NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE
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Instructions for manufacturers and sponsors

This specification for submission of evidence to the National Institute of Health and Clinical Excellence (NICE, or the Institute) as part of the single technology appraisal (STA) process is designed to indicate to manufacturers and sponsors the information required by the Institute and the format in which it should be presented. Use of the specification and completion of Appendices 9.1 to 9.3 are mandatory, and the format should be adhered to wherever possible. Reasons for not adhering to this format must be clearly stated. Sections that are not considered to be relevant should be marked ‘N/A’ and a justification given for this response. The specification should be completed with reference to the NICE document ‘Guide to the methods of technology appraisal’ (www.nice.org.uk), particularly with regard to the ‘reference case’.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise the Institute immediately of any variation between the preliminary and final approval.

A submission should be as succinct and informative as possible. It is expected that the main body of the submission will not usually exceed 75 pages. The submission should be sent to the Institute electronically in Word or a compatible format, and not as a PDF file. A list of all references must be provided, together with paper or electronic copies.

For model-based economic evaluations, a transparent and fully executable electronic copy of the model should be submitted. The Evidence Review Group should have full access to the programming code, and running of the model should be unhindered. Please ensure that the submitted versions of the model program and the content of the submission match. The model should be constructed using standard software, such as Excel or DATA. If non-standard software is required for the construction of the model, please discuss this with the Institute at the earliest opportunity in advance of submission.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but which is considered to be relevant to the submission.
Any additional appendices should be clearly referenced in the body of the submission and should not be used to present core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the efficacy section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID rather than relying on numerical referencing alone (for example, ‘Trial 123/Jones et al. ¹²⁶ found ABC’ rather than ‘One trial ¹²⁶ found ABC’).

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to the Institute at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by the Institute.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to the Institute with all confidential information highlighted and underlined
- a fully executable electronic copy of the economic model has been submitted
- all key references have been made available (electronic or hard copy versions as appropriate)
- the checklist of confidential information has been completed and submitted.

**Disclosure of information**

To ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Appraisal Committee’s decisions should be publicly available. The Institute recognises, however, that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the Final Appraisal Determination
(FAD) or Appraisal Consultation Document (ACD) to consultees and commentators, all the evidence seen by the Committee should ideally be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). As a minimum, a structured abstract will need to be made available for public disclosure, using a recognised format such as that provided by the CONSORT statement (www.consort-statement.org).

Where data are commercial in confidence or academic in confidence, it is the manufacturer's or sponsor’s responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The NICE checklist of confidential information should be completed. If no checklist of confidential information is provided, the Institute will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor will be requested to supply a second ‘stripped’ version of the submission from which any information that is to remain confidential has been removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear how much data have been removed and where they have been removed from.

The Institute will request the stripped version of the submission at least 2 weeks before the anticipated date of issue of the FAD or ACD to consultees and commentators. The stripped version will be issued to consultees and commentators along with the ACD or FAD, and made available on the Institute’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the
stripped version of the submission does not contain any confidential information. **No further amendments or corrections may be made to the submission at this stage.** The NICE checklist of confidential information should be updated and submitted at the same time. The Institute will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for the Institute to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Appraisal Committee. Confidential information may be distributed to consultees with the permission of the manufacturer or sponsor. The Institute will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by the Institute that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

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 the Institute to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to the Institute. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed as commercial in confidence before making any decision on disclosure.

For further information, please see the NICE website (www.nice.org.uk).
Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the ‘Guide to the single technology appraisal process’ – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

[Response]

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

[Response]

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

[Response]

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

[Response]
1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

[Response]

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

[Response]

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

[Response]

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

[Response]

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

[Response]

1.10 What is the setting for the use of the technology?

[Response]
1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

[Response]

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

<table>
<thead>
<tr>
<th>Final scope issued by NICE</th>
<th>Decision problem addressed in the submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
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<tr>
<td>Comparator(s)</td>
<td></td>
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<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Economic Analysis</td>
<td></td>
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<tr>
<td>Special considerations and other issues</td>
<td></td>
</tr>
</tbody>
</table>
Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.
- The main clinical results of the randomised trials and any relevant non RCTs.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the incremental ratios from the evaluation.

[Executive summary]
4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

[Response]

4.2 What was the rationale for the development of the new technology?

[Response]

4.3 What is the principal mechanism of action of the technology?

[Response]

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

[Response]

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

[Response]

4.6 Provide details of any relevant guidelines or protocols.

[Response]
5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from ‘head-to-head’ randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head–to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.
5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.
Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

[List]

5.2.4 List of relevant non-randomised controlled trials
Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

[List]

5.2.5 Ongoing studies
Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

[Details]

[Flow diagram described in 5.3]

5.3 Summary of methodology of relevant RCTs
As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.
5.3.1 Methods
Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

[Response]

5.3.2 Participants
Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

[Response]

5.3.3 Patient numbers
Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

[Flow chart]

5.3.4 Outcomes
Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

[Response]
5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

[Response]

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any ‘commercial in confidence’ data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- How was allocation concealed?
- What randomisation technique was used?
- Was a justification of the sample size provided?
- Was follow-up adequate?
- Were the individuals undertaking the outcomes assessment aware of allocation?
- Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.
- Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?
- How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to
affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.

- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?
- Were the study groups comparable?
- Were the statistical analyses used appropriate?
- Was an intention-to-treat analysis undertaken?
- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

[Response]

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any ‘commercial in confidence’ data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both 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 patients included in the analysis.
- The median follow-up time of analysis.
- State whether intention-to-treat was used for the analysis and how data were imputed if necessary.
- Discuss and justify definitions of any clinically important differences.
Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.

If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.

Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

5.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate.
- Tabulate and/or graphically display the individual and combined results.

[Meta-analysis methods/results table/graph]
5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4. Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

[Response]

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be
reported here in the same detail as described in the previous sections relating
to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision
problem.. Give incidence rates of adverse effects if appropriate.

[Response]

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will
be considered, with reference to the inherent limitation inferred by the study
design. The level of detail provided should be the same as for RCTs and
where possible more than one independent source of data should be
examined to explore the validity of any conclusions. Inferences about relative
treatment effects drawn from observational evidence will necessarily be more
circumspect from those from RCTs.

5.8.1 Summary of methodology of relevant non-RCTs

[Response]

5.8.2 Critical appraisal of relevant non-RCTs

[Response]

5.8.3 Results of the relevant non-RCTs

[Response]

5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the
decision problem. Include a discussion of the relevance of the outcomes
assessed in clinical trials to the clinical benefits experienced by patients
in practice.

[Response]
5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

[Response]

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies
Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

[Response]

6.1.2 Description of identified studies
Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

[Response]
### 6.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the ‘reference case’ (see the NICE document ‘Guide to the methods of technology appraisal’). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Reference case</th>
<th>Section in ‘Guide to the methods of technology appraisal’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator(s)</td>
<td>The comparator that has been specified in the decision problem</td>
<td>5.3.2</td>
</tr>
<tr>
<td>Perspective costs</td>
<td>NHS and Personal Social Services</td>
<td>5.3.3</td>
</tr>
<tr>
<td>Perspective benefits</td>
<td>All health effects on individuals</td>
<td>5.3.3</td>
</tr>
<tr>
<td>Form of economic evaluation</td>
<td>Cost-effectiveness analysis</td>
<td>5.3.4</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Sufficient to capture differences in costs and outcomes</td>
<td>5.3.5</td>
</tr>
<tr>
<td>Synthesis of evidence</td>
<td>Systematic review</td>
<td>5.4.1</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>Quality-adjusted life years (QALYs)</td>
<td>5.5</td>
</tr>
<tr>
<td>Health states for QALY measurement</td>
<td>Described using a standardised and validated instrument</td>
<td>5.5</td>
</tr>
<tr>
<td>Benefit valuation</td>
<td>Time trade-off or standard gamble</td>
<td>5.5</td>
</tr>
<tr>
<td>Source of preference data</td>
<td>Sample of public</td>
<td>5.5</td>
</tr>
<tr>
<td>Discount rate</td>
<td>Health benefits and costs – both 3.5%</td>
<td>5.7.2</td>
</tr>
<tr>
<td>Equity</td>
<td>No additional weighting to QALYs</td>
<td>5.9.7</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Probabilistic sensitivity analysis</td>
<td>5.9.3</td>
</tr>
</tbody>
</table>
6.2.1 Technology
How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

[Response]

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

[Response]

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

[Response]

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

[Response]

6.2.2.4 At what points do patients ‘enter’ and ‘exit’ the evaluation? Do these points differ between treatment regimens? If so, how and why?

[Response]

6.2.3 Comparator technology
What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).
6.2.4 Study perspective

If the perspective of the study did not reflect NICE’s reference case, provide further details and a justification for the approach chosen.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.6.1 Please provide the following.

- A description of the model type.
- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

6.2.6.2 Why was this particular type of model used?
6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

[Response]

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

[Response]

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

[Response]

6.2.6.6 For discrete time models, what was the model’s cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

[Response]

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

[Response]

6.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

[Response]

b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

[Response]
6.2.6.10  Provide details of the clinical trial, including the rationale for its selection.

[Response]

6.2.6.11  Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

[Response]

6.2.6.12  Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

[Response]

6.2.6.13  Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

[Response]

6.2.7  Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.
6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

[Response]

6.2.7.2 How were the relative risks of disease progression estimated?

[Response]

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

[Response]

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

[Response]

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

[Response]

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

[Response]

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

[Response]
6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

[Response]

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE’s reference case? If not, which approach was used?

[Response]

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

[Response]

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

[Response]

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

[Response]

6.2.9.2 How were the resources measured?

[Response]

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

[Response]

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?
Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

[Response]

6.2.9.5 What source(s) of information were used to value the resources?

[Response]

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

[Response]

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

[Response]

6.2.9.8 Were resource values indexed to the current price year?

[Response]

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

[Response]

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE’s reference case?

[Response]
6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

[Response]

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of ‘priors’.

[Response]

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

[Response]

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

[Response]

6.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this 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.

[Response]
6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

[Response]

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves
- scatterplots on cost-effectiveness quadrants.

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

[Response]

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

[Response]

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

[Response]
6.3.4 Interpretation of economic evidence

6.3.4.1 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?

[Response]

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

[Response]

6.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

[Response]

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

[Response]

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document ‘Guide to the methods of technology appraisal’.

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

[Response]
7.2 What number of patients were assumed to be eligible? How was this figure derived?

[Response]

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

[Response]

7.4 What assumption(s) were made about market share (where relevant)?

[Response]

7.5 What unit costs were assumed? How were these calculated?

[Response]

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

[Response]

7.7 Were there any estimates of resource savings? If so, what were they?

[Response]

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

[Response]

8 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

[References]

9 Appendices

9.1 Appendix 1

Summary of Product Characteristics or Technical Manual or drafts

9.2 Appendix 2: search strategy for section 5

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

[Response]

9.2.2 The date on which the search was conducted.

[Response]

9.2.3 The date span of the search.

[Response]

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

[Response]

9.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

[Response]
9.2.6 The inclusion and exclusion criteria.

[Response]

9.2.7 The data abstraction strategy.

[Response]

9.3 **Appendix 3: search strategy for section 6**

The following information should be provided.

9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED).

[Response]

9.3.2 The date on which the search was conducted.

[Response]

9.3.3 The date span of the search.

[Response]

9.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

[Response]

9.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

[Response]