evaluations 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).

3.3.5 Details to report in this section include:

- subsequent treatments included in the model and a discussion of, and rationale for, any differences from the subsequent treatments' data in the trial(s)
- drug exposure data used in the model and the source of this data
- treatment discontinuation data used in the model and a rationale if different from the data in the trial(s).

3.4 Measurement and valuation of health effects

This section should be read with the NICE's health technology evaluations 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). Also consider the NICE Decision Support Unit report on methods for mapping between the EQ-5D-5L and the 3L for technology appraisal, where relevant.
- 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 evaluations 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 F, describe how systematic searches for relevant health-related quality-of-life data were done.

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

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 evaluated. 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 is provided after section 3.5.6. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 3.1. Analyses should be based on prices that reflect as closely as possible those paid in the NHS, including any known price reductions available across the NHS. Please include the price from the electronic market information tool (eMIT) if available for the treatment. eMIT prices should reflect the current version of eMIT, within 2 months of the company submission.

3.5.5 State where the medicine is likely to be commissioned and prescribed (for example, in primary care, by integrated care boards or in secondary care).

3.5.6 Drug wastage should be taken into account in calculating drug costs. For oral treatments dispensed in tablet packs, NICE will evaluate oral treatments costed on a per pack basis, unless clinical experts or other evidence suggests that prescribing and dispensing is done such that there would be no wastage.

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

3.5.7 Summarise and tabulate the costs included in each health state. See the

following suggested format for a table. 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		
Health state 1	Staff		
Health state 1	Hospital costs		
Health state 1	[Add more rows as needed]		
Health state 1	Total		
Health state 2			
[Add more rows as needed]			

Adverse reaction unit costs and resource use

3.5.8 Summarise and tabulate the costs for each adverse reaction listed in section 2.10 and included in the cost-effectiveness analysis. See the following suggested format for a table. 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		
Adverse reaction 1	Staff		
Adverse reaction 1	Hospital costs		
Adverse reaction 1	[Add more rows as needed]		
Adverse reaction 1	Total		
Adverse reaction 2	Technology		

Adverse reactions	Items	Value	Reference in submission
Adverse reaction 2	Staff		
[Add more rows as needed]			

Miscellaneous unit costs and resource use

3.5.9 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 evaluations 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 after 3.6.2 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.

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]

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
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	
[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 evaluations 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 who 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. See the following suggested table format.

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

Clinical uncertainty	Outcome data	Data source
[Add 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. The following is a suggested format for clinical trial data sources and data collected through the Systemic Anti-Cancer Therapy (SACT) dataset.

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 evaluations manual, section 5.8.

3.9 Summary of base-case analysis inputs and assumptions

This section should be read with NICE's health technology evaluations 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 after 3.9.2, which 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 evaluations 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 following table, 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 H, please provide the clinical outcomes and disaggregated results from the model.

3.11 Exploring uncertainty

This section should be read with NICE's health technology evaluations 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 evaluations 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 following information:

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 evaluations 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 trial[126]').

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.

> All information that should be provided in appendices A to I is outlined in the following sections. Any additional appendices should start at appendix J.

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

1.1 SmPC

Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in appendix A.

1.2 UK public assessment report

Provide the (draft) UK public assessment report for pharmaceuticals, or a (draft) technical manual for devices in appendix A.

Appendix B: Identification, selection and synthesis of clinical evidence

1.1 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.

To identify and select relevant studies, it is expected that a systematic literature search will be carried out in line with NICE's health technology evaluations manual, sections 3.4.2, 3.4.4 and 3.4.5.

In exceptional circumstances 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.

Advise whether a search strategy was developed to identify relevant studies. 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 (University of York Centre for Reviews and Dissemination).

Search strategy

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.

Study selection

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 to make a connected network for a mixed treatment comparison.

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. See the following suggested table format.

Table [X] Eligibility criteria used in the search strategy

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

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. The total number of studies in the statement should equal the total number of studies listed in section 2.1.

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.

- Provide a complete reference list of included studies.
- Provide a complete reference list of excluded studies.

For indirect and mixed treatment comparisons

Summary of trials included in indirect or mixed treatment comparisons

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 at the end of this section. When there are more than 2 treatments in the comparator sets for synthesis,

include a network diagram.

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.

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

	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]				

Methods and outcomes of studies included in indirect or mixed treatment comparisons

Provide the rationale for the choice of outcome measure chosen, along with the rationale for the choice of outcome scale selected.

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.

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.

For each trial included, provide table(s) of the:

- methods

- outcomes and results
- participants' baseline characteristics.

Methods of analysis of studies included in indirect or mixed treatment comparisons

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).

For analyses of overall survival, provide and discuss the subsequent treatment data for each trial and how this informed the feasibility assessment for the indirect or mixed treatment comparison.

Refer to NICE's health technology evaluations manual, sections 3.4.11 to 3.4.21.

For studies which will be detailed in section 2.4 of the main submission (that is, studies assessing the intervention technology), cross reference the submission rather than repeating the information in appendix B.

Supply any programming language used (for example, the WinBUGS code).

Risk of bias of studies included in indirect or mixed treatment comparisons

- Provide a complete quality assessment of each trial.
- Identify any risk of bias within the trials identified, and describe any adjustments made to the analysis.

1.2 Participant flow in the relevant randomised controlled trials

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 showing the flow of

participants through each stage of each of the trials.

> See section 2.4 for full details of the information required here.

1.3 Critical appraisal for each study

> See section 2.5 for more details of what should be included here.

For studies that will be detailed in section 2.5 of the submission (that is, studies assessing the intervention technology), cross reference the submission rather than repeating the information in appendix B.

Appendix C: Subgroup analysis

Provide a summary of the results for the subgroups in appendix C.

See section 2.8 for full details of the information required here.

Appendix D: Adverse reactions

In appendix D, provide details of any studies that report additional adverse reactions to those reported by the studies identified in section 2.2. Include the following:

- Details of the methodology used for the identification, selection and quality assessment of the studies.
- 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 (University of York Centre for Reviews and Dissemination). Exact details of the search strategy used and a complete quality assessment for each trial should also be provided in appendix D.
  - Details of the methodology of the studies.
  - 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 adverse reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

See section 2.11 for full details of the information required here.

Appendix E: Published cost-effectiveness studies

Please provide the following information in appendix E.

Identification of studies

Describe the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England from published NICE technology evaluations, 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.

Description of identified studies

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.

Critical appraisal of the identified studies

Provide a complete quality assessment for each relevant cost-effectiveness study identified. Use an appropriate and validated instrument, such as Drummond and Jefferson, guidelines for authors and peer reviewers of economic submissions to the BMJ (1996) or quality assessment in decision-analytic models: a suggested checklist (appendix 3) in Philips et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment (2004).

This section should be read with NICE's health technology evaluations manual, section 3.3.26 to 3.3.27.

See section 3.1 for full details of the information required here.

Appendix F: Health-related quality-of-life studies

Describe how systematic searches for relevant health-related quality-of-life 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 the appendix.

Tabulate the details of the studies in which health-related quality of life 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.

See section 3.4.3.

Appendix G: Cost and healthcare resource identification, measurement and valuation

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 also be provided in the appendix. 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.

See section 3.5.

Appendix H: Clinical outcomes and disaggregated results from the model

1.1 Clinical outcomes from the model

For the outcomes highlighted in the decision problem (see section 1), 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 following table. 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	C_1	R_1
Post-progression survival	C_2	R_2
Overall survival	C_{1+2}	R_{1+2}
Adverse reaction 1	C_3	R_3
[Add more rows as needed]		

Provide (if appropriate) a graphical representation of how QALYs accrue over time in the economic model (for example, Markov trace, active partitioned survival curves or equivalent). Supply 1 for each comparator, showing the proportion of time spent in each health state over the full time horizon. Other time horizons may also be appropriate.

1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

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

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 following are 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).

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]	[X_{HS1}]	[Y_{HS1}]	[$X_{HS1} - Y_{HS1}$]	[$\lvert X_{HS1} - Y_{HS1} \rvert$]	[$\lvert X_{HS1} - Y_{HS1} \rvert$/(Total absolute increment)]
[Health state 2]	[X_{HS2}]	[Y_{HS2}]	[$X_{HS2} - Y_{HS2}$]	[$\lvert X_{HS2} - Y_{HS2} \rvert$]	[$\lvert X_{HS2} - Y_{HS2} \rvert$/(Total absolute increment)]
[Add more rows as needed]					
Total	[X_{Total}]	[Y_{Total}]	[$X_{Total} - Y_{Total}$]	Total absolute increment	100%

Abbreviations: HS1, health state 1; HS2, health state 2; QALY, quality-adjusted life year. 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 ($_{HS1}$)]	[X_{HS1}]	[Y_{HS1}]	[$X_{HS1} – Y_{HS1}$]	[$\|X_{HS1} – Y_{HS1}\|$]	[$\|X_{HS1} – Y_{HS1}\|$ / (Total absolute increment)]
[Health state 2]	[X_{HS2}]	[Y_{HS2}]	[$X_{HS2} – Y_{HS2}$]	[$\|X_{HS2} – Y_{HS2}\|$]	[$\|X_{HS2} – Y_{HS2}\|$ / (Total absolute increment)]
[Add more rows as needed]					
Total	[X_{Total}]	[Y_{Total}]	[$X_{Total} – Y_{Total}$]	Total absolute increment	100%

Abbreviations: 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]	[X_{tech}]	[Y_{tech}]	[$X_{tech} – Y_{tech}$]	[$\|X_{tech} – Y_{tech}\|$]	[$\|X_{tech} – Y_{tech}\|$ / (Total absolute increment)]
[Mean total treatment cost]	[X_{treat}]	[Y_{treat}]	[$X_{treat} – Y_{treat}$]	[$\|X_{treat} – Y_{treat}\|$]	[$\|X_{treat} – Y_{treat}\|$ / (Total absolute increment)]
[Administration cost]	[X_{admin}]	[Y_{admin}]	[$X_{admin} – Y_{admin}$]	[$\|X_{admin} – Y_{admin}\|$]	[$\|X_{admin} – Y_{admin}\|$ / (Total absolute increment)]
[Monitoring cost]	[X_{mon}]	[Y_{mon}]	[$X_{mon} – Y_{mon}$]	[$\|X_{mon} – Y_{mon}\|$]	[$\|X_{mon} – Y_{mon}\|$ / (Total absolute increment)]
[Tests]	[X_{tests}]	[Y_{tests}]	[$X_{tests} – Y_{tests}$]	[$\|X_{tests} – Y_{tests}\|$]	[$\|X_{tests} – Y_{tests}\|$ / (Total absolute increment)]

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
[Add more rows as needed]					
Total	[X_{Total}]	[Y_{Total}]	[$X_{Total} – Y_{Total}$]	Total absolute increment	100%

Abbreviations: admin, administration; mon, monitoring; tech, technology; treat, treatment.

See sections 3.10.1 to 3.10.2.

Appendix I: Price details of treatments included in the submission

Provide the relevant details for each treatment, including the intervention, comparator and subsequent treatments used in the model, including concomitant treatments. Please give the following details of each formulation used in the modelling:

- the name of the technology
- the mode of administration
- dose per unit
- pack size
- list price (and the source of the list price)
- electronic market information tool (eMIT) price, if applicable
- patient access scheme price, if applicable.

Provide prices that reflect as closely as possible those paid in the NHS, including price reductions when it is known that a price reduction is available across the NHS, such as eMIT prices, when available.

Update information

December 2024: A company submission summary (previously Document A) is no longer required when submitting to NICE for a medicines evaluation, so we updated the user guide to reflect this. We also clarified and added detail on the types of evidence required in different sections of the company evidence submission.

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