NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

User guide for evidence submission template

July 2022

Contents

What is the user guide for?

This user guide is intended to help you complete the submission of evidence to inform the development of NICE medical technologies guidance.

See NICE's health technology evaluations manual for further information on the methods and processes that NICE follows when carrying out health technology evaluations.

General advice for completing the evidence submission

The evidence submission is your opportunity to collate, analyse and present all relevant evidence for the technology and the benefits it can offer to patients and the NHS. See section 3.3 of NICE's health technology evaluation manual for further information on the types of evidence that NICE considers.

The submission should be as concise and informative as possible. Try to avoid repeating information. You may copy and paste information directly from NICE documents (for example, the scope or relevant medtech innovation briefing) but do not copy from any external sources (for example, published papers). This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

The submission should be sent to NICE electronically in Microsoft Word or a compatible format, and not as PDF files.

Clinical-effectiveness evidence

Clinical-effectiveness evidence should be described in section 2 of the submission and used to inform the de novo economic decision modelling in section 4. This is your opportunity to critique the available evidence. A systematic review of the relevant evidence relating to a technology should be done using a pre-defined protocol. This protocol should allow evidence to be included from all sources likely to inform the decision about using the technologies by the NHS. A systematic review attempts to assemble all the available relevant evidence using explicit, valid and replicable methods in a way that minimises the risk of biased selection of studies.

When completing the template, also refer to section 3 of NICE's health technology evaluation guidance development manual.

The types of evidence may include:

- Peer-reviewed published journal articles – Although high-quality randomised controlled trials are preferred for relative treatment effects (see section 3.3.2 and sections 3.3.5 to 3.3.8 of NICE's health technology evaluation manual) we will consider any study methodology, including non-randomised evidence (see sections 3.3.9 to 3.3.15 of NICE's manual and the NICE RWE framework).
- Meta-analyses – Although evidence synthesis and meta-analyses are not mandatory for a submission to be accepted, they are strongly encouraged if data is available to support such an

approach. For more information on meta-analyses, see below, and chapter 40 of Introduction to Meta-Analysis, 'When does it make sense to perform a meta-analysis?'.

- Unpublished studies – These should be submitted as manuscripts or structured abstracts (see also Confidential information).
- Registry or other real-word data sources – These will also be considered; provide data analysis when appropriate.
- Expert elicitation – In the absence of empirical evidence from randomised clinical trials, non-randomised studies, or registries, or when considered appropriate by the committee, considering all other available evidence, expert elicitation (see sections 3.3.21 and 3.3.23, section 4.6.28 and section 4.7.10 of NICE's health technology evaluation model) can be used to provide evidence. Expert elicitation may use either structured or unstructured methods. Structured methods are preferred, to minimise biases and provide some indication of the uncertainty. Expert elicitation may be used to agree on plausible parameter ranges and scenarios for economic modelling, and to define which uncertainties are unresolvable. Expert elicitation methods are expected to be particularly important when economic results are sensitive to a particular parameter and the range of potential values is indeterminate.
- Expert opinion – The submission may also include advice from clinicians or patients (both quantitative and qualitative). This can be in the form of validation, surveys or statements and is different to the methods applied for expert elicitation. Note that any experts who receive renumeration or other incentives during their involvement in the company submission may not be eligible to act as expert advisers to NICE because of a potential conflict of interest.

If possible, provide PDF copies of full journal articles or reports in the submission (in electronic format). Only submit copies of full papers if you own the copyright, or if you have adequate copyright clearance to permit the intended use by NICE (that is, making further copies and storing the article electronically for a limited period to be accessed by a limited number of staff). If you do not have copyright clearance, then you can submit links as part of the list of references in the submission, or contact details for unpublished studies.

All studies and data included in the submission must be referenced. Use the NICE referencing style and include a list of references at the end of each part of the submission.

Submitting economic decision models

An executable version of the decision model (with full access to the programming code) should be included with the submission. Ensure that the decision model is consistent with the written content of the submission. If the economic model contains confidential values, these should be clearly

labelled as such within the model itself. If possible, a redacted version of the model should also be supplied with the submission. Note that NICE may distribute the executable version of the cost model to a stakeholder if they request it during technical engagement or consultation (see section 5.5.17 of NICE's manual). If a request is received, we will release the model as long as any confidential data can be redacted without limiting its functionality.

Acceptable software options for model submissions are Excel, R, Data/Treeage, or WinBUGs. If using an alternative software, NICE, with the external assessment group (EAG), will investigate if the requested software is acceptable. NICE reserves the right to reject models in non-standard software format.

Equality issues and considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others and society as a whole, and to complying with its legal obligations on equality and human rights. For further information about equality issues see NICE's equality scheme.

An equality issue may arise if using the technology:

- could exclude any people protected by the equality legislation who fall within the patient population for the technology
- 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 disabled people.

An equality consideration may be appropriate if using the technology would benefit a specific group with protected characteristics without causing any disadvantages to any other groups.

Adapting tables and figures

The evidence submission contains suggestions for tables and figures to present information on your technology. These have been designed based on our experiences of evaluating medical technologies and what is considered best practice from an editorial perspective. Each evaluation is unique, however, so there may be instances when you need to adapt tables and figures within the submission to suit your technology and to ensure all relevant information is reported.

For a submission to be accepted all sections of the submission template need to be completed where possible. If some of the requested information is not relevant to your technology then

provide the reasons in your submission. For example, if there are no relevant published economic evidence for the technology, this should be clearly stated as justification for why it was not possible to complete section 3.

Confidential information

To ensure that the assessment process is as transparent as possible, NICE strongly prefers any evidence used in making decisions to be publicly available (see section 5.4 of NICE's manual; information handling – confidential information).

Commercial in confidence (CIC) information would include for example, the findings of a research project considered confidential because public disclosure could have a significant impact on the commercial interests of a particular company.

Academic-in-confidence (AIC) information refers to data where public disclosure would seriously jeopardise the ability of the data owner to publish the information in a scientific paper. NB: In May 2022 the International Consortium of Medical Journal Editors, representing the bulk of medical journals, has updated its recommendations to include the following statement:

The ICMJE does not consider results or data contained in assessment reports published by health technology assessment agencies, medical regulators, medical device regulators, or other regulatory agencies to be duplicate publication.

Companies should be mindful of the above and we envisage it will enable full disclosure of clinical data relied without threatening the subsequent full publication of the data in an ICMJE journal. This position also enables pressure to be put on medical journals which are not within the ICMJE to explain why a different position might be taken. [1]

Depersonalised data (DPD) refers to data that is stripped of direct identifiers but contains data which could be used to indirectly identify an individual through combinations of information. This may be applicable to real world data reports, for example, registry reports containing data on very small patient numbers (e.g. <6 individuals).

Any 'commercial in confidence' (CiC) information in the submission document should be underlined and highlighted in turquoise.

Any 'academic in confidence' (AiC) information in the submission document should be underlined and highlighted in yellow.

[1] Note this change in policy, where we now expect less (or even no) AiC going forward. We are expecting NICE to write a formal position statement on this soon

Any 'depersonalised data' in the submission document should be underlined and highlighted in pink.

You may be asked to reconsider restrictions on the release of data if the data does not seem to fit into 1 of these 2 categories, or if such restrictions would make it difficult for NICE to show the evidential basis for its guidance.

It is your responsibility to highlight any commercial- or academic-in-confidence data clearly and correctly:

- information that is commercial in confidence should be underlined and highlighted in blue
- information that is academic in confidence should be underlined and highlighted in yellow.
- Information that is depersonalised data should be underlined and highlighted in pink.

You must also complete the confidential information checklists in both parts of the submission (see appendix G).

Any confidential information submitted will be shared (in confidence) with the medical technologies advisory committee, EAG and expert advisers. Information marked as academic in confidence may be presented and discussed during public meetings (part 1). Commercial in confidence or depersonalised data can be presented and discussed during the closed part of the meeting (part 2).

Please also save file names by adding the following to the end of the file name:

- [AIC] = document contains academic in confidence information
- [CIC] = document commercial in confidence information
- [ACIC] = document contains both academic and commercial in confidence information
- [DPD] = document contains depersonalised data
- [AICDPD] or [CICDPD] or [ACICDPD] (use 1) = document contains academic and/or commercial in confidence information and contains depersonalised data.
- [noACIC] = document contains no confidential information
- [redacted] = document originally contained confidential information, which has all been replaced (the NICE team will redact the marked information)

Confidential data in the decision model

It is strongly recommended that companies are transparent in the base case of its decision model i.e. using publicly available evidence/prices/sources. Strong justification will be needed for using confidential values, and these should be clearly labelled as such within the model itself. In this situation, a redacted version of the model should also be supplied with the submission. Note that NICE may distribute the executable version of the decision model to a stakeholder if they request it during technical engagement or consultation (see section 5.5.17 of NICE's manual). If a request is received, we will release the decision model, so any confidential data will need to be redacted without limiting its functionality where possible.

NICE adheres to the principles and requirements of data protection legislation, including the General Data Protection Regulation and the Freedom of Information Act, when dealing with information received during an evaluation (see section 5.3.1 of NICE's manual).

Take care when submitting information about individual people. When possible, personal and sensitive information should be removed from submissions, unless critical to the submission. If this information is critical to the submission, it should be highlighted as confidential..

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people right of access to that information. This obligation extends to submissions made to NICE. Information that is marked as commercial in confidence may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed commercial in confidence before making any decision on disclosure.

All evidence submissions and other information supplied as part of the evaluation process will be published on the NICE website and must therefore meet legislation to ensure content is accessible to everyone including users with impairments to vision, hearing, mobility, thinking and understanding. NICE requires stakeholders to ensure their submissions meet formal accessibility standards.

Section-by-section guide

1.1 Decision problem, the technology and clinical context

Decision problem

The decision problem outlines the main factors that the evaluation will consider (such as population, intervention, comparator and outcomes). The decision problem is finalised by NICE and published in the scope.

To complete the table, copy and paste the information from the scope into the first blank column. Use the other columns to describe and explain any variations from the scope issued by NICE. It is recommended to discuss any significant deviations from the scope with the NICE technical team in advance to ensure that the remit of the decision problem remains appropriate, and changes are reasonable and justified. Any changes to the published scope will need to be appropriately explained, providing relevant references when needed (use the last column to provide this information).

The technology

The information in this section should relate to the technology and its use, as set out in the decision problem.

Provide details of the brand name, approved name (if different) and details of the UKCA/CE-mark class and date of authorisation for all components of the technology. In addition, details of the wording or indications and restriction(s) as described in the labelling or instructions for use should be provided.

Provide details of any previous versions of the technology, including when the version was in use, differences between the versions and details of any evidence demonstrating equivalence. The instructions for use for each version of the technology should also be provided with the submission documents.

Describe the key claimed benefits for using the technology as described in the scope. Ensure claims made are relevant, plausible, and have an evidence base. These may include patient benefits (such as reduced pain), carer benefits (such as less frequent dressing changes), system benefits (such as reduced need for testing), and sustainability benefits (such as reduced disposable consumables). These benefits can be copied directly from the scope document. As part of your submission, you will have to support the claimed benefits with evidence, including providing appropriate references. When you do not have evidence to support a claimed benefit,

you should provide further information in the rationale column to explain the reasons for including it.

Briefly describe how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology. Refer to any relevant evidence.

Briefly describe the environmental impact of the technology (positive or negative) and any sustainability considerations for adopting the technology across the NHS.

Briefly provide an assessment of whether the use of this technology is likely to raise any equality issues. These may be copied directly from the scope document.

Further information can be added to the appendix, if needed.

Clinical context

In this section, provide a diagram (or other suitable description) of the clinical pathway that includes the technology. Ensure the clinical pathway is informed by any relevant NICE guidance. If relevant NICE guidance is not available, then reference other relevant national and/or international guidelines that guide clinical decision making in the UK. If clinical expert input has been used to inform your description of the clinical pathway, make this explicit in your submission.

Describe any training needed to use the technology, for both patients and NHS staff. Include how the training will be delivered, how long it takes and whether training will need to be updated regularly. Include details of any service changes that will be needed to adopt the technology (for example, differences in treatment for patient subgroups, additional tests for patient selection or monitoring and details of any additional systems or infrastructure needed to use the new technology).

1.2 Clinical-effectiveness evidence

Identification and selection of studies

Provide brief results of the systematic search in the table provided in section 2.1. A full description of the search methods used should be included in appendix A. The detail should allow the EAG to re-create the searches. In the inclusion criteria, list criteria such as age groups, study designs, etc., to be included, and in the exclusion criteria, list any study designs, date limits, etc., to be excluded. This section should also include a flow chart (e.g. using PRISMA Flow Diagram) of the results, and please state the number of reviewers used to screen studies (e.g. two independent reviewers screen all studies, resolving areas of disagreement by consensus).

List of relevant studies

In this section, list all relevant studies identified through the systematic search in table 1, see section 3.3.4 of the manual for more information on systematic reviews. This should include only studies relevant to the decision problem from the scope. Provide details related to the studies methods (for example, study design) and outcomes in the tables provided.

For any unpublished studies, provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data. The information required includes the study title and authors, introduction, objectives, methods, results, conclusion, status and expected publication date.

Critical appraisal of relevant clinical-effectiveness studies

The quality of each study identified as relevant to your submission in section 2.2 should be appraised. Provide the complete quality assessment for each study in appendix B.

The studies should be appraised using validated tools specific to the study design and use case. Appendix B contains suggested tools for:

- randomised controlled trials (adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care; University of York Centre for Reviews and Dissemination)
- non-randomised and non-controlled studies (adapted from Critical Appraisal Skills Programme [CASP]). ROBIS-A or another relevant tool is recommended for quality assurance of systematic reviews and meta-analyses. Other validated tools can be used if these are considered appropriate for the study design.

ROBIS A or another relevant tool is recommended for quality assurance of systematic reviews and meta-analyses. This should be done for all SRs and meta-analyses, even if company does a de novo review/analysis.

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 external assessment group (EAG).

Table 2 should be used to critically appraise the methodological quality of the included clinical and economic studies, respectively. The prompts are designed to help you explain the relevance of the included studies to the decision problem. You can add additional columns and questions if there is any particularly relevant information that might be missed.

Results from the clinical evidence base

In this section provide a summary of results from the evidence base. Use the table provided (Table 3), adapting if needed, to present the key results from each of the included studies from section 2.2 of your submission. Note when data is 'not reported'.

Comment if any of the key outcomes are a surrogate endpoint; see the NICE health technology evaluations: the manual (see sections 4.6.6 to 4.6.10) – discuss what level of evidence (1-3) supports the surrogate relationship for decision making, and comment whether the surrogate endpoint is considered validated. This is particularly important for clinical parameters that are used to inform the decision model.

Adverse events

Provide details of any adverse events associated with the technology that are logged in regulatory databases, such as those maintained by Medicines and Healthcare products Regulatory Authority (MHRA) and the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE). If appropriate, do a systematic review and provide details in appendix C. If necessary, add tables to describe and appraise the evidence for adverse events. Highlight any planned or ongoing studies that are related to regulatory requirements to collect long-term data on safety, for example post-market surveillance studies.

Evidence synthesis and meta-analysis

In this section, you can report any evidence synthesis done, such as meta-analyses. This may be a de novo analysis done for the purpose of the submission or details of a relevant recently published analysis. Chapter 9 of the Cochrane handbook for systematic reviews of interventions provides guidance on evidence synthesis. If there is not enough information available for a meta-analysis or quantitative evidence synthesis, provide a qualitative review. However if there is any uncertainty about whether a meta-analysis is possible, we recommend carrying it out and acknowledge the limitations.

Reporting methods

Ensure the methods includes a description of the processes used to decide which studies were eligible for the synthesis. Describe the model, and the method to identify the presence and extent of statistical heterogeneity. Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). Provide details of the software package used. As part of the independent assessment of your submission by an EAG, you may be asked to provide an executable format of the software file that you used for the meta-analysis.

Describe the methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. The EAG

should be able to reproduce the analysis, so the methods need to provide complete clarity for what was done. Sometimes it is not clear where the numbers in a meta-analysis have come from, particularly where companies use specialised software (such as STATA) to produce the analysis. Sometimes, there is a need to do calculations around the event numbers from individual papers (for example if the paper reports how many people survived but the meta-analysis event is how many people died). In these situations, it can be more difficult for the EAG to understand if the company has worked the numbers out correctly. It therefore needs to be clear for example that published figures were converted with clear details of calculations. There is further example text in Table 4 showing the typical details needed. Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.

Reporting results

Report all relevant results, including diagrams if appropriate. Briefly summarise the characteristics and risk of bias among contributing studies. Provide the results in an appropriate format (i.e. so it is accessible and can clearly be followed by an EAG so they can quality assure the analyses). Results should include the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. Present results of all investigations of possible causes of heterogeneity among study results. Present assessments of risk of bias due to missing results (arising from reporting biases), for example, funnel plots. Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

Summary and interpretation of clinical evidence

This section should be used to critically appraise the evidence base for the technology and explain how it supports the decision to adopt the technology for use in the NHS. You should describe the clinical benefit and any risks of using the technology and how the evidence supports the key claimed benefits. It is also important to identify any external factors that may have influenced the study results (such as training or auditing) and whether these factors will affect implementation in the NHS.

Ongoing studies

In this section, provide details of any relevant ongoing or planned studies using the technology. For each study, provide information on the patient population, the intervention (including version), comparator(s), outcomes and expected completion date. If the study is registered on a clinical trials database, provide a hyperlink to the study record along with the identifier number. Below is a suggested table format in which you can provide this information.

Suggested table format for providing details of any relevant ongoing or planned studies using the technology

Principal investigator and location	Year (expected completion date)	Patient population, setting, and withdrawals/ lost to follow up	Intervention and version(s)	Comparator(s)	Outcomes
–	–	–	–	–	–
–	–	–	–	–	–

1.3 Published economic evidence

Identification and selection of studies

Provide brief results of the systematic search in the table provided in section 3.1. A full description of the search methods used should be included in appendix D. A pragmatic literature search is acceptable but it should be justified and it should be clear how the search was adapted and what additional limits to the search have been applied. If there are no economic studies relevant to the decision problem, use this section to describe the search that was done and delete the subsequent sections (List of relevant economic studies, Critical appraisal of relevant economic studies and results from the economic evidence base).

List of relevant studies

In table 4, summarise the details of all relevant studies identified through the systematic search. This should include only studies relevant to the decision problem

from the scope. When studies have been identified and not included, justification for this should be provided in the table provided in appendix D.

Critical appraisal of relevant economic studies

The quality of each economic study identified as relevant to your submission in section 3.2 should be appraised. Provide the complete quality assessment for each study in appendix E (a suggested quality assessment checklist is provided in the submission).

The prompts in table 5 are designed to help you explain the relevance of the included economic studies to the decision problem. You can add additional columns and questions if there is any particularly relevant information that might be missed.

Results from the economic evidence base

In this section, describe the results from each of the relevant economic studies, including results from any sensitivity or scenario analyses done. Each study's results should be interpreted with reference to a critical appraisal of its methodology.

Company decision model

This section refers to the de novo economic decision model that is submitted. When developing the model and completing the submission template, also refer to section 4 of NICE's health technology evaluation guidance development manual.

During the evaluation an external assessment group (EAG) will provide a detailed critical appraisal of your submission, including the decision model. The submitted model plays a key role in evaluating if the technology should be recommended as a cost saving option in the NHS. Submission of a low-quality model can have a negative impact on guidance development, often requiring more work from the EAGs and increasing the difficulties in the committee’s decision-making. Both scenarios can result in delaying publication of guidance and may make it more difficult for the committee to recommend the technology.

NICE medical technologies evaluations use a cost comparison analysis (CCA) framework, which comprises an analysis of the costs and resource use associated with the technology being evaluated compared with that of the comparator(s). The

cost comparison analyses submitted to the medical technologies evaluation programme (MTEP) should incorporate clinical parameters based on appropriate estimates of clinical effectiveness, as well as relevant differences in health outcomes that affect resource use (for example, managing adverse events). Further information on CCA can be found in section 4.2.18 to 4.2.21 of NICE's methods manual.

To ensure economic analyses are consistent across different technologies and disease areas, NICE has defined a reference-case framework (see section 4.2 of NICE's manual). The reference case specifies the methods NICE considers to be most appropriate for estimating clinical effectiveness and value for money. Economic evaluations submitted to MTEP should include an analysis of results using these reference-case methods.

Although reference-case methods are preferred by NICE, it does not prevent additional analyses from being presented, if appropriate, for example, in circumstances when a particular cost is apportioned or adjusted. Examples of circumstances when costs may need adjusting or apportioning are given in section 4.4.15 of NICE's methods manual. If presenting an additional non-reference-case analysis, this should be justified and clearly distinguished from the reference-case analysis.

Decision model description

In this section, use the prompts to describe the decision model, its structure and the assumptions used. Provide information on the patient groups and comparators included in the model, as well as the type of analysis (for example, decision tree or Markov model) and justification of the chosen structure, in line with the clinical pathway described in section 1.3. Provide a diagram of the submitted model in appendix F of the submission.

In table 8, list the main assumptions that underpin the model. Provide a justification and a source for each assumption. When relevant, these assumptions and justifications should be consistent with the clinical evidence in section 2 of the submission.

The following principles should guide the modelling approach:

- Patient population: The patient groups included in the economic evaluation should reflect the population defined in the scope. If there are differences, provide the rationale. If published evidence or advice from clinical experts demonstrates that resources required, or saved, vary for different population subgroups, (for example, by disease severity, age, comorbidities, or gender) the model should report results for each subgroup separately. Such subgroups may have been included in the scope, but it is possible to include results for subgroups that have not been captured in the scope with appropriate justification provided.
- Intervention and comparator(s): the model should compare the technology under review with the comparator(s) listed in the scope developed by NICE. If any comparators defined in the scope are not included in the model, provide the rationale. A new technology may replace 1 or more current interventions, be additional to current interventions, or provide a new service. The model should capture the relevant option. This may differ by setting. For example, a new device may replace a service currently only provided in tertiary services. On implementation, the technology could enable a new service to be offered in secondary care but be an additional or replacement service in the tertiary setting. The impact on both settings should be modelled. If the clinical pathways differ between the settings, it may be necessary to submit 2 decision models to capture these differences.
- Decision model structure: The structure of the model should capture all points on the clinical pathway which will be impacted by a decision to adopt the technology under review. When the technology will impact on personal social services (PSS) resources this effect should also be captured. When there are alternative plausible assumptions and inputs, sensitivity analyses of their effects on model outputs should be done. The chosen type of model (for example, Markov cohort model) and model structure should be justified.

Time horizon and discount rate: The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. If the benefits exceed 1 year, then costs and benefits should be discounted at the NICE defined cost of capital, currently 3.5% per annum. While

longer time horizons increase the complexity of the modelling, often requiring data to be extrapolated from studies of under a year to many years, it is important to capture these longer-term benefits, particularly those that improve patient outcomes and thereby avoid future costs for the NHS. Before developing the decision model, consult the scope published by NICE which clearly defines and describes the care pathway relevant to the evaluation. You may also wish to consult appropriate NICE guidance products, or other available guidelines, for further details on the care pathway. In most cases, the scope published by NICE will provide information on relevant existing national and international guidelines to consult. In cases with no relevant clinical guidance, additional advice can be sought from clinical experts, with the process to identify experts, the questions asked, and their responses, clearly documented in the submission.

Clinical parameters and variables

In table 9, describe the clinical parameters, patient and carer outcomes and system outcomes from the clinical evidence that were used in the model. Any data values taken from clinical evidence that are used in the model should be listed and referenced in this section.

Model parameters based on clinical effects should be informed when possible by the most robust and relevant outcomes. Such outcomes should be listed in the scope developed by NICE. The synthesis of evidence on health effects should be based on systematic review. In general, all model parameter values used should be both clinically plausible and should use methods that are consistent with the data.

In the absence of empirical evidence from randomised clinical trials, non-randomised studies or registries, expert elicitation can be used. If expert elicitation methods were used to identify any model parameters or plausible parameters ranges, this should be fully justified, and the methods outlined in the submission.

If the model extrapolates any clinical data beyond the study follow-up period, explain the rationale for this assumption.

List any other parameters in the model in table 10. Example parameters are provided; adapt them as necessary. If transition probabilities have been used in the

model, explain how they were calculated from the clinical data. If appropriate, provide the transition matrix and details of the transformation of clinical outcomes.

For tables 8, 9 and 10, the sources used to identify and critically evaluate sources of data for decision models should be stated and the choice of particular data sets should be justified with reference to their suitability to the population of interest and the clinical pathway, as specified in the scope of the evaluation.

Resource identification, measurement and valuation

This section should detail the costs of using the technology and the comparator. Describe any relevant NHS costs and unit costs and reference them if possible. Describe resource use costs in table 11. Adapt the table as necessary to suit the data included in the model.

The decision model should include net change in costs to the NHS and PSS. All costs used in the model should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS. The decision model should estimate the impact of adopting the technology on the demand for all resources, such as:

- costs to acquire the technology and comparator(s) including any associated with infrastructure changes or training
- annual operating costs such as consumables, repair and maintenance of the device and warranties
- impact on NHS resources such as staff time by grade, bed days, existing equipment, diagnostic and other tests, imaging, surgical procedures, pathology, unscheduled care, outpatient or primary care appointments, day cases, and medication
- impact on PSS resources such as discharges to care homes and number of care packages required.

The range of costs and resource parameters to be included in the model depends on the clinical characteristics of the individual technology and its comparator(s) and their impact on the clinical pathway. Only incremental costs, such as those which differ between the technology and its comparator(s) need to be measured.

Preferred sources for resource use:

- NHS England's National Cost Collection (NCC), previously called **'reference costs'** (provider perspective) should be used for other activities and estimates of resource when available and appropriate. NCC costs are preferred over national tariff costs. Source *data* for NHS reference costs would ideally include the HRG group and specify if it is all HRGs, inpatients, elective etc.
- Personal Social Services Research Unit (PSSRU) for NHS staff costs. Banding of staff for specific roles can vary; it is best practice to ask clinical experts and apply scenario analysis to cover the range of possible costs.
- Note that lower bands are not included in PSSRU staffing costs, and in these instances, agenda for change bands should be used (pro-rata), with additional uplifts. Add payroll-related costs onto the agenda for change salaries; these add-on costs are the employers' contribution to superannuation (pension) and employers' National Insurance costs. This gives a more accurate estimate of the cost to the organisation of the staff member. Salary should then be adjusted to take into account actual working hours (37.5 hours per week) and weeks worked per year (assume 42 weeks, which allows for annual leave, training and sickness).
- For primary/community care, NCC costs may not be available, so staff time costs (based on PSSRU when possible) should be used.

Challenges using HRGs/NCCs/reference costs:

- Clear justification is needed if using alternative sources to NCC costs in the base-case analysis, otherwise the preference is to use NCC costs in the base-case analysis and other approaches such as micro-costing or PLICS in sensitivity analyses.
- Potential reasons why NCC costs may not be appropriate in the base case may be that it does not reflect the new intervention, particularly when changes are expected in the way the intervention is delivered compared with standard care. This should be clearly outlined in the submission. Examples include:
  - When there is no appropriate HRG / clinical coding.
  - When clinical coding aggregates (does not differentiate) with another intervention.

  - When there is a new pathway or a change in setting, inpatient compared with outpatient, local compared with general anaesthetic and so on.
  - When a reduced length of stay is expected with the new intervention.
  - When the health resource group (HRG) represents a different risk group who are expected to have higher/lower level of complications or different procedure length.
  - When there are differences in staff involved in the procedure or different test/scan requirements.
- Other reasons HRGs have not been appropriate to use in the base case previously have included:
  - If the HRG has some incentives attached that means it is not reflective of the true cost.
  - If there are a very low number of submissions for the reference cost and so they are deemed unreliable.

Micro-costing:

- The preferred approach for micro-costing is to use prospective comparative studies so that similar methods for collecting the costing data are used between the intervention and the comparator(s). National/large-scale audits and routine administrative data can provide reliable sources of procedure duration and length of stay outcomes.
- Refer to the NICE real-world evidence (RWE) framework for further information about the requirements for the use of RWE in health technology assessment.
- In the absence of other means, expert elicitation is a potential option to obtain micro-costing estimates.
- Avoid inconsistencies and biases between how the intervention and comparator technologies have been costed.

When presenting the CCA you should:

- Identify and describe resource use changes and the method used to estimate them, and support this with evidence to justify the values adopted.
- Quantify each resource in physical units (for example, 3 bed days, 1 MRI scan and 2 X-rays).

- Identify the unit cost for each resource, (for example, cost per bed day: £400 per day; MRI scan: £120 and X-ray: £50) together with a supporting reference and date on which the price was recorded (for example, the source is NHS Reference Costs [year]).
- In cases in which current costs are not available, costs from previous years should be adjusted, to present the value using inflation indices appropriate to the cost perspective, such as the hospital and community health services index and the PSS pay and prices index, available from the PSSRU report on unit costs of health and social care 2021, or the Office for National Statistics consumer price inflation tables.
- Wherever possible, costs relevant to the healthcare system in England should be used. However, in cases when only costs from other countries are available these should be converted to British Pound Sterling using an exchange rate from an appropriate and current source (such as HM Revenue and Customs or Organisation for Economic Co-operation and Development). The date and conversion rate should be explicit.
- Estimate the value of each resource (that is, the quantity of resources impacted multiplied by their unit cost).

Unit costs for each resource should be shown separately in the model. Total costs for each additional or saved resource should be calculated by multiplying the unit cost by the number impacted to show the total cost for each, before aggregating across all resources.

Describe the adverse event costs included in the model. Adapt table 12 as needed. Refer to the adverse events section of section 2.5 of the submission when possible.

The section on miscellaneous costs should only be completed if there is relevant information on costs that has not been included in previous sections.

Price of intervention and comparator

The total costs of the technology and the comparator should be described in tables 13 and 14 respectively. Adapt the tables as needed.

Capital costs for the intervention and comparator(s) should be expressed as a cost per year, to provide a comparison of the annual costs of the technologies. If relevant, the annualised capital costs plus other annual costs can be expressed as a cost per use of the technology and its comparator(s).

When providing the capital costs associated with the intervention and comparator(s), it should reflect as closely as possible the price(s) paid in the NHS and exclude VAT. Companies for the intervention technology are therefore expected to be publicly forthcoming with their prices and potential existing discounts. The EAGs can check the intervention price on NHS Supply Chain for significant deviations from the publicly available prices, and it is therefore expected that this price will be used in the base case when possible and explored adequately with sensitivity analyses. Ensure that VAT is excluded from all technology costs.

It can sometimes be difficult to access up-to-date, accurate comparator prices and sometimes the most accurate price source may be confidential outside of the NHS (for example, supply chain prices) or may lack transparency (for example, when provided by clinicians or contacts within the NHS). In addition, there may be variability in the prices depending on the source used, or depending on the volume purchased and so on. Some prices or discounts may only be available to some trusts and not across the NHS. Recommendations for dealing with comparator prices include:

- A public list price for technologies (that is, a publicly available price) is generally preferred, but as outlined in NICE health technology evaluations: the manual (2022), reference-case analyses should be based on prices that reflect as closely as possible the prices that are paid in the NHS for all evaluations. Ensure the source(s) of the price is stated in the submission and that the price excludes VAT.
- Potential discounts or alternative prices should then be explored in sensitivity analyses. Ensure any confidential prices, such as from Supply Chain, are marked as commercial in confidence,
- If there is uncertainty about the most appropriate comparator price, and the cost case is sensitive to this parameter, efforts should be made to ensure the range of potential prices is explored in scenario and threshold analyses.

- When there is uncertainty, it may be prudent to use price estimates in the base case that ensure the model's cost savings are conservative.
- Where possible, it is preferable to try and avoid or minimise inconsistencies and biases between how the intervention and comparator technologies have been costed. Where this is not possible, the potential for bias (and possibly the direction of bias) should be clearly described.

If there are different versions of the intervention/comparator technology or the consumables (for example, different sizes of the same product) then an average price across the different versions may be reasonable.

Prices of drugs

The public list prices for medicines or medical devices should be used in the base-case analysis, but prices should reflect as closely as possible the prices that are paid in the NHS for all evaluations. When there are nationally available price reductions (for example, for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit), the reduced price should be used in the base-case analysis to best reflect the price relevant to the NHS. The Commercial Medicines Unit publishes information on the prices paid for some generic medicines by NHS trusts through its electronic market information tool (eMIT), focusing on medicines in the national generics programme framework for England. If the price is not listed on eMIT, then the current price listed on the BNF should be used.

For medicines that are predominantly dispensed in the community, prices should be based on the Drug Tariff.

When a reduced price is available through a patient access scheme that has been agreed with the Department of Health and Social Care, the analyses should include the costs associated with the scheme. The possibility of such a discount should be flagged during scoping. Company submissions may not have access to the size of the discounts because of confidentiality; companies are advised to explore a range of discounts in sensitivity analysis and the EAG can further explore the use of the discounted price for the base case in its assessment.

Base-case results

In this section, report the results of the base-case analysis for the technology and comparator(s). These costs may be 'per patient', 'per treatment' or 'per year' depending on which is most appropriate for the technology. This should be clearly specified in the base-case results table. Adapt the table as needed. Use negative values to indicate cost savings.

The results should be derived from probabilistic analysis when possible unless the model is linear. If deterministic model results are used, this should be clearly justified, and the committee should take a view on if the deterministic or probabilistic estimates are most appropriate. However, in general, uncertainty around individual parameters is not a reason to exclude them from probabilistic analyses; rather, that uncertainty should be captured in the analysis (Section 4.7.12 of the manual).

Based on the above, where possible the cost saving estimates presented should be based on **probabilistic analyses** unless a deterministic approach can be justified.

Scenario analysis

Scenario analyses are used to explore uncertainty around the structural assumptions used in the analysis. It may be useful to capture differences in the setting when a device is used, and regional and local differences. For example, a new device may be used on patients in the community or as day cases or after an inpatient admission. Each setting may have a different clinical pathway, comparator, resource use and potential savings associated with the device. These can be captured using, for example, different decision trees, with 1 tree for each setting. The combination of parameters used in the base case can also be changed to reflect regional or local differences in pathways or resource use. Using the results from local scenarios to inform recommendations, in addition to those representing a national average, should ensure that recommendations are robust to local variation. When planning scenario analyses it may be helpful to refer to the subgroups and outcomes identified in the scope.

Describe the methods and tabulate the results of any scenario analyses done. When completing this section of the submission, also refer to section 4.7 of NICE's health technology evaluation guidance development manual.

Present results of the scenario analyses in table 16. Adapt the table as needed. Similar to the above for the base case results, scenario analysis results should also be **probabilistic** where possible. When only deterministic scenario analyses are provided, this should be justified.

Sensitivity analysis

Sensitivity analyses should be done to describe the relative effect of different types of uncertainty (for example, parameter or structural) on cost saving estimates. When completing this section of the submission, also refer to section 4.7 of NICE's health technology evaluation guidance development manual.

Sensitivity analysis should be done around the key parameter values of the model. The form of sensitivity analysis applied should reflect the type of uncertainty and be appropriate for the technology and users. In principle, probabilistic analyses are preferred over deterministic analyses. It is acknowledged such analyses can be unnecessarily complex for some decision problems, but the expectation is that probabilistic analyses are routinely carried out, particularly for models that are 'non-linear' (such as when there are interacting parameters, including most Markov models). The company should document and justify decisions not to carry out probabilistic analyses. The more uncertainty around the model's structure and parameters values, the more sensitivity analyses should be done to ensure the extent of uncertainty has been captured adequately for decision making.

Probabilistic sensitivity analysis

Where possible, probabilistic sensitivity analysis should be used to assess uncertainty around parameter precision. In most decision models, each parameter (for example, the probability of a treatment being successful) is assigned a point estimate value. In probabilistic sensitivity analysis, rather than assigning a single value to each parameter, a distribution is assigned to determine the mean, variance and shape of the spread of data (for example, using the 95% confidence intervals).

Each time the model is run, the software randomly 'selects' 1 value for each parameter and records the model's results. The model is usually run several thousand times, with the results recorded each time. The spread of the results presents a measure of uncertainty in the model.

In this section describe the methods used and tabulate the results of the probabilistic sensitivity analyses. This should include the distributions and their sources for each parameter. If any parameters or variables were omitted from the probabilistic sensitivity analysis, provide the rationale for the omission(s). Present results in a table, identifying parameters that have a substantial effect on the modelling results. Provide expected mean cost estimates and the probability that the treatment is cost saving.

Deterministic sensitivity analysis

Deterministic sensitivity analyses exploring individual or multiple correlated parameters may be useful for identifying parameters to which the decision is most sensitive and explaining key drivers of the decision model. In DSA, 1 or more parameters are changed and the impact of these changes on cost estimates is explored. In univariate (one-way) sensitivity analysis, 1 parameter is changed at a time, while a multivariate sensitivity analysis involves varying more than 1 parameter simultaneously.

In this section, describe the methods and present the results of the deterministic sensitivity analysis, focusing on the key drivers of the model. This should include a summary of the variables subject to a deterministic sensitivity analysis, how they were varied, and the rationale behind this. When presenting the results of the deterministic sensitivity analysis, consider the use of tornado diagrams.

Threshold sensitivity analysis

Threshold analysis may also be helpful to identify relevant parameter boundaries, especially if there are influential but highly uncertain parameters. The threshold analysis assesses the tipping point for a given parameter, for example, the purchase cost which would result in the new technology having the same costs as current practice.

In this section, describe the methods and present the results of any threshold analyses done. Explain whether the parameter boundaries identified will fall within the expected uncertainty boundaries (for example, based on published evidence or expert opinion/elicitation).

Summary of sensitivity analysis results

Use this section to summarise the main findings and conclusions of the sensitivity analyses done. Present an overall assessment of uncertainty, highlighting the presence of any uncertainties that are unlikely to be reduced by further evidence or expert input.

Miscellaneous results

The section on miscellaneous results should only be completed if there are relevant results that have not been included in previous sections.

Validation

In this section, describe the methods used to validate the cost model.

The structure of the model, choice of input parameters, and assumptions used should be validated by clinical experts to reduce the risk of bias and improve the likelihood that the results of the model can be considered representative of what may happen in real clinical settings (external validity). Provide contact details for any clinical experts, ensuring you have permission to share this information with NICE. Mark any personal information in the evidence submission as confidential.

Separately, all formulas in the model should be checked, ideally using a verification checklist such as the TECH-VER checklist (Büyükkaramikli et al. 2019). This will increase the credibility of the model and its results and reduce the incidence of errors. This step is essential, and an explanation of the selection process used must be given.

Summary and interpretation of economic evidence

In this section, you can critically appraise any economic evidence for the technology and explain how the results of the model support adopting the technology for use in the NHS. You should describe how the model was designed to support decision

making in the NHS, how it is relevant to the NHS patient population and how the comparator represents current NHS standard care. It is also important to identify any limitations in the model and how these were explored using sensitivity analyses.

References

List references in alphabetical order using NICE's referencing style.

Appendices

Appendix A and appendix D should contain the search methods used to identify the clinical effectiveness and economic evidence, respectively. If separate searches were done for abstracts and ongoing studies, provide details of these in separate tables.

Clinical effectiveness and economic evidence 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. Further information on systematic reviews can be found in section 3.3.4, and sections 3.4.2 and 3.4.3 of NICE's health technology evaluations manual and Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

List any excluded studies, along with the rationale for exclusion, in the relevant tables in appendix A (for clinical-effectiveness studies) and appendix D (for economic studies). Report the number of published studies included and excluded at each stage, preferably as a PRISMA statement flow diagram.

You can also provide a structured abstract for any unpublished clinical-effectiveness studies in appendix A.

Appendix B and appendix E should contain the complete quality assessments for each included clinical effectiveness and economic study, respectively. Example critical appraisals tables are provided. Quality assessments should be done using validated tools appropriate to the study design and use case.

Appendix C should contain the search methods used to identify adverse events for the technology (if done). Brief details on the relevant evidence can be added in the

appendix or moved up to the adverse events section if there is substantial information.

Appendix F should include a diagram of the decision model structure.

Appendix G is the checklist for any confidential information. Provide reasons for marking any information as confidential and say when the information will be available to share publicly (if applicable). The declaration on confidential information should be signed by someone in a senior position at the company (such as a medical director or company director).

Appendix A: Epidemiology and cost sources

This appendix provides links to sources of national data providing information on epidemiology, and volumes and unit costs of NHS and social care activities in England, as of 2022. Note that this list is not exhaustive, and companies must take responsibility for identifying relevant data inputs.

Population estimates

- Population estimates for England are available from the Office for National Statistics.
- National catchment populations for all acute trusts in England are available from Office for Health Improvement and Disparities.
- GP-registered populations information is available from NHS Digital.

Mortality statistics

- Mortality statistics by cause of death are available from Office for National Statistics

Incidence and prevalence data

- NICE guidance often publishes epidemiological data for disease areas.
- NHS Digital's annual hospital episode statistics publishes data on inpatient episodes, outpatient appointments, A&E attendances, maternity and adult critical care in NHS hospitals in England.
- NHS Digital's hospital admitted patient care activity publishes data on the number of admissions, length of stay and age. Data is available by clinical commissioning group, diagnosis, healthcare resource group (HRG), procedures and treatment speciality.
- NHS Digital's Hospital outpatient activity publishes data on the number of outpatient appointments. Data is available for all attendances, first attendances, and by main procedure or intervention, main specialty, primary diagnosis and treatment specialty.
- NHS Digital's hospital A&E activity publishes data on the number of A&E attendances by gender, age, treatment, diagnosis and duration.

- Key national patient organisations for the disease under review often publish incidence and prevalence data. For example, Cancer Research UK has incidence, prevalence and mortality statistics on all cancers, analysed by cancer type.
- Office for Health Improvement and Disparities has several data and analysis tools and publishes numerous statistics, including the prevalence of infections such as methicillin-resistant Staphylococcus aureus (MRSA). A full list of can be found on the GOV.UK website.
- NHS Digital's community services dataset and measures from the adult social care outcomes framework publishes data on the numbers and type of support received in the community.
- NHS England has 6 National Programmes of Care (NPoC). The 6 NPoCs are internal medicine, cancer, mental health, trauma, women and children, blood and infection; and these are broken down into clinical reference groups. Each clinical reference group has service specifications and standard contracts, which provide epidemiology data and cost of illness data for different disease areas and describe current service provision.

Unit costs

- The National Cost Collection for the NHS publishes aggregated costs (the average unit cost of providing defined services to NHS patients in England) and patient-level information and costing systems (PLICS; a cost based on the specific interactions a patient has, and the events related to their healthcare activity).
- Personal Social Services Research Unit publishes the unit costs of health and social care. This includes hourly costs for community-based healthcare staff such as GPs and practice nurses; hospital-based staff, such as consultants, ward nurses, physiotherapists and radiographers; and social care and care home costs. It also provides inflation indices for the previous 10 years for hospital community health services.
- NHS Digital publishes expenditure and unit costs in England, which includes the number and unit cost of patients receiving nursing or residential support for physical, sensory, learning disability, memory and cognition or mental health.

- The NHS Supply chain catalogue publishes costs and volumes for most items, including devices bought. This is only available with an NHS login, but you can submit a freedom of information request to gain access to specific information. NHS Business Services Authority provides guidance on how to submit a freedom of information request.

Medication costs

- NHS Business Services Authority's Drug Tariff publishes the prices of various drugs.
- The Department of Health and Social Care's drugs and pharmaceutical electronic market information tool (eMIT) provides information about prices and usage for generic drugs and pharmaceutical products in secondary care.
- NHS Digital's prescription cost analysis provides details of the number of items and the net ingredient cost of all prescriptions dispensed in the community in England.
- Medication costs per item dispensed are available from the BNF.

