



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

Implementation support

Published: 8 January 2015

Last updated: 10 February 2022

www.nice.org.uk

Contents

Instructions for companies	3
Appendices	4
Appendix C: Summary of product characteristics (SmPC) or information for use (IFU) and UK public assessment report, scientific discussion or drafts	6
C1.1 SmPC	6
C1.2 UK public assessment report	6
Appendix D: Identification, selection and synthesis of clinical evidence	7
D1.1 Identification and selection of relevant studies.....	7
D1.2 Participant flow in the relevant randomised control trials	10
D1.3 Quality assessment for each trial.....	11
Appendix E: Subgroup analysis.....	12
Appendix F: Adverse reactions	13
Appendix G: Published cost-effectiveness studies	14
Appendix H: Health-related quality-of-life studies	16
Appendix I: Cost and healthcare resource identification, measurement and valuation	17
Appendix J: Clinical outcomes and disaggregated results from the model	18
J1.1 Clinical outcomes from the model	18
J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis.....	18
Appendix K: Price details of treatments included in the submission	22
Appendix L: Checklist of confidential information	23

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.

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.

Info boxes highlight areas where further detail is also outlined in the [main submission user guide](#), or [NICE's health technology evaluation guidance development manual](#)

Appendix C: Summary of product characteristics (SmPC) or information for use (IFU) and UK public assessment report, scientific discussion or drafts

C1.1 SmPC

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

C1.2 UK public assessment report

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

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 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.

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 evaluation guidance development 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. A suggested table format is provided below.

Table [X] Eligibility criteria used in the search strategy

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

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 below. 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.

Provide the following for each trial included:

- table(s) of the methods
- table(s) of the outcomes and the results
- table(s) of the 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).

Refer to [NICE's health technology evaluation guidance development 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 D**.

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.

D1.2 Participant flow in the relevant randomised control 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 of the main submission user guide for company evidence submission](#) for full details of the information required here.

D1.3 Quality assessment for each trial

See [section 2.5 of the main user guide for company evidence submission](#) for more details of what should be included here.

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

Appendix E: Subgroup analysis

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

See [section 2.7 of the main user guide for company evidence submission](#) for full details of the information required here.

Appendix F: Adverse reactions

In appendix F, 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 F.
 - 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 2.10 of the main user guide for company evidence submission](#) for full details of the information required here.

Appendix G: Published cost-effectiveness studies

Please provide the following information in appendix G:

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 as suggested below.

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 evaluation guidance development manual](#) section 3.3.26 to 3.3.27.

See [section 3.1 of the main user guide for company evidence submission](#) for full details of the information required here.

Appendix H: 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.

Appendix I: 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.

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 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 table below. Discuss reasons for any differences between the modelled results in the cost-effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover).

Table [X] Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Progression-free survival	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.

J1.2 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 tables that should be completed summarising the disaggregated results (for example, QALY gain by health state, costs by health state, predicted resource use by category of cost) are presented below.

Table [X] Summary of QALY gain by health state

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
[Health state 1]	[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: QALY, quality-adjusted life year; HS1, health state 1; HS2, health state 2. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table [X] Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
[Health state 1 (HS1)]	[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)]

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
[Administration cost]	$[X_{\text{admin}}]$	$[Y_{\text{admin}}]$	$[X_{\text{admin}} - Y_{\text{admin}}]$	$[X_{\text{admin}} - Y_{\text{admin}}]$	$[X_{\text{admin}} - Y_{\text{admin}} / (\text{Total absolute increment})]$
[Monitoring cost]	$[X_{\text{mon}}]$	$[Y_{\text{mon}}]$	$[X_{\text{mon}} - Y_{\text{mon}}]$	$[X_{\text{mon}} - Y_{\text{mon}}]$	$[X_{\text{mon}} - Y_{\text{mon}} / (\text{Total absolute increment})]$
[Tests]	$[X_{\text{tests}}]$	$[Y_{\text{tests}}]$	$[X_{\text{tests}} - Y_{\text{tests}}]$	$[X_{\text{tests}} - Y_{\text{tests}}]$	$[X_{\text{tests}} - Y_{\text{tests}} / (\text{Total absolute increment})]$
[Add more rows as needed]					
Total	$[X_{\text{Total}}]$	$[Y_{\text{Total}}]$	$[X_{\text{Total}} - Y_{\text{Total}}]$	Total absolute increment	100%

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

Appendix K: 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)
- patient access scheme price, if applicable.

Appendix L: Checklist of confidential information

ISBN: 978-1-4731-0933-9