

Guidance to submitting companies for completion of New Product Assessment Form (NPAF)

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Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ADTC	Area Drug and Therapeutics Committee
AI	Artificial intelligence
AIC	academic in confidence
AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CEACs	cost-effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIC	commercial in confidence
CMA	cost minimisation analysis
CUA	cost utility analysis
DCEA	distributional cost-effectiveness analysis
DIC	deviance information criterion
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
FDA	Food & Drug Administration
FOI	Freedom of Information
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ILAP	Innovative Licensing and Access Pathway
MHRA	Medicine and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MTA	multiple technology appraisal
NDC	New Drugs Committee
NHB	net health benefit
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
NPAF	New Product Assessment Form
OS	overall survival
PACE	Patient and Clinician Engagement
PAS	Patient Access Scheme
PASAG	Patient Access Scheme Assessment Group
PFS	progression-free survival
PICOS	Population, Intervention, Comparison, Outcome, Study design
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
RCT	randomised controlled trial
SG-TAG	Scottish Genomic Test Advisory Group
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPAN	Scottish Pathology Network
SPC	Summary of product characteristics
UK	United Kingdom
UK PAR	United Kingdom Product Assessment Report
VAT	value-added tax

Introduction

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland about the status of newly licensed medicines, new indications and formulations of existing medicines. SMC aims to issue its advice as soon as is practical after a new medicine becomes available for use.

About this guide

This guide provides information to submitting companies about the methods that are expected to be followed and evidence required to demonstrate the clinical and cost effectiveness of a new medicine to SMC. It should be read in conjunction with the SMC Process guide for submitting companies, available on the [Making a submission](#) page of the SMC website.

The New Product Assessment Form (NPAF) provides a template for the evidence required by SMC to issue advice to NHS boards ADTCs. This form should be used for all full submissions (including resubmissions and reassessments).

A separate submission template and additional accompanying guidance are available on the [Making a submission](#) page of the SMC website for submissions for ultra-orphan medicines. There is also a specific template for abbreviated submissions where appropriate.

Guidance on completion of all sections of the NPAF are provided in this document as follows:

- For sections 1 through 5 and section 8 of the NPAF, these are set out as 'Guidance notes' including a description of the type of information expected to be submitted within relevant sections of the form, an indication, where appropriate, of the expected source of the information and how the information should be presented.
- For completion of section 6 of the NPAF, the submitting company should provide a summary of their economic case and within this guide, detailed information is provided on the methods to be used in the preparation of the economic case.
- This guide also provides detailed guidance on the completion of the SMC budget impact template, a summary of which must be provided in the section 7 of the NPAF.

Completion of introductory sections of the NPAF

Title page

Guidance notes:

Please complete the table on the title page of the NPAF.

The name and position of the person responsible for compiling the submission should be entered, and this person should sign a master copy.

A contact person and contact details should be given. This need not be the person making the submission. The purpose is to identify a single contact for enquiries about the submission. It need not be someone who can directly answer enquiries, but the contact person should have sufficient knowledge to be able to relay enquiries to the appropriate person within the company.

Checklist of confidential information

Guidance notes:

The appropriate box should be ticked to indicate the presence or absence of confidential information within submission documentation. Where the submission does contain confidential information, the table should be completed to provide full details as requested.

The appropriate box should be ticked to indicate whether the medicine is being submitted with a Patient Access Scheme (PAS). If a PAS is submitted, the appropriate checkbox should be selected to indicate if the 'with PAS' results can be discussed in the open session of the SMC meeting and presented in the published advice document. Where a company indicates the results cannot be used in this way, the reason for this should be provided as text.

In relation to budget impact templates, the appropriate box should be ticked to indicate if the submitted budget impact template can be shared in confidence with NHS boards in NHSScotland if the medicine is accepted for use. If 'no' is selected, the reason for this should be provided as text.

Freedom of Information (FoI)

Guidance notes:

Full contact details of the appropriate company representative to be contacted by the SMC Secretariat in the event that SMC receives a FOI request must be entered in the NPAF.

Declaration of Artificial Intelligence (AI) use

Guidance notes:

In order for SMC to understand any use of AI in the preparation of submissions it receives, submitting companies should ensure that the questions in this section of the NPAF are completed. Please refer to the SMC Position Statement on the use of Artificial Intelligence in Medicines Submissions, available on the SMC website, for further details.

Checklist for completion of New Product Assessment Form

Guidance notes:

To ensure efficient processing of your submission at the point of receipt by SMC, the second column in the table should be completed to indicate that the appropriate documentation has been provided. Failure to provide relevant documentation may result in delays to the scheduling of your submission.

1 Registration details

- a) State the indication(s) for the product that is under review in the submission, as described in the Summary of Product Characteristics.

Guidance notes:

Include the full indication under review in this submission. Other indications not included in this submission should be described in 1c).

If the medicine under review is given as part of a combination regimen, please specify the formulation(s) of the other medicine(s) relevant to the submission.

If the other medicine(s) is marketed by a different company and available under a PAS or a national contract price in NHSScotland, the submitting company is required to provide an economic model that facilitates the input of the confidential PAS price or national contract price. Please refer to the further guidance provided in section 6 of this guide relating to the handling of combination or comparator discounted prices within the economic analysis.

- b) If the submission positions the medicine for use in a subpopulation of the licensed indication, please state the focus of the submission clearly and the context in which you wish SMC to consider the use of the medicine.

Guidance notes:

A submission that either (i) covers only part of the marketing authorisation or (ii) requests that SMC consider the medicine when positioned for use in a specific population of patients narrower than that covered by the marketing authorisation is termed a selective submission. A selective submission may relate to either part of the indication (selective by indication) or to a subgroup of the population eligible under the marketing authorisation (selective by population).

Where a submission covers only part of the marketing authorisation for a product the submitting company must detail under 1c) on the registration page all other aspects of the marketing authorisation that are within SMC remit but have not yet been submitted.

Where a submission proposes the use of a medicine when positioned for use in a subgroup of patients narrower than that covered by the marketing authorisation the submitting company should ensure that the proposed population for treatment is appropriate and valid within the licensed indication for the product.

The submitting company must state explicitly on the registration page under 1b) that SMC is asked to consider the use of the medicine when positioned for use in a subgroup of the population covered by the marketing authorisation. The focus of the submission must be clear and refer to a single population; either the full licensed population or a subpopulation. This must match the clinical and economic case presented and be reflected in the budget impact template.

- c) State any other indication(s) for the product which fall within the remit of SMC.

Guidance notes:

A separate NPAF should normally be submitted for each indication. If the company considers that one submission for multiple indications is appropriate to reduce duplication, for example, one clinical study covers two indications this should be discussed with SMC in advance of submission.

- d) Provide details of the licence status of the product for the indication(s) detailed in the submission, including dates of granted or expected Medicine and Healthcare products Regulatory Agency (MHRA) marketing approval, and if this is a conditional marketing authorisation.

Guidance notes:

A company may make a submission for a product once it has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) or up to 2 months before final approval from the MHRA.

- e) Provide details of the confirmed or estimated United Kingdom (UK) launch date for the product in the indication(s) detailed in the submission.

Guidance notes:

The launch date should be the date that the product first becomes available for prescribing in the UK. SMC will only issue advice to NHSScotland once a medicine is available to prescribe. This may be different from the launch of a promotional campaign for the product or availability via an early access programme.

For the first indication for a medicine, please provide the date when product is expected to be in the UK supply chain (in the country).

For a submission relating to a new indication for a product already marketed in the UK, a launch date is not required and the MHRA marketing authorisation date is sufficient.

This information may also be used to prioritise SMC workload and therefore even an estimated time period for launch would be useful.

- f) In the event of New Drugs Committee (NDC) preliminary 'not recommended' advice, if at the request of the company, SMC has validated the medicine as eligible (described below), a Patient and Clinician Engagement (PACE) meeting will be held.

If you wish SMC to assess eligibility for a PACE meeting, please answer the following:

Is this submission for:

an end-of-life medicine (a medicine used to treat a condition at a stage that usually leads to death within 3 years with currently available treatments)?

YES/NO

a medicine with an MHRA orphan marketing authorisation (conditions affecting fewer than 2,500 people in a population of 5 million) or a medicine to treat an equivalent size of population (<5 per 10,000) irrespective of whether it has designated orphan status.

YES/NO

Guidance notes:

Supporting evidence and rationale for end-of-life and orphan status must be included in section 2.2.

The definition of orphan status is based on the full population of the licensed indication relevant to the submission, irrespective of whether or not the company wishes SMC to consider the product when positioned for use in a subpopulation of the licensed indication. The definition of end-of-life medicine may be based on a subpopulation of the licensed indication where the submission is positioned for use in this subgroup and the submitting company provides adequate justification.

- g) Has the product received a positive MHRA Early Access to Medicines Scheme (EAMS) scientific opinion for the indication(s) detailed in the submission?

YES/NO

If YES, please include the EAMS number and the positive opinion date:

- h) Does the product have an 'Innovation Passport' allowing entry into the Innovative Licensing and Access Pathway (ILAP)?

YES/NO

If YES, please provide the date that the Innovation Passport was granted:

- i) Does the product require a diagnostic test (for example somatic, germline or biomarker test) in order to identify patients eligible for treatment within the licence/target population?

YES/NO

If YES, and this represents a **change in clinical practice**, Appendix A – Diagnostic Testing (for example somatic, germline or biomarker test) should be completed.

Guidance notes:

The implications of additional diagnostic testing should be reflected in the economic analysis as detailed in section 6 of this guidance document.

- j) Provide details of the formulation(s) of the product that are or will be licensed for the indication(s) detailed in the submission and their confirmed or anticipated list price(s).

k) Has a PAS been included within this submission?

YES/NO

If yes, please specify if this is a simple or complex scheme.....

l) Please complete the table below providing details of any relevant active comparator(s)/combination medicines and subsequent treatments for the product in the indication(s) (with respect to any positioning, if relevant) detailed in the submission and indicate whether any of these treatments are available under a PAS. Additional information on the rationale for the choice of comparator(s) can be provided below the table.

Medicine name*	Company	Strength	Form	Pack size	NHS List price	PAS (Y/N)	Use in model**

*Include both generic and brand name where applicable

** Indicate if medicine is a comparator, combination or subsequent treatment in the economic model

Guidance notes:

Provide details of any relevant active comparator(s) for the product in the indication(s) detailed in the submission, with respect to the proposed positioning, if relevant. If appropriate specify the formulation(s) of those comparators that are relevant to the submission.

If comparator/combination/subsequent treatments detailed in the table are available under a PAS or a national contract price in NHSScotland, the submitting company is required to provide an economic model that facilitates the input of the confidential PAS price or national contract price. Please refer to the further guidance provided in section 6 of this guide relating to the handling of combination or comparator discounted prices within the economic analysis.

m) Provide details of any scheduled or ongoing health technology assessment (HTA) of this product in the UK.

Guidance notes:

Provide details of any other HTAs, such as those performed by the National Institute for Health and Care Excellence (NICE) (with expected dates for the draft guidance/final draft guidance) or the All Wales Medicines Strategy Group (AWMSG) that include the medicine or a relevant comparator in the indication(s) under review. Details should include the organisation conducting the review, title of the review and expected date of publication. If

available, also summarise details of the scope of the review or any initial recommendations of the assessment relating to the product that is the subject of the SMC review, or any relevant comparator(s).

- n) Provide details of any upcoming data cuts or additional clinical study results relating to the indication(s) detailed in the submission that are expected to become available within the next 6 months.

2 Overview and positioning

2.1 Overview of the condition and target population

In no more than one page describe the context for this submission and the proposed position of this medicine in the pathway of care.

Guidance notes:

The summary should include:

- Brief overview of the condition and target population.
- The rationale for the development of the new product, indication or formulation, including perceived gaps in therapy and the underlying pharmacological and/or pharmacokinetic principles.
- Brief overview of current treatment options within Scotland, which may include treatment options other than medicines.
- The suggested place in therapy for this treatment with respect to treatments currently available.
- The rationale supporting the company's proposed positioning, where applicable.
- Brief summary of the economic case.

2.2 Eligibility for Patient and Clinician Engagement (PACE) meeting

If the product is noted as eligible for the option of a PACE meeting in the event of NDC preliminary 'not recommended advice' in section 1f, in no more than two pages please provide supporting evidence and rationale for this designation.

Guidance notes:

- For end-of-life medicines this should include an estimate of median overall survival (OS) with currently available treatments for the relevant population. Please include references to support the estimate of median OS.
- For medicines that will be used to treat an orphan equivalent condition this should include supporting data on disease prevalence in NHSScotland for the full licensed indication.
- For MHRA orphan medicines provide the designation number and the date of designation.

3 Direct evidence

Efficacy

- a) Provide details of studies which evidence the clinical benefits with the medicine in the indication(s) under review relative to active comparator(s) used in clinical practice. The most relevant are active-controlled studies but if these are not available, details of placebo-controlled or uncontrolled studies should be included. Placebo-controlled and uncontrolled studies can also be included if they provide evidence of relevant clinical benefits not demonstrated in active-controlled studies.

Guidance notes:

Important: any direct evidence used in the economic base case or scenario analyses **must** be identified and appraised in this section.

Types of studies to be included and sources

This section should include details of randomised controlled trials (RCTs), meta-analyses and other studies that provide evidence of the clinical benefits of the medicine in its licensed dose within the indication(s) under review relative to active comparator(s) used in routine clinical practice.

The most relevant are active-controlled studies. However, if active-controlled studies are not available or do not demonstrate relevant clinical benefit, details of placebo-controlled or uncontrolled studies that provide evidence of the clinical benefits of the medicine in its licensed dose within the indication(s) under review should be included.

Real-world data can be included where evidence gaps exist or where clinical study data are limited or not feasible, if it provides further evidence and insights to support the SMC Committees with informed decision making. Please refer to [Scottish Medicines Consortium \(SMC\) Position Statement on the Use of Real-World Evidence \(RWE\)](#) on the SMC website for further guidance on methodological standards. Where randomised comparative evidence is unavailable or insufficient, companies should justify the external control source (if applicable), describe methods used to address confounding and selection bias, and explain how remaining uncertainty is carried into the economic model.

Details of the clinical studies used to inform the assessment of efficacy should be taken from peer reviewed publications or reports published by regulatory authorities, such as the UK Public Assessment Report (UK PAR) produced by the MHRA, the European Public Assessment Report (EPAR) produced by the European Medicines Agency (EMA) and medical reviews produced by the United States Food & Drug Administration (FDA). If a published report of the study is not available, details should be taken from clinical study reports. These references (including any appendices from which data have been extracted) should be provided with the submission to SMC. Where confidential data have been taken from a clinical study report, these should be clearly highlighted by underlining and shading appropriately as commercial in confidence (CIC) or academic in confidence (AIC) and will be treated as confidential.

Abstracts and posters may be provided to demonstrate that information is in the public domain but are NOT appropriate sources for descriptions of the study methodology or primary outcomes of studies. However, if adequately detailed, they may be references for some relevant additional data, for example:

- updates of data subsequent to the primary analyses
- analyses of secondary outcomes not detailed in the published report.

Where data for a single study have been taken from more than one source this should be made clear. Examples of this include:

- a clinical study report and a published paper where the clinical study report provides additional detail
- an open-label extension to a study
- additional analyses (e.g. interim or post-hoc).

Description of the study methodology

For each study the following details should be included. It is not sufficient to state that there is a description of the study in an accompanying document or an appendix.

In general, each study should be described in full before proceeding to a description of the next study. This allows the assessor to evaluate individual studies without having to search through the document in a piecemeal fashion to gather all the details of that study.

However, there will be exceptions, for example:

- where summarising details of some aspects of all studies together, such as in a table, will help understanding of the overall study programme
- where studies are so similar in design that full sequential description of each study would result in excessive duplication.

Inclusion criteria common to all studies could be described once and cross-referenced for individual studies. The priority in presenting study details should be that there is a logical flow without undue duplication of information.

Title and/or study number: details of study title from published paper or clinical study report and/or study number.

Study design: brief description of study design, including details of blinding and randomisation.

Inclusion criteria: details of inclusion criteria including any definitions, especially for potentially ambiguous terms (for example, 'treatment-resistant'), and any assessments used in recruitment.

Exclusion criteria: details of exclusion criteria including any definitions, especially for potentially ambiguous terms, and any assessments used in recruitment.

Study medicines: details of study medicine and comparator(s), with dosing information, including routes of administration and titration schedules where appropriate. Where dosing schedules are unlicensed this should be stated.

Permitted and disallowed concomitant medications: provide an overview of concomitant medications permitted and disallowed during the study.

Primary outcome: definition of the primary outcome, including details of the methods of collecting these data and timing of assessments. If the primary outcome is measured on a scoring system, brief details of this should be provided, including an indication of the relevance of the score (for example, higher scores=better quality of life).

Population included in primary analysis of primary outcome and methods for handling missing data: details of the study population included in the primary analysis of the primary outcome and methods to take account of missing data.

Statistical test in primary analysis of primary outcome: details of the statistical test used in the primary analysis of the primary outcome.

Primary hypothesis under investigation and power calculation: details of the primary hypothesis or hypotheses under consideration and statement about the power of the study including assumptions in the sample size calculation.

Relevant secondary analyses of primary outcome and analyses of relevant secondary outcomes: for any relevant secondary analyses of the primary outcome (such as analyses in a subgroup within which the medicine is licensed) or analyses of relevant secondary outcomes (such as survival when primary outcome was tumour response), provide details of the study population included in these analyses, methods to take account of missing data and details of the statistical tests used. If any of these analyses were designed post-hoc, note this and provide details of the rationale supporting these post-hoc analyses.

It may be useful to consider presenting study methodology in a table such as this:

Sample table 1 Study methodology

	Study 1 [add name]	Study 2 [add name]
RCT/Single-arm/RWE		
Eligible patients		
Treatments		
Randomisation		
Primary outcome		
Secondary outcomes		
Results inform economic base case yes/no		
Results inform economic scenario analysis yes/no		

Reporting results

For each study the following details should be included. It is not sufficient to state that outcomes of the study are detailed in an accompanying document or an appendix.

Patient disposition: details of the number of patients randomised, treated and discontinued from the study and the number of patients who completed the study or are ongoing in the study. A participant flow diagram is useful, see [CONSORT 2025 statement](#).

Baseline demographics: details of baseline demographics, including age, sex and relevant variables describing disease duration/severity and, if appropriate, previous treatments. If there are any significant differences between study groups, these should be noted. Please complete the PRO EDI table in appendix B to report patient characteristics for each clinical study which informs the economic model.

Results of the primary analysis of the primary outcome: details of results from the primary analysis of the primary outcome with a measure of variance, preferably 95% confidence intervals (CIs). Graphical presentation of data may be appropriate but should be a supplement to text and tabulated data NOT an alternative. Complex graphics that markedly increase the size of the electronic document should not be included.

Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes: details of results of relevant secondary analyses of the primary

outcome and any analyses of relevant secondary outcomes in the format described previously for the primary analysis of the primary outcome.

It may be useful to consider presenting study results in a table such as this:

Sample table 2 Study results

	Medicine 1 [specify] (n=)	Comparator [specify] (n=)
Primary outcome: OS/PFS/etc		
Events, n		
Median OS/PFS/etc		
Hazard ratio (95% CI)		
OS/PFS/etc rate at 12/18/24 months		
Key secondary outcome: OS/PFS/etc		
Events, n		
Median OS/PFS/etc		
Hazard ratio (95% CI)		
OS/PFS/etc rate at 12/18/24 months		

PFS = progression-free survival

Additional information: details of any relevant additional information.

- b) If the clinical and/or economic case is made for only part of the marketing authorisation, or if SMC is requested to consider the use of the medicine when positioned for use in a specific population of patients narrower than that covered by the marketing authorisation, the clinical evidence base to support the use of the product in that population should be described.

Guidance notes:

Protocol specified subanalysis of a primary outcome or a secondary outcome measure of an active-controlled study would be the most relevant. However, other placebo-controlled and uncontrolled studies or real-world data may be included if they provide relevant evidence. Please refer to [Scottish Medicines Consortium \(SMC\) Position Statement on the Use of Real-World Evidence \(RWE\)](#) on the SMC website for further guidance.

- c) If the medicine has an MHRA conditional marketing authorisation, then provide details of the evidence required to meet the Specific Obligations set out by the MHRA.

Guidance notes:

For medicines with conditional marketing authorisation, provide details of studies that will fulfil the Specific Obligations set out by the MHRA.

For each study provide a brief description of:

- the study design, including details of blinding and randomisation;
- the main inclusion criteria, that define the patient population included in the study;
- the primary and/or other relevant outcome(s) measured in the study and likely timescale for reporting of these.

- d) If the medicine has an 'Innovation Passport' and is included in the MHRA ILAP or had a positive EAMS scientific opinion, please provide details of key efficacy data awaited from ongoing studies in this indication.

Guidance notes:

For each study provide a brief description of:

- the study design, including details of blinding and randomisation;
- the main inclusion criteria, that define the patient population included in the study;
- the primary and/or other relevant outcome(s) measured in the study and likely timescale for reporting of these.

Safety

- e) Provide details of studies that provide evidence of the clinical adverse effects with the medicine in the indication(s) under review relative to active comparator(s) used in clinical practice. The most relevant are active-controlled studies. However, if active-controlled studies are not available, details of placebo-controlled or uncontrolled studies should be included.
- (i) For studies primarily designed to investigate differences between the medicine under review and a placebo or active comparator in a safety outcome as the primary endpoint, provide complete details of the study, as described above.
 - (ii) For active-controlled studies that primarily assessed an efficacy outcome, provide details of any analyses, indicating significant differences in adverse event rates between the medicine under review and an active comparator.

- (iii) For placebo-controlled and uncontrolled studies that primarily assessed an efficacy outcome, provide details of the type and frequency of adverse effects that might be expected in clinical practice with the medicine in the indication(s) under review.

Guidance notes:

For (i) to (iii) details of these studies should be taken from complete published reports of the studies. However, if a published report of the study is not available, details should be taken from clinical study reports. These references should be provided with the submission to SMC. Where confidential data have been taken from a clinical study report, these should be clearly highlighted by underlining and shading appropriately as CIC or AIC and will be treated as confidential.

SMC is specifically interested in comparative safety. There is no requirement for highly detailed safety summaries versus placebo as provided to the regulatory authorities.

- f) Provide details of any additional safety issues for the medicine in the indication(s) under review compared with relevant active comparator(s) that were not identified in the studies described previously.

Guidance notes:

This section should include a brief summary of additional safety issues for the medicine under review compared with relevant comparator(s) that were not identified in the studies described previously and would include, but not be limited to, the following:

- details of any additional safety issues identified by the regulatory authorities, for example requirements for post-marketing surveillance of theoretical but rare potential adverse effects.
- details of adverse effects not yet identified with the medicine under review that have been observed with comparator(s). Similarly, details should be provided of adverse effects identified with the medicine under review that have not been observed with relevant comparator(s). Any limitations of available data for these comparisons should also be stated.

This information may be taken from publications produced by regulatory authorities, including Summary of Product Characteristics (SPCs), published papers and clinical study reports.

4 Indirect evidence

If results from indirect or mixed treatment comparisons have been **used in the economic model** to define clinical benefits and adverse effects to be expected in practice with the medicine and relevant comparator(s), complete the following checklist to show on what page of the NPAF the points have been addressed. (Information can either be included in the main document or as an appendix.)

Checklist of information for indirect evidence		Page no. in submission
1.	What type of indirect comparison has been performed? Describe and justify the methods used. Guidance notes: Describe the type of indirect comparison performed, for example, indirect treatment comparison, mixed treatment comparison, matching-adjusted indirect comparison, simulated treatment comparison. Please justify why you have chosen this particular method.	
2.	What are the comparators? Give the rationale for selecting these comparators, with reference to the clinical and economic case.	
3.	Have the results of this indirect comparison been used in the economic analysis? (base case/sensitivity analysis – please specify which). Guidance notes: Important: any indirect evidence used in the economic base case or scenario analyses must be identified and appraised in this section.	
4.	Describe the target population, this should match the clinical and economic case.	
5.	Provide details of the data sources used and the search strategies employed. Guidance notes:	

	See section 4 b) for further information.	
6.	Provide a PRISMA diagram showing studies included and excluded from the indirect comparison (studies which were eligible for inclusion in the systematic review and were excluded from the analysis).	
7.	Where additional eligibility criteria were used to inform study selection for the indirect comparison please specify.	
8.	Provide a tabulated list of studies excluded from the indirect comparison with reasons for exclusion in accordance with the Population, Intervention, Comparison, Outcome, Study design (PICOS) framework.	
9.	Which individual studies (and not records) have been used in the indirect comparison? Guidance notes: Indicate the sources of specific data used in the indirect comparison and include the supplied reference publications for these studies in a separate reference folder titled 'Indirect comparisons references'.	
10.	Provide a diagram of the complete network showing the connection between treatment nodes and provide a network diagram of any restricted networks used in any sensitivity analyses.	
11.	Provide a quality assessment of included studies indicating which tool has been used. Guidance notes: A quality assessment of the studies included should be provided and the tool used should be specified (for example, the Cochrane Risk of Bias Tool or the Newcastle Ottawa Scale). The risk of bias for each domain assessed by the specific tool should be tabulated and reported and an overall assessment of the risk of bias stated.	
12.	Do some studies include patients outside the target population? Have subgroups of some studies been used?	
13.	Briefly describe the methods used for the indirect comparison. Include details of any statistical or clinical assumptions made.	

	Guidance notes: For example, are proportional hazards assumed in the analyses or are methods used to account for non-proportional hazards?	
14.	Include evidence to support choice of fixed or random effects model (for example goodness of fit statistics, Deviance Information Criterion [DIC]).	
15.	What clinical and safety outcomes have been assessed in the indirect comparison? Provide adequate justification.	
16.	Provide tabulated details for each treatment group of each study included in the indirect comparison, paying particular attention to any treatment effect modifiers or prognostic factors, including: • number of patients in each treatment group or relevant subgroup • patient characteristics • baseline severity of condition • previous treatments • interventions and any additional medication used • length of follow up and/or data maturity • primary outcome (with definition).	
17.	If a matching-adjusted indirect comparison has been performed, please state how many baseline characteristics have been matched, provide details of the treatment group before and after matching and of the weights applied. Guidance notes: If an anchored analysis has been conducted, then treatment effect modifiers should be outlined. However, if an unanchored analysis has been undertaken treatment effect modifiers and prognostic factors should be outlined.	
18.	If a simulated treatment comparison has been undertaken, please outline the baseline characteristics identified and include the degree of systematic error for the analysis.	

	Guidance notes: If an anchored analysis has been conducted, then treatment effect modifiers should be outlined. However, if an unanchored analysis has been undertaken treatment effect modifiers and prognostic factors should be outlined.	
19.	Provide tabulated details of data input to the analysis for each treatment group (and relevant subgroups when appropriate) of each study included in the indirect comparison and the time point at which these results were assessed.	
20.	Comment on any differences between the included studies in terms of: • study methods • patient or disease characteristics • previous treatments • interventions and assessment time points • outcomes or durations of follow up • common comparator used • results in common comparator groups • statistical analysis	
21.	Provide the results of the indirect comparison in terms of the relative treatment effect of the medicine under review versus the selected comparators. Guidance notes: This should include the relative treatment effect (hazard ratio, difference, odds ratio [with justification for choice]) and the 95% CI or credible interval around this. In addition, ranking of treatments should be reported.	
22.	Where relevant, describe any evidence of inconsistency between direct and indirect results.	

23.	Report any measures or assessment of heterogeneity. Guidance notes: Further information can be found in the Cochrane Handbook for Systematic Reviews of Interventions available from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current .	
24.	Provide details of any sensitivity analyses performed to explore uncertainty, including justification and relevance to the economic analysis.	
25.	Conclusions of the indirect comparison.	

- a) Provide an overview and brief details of the presented analysis.

Guidance notes:

This should include

- a description and justification for the type of methodology used in the indirect or mixed treatment comparison
- the population of interest
- the rationale for the identified comparator(s)
- the intervention
- and the outcomes of interest with reference to both efficacy and adverse events.

- b) Provide details of the search strategies and rationale for identification of data sources used in the indirect or mixed treatment comparison, detailing inclusion and exclusion criteria, to provide evidence of clinical benefits and adverse effects.

Guidance notes:

This should include criteria for inclusion and/or exclusion of studies from the evidence base, preferably using the PICOS framework. If a search has not been performed, provide details of the rationale supporting the choice of data sources to provide clinical evidence.

Using the checklist below as a guide, provide details of the search strategies undertaken to identify data sources used in the indirect comparison that provide evidence of the clinical benefits and adverse events. The checklist is based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement and supporting checklist. This approach provides transparency and a reproducible method for reporting search strategies.

Section	Details
Title	Include the new medicine name and indication
Summary	Provide a summary of the submission including data sources, study eligibility criteria (inclusion and exclusion) and key findings
Eligibility criteria	- PICOS - Date limits - Language limits - Publication or study type limits - Human/animal limits applied
Information sources	List all information sources, including: - platform used (e.g. OVID, Dialog), - databases searched and years of coverage, - date search was conducted, - details of any personal communications
Search	Present full electronic search strategies for all databases, including any limits applied (please include origin/name of filters used, such as McMaster or Scottish Intercollegiate Guidelines Network [SIGN]) and the number of results retrieved
Study selection	Provide details of the process for selecting studies, including: - number of studies identified through searches - number of studies screened - number assessed for eligibility - number included in the review with reasons for all exclusions at each stage
Reference lists	Complete reference details for included and excluded studies

- c) Provide a diagram of the network and a table with details of the data sources used in the indirect or mixed treatment comparison(s) to provide evidence of clinical benefits and adverse effects. Include an assessment of the quality of the data sources and specific reasons for excluding any additional studies.

Guidance notes:

This should include:

- a pictorial representation of the complete network(s) used in any indirect or mixed treatment comparison(s) and any restricted networks that may have been used in any sensitivity analyses.
 - a list of studies included in the indirect comparison or networks(s); when describing clinical studies, provide the study title, study acronym, national clinical trials register number and/or clinical study report number where appropriate. This list of studies should be referenced and the references supplied with the submission to SMC. Such information may be best supplied in appendices.
 - reasons for the exclusion of additional studies with an assessment of the quality of the data sources and identify any potential sources of bias in included studies.
 - report in tables the relevant baseline demographics of the included studies and individual study results for all outcomes analysed in the indirect comparison or mixed treatment comparison. Such information may be best supplied in appendices.
- d) Provide results (hazard ratios and 95% CI or credible intervals) and where appropriate include ranking of treatments, a measure of heterogeneity or sensitivity analysis to account for heterogeneity, description of evidence consistency, use of random or fixed effects or other relevant information. Clearly identify any results that have been used in the economic model.

5 Clinical effectiveness

Describe any limitations of the methodology and conduct in the key clinical efficacy or clinical effectiveness studies affecting the quality of the evidence of clinical benefits and adverse effects with the medicine in the indication(s) under review relative to relevant active comparator(s) (with respect to the proposed positioning of the product within the submission, if relevant).

a) Relative to relevant active comparator(s)

Guidance notes:

Examples include, but are not limited to, the following:

- open-label design for measurement of subjective outcomes, such as quality-of-life and adverse events
- non-random assignment to treatment
- effect of high dropout rates on study power.

If you have chosen to make a clinical and/or economic case for only part of the licensed indication under review or for a specific subgroup of the eligible patient population, any limitations to the evidence base to support this positioning should be identified, justified and discussed, including any 'mismatch' between the clinical evidence base and the economic analysis.

b) Describe the relevance of the outcomes assessed in clinical studies to clinical benefits, health-related quality of life (HRQoL) and adverse effects expected in practice and how the medicine would be expected to address any areas of unmet need.

Guidance notes:

Include relevant details from guidance, such as that from regulatory authorities or professional bodies, on preferred outcome measures for the condition under review. Describe details of whether studies have directly measured health outcomes such as mortality, survival, incidence of disease, morbidity, functional performance, quality of life or whether surrogate outcomes have been measured, such as reduction in blood pressure.

Surrogate outcomes should only be used when final patient-relevant outcomes are not possible and when essential to inform the clinical or economic case. For a surrogate outcome to be considered valid, there should be evidence that the relative effect of the medicine on the surrogate outcome is predictive of its relative effect on the final outcome. Evidence of a predictive relationship should be supported by robust empirical evidence and should be in the population, disease stage and type of technology relevant to the medicine being assessed by SMC. The degree of uncertainty around the predictive relationship should be addressed. If the surrogate-final outcome relationship has been borrowed from another clinical context or population, this should be explicitly justified and uncertainty explored. All

surrogate outcomes used should be biologically plausible and fully justified and validated appropriately for the population under consideration. For use in a cost-utility analysis (CUA) the most useful surrogate outcomes are those that predict HRQoL and/or survival.

The multi-agency white paper 'Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment' was developed in 2024 to offer guidance in best practice for technology developers in the use and reporting of surrogate endpoints in HTA.

It is accepted that for rare conditions the level of evidence to support the association between the surrogate and final outcome may not be high.

- c) Describe any factors that may influence the applicability of study results to patients in routine clinical practice in Scotland.

Guidance notes:

Provide details of differences between the patient populations included in the studies that provided evidence of clinical benefits and adverse effects compared with the Scottish population likely to receive the medicine in clinical practice. Examples of this include, but are not limited to, the following:

- differences in baseline demographics, such as age, performance status, previous treatments, severity of disease
- differences in clinical management such as the dose schedule of comparator(s) or permitted/disallowed concomitant medicines, monitoring or assessment frequency.

- d) If the medicine has a MHRA conditional marketing authorisation outline how the data requirements for the Specific Obligations could address key uncertainties in the clinical evidence.
- e) If the medicine has an 'Innovation Passport' and is included in ILAP or had a positive EAMS scientific opinion, please outline how further data could address key uncertainties in the clinical evidence.

The following questions should be completed to provide a balanced account of the advantages and disadvantages of the medicine in the indication(s) under review relative to relevant active comparator(s).

- f) Provide details of the main alternative treatments used for the indication(s) under review within the Scottish clinical practice.

Guidance notes:

The comparator should reflect any proposed positioning of the product within the submission, if relevant. If the relevant comparator is a medicine, it is expected to be a licensed product in most circumstances; however, comparators may include off-label or unlicensed products, provided they are in routine clinical use in NHSScotland.

The assertion that a treatment represents routine use or best practice should be supported by data confirming that the treatment is routine, established and accepted clinical practice in the majority of NHS boards in NHSScotland. Recommendation of the treatment in national clinical guidelines or clinical management pathways may also be relevant (for example see [Right Decision Service](#)).

- g) Provide details of relevant guidelines and protocols relating to the medicine for the indication(s) under review, including previous SMC guidance for medicine(s) that may also be used for the indication(s) under review.

Guidance notes:

Relevant clinical guidelines include those from national organisations such as SIGN and NICE and professional bodies such as the Royal Colleges. If the guideline development was supported by a grant (such as from a pharmaceutical company) this should be noted. The following information should be included:

- the organisation responsible for the guideline
- the title of the guideline
- the date the guideline was published
- brief details of recommendations within the guideline for the medicine and relevant comparator(s) within the indication(s) under review.

Provide full details of the final advice paragraphs for previous advice from SMC for medicines that may also be used for the indication(s) under review.

- h) Provide details of any advantages or disadvantages, other than clinical benefits and adverse effects with the medicine in the indication(s) under review compared with usual clinical practice with the relevant active comparator(s). These would include, but are not limited to, differences in terms of: (a) tests or investigations for selection or monitoring of patients; (b) routes or schedules of administration; and (c) service changes.

Guidance notes:

- Tests or investigations for selection or monitoring of patients: provide details of any additional tests or investigations needed for selection or monitoring of patients over and above usual clinical practice with the relevant active comparator(s). For example, in terms of efficacy to establish eligibility for treatment (e.g. measure a pre-specified severity of disease for which the product is licensed) or monitor effect (e.g. assess response necessary for continuation of treatment). In terms of safety, to identify patients in whom the treatment is contraindicated and/or who are particularly at risk from known adverse effects or monitoring to detect potential adverse effects. If the recommended testing/monitoring regimens are extensive, these may be included as an appendix.

- Routes or schedules of administration: provide details of any differences in routes or schedules of administration compared with usual clinical practice with the relevant comparator(s). For example, fewer visits to hospital for administration of infusion.
- Service changes: provide details of any service changes that would be associated with use of the medicine in the indication(s) under review, compared with usual clinical practice with the relevant comparator(s). For example, increase or reduction in healthcare facilities.

Where these aspects are associated with changes in resource use, this should be reflected within the economic analysis and budget impact template, where relevant.

i) If an indirect or mixed treatment comparison has been conducted:

- Discuss details of any relevant differences between the data sources providing evidence of clinical benefits and adverse effects with the medicine in the indication(s) under review and those providing evidence for indirect comparator(s).

Guidance notes:

These would include, but not be limited to, differences which might bias or otherwise adversely impact the indirect or mixed treatment comparison in terms of:

- patient populations, by comparing inclusion/exclusion criteria, baseline demographics, including defining relevant variables such as disease severity and previous or additional treatments;
- medicine treatments, by comparing dosing schedules of study medicines and concomitant study medications that were allowed and disallowed;
- methodology, by comparing phase (II/III/IV), methods of measuring primary/secondary end points, randomisation method, any stratification, blinded/open-label, placebo or active comparator-controlled, any important subgroups, treatment switching, imputation of missing data methods;
- length of study, by detailing any differences;
- results, by listing study results highlighting any inconsistent findings;
- study limitations, by comparing limitations in methodology including any potential sources of bias in the individual studies and application of results to practice.

Where relevant this should reflect any proposed positioning for the product in the submission.

- Provide a conclusion detailing any limitations in terms of the evidence synthesis or extrapolation to the Scottish population.

Guidance notes:

Summarise the key results from the evidence and provide details/background/explanation for any limitations in the evidence synthesis and if these might affect the extrapolation of the results to the relevant Scottish population.

- j) Are there any potential equality issues that should be taken into account when considering this condition and medicine?

Guidance notes:

These would include, but not be limited to, any potential equality issues that affect groups of people:

- who share the protected characteristics of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation
- who may be affected by health inequalities (especially if these involve one or more protected characteristics)
- with the condition who have difficulties using currently available treatments
- with the condition who may have difficulties using the new medicine.

6 Pharmaco-economic evaluation

6.1 Introduction

Section 6 of the NPAF must be completed by reporting the design, methods and results of the economic evaluation. Detailed guidance is provided on all of the relevant aspects below.

For ease of reference, the checklist contained in this section must be completed to denote where in the submission each of the aspects has been covered.

6.2 Economic checklist

The design of the evaluation		Page no. in submission
1.	The alternatives compared are clearly described.	
2.	The rationale for choosing the alternative programmes or interventions compared is stated.	
3.	The patient group(s) considered in the economic evaluation is clearly stated and justified.	
4.	The viewpoint of the analysis is clearly stated and justified.	
5.	The time horizon over which costs and benefits were calculated is stated and justified.	
6.	The primary outcome measure(s) for the economic evaluation is clearly stated and justified.	
7.	Evidence is provided linking proxy or disease-specific outcomes to final health outcomes.	
Data collection		
8.	The source(s) of effectiveness estimates used are stated and cross-referenced to the clinical section of the submission.	
9.	Methods to value health states and other benefits are stated and details of the subjects from whom valuations were obtained are given.	
10.	Quantities of resources are reported separately from their unit costs.	

11.	Methods for the estimation of quantities and unit costs are described.	
12.	If a model is used, the choice of approach is justified.	
Analysis and interpretation of results		
13.	The approach to sensitivity analysis is stated.	
14.	The choice of variables for sensitivity analysis and the ranges over which the variables are varied is stated and justified.	
15.	Major outcomes are presented in a disaggregated as well as aggregated form	
16.	The relevance (generalisability) of the analysis to Scotland is discussed.	
17.	Any equity implications of the analysis are discussed.	

Submitting companies may enter N/A for items 7, 9, and 12.

Where the medicine is an ultra-orphan, please see the Guidance to submitting companies for completion of New Product Assessment Form (NPAF) for ultra-orphan medicines on the [Making a submission](#) page of the SMC website, where the submission template for ultra-orphan submissions can also be found.

6.3 Remit and exceptions to the guidance

The SMC process requires an economic evaluation of a medicine within the context of the NHS in Scotland. If the submitting company does not submit economic evidence according to the principles and standards outlined in this guidance SMC will be unable to accept the medicine for use in NHSScotland.

The only exception to the requirement for an economic evaluation is for medicines that fulfil the SMC criteria for an abbreviated submission, details of which can be found in the SMC Process guide for submitting companies on the SMC website.

6.4 Responsibility of the submitting company

SMC issues advice on new medicines to NHS boards and prescribers in Scotland based on an assessment of the likely clinical and cost effectiveness. The principal source of evidence for this assessment is the submission made by the pharmaceutical company. **The onus is on the company to clearly demonstrate the case that the medicine is cost effective in the positioning proposed.** To achieve this, the submitting company must provide a clear, concise, unbiased and robust case to support the application. Robustness will be judged on the basis of the methodological quality of the case submitted. The application needs to show that the medicine will:

- (i) provide additional health benefits that are valued by patients compared with current Scottish practice and that this is at a net cost to the NHS that offers acceptable value in relation to other uses of the same resources,
- or
- (ii) offer equivalent levels of health benefit to patients at an equivalent or lower net cost to the NHS.

6.5 SMC reference case summary

This section of the guide sets out SMC's expectations on a range of factors around the preparation of the economic case. SMC expects companies to use the reference case as summarised in Guidance table 1 in their base case analysis. Relevant sections thereafter will provide further information on the expectations within each aspect of the reference case.

Guidance table 1: Summary of reference case

Defining the decision problem	Submitting company must clearly define the patient population and interventions compared. Selective submissions (as per section 1b of this guide) are permissible. SMC does not offer scoping pre-submission to define the decision problem.
Comparator	Treatment most likely to be displaced in NHSScotland.
Perspective (costs and outcomes)	Effects: all direct effects whether for patients or where relevant, carers. SMC requires the patient perspective as the base case and where relevant, a patient and carer perspective as additional analysis (including accompanying key sensitivity analyses to be presented with both the patient-only perspective and patient and carers perspectives). Costs: NHSScotland and social work (Personal Social Services [PSS]). Non-reference case costs only as additional sensitivity analysis.
Type of economic evaluation	Cost utility analysis (CUA) preferred. Cost minimisation analysis (CMA) acceptable where equivalence in relevant outcomes can be demonstrated. Other approaches only acceptable where quality adjusted life years (QALYs) can be demonstrated to be inappropriate.
Time horizon	Sufficiently long to reflect any differences in costs and outcomes between the interventions being compared.

Synthesis of evidence on health effects	Evidence assembled systematically; synthesised transparently/reproducibly.
Measuring health outcomes/effects	QALYs preferred.
Data for HRQoL	EQ-5D reported directly in patients (and carers where relevant) as the preferred measure.
Valuation of HRQoL	Representative sample of the UK.
Evidence on resource use and costs	Resource use and cost data should be clearly presented, justified, and sourced transparently. Costs should reflect NHSScotland and social work)/PSS resource use where relevant.
Discounting	Annual discount rate of 3.5% on costs and benefits.
Sensitivity analysis/uncertainty	Deterministic, probabilistic and scenario-based sensitivity analysis should be provided.
Equity	Additional QALYs have the same weight irrespective of the circumstances of those receiving the health benefit.

Submitting companies may consider it appropriate to present analyses that differ from the reference case in one or more aspects. These should be appropriately justified and clearly marked as additional analyses. If the base case economic evaluation does not comply with the reference case, SMC will request a revised NPAF to include a compliant version.

6.6 Consistency of requirements across the UK

SMC recognises that the pharmaceutical industry engages with organisations across the UK performing similar roles, notably NICE and AWMMSG. A key theme in developing and updating this SMC guide was consistency with existing, authoritative guidance where possible; in the UK context this means the NICE document, NICE technology appraisal and highly specialised technology guidance: the manual (henceforth ‘the NICE guide’). This document was drawn up by experts, following extensive discussions and consultation and many of the principles can be accommodated within the SMC guide.

6.7 Design of the economic evaluation

6.7.1 Defining the decision problem

SMC does not offer pre-submission scoping. The submitting company should therefore provide a clear statement of the decision problem. This will require a definition and justification of the medicines being compared and the relevant patient group(s). If the submission applies only to part of the indication (a selective submission) then this should be stated. SMC advice may then necessarily be limited to the element of the indication for which evidence is submitted. Populations/indications for which there is no economic evaluation will be explicitly excluded from SMC advice.

The economic and budget impact analyses presented in sections 6 and 7 of the NPAF should always relate specifically to the target population that is the focus of the company submission. The advice box in the SMC published advice will make clear the elements of the marketing authorisation covered by the advice if a selective submission has been made.

6.7.2 Comparator

A comparator may be any medicine or non-medicinal treatment that is used in current clinical practice in Scotland for the indication(s) under review in the submission. Relevant comparators are those that are considered to be in routine use or represent best practice in NHSScotland and are the treatments that are most likely to be replaced if the medicine under review is accepted by SMC. All relevant comparators must be identified, although a full comparison will not always be appropriate for every one of these comparators; companies would however be expected to provide analysis versus the predominant comparator(s). The relevant comparator might also involve no active treatment of the condition.

The assertion that a treatment represents routine use or best practice should be supported by data confirming that the treatment is routine, established and accepted clinical practice in the majority of NHS boards in NHSScotland (for example, data from the Cancer Medicines Outcomes Programme [CMOP] if available). Recommendation of the treatment in national clinical guidelines may also be relevant, particularly where these are informed by cost-effectiveness analysis. If current treatment patterns are highly variable, the SMC preference would be for the comparator to be based on Scottish treatment or audit data. Where data do not show the predominance of one treatment, SMC would not expect to see comparisons against every possible treatment. Instead, the submitting company should select (and justify) a base case comparator treatment but also provide supplementary analysis against another treatment(s) where possible, particularly if there are known to be large cost or effectiveness differentials between the relevant treatment options which are likely to influence the cost-effectiveness results.

A relevant comparator medicine is expected to be a licensed product in most circumstances; however, comparators may include off-label or unlicensed products, provided they are in routine clinical use in NHSScotland. SMC recognises that submitting companies have strong reservations about comparing with unlicensed or off-label medicines. However, in judging the comparator to use, the submitting company must bear in mind that some unlicensed or off-label medicines are so widely used that any economic comparison that did not include them would have neither relevance nor credibility for the NHS in Scotland. If an unlicensed or off-label medicine is chosen as the comparator then indirect comparison might be the appropriate basis on which to base the cost-effectiveness assessment. In such circumstances, where there is a lack of robust data on the comparator product, SMC appreciate that such analyses may be associated with higher levels of uncertainty.

The submitting company may need to consider whether a medicine that is currently being appraised by SMC or for which SMC has recently issued advice should be included as a comparator. Where the SMC advice on a new medicine that would be considered a relevant comparator has been in the public domain for 6 months at the time of the submission, SMC would normally expect the company to include this comparator in the analysis.

If current practice is not 'best practice', for example, where SMC advice (or NICE/SMC collaborative multiple technology appraisal [MTA] guidance if relevant) has been issued but not implemented and data on prescribing trends suggest the SMC accepted medicine is likely to become standard practice in the near future (for example, the next 12 months)

then it should be selected as the comparator; this will be a matter for judgement and the rationale for the approach used should be set out. However, if there is no such evidence then current Scottish practice is the preferred choice of comparator. Medicines that are not recommended for use by SMC can be used as comparators on a case-by-case basis but would need to be supported by appropriate data showing established and predominant usage of the medicine in the population of interest in NHSScotland. In these circumstances, SMC may also require a comparison against an alternative medicine accepted by SMC or against a placebo/best supportive care option.

Medicines that are accepted for use on an interim basis can be considered as relevant comparators on a case-by-case basis but would need to be supported by appropriate data. In these circumstances, SMC may also require a comparison against an alternative medicine accepted by SMC or against a placebo/best supportive care option.

In the case of medicines that are in use following an SMC initial assessment through the ultra-orphan pathway, these may also be considered a relevant comparator provided the new treatment itself is being considered as part of the ultra-orphan pathway. For new treatments that are not being considered as part of the ultra-orphan pathway, an alternative comparator should be selected such as the previous standard treatment or best supportive care.

If the key comparator medicine is available under a PAS, then please refer to Section 6.10.3 in terms of how the pricing of the comparator medicine is approached in the economic model.

6.7.3 Perspective

For the base case, the perspective on outcomes should be all direct health effects for patients. Where relevant, analysis incorporating both patient and carer effects should be presented as additional analysis. The perspective adopted on costs should be that of the NHS in Scotland and social work (referred to as PSS in England).

If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, these should be reported in a sensitivity analysis. They can also be included in a discussion although this may limit their impact on the decisions.

6.7.4 Type of economic evaluation

In general, CUA is the appropriate form of economic evaluation to be used in SMC submissions, with health effects expressed in terms of QALYs.

CMA may be appropriate if the proposed medicine is demonstrated by studies to be therapeutically equivalent to the relevant comparator(s), as assessed using an adequately designed and powered non-inferiority or equivalence or superiority study. Companies should consider using the SMC abbreviated submission process where cost minimisation is the key analysis used. This is a simpler, less resource-intensive process.

Therapeutic equivalence may be established on the basis of final patient outcomes, preferably, but evidence from surrogate endpoints (see guidance notes in section 5b), may also be acceptable. CMA may also be an appropriate choice of economic evaluation where

the results of appropriately conducted indirect comparisons show statistically insignificant differences in clinical effectiveness (either on final patient outcomes or accepted surrogate endpoints). Uncertainty associated with use of surrogate outcomes in an economic model should be quantified and explored using probabilistic sensitivity analysis (PSA) and scenario analyses. Where multiple potential valid surrogates exist, this should also be reflected in the analysis of uncertainty.

Where a CUA shows extremely small differences between treatments in terms of QALYs, it may also be helpful for submitting companies to provide sensitivity analysis showing the impact of assuming a CMA approach (such as no differences in QALYs).

Submitting companies should note that failure to collect data to measure and value QALY gains in the clinical study programme is not an adequate reason for not using QALYs. Similarly, disease-specific outcomes as the outcome measure in the economic evaluation are not helpful since they do not give comparability of the cost effectiveness of a medicine against other uses of healthcare resources.

Alternative approaches can be considered in those circumstances in which the QALY may not to be the most appropriate outcome measure. For example:

- The QALY does not capture the main health benefit of the medicine – contraception is one example. In this situation, cost- effectiveness analysis is acceptable.
- The QALY does not capture the main benefit of the medicine where this is something other than health. For example, the main advantage of a new medicine might be patients prefer the delivery system. However, submitting companies need to be cautious because the SMC may ask whether this preference translates into better concordance and whether this translates in turn into health gain. The company must make a careful argument for not using a QALY in these circumstances.
- Utility values used to generate QALYs appear to lack sensitivity in circumstances where other measures suggest health improvements or disease reductions. Again, this should be demonstrated and not simply asserted. SMC would need to be assured that the changes in alternative outcome measures are valued by patients.
- Utilities used to generate QALYs cannot be adequately measured for the main health states generated by the condition in question (e.g. this may be the case with some mental health states).
- Cost-consequence analysis is not generally useful to the SMC as the trade-offs between different dimensions of benefit are not made clear; however in the case of ultra-orphan medicines, SMC may consider this form of analysis; see the Guidance to submitting companies for completion of New Product Assessment Form (NPAF) for ultra-orphan medicines on the [Making a submission](#) page of the SMC website for more details.

Submitting companies are urged to think carefully before deciding not to use CUA as the SMC regards this methodology to be the most appropriate to make comparisons of value across healthcare interventions.

6.7.5 Time horizon for the economic evaluation

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the medicines being compared.

Results (in terms of net cost per QALY gained) need to be reported at different time horizon intervals, for example at end of study follow up, at 5-year follow up and at 5-year intervals thereafter.

A time horizon shorter than lifetime is justifiable when there is no differential mortality effect between options and differential costs and HRQoL relate to a relatively short period, for example, in the case of an acute infection.

6.8 Synthesising evidence on outcomes

All the relevant clinical literature relating to the medicine under evaluation will be included in sections 3 and 4 of the submitting company's submission. Data cuts used in the clinical and economic section should not differ (any difference should be highlighted and justification provided). NICE describe an approach that will synthesise these data into a point estimate of treatment effect plus the variance around that estimate. This approach is valid, but the SMC will also accept an economic evaluation based on a single clinical study provided:

- (i) the patients recruited to the study are broadly representative of a Scottish or UK population,
 - (ii) the study provides direct evidence with the relevant comparator
- and
- (iii) it is demonstrated by the submitting company that this study does not have notably different results to the studies that are not used. In other words, the SMC requires consistency of clinical effects between sections 3 and 6 of the submitting company's submission and no bias.

6.8.1 Indirect comparison

See sections 4 and 5 for details on advice for conducting and reporting of indirect treatment comparisons. Note that for the purposes of the economic analysis, the values elicited from the indirect comparison (including the upper and lower limits) should be a key part of the base case results and sensitivity analysis.

6.8.2 Systematic review

This involves the systematic location, appraisal and synthesis of evidence in order to obtain a reliable overview. Databases searched and literature searching strategies should be reported. There should be a clear rationale for selecting specific studies from those identified.

6.8.3 Study selection and data extraction

In order to reduce the risk of selective use of single studies, submitting companies should demonstrate that a systematic literature search has been undertaken and state the inclusion criteria for studies. Each study meeting the criteria for inclusion should be subjected to critical appraisal.

6.8.4 Meta-analysis

Synthesis of outcome data through meta-analysis is appropriate provided there is sufficient, relevant and valid data that uses comparable measures of outcome. Where such data are not available, the analysis may have to be restricted to a qualitative overview that critically appraises individual studies and presents their results. Forest plots are a useful tool to illustrate the individual study population results. The characteristics and limitations of the data (that is population, intervention, setting, sample size and validity of the evidence) need to be fully reported.

Before any statistical pooling is carried out an assessment of the degree of, and the reasons for, heterogeneity in the study results should be undertaken – that is, any variability in addition to that accounted for by chance. Statistical heterogeneity of study results can, to some extent, be addressed using a random (as opposed to fixed) effects model. Known clinical heterogeneity (for example patient characteristics or intervention dose or frequency) can be managed by judicious use of methods such as subgroup analyses and meta-regression. For methodological heterogeneity (for example where different studies are of different quality) the results of sensitivity analyses (varying the studies in the meta-analysis) should be reported. If the risk of an event substantially differs among the control groups of the studies included in a meta-analysis, an assessment of whether the relative risk is constant over different baseline risks should be undertaken. This is especially important when the relative risk is to be used within an economic decision model and the baseline rate in the model is very different to the control event rates of the studies in the meta-analysis.

Forest plots should include lines for studies that are believed to contain eligible data even if the data are missing from the analysis in the published study. An estimate of the proportion of eligible data that are missing (because some studies will not include all relevant outcomes) will be needed for each analysis.

6.8.5 Role of expert opinion

Where data from studies are absent or insufficient to provide values for relevant parameters, estimates from expert elicitation exercises may be included. Structured elicitation approaches are preferred, using established methods such as The Medical Research Council protocol, the Sheffield Elicitation Framework, the Cook Method, IDEA (Investigate, Discuss, Estimate, Aggregate) and Modified Delphi. Outside of structured expert elicitation methods, SMC may accept the use of expert opinion to inform key parameters if appropriate justification can be given, on a case-by-case basis.

Given the inherent uncertainty associated with such a data source, it is important that sufficient information on the method used is provided to help inform an assessment of bias that could be associated with parameter estimates obtained in this way. Submitting

companies should provide detailed information covering aspects such as rationale for use of expert elicitation, selection of experts, declarations of interest, data collection approach, aggregation method and presentation and interpretation of results.

Variables obtained through expert elicitation methods must be tested in appropriate sensitivity analysis.

6.9 Measurement and valuation of health effects in the economic evaluation

SMC has a preference for CUAs using QALYs as the primary outcome measure.

HRQoL for inclusion in the CUA should be measured directly in patients relevant to the decision problem, or if this is not possible, from their carer. The utility of changes in HRQoL should be based on public preferences using a choice-based method.

6.9.1 Patient health-related quality of life

EQ-5D is the preferred measure of HRQoL in adults.

Utility values used where there has been extrapolation of effects over extended time horizons in the economic model should be adjusted to reflect decreases in HRQoL seen in the general population and to make sure that they do not exceed general population values at a given age.

Where EQ-5D data are not available from the key clinical study supporting the submission, other literature sources can be used. This should be done in a transparent and systematic way, with justification for the values selected and any uncertainty addressed through sensitivity analysis.

Mapping from other HRQoL measures or clinical study outcomes may be used when data from EQ-5D are not available. The choice of mapping approach should be fully documented and justified and uncertainty from the use of mapping should be addressed as part of sensitivity analysis.

There may be instances where the EQ-5D is not the most appropriate measure. If a submitting company considers this to be the case, this should be evidenced with respect to the content and construct validity of the tool. Alternative HRQoL measures can be used where this has been appropriately evidenced.

In circumstances where EQ-5D is not available or appropriate, SMC refers to the hierarchy of preferred HRQoL methods set out in the NICE guide in terms of good practice.

Measurement of HRQoL in children can be approached using generic measures developed for use in children and young people.

Submitting companies should refer to the NICE guide in terms of good practice in usage of the 3L and 5L versions of EQ-5D and their valuation.

6.9.2 Carer health-related quality of life

Where appropriate, data on utilities/QALYs for carers can be incorporated into the economic evaluation as a scenario analysis to the patient-only base case.

If health impacts on carers are included in the economic analysis, their impact should be measured directly using validated generic HRQoL instruments consistent with that used for the patient for example, EQ-5D-5L with valuation based on value sets obtained from a representative sample of the UK population.

A decrement approach should generally be taken to model carer quality of life associated with health states. A single carer should be assumed as standard.

Should the submitting company wish to present different estimates of carer HRQoL using alternative assumptions, this must be fully justified and presented as additional scenarios.

6.10 Evidence on costs

The central aim of costings in an economic evaluation is to accurately capture, value and report the resource implications of introducing a new health technology. The costing methods used should be transparent and sufficiently well described that they can be assessed and critiqued.

6.10.1 NHS and social work resource costs

The costs perspective that should be adopted within SMC submissions is that of NHS in Scotland and social work (equivalent to PSS in England). All activities and resources which would occur within the scope of the analysis should be identified through a detailed understanding of the current clinical or care pathway for the health condition in Scotland, and how this would change through the introduction of the new medicine.

The identified resources should be quantified appropriately. Where resource quantities come from clinical studies, consideration should be given to whether these are protocol-driven and therefore do not reflect Scottish practice. Resource units should be valued using costs relevant to the NHS in Scotland and social work. The range of sources that are suitable for valuing resources is extensive; however, a first point of reference should be any current official listing published by the Scottish Government Health and Social Care Department, Public Services Delivery Scotland, Public Health Scotland, the Department of Health and Social Care in England and/or the Welsh Assembly Government. Data on Scottish hospital costs are available on a per diem basis from Scottish Health Service Costs, which can be found on the Public Health Scotland website. [NHS Reference Costs](#) from NHS England are acceptable.

Primary care and community costs from the [Unit Costs of Health and Social Care Programme](#) publication by the Care and Outcomes Research Centre (previously known as Personal Social Services Research Unit [PSSRU], University of Kent), are also acceptable. As social service costs are hard to find for Scotland, English data (such as those from PSSRU) are acceptable. Other sources of cost data should be clearly explained and referenced.

If the medicine under review requires a diagnostic test (for example somatic, germline or biomarker test) in order to identify patients eligible for treatment within the marketing authorisation/target population and this represents a change in clinical practice this should be reflected in the economic analysis.

Appendix A of the NPAF should be completed by the submitting company based on the data used in the economic and budget impact models. This will allow the information to be shared in confidence with the Scottish Genomic Test Advisory Group (SG-TAG) or Scottish Pathology Network (SPAN), as appropriate, who will advise SMC on the diagnostic testing aspects of the economic case.

Where cost and resource use data are taken from literature, the methods used to identify the sources should be defined. Where several alternative sources are available, a justification for the costs chosen should be provided. Where appropriate, sensitivity analysis should be used to assess the implications for results of using alternative data sources.

Resource use and costs are two aspects of an economic evaluation that are least likely to be generalisable across countries. For resource use, data from elsewhere in the UK are acceptable. Resource use data from other countries or estimated by a panel of experts should be avoided if possible or at least validated for the Scottish setting (for example by demonstrating that treatment patterns are similar between the country in question and Scotland) and included in a sensitivity analysis. If cost conversion is required from international prices, this should be done using a common measure of exchange rate, with justification on the price comparability between the source country and Scotland.

As in all areas of the evaluation, where there is uncertainty in relation to resource use and cost values, the implications of that uncertainty upon results should be explored through appropriate sensitivity analysis.

Value-added tax (VAT) should be excluded from the economic evaluation but included in the budget impact calculation at the prevailing UK rate when the resources in question are liable for the tax.

6.10.2 Medicine costs

Where a PAS is proposed for the medicine under review, the PAS price should be used for calculating the base case results and all sensitivity analyses. Only PAS accepted by the Patient Access Scheme Assessment Group (PASAG) at the time of the SMC meetings will be considered in decision making. Where no PAS has been accepted, SMC will consider the submitted medicine using results at list price.

Typically, medicine costs for combination, comparator and subsequent treatments should be based on unit prices listed in the British National Formulary (BNF) or the Monthly Index of Medical Specialties (MIMS). Note that the Electronic Market Information Tool (eMIT) is not a suitable source for medicine costs within SMC submissions. SMC takes confidential national contract prices into account in its decision making. Specifically, the contract price of a medicine will be included if it is in one arm of the model only (used in combination or as a comparator) or is a subsequent treatment which is a key driver of the results. SMC does not take account of any other type of discount that may be applied to the list price of

comparator products and these should not be included within the economic evaluation; only PAS and national contract discounts are relevant.

In cases where the same submitting company manufactures the medicine under review and a combination/comparator/subsequent treatment, all known PAS can be included directly in the modelling.

Where a generic medicine is available at multiple price points, the cheapest cost should be used. If a volume-weighted average based on Scottish practice is used, a comparison with the cheapest medicine should be included in a sensitivity analysis.

Where the comparator, combination or subsequent treatment medicine has a confidential PAS or national contract price which is not known to the submitting company, this will be included in results used for decision making by the SMC assessment team. Further guidance on how this should be approached is provided in section 6.10.3.

As far as possible, SMC will look to base its final decision on the relevant medicine prices prevailing on the day of the SMC meeting when the medicine is assessed. Price changes for any medicine included in that pathway, which come into force greater than 10 working days of the SMC meeting will be incorporated into decision-making results. Changes made less than 10 working days in advance of the SMC meeting will be included at the discretion of SMC staff.

6.10.3 Medicines available under a PAS or national contract price

Where a relevant comparator medicine, medicine used as part of an inter-company combination or a medicine used as a subsequent treatment are applicable to the submission the 'with PAS' or contract prices will be relevant for SMC decision making. Guidance on the approach to each of these scenarios is provided in section 6.10.3.1 and appendix C outlines these for a range of possible scenarios.

6.10.3.1 *Comparator medicines available under a PAS or national contract*

If one or more key comparators in the economic case are available through a PAS discount or contract price, the submitting company should provide an economic model that facilitates the input of any confidential PAS or contract price discounts for the comparator medicines. The submitting company should ensure that the base case results, all scenario analysis results, probabilistic sensitivity analysis, and one-way deterministic sensitivity analysis can be re-run within the economic model by SMC using inputted confidential PAS/contract price discounts for the comparators.

If this cannot be provided by the submitting company, then the submitting company must provide the cost-effectiveness results of their product under its PAS against each comparator at list price as the base case and also using the full range of potential discounts for the comparator price between 5% and 95% in 5% increments (so for each comparator provide base case estimates accompanied by 20 sensitivity analysis for each 5% price discount level). These additional analyses should be provided as an appendix within the NPAF. Note that it is not acceptable for companies to provide only a set of analyses using a

single estimate of the anticipated discount for the comparator product (unless the submitting company also owns the comparator product).

During the assessment, further sensitivity analyses may be considered by the economic assessor. The submitting company may be asked to confirm the appropriate model options to select, or to validate the QALY outputs generated by the model for such analyses. If these considerations are not possible within the existing model, the submitting company should seek to update the model to facilitate such analysis under any comparator PAS/contract price. If this is not possible, the company may provide analysis results using a range of potential discounts for the comparator, from 5% to 95% in 5% increments.

The preference is for the submitting company to provide a suitable model to readily facilitate the input of the PAS discounts for the comparator medicines. In such a case where the company provides analysis in 5% to 95% increments, SMC will select the cost-effectiveness results that use the 5% increment closest to the actual PAS discount in place for the comparator and will use these for decision-making purposes.

In the event of comparator PAS discounts in the economic analysis, no results will be reported in the detailed advice document (DAD) issued to the submitting company following the NDC meeting and in the final published SMC DAD. Such results will only be presented in confidence to committee members as part of meeting paperwork (referred to as a 'Results for decision-making' document). A standard statement in the DAD will note that the results using the 'with PAS' or contract price for the comparator medicines were used for decision making but cannot be reported.

If the comparator medicine is available under a simple PAS/contract price, this PAS discount will be applied. If a comparator medicine is available through a complex PAS (defined in [NHS Scotland Patient Access Scheme \(PAS\) Guidance](#)), an equivalent simple PAS discount will be considered in the economic assessment.

6.10.3.2 Combination regimens available under a PAS or national contract

Where a submission involves the medicine under review being given as part of a combination regimen with another medicine that is available through a PAS or contract price and this medicine is also marketed by the submitting company, it is acceptable to use the 'with PAS' price of this medicine in the base case.

Where a submission involves the medicine under review being given as part of a combination regimen with another medicine that is available through a simple PAS or contract price and is marketed by a different company (an inter-company combination regimen), the submitting company should follow the approach outlined in section 6.10.3.1. This involves either providing an economic model that facilitates input of the discount for the other medicine, or, if this is not possible, submitting a table of results using a range of potential discounts for the other medicine, from 5% to 95% in 5% increments.

6.10.3.3 Subsequent therapy available under PAS or national contract

Where a subsequent therapy is available to patients in NHSScotland through a PAS or contract price, the submitting company should follow the approach outlined in section

6.10.3.1. This involves either providing an economic model that facilitates input of the PAS discounts for the subsequent therapy, or, if this is not possible, submitting a table of results using a range of potential discounts for the subsequent therapy, from 5% to 95% in 5% increments.

6.10.4 Reporting of cost-effectiveness estimates in the NPAF

Where the medicine submitted for review has a PAS, cost-effectiveness estimates should normally be provided both with and without the PAS. However, in a submission where both the new medicine under review and the comparator (or another medicine in an inter-company combination regimen) has a PAS, the cost-effectiveness estimates should apply the proposed simple PAS (or a simple equivalent in the case of a complex PAS) to the medicine under review and the list price of the comparator/combination/subsequent medicines should be used. As noted above, the company should provide an economic model that facilitates input of the discounts for the other medicines, or, if this is not possible, a table of results using a range of potential discounts for the other medicine, from 5% to 95% in 5% increments.

6.10.5 Resource implications (budget impact template)

Where the comparator (displaced medicine) is available through a PAS/contract price and/or the medicine under review is given as part of an inter-company combination regimen and the other medicine is available through a PAS/contract price, the budget impact template should use the list price for these medicines. There is no requirement to provide templates using a range of possible discount levels for the comparator/other medicine.

Please contact the SMC Secretariat for advice on complex situations where this guidance may not be sufficient.

6.10.6 Non-NHS and non-social work costs

All SMC submissions should maintain the cost perspective of NHS in Scotland and social work in the base case. However, it is acknowledged that there will be occasions where non-NHS/social work costs will be differentially affected by the medicines under comparison. In these situations, the submitting company should provide a clear justification as to why wider costs should be considered as part of decision making. As far as possible, this justification should be evidence based. Results inclusive of non-NHS/social work costs can be presented as part of sensitivity analysis. It remains the prerogative of the SMC Committee how non-NHS/social work will be considered in their decision making.

6.11 Discounting

Economic results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. The discount rates to be applied to costs and benefits should be an annual discount rate of 3.5%. When results are potentially sensitive to the discount rate used, sensitivity analysis should vary the rate between 0% and 6%.

6.12 Modelling methods

Modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost effectiveness relevant to the SMC's decision-making process. It is expected that submissions made to SMC, outside of abbreviated submissions, would use some type of economic modelling.

Models should be designed to explicitly address the decision problem at hand. They should look to reflect the current clinical and care pathways in Scotland, and how this would change through the introduction of the new medicine. Models are, by necessity, a simplified representation of reality, but care should be taken that sufficient granularity is included to allow for informed decision making. However, submitting companies should avoid unnecessary and unhelpful complexity. An example of this would be use of individual simulations to analyse a Markov model, as opposed to a more traditional cohort analysis and would require thorough justification, given the limitations for transparency in what is driving the model outputs, and difficulties for undertaking additional scenario analyses. It is also useful to frame any bespoke modelling in the context of other economic models which have been used in the same or similar disease areas. Where deviations are made from the structures and assumptions previously employed, these should be justified.

Modelling should be conducted to an appropriate standard, although providing an all-embracing definition of what constitutes a high-quality model is not possible. Some guidelines are available, such as the [Technical Support Documents](#) created by the NICE Decision Support Unit and ISPOR The Professional Society for Health Economics and Outcomes Research '[Modelling Good Research Practices](#)' reports.

Modelling work should be subject to quality assurance by the submitting company, to check for internal consistency, errors and face validity. Details of the quality assurance procedures undertaken should be summarised within the submission. Where external validation of the modelling has taken place, details of this should also be given. This includes the comparison of modelled outcomes with secondary sources and seeking the opinions of clinical experts.

In general, all structural assumptions and data inputs must be clearly documented and justified. This is particularly important in the case of modelling to extrapolate costs and health benefits over an extended time horizon. In such circumstances the results of using alternative time horizon scenarios must be reported to compare the implications of different assumptions for the results. Where data limitations have meant compromises and omissions within the modelling approach, these should be clearly highlighted and the implications described.

Given that one important and common role of economic models is to extrapolate observed outcomes to longer time horizons, the maintenance or otherwise of a medicine's treatment effect is an important consideration. All assumptions about the long-term treatment effect of a medicine made in the base case (including any assumption that the treatment effect would be maintained), should be explicitly addressed and justified. Where appropriate, alternative treatment effect durations should be explored in scenario analysis.

More broadly, it is important for models to quantify the decision uncertainty associated with a medicine – that is, the probability that a different decision would be reached if it were possible to ascertain the true cost effectiveness of each medicine before making the decision. Modelling parameters and structural assumptions which are a source of uncertainty and are likely to have a material result on the economic outcomes must be included in a sensitivity analysis.

6.13 Exploring uncertainty

As well as modelling a base case estimate of cost effectiveness, submitting companies must explore the full uncertainty in the economic analysis. This includes uncertainty about the clinical efficacy, costs, health impacts, the results of indirect treatment comparisons and the structural assumptions made in a model.

The following analyses should be presented to explore uncertainty in an SMC submission:

Deterministic sensitivity analysis

Deterministic (often one-way) sensitivity analysis helps identify the key drivers of the model results by showing how much the incremental cost-effectiveness ratio (ICER) (or other metric) changes when one input is varied at a time. It is most useful for understanding which parameters matter most and where additional evidence (or clearer justification of ranges) would most improve confidence in the decision.

The list of parameters and their sources included in the deterministic sensitivity analysis should be extensive and include the key measures of clinical effect and any results from an indirect treatment comparison. Those parameters should then be varied through a range that is sufficient to test the extent of the uncertainty, for example using 95% CIs where available. Where 95% CIs are unavailable, as a general rule a minimum of $\pm 20\%$ should be used but in certain circumstances a wider range may be required.

Probabilistic sensitivity analysis

PSA propagates parameter uncertainty jointly by repeatedly sampling from the specified input distributions. PSA therefore quantifies decision uncertainty—for example, the probability the intervention is cost effective at different willingness-to-pay values (commonly presented via cost-effectiveness acceptability curves [CEACs]) and the spread of results on the cost-effectiveness plane.

Many of the principles provided in relation to deterministic sensitivity analysis (see above) are relevant for probabilistic sensitivity as well. The selection of variables should be comprehensive, and they should be altered across an appropriate range. Where parameters included in the PSA are likely to be correlated, this should be reflected in the applied distributions.

Scenario analysis

Scenario analyses are primarily used to explore structural uncertainty and other ‘choice’ uncertainties (for example alternative extrapolation assumptions, alternative data sources,

different modelling approaches) that are not well represented by varying single parameters. They show whether conclusions are robust to plausible alternative assumptions, and they help committees understand which modelling choices are most decision-relevant—especially when combined scenarios are used to reflect ‘realistic worst/best case’ combinations.

Due to its direct interpretability, scenario analysis is often a way that uncertainty is explored in SMC appraisals. As standard, it is expected that scenario analysis should include alternative discount rates, time horizons, efficacy estimates/results from indirect treatment comparisons (where relevant) and any particularly influential resource use aspects. The submitting company should consider carefully what additional scenarios to include and provide sufficient commentary on them to enable an understanding of their relevance to identified sources of uncertainty. Combined scenarios are also expected where the scenario is plausible and is likely to have impact on the ICER.

Uncertainty associated with use of surrogate outcomes in an economic model should be quantified and explored using PSA and scenario analyses. Where multiple potential valid surrogates exist, this should also be reflected in the analysis of uncertainty.

If the submitting company presents a clinical case, based on either direct or indirect treatment comparisons, which show no statistical differences in treatment effect, a scenario with no additional treatment benefit from the new medicine should be included in scenario analysis.

6.14 Presentation of data and results

Clarity and transparency are key features of a high-quality economic evaluation. This section describes how submitting companies should structure and present data and results to allow for assessment and critique.

6.14.1 Presenting data

All data used to estimate clinical and cost effectiveness must be presented clearly, typically in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. Measures of precision should be detailed for all variables. As well as presenting details of inputs in relevant sections of the NPAF, it is particularly useful to present a summary table of inputs prior to the presentation of the results which draws together details in a single location.

Consideration should be given to how complex information can best be presented to decision makers, particularly how graphical representation can lead to greater interpretation of the model. This may include, but is not limited to, Kaplan Meier curves, survival projections and cohort traces.

6.14.2 Presenting expected cost-effectiveness results

The base case results should represent the submitting company’s best estimate of the economic impact of the introduction of the medicine under consideration. Base case results may be calculated deterministically or probabilistically. ICERs must be reported for all CUAs

and is calculated as the ratio of expected incremental cost to expected incremental QALYs. The ICER will be the main economic metric brought forward into decision making. Submitting companies may choose to present additional metrics where they are viewed as helpful. While net health benefit (NHB) and net monetary benefit (NMB) can be presented, given the lack of fixed upper threshold in the SMC process, these can be challenging to interpret in a Scottish context. If these approaches are provided, they should be used with reference to the values from NICE set out in section 6.16.

SMC make decisions based on pairwise comparisons. Where multiple comparators are relevant, full incremental analysis can be provided, but this should be considered supplementary.

Results from a CUA must be set out as follows:

Sample table 3 Base case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental life years gained	Incremental QALYs	ICER (£/QALY)
New intervention			-	-	-	-
Comparator A						
Comparator B						

Separate disaggregation of total QALYs and total costs across model states and cost categories is useful for helping decision makers understand the dynamics of the model and where the benefits of a new medicine are generated.

6.14.3 Presenting results from sensitivity and scenario analysis

The standard means of presenting deterministic sensitivity analysis should be a tornado diagram. This can be supplemented by results tables as appropriate. It is expected that submitting companies will provide meaningful commentary on how the results of deterministic sensitivity analysis should be interpreted.

In cases where altering the value of parameters leads to economic results shifting in directionality (such as moving from the northeast to southwest quadrant of the cost-effectiveness plane), presenting a tornado diagram of ICERs can be challenging. In this case it may be more informative to use NMB as the unit of measurement. As described in this guide, SMC does not have a fixed upper threshold value. Despite this, in these circumstances, NMB can be a useful means of highlighting the main drivers of uncertainty within the model and can be illustrated with reference to the values from NICE set out in section 6.16.

The results of PSA should be presented through scatter plots, confidence ellipses and CEACs. This can be supplemented by results tables as appropriate.

The results of scenario analysis should be presented as follows:

Sample table 4 Scenario analyses results

	Parameter	Base case	Scenario	Incremental costs (£)	Incremental life years gained	Incremental QALYs	ICER (£/QALY)
	Base case	-	-				
1	Parameter description 1	Base case value 1	Scenario value 1				
2	Parameter description 2	Base case value 2	Scenario value 2				
3	Parameter description 3	Base case value 3	Scenario value 3				

6.15 Supplementary analysis

6.15.1 Presenting analysis of clinical and cost effectiveness for patient subgroups

Given the SMC's focus on maximising health gain from limited resources, it is important to consider how clinical and cost effectiveness may differ because of differing characteristics of patient populations. Typically, the capacity to benefit from treatment will differ between patients, but this may also impact on the subsequent cost of care. There should be a clear clinical justification and, where appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect. Subgroup analysis based on ad hoc 'data mining' in search of significant subgroup effects would not be accepted. The characteristics of the patients associated with the subgroups presented should be clearly specified to allow the SMC to judge the appropriateness of the analysis with regard to the decision problem.

Care should be taken to specify how subgroup analyses were undertaken. This should include a clear description of what parameters have been altered between the full population analysis and the subgroup analysis. Given that subgroups will be smaller, and subgroup analysis may be supported by weaker evidence, the associated greater uncertainty should be appropriately explored in sensitivity analysis.

6.15.2 Reflecting equity considerations in cost-effectiveness analysis

The estimation of QALYs implies a particular position regarding the comparison of health gained between individuals. Thus, an additional QALY is of equal value regardless of other characteristics of the individuals such as their sociodemographic details, or their pre- or post-treatment level of health.

Distributional cost-effectiveness analysis (DCEA) is an analysis technique which allows societal preferences over inequalities to be factored into economic evaluations using a system of weightings on health benefits. DCEA is an evolving topic, SMC allows its inclusion as additional (not base case) sensitivity analysis where it can be shown that the medicine under consideration has a clear and significant impact upon inequalities. Submitting companies should provide detail on the sources, type and quality of the data used to underpin the DCEA and conduct the analysis with reference to the DCEA methods set out in the NICE Support Document on Health Inequalities.

In instances where the impact on inequalities is not quantified through DCEA, the submitting company can describe the impacts narratively in their discussion of the economic analysis, allowing the SMC to take them into account during decision making.

6.15.3 Reflecting environmental impacts in cost-effectiveness analysis

The inclusion of environmental impacts into cost-effectiveness analysis is another area of ongoing development, with no consensus on how it should be approached. SMC is keen to explore environmental impacts in its decision making where possible. Submitting companies are encouraged to consider how environmental impacts could be included, either analytically or narratively, in their submission.

6.16 Decision making incorporating economic analysis

The SMC does not have a fixed upper limit on willingness-to-pay for a QALY.

The challenge for decision making is to strike a balance between decision making based upon explicit, stated principles and the need to retain some flexibility to respond to the circumstances of any particular case. This section sets out some general principles but in any individual decision it is the responsibility of the SMC to weigh the factors and issue guidance that it feels to be consistent with the full range of evidence (economic and other, quantified and qualitative).

SMC may also consider other factors in relation to end-of-life and orphan medicines such as added benefit from the patient and clinician perspective that may not be fully captured in conventional clinical and economic analysis (these are included in the PACE statement). The output from the PACE meeting will be an important factor in the SMC decision.

In some specific situations, with or without PACE, SMC may also exercise greater flexibility in its decision making to allow consideration of additional factors. These may allow SMC to accept either more uncertainty in the health economic case or a higher cost per QALY. The modifiers are only applied for a relatively high cost per QALY when the committee is satisfied that the clinical and economic case for the medicine is robust. Full details of these decision modifiers can be found in the SMC Process guide for submitting companies on the SMC website.

Where a pharmaceutical company wishes SMC to consider the medicine under review in the context of these modifiers it is helpful to make reference to this in section 6 (discussion) of the NPAF, using appropriate supporting references where possible. It should be noted that

NDC does not consider the application of the modifiers; these are considered and taken into account only in the decision made by SMC.

Further details with respect to decision making for medicines in the ultra-orphan pathway can also be found in the Guidance to submitting companies for completion of New Product Assessment Form (NPAF) for ultra-orphan medicines on the SMC website.

In making its decisions, SMC notes sections 6.3.4 to 6.3.9 from the NICE guidance, as follows:

NICE guidance section 6.3.4

Below a most plausible ICER of £25,000 per QALY gained, or £100,000 per QALY gained for highly specialised technologies, the decision to recommend a technology is normally based on the cost-effectiveness estimate and the acceptability of a technology as an effective use of NHS resources. When the estimated ICERs are less than £25,000 per QALY gained, or £100,000 per QALY gained for highly specialised technologies, and the committee decides that the technology should not be recommended, the committee will make specific reference to its view on the plausibility of the inputs to the economic modelling, or the certainty around the estimated ICER, or both. This might be affected, for example, by sensitivity analysis or limitations to the generalisability of findings about effectiveness.

NICE guidance section 6.3.5

Above a most plausible ICER of £25,000 per QALY gained, or £100,000 per QALY gained for highly specialised technologies, decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider the following factors:

- the degree of certainty and uncertainty around the ICER
- aspects that relate to uncaptured benefits and non-health factors
- aspects that relate to health inequalities.

NICE guidance section 6.3.6

For highly specialised technologies the committee may give particular consideration to:

- the impact of the technology on the overall delivery of the specialised service
- additional staffing and infrastructure requirements, including training and planning for expertise.

NICE guidance section 6.3.7

As the ICER for a technology increases in the range of £25,000 to £35,000 per QALY gained, the committee's decisions about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed in section 6.3.5.

NICE guidance section 6.3.8

Above a most plausible ICER of £35,000 per QALY gained or £100,000 per QALY gained for highly specialised technologies, the committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, considering the factors listed in sections 6.3.5 and 6.3.6.

NICE guidance section 6.3.9

For technologies that provide less health benefit at a lower cost compared with the relevant comparator(s) (that is, that fall in the south-west quadrant of a cost-effectiveness plane), cost-effectiveness considerations should consider the usual cost-effectiveness levels of £25,000 to £35,000 per QALY. Any relevant additional factors and modifiers should also be taken into account.

6.17 Patient Access Schemes

Patient Access Schemes (PAS) are schemes proposed by pharmaceutical companies to improve the cost effectiveness of medicines, thereby facilitating patient access. PAS will be considered by NHSScotland to facilitate access by patients to medicines that are not, or might not be, in the first instance found to be cost effective by SMC.

PASAG undertakes an objective and independent assessment of PAS submitted by companies and advise SMC on their acceptability for implementation by NHS boards in NHSScotland. Full guidance covering submission of a PAS and links to the most up-to-date PAS application forms to be used with submissions are available on the SMC website. Further details on the processes around the PAS can also be found in the SMC Process guide for submitting companies.

In terms of specific guidance to submitting companies on the methods for handling a submitting company PAS within the economic evaluation of the NPAF, the following should be noted, along with any relevant points in section 6.10.3:

- Section 6 of the NPAF should include a brief description of the PAS being offered to NHSScotland. This should make clear the type of scheme that is being offered (for example simple discount, responder-based scheme, fixed price per patient), the patient population who would be eligible under the scheme and a clear statement of the price being charged for the product under the PAS. In addition to this detail in the NPAF, the submitting company must provide a PAS application form.
- If a complex PAS is proposed, then the 'without PAS' sensitivity analysis should also include varying the list price of the medicine from 5% to 95% to provide an estimate of the discount of the complex PAS in the event that the medicine is used as a comparator in a future submission.
- It is the role of PASAG to verify and assess any administrative costs to NHSScotland associated with implementing the scheme. Where PASAG estimates these costs to be very high in comparison to the discount offered, SMC reserves the right to ask the

submitting company to provide revised base case results to show the impact of incorporating the additional NHS administration costs.

- Where a PAS has been accepted by PASAG, SMC will consider the 'with PAS' ICERs as relevant for decision making. The DAD on the product will indicate that a PAS has been proposed and, where possible accounting for any CIC stipulations, provide the ICERs used for decision making. Therefore, if the PAS has not been accepted by PASAG, the 'without PAS' ICERs are the figures relevant for SMC decision making. In such cases, the DAD will still indicate that a PAS had been submitted by the company but the 'with PAS' ICERs will not be presented.
- Note that in the PAS application form, the submitting company has the option to list as confidential any relevant information, and SMC will give due consideration to such requests.
- If a key comparator medicine, medicine used in combination or medicine used as a subsequent treatment in the economic case is available with a PAS, please refer to section 6.10.3.

Additional requirements for submitting a new/revised PAS post NDC

Following issue of preliminary NDC advice, the submitting company has the opportunity to submit a new or revised PAS aimed at improving the cost effectiveness of the medicine. The PAS may be simple or complex and may be submitted for any medicine, whether accepted for use, accepted for restricted use or not recommended by NDC, including those that are eligible for PACE.

The new or revised PAS application form should be sent to the secretariat at the same time as the post-NDC company comments. The following information should be included with the company comments with respect to the economic analysis:

- A table of results, which clearly shows the impact of the new/revised PAS on the base case ICER and all sensitivity analysis ICERs currently reported in the NDC DAD. This should include the revised incremental cost figures where these have been quoted in the NDC DAD.
- A copy of the summary table on budget impact for the new/revised 'with PAS' scenario
- In addition, the company should provide a supplementary document showing the impact of the new/revised PAS on all the ICERs presented as sensitivity analysis within the NPAF (any results tables and tornado diagrams) and also the 'with PAS' results corresponding to any additional analyses that had been requested by the economic assessor prior to or following the NDC meeting.
- It should be noted that if the comparator is associated with a PAS (and/or the medicine under review is used as part of a combination regimen where a confidential PAS applies for the combination medicine), the guidance referred to above in relation to comparator PAS will be relevant and should be taken account of in providing the analysis above for the new/revised PAS.

In addition, a revised budget impact template to take account of the new/revised PAS should be provided.

The additional information will then be reviewed by the economic assessor prior to the SMC meeting.

7 Resource implications

7.1 Background

SMC provides advice on the clinical and cost effectiveness of all new medicines for NHSScotland. As part of the assessment process, submitting companies are required to provide an estimate of the potential budget impact of the new treatment relative to existing practice for planning and implementation purposes. This is provided through completion of a standardised SMC budget impact template which is issued in confidence to NHS boards for medicines accepted for use by SMC.

Budget impact information is not taken into account in the SMC decision on whether or not to accept a medicine for use.

This section provides guidance for submitting companies on the key principles that should be followed when completing the SMC budget impact template. Templates (including a worked example) are available on the [Making a submission](#) page of the SMC website. Information included in section 7 of the NPAF, should be consistent with the completed budget impact template.

7.2 What is budget impact assessment?

A budget impact assessment is an evaluation of the expected cost or saving that results from implementing SMC advice.

The focus of the SMC budget impact template is to show whether the cost or saving associated with the introduction of the new medicine is expected to have a financial impact for NHS boards in Scotland. A non-financial impact may also be relevant if, for example, there are administration capacity benefits that do not result in money being saved.

7.3 Budget impact principles and perspectives

7.3.1 Time frames

SMC's budget impact template covers a period of up to 3 financial years (April to March) from the point of launch. This means the calculations should cover the remainder of the current financial year followed by 2 full financial years to provide an estimate of the predicted 'steady state' budget impact and patient numbers.

7.3.2 General principles for assessing budget impact

Using standard accounting principles

- Standard accounting principles are applied.

- These principles are similar to health economic principles used in the cost-effectiveness calculations underpinning SMC advice but there are some differences, such as the budget impact template considers the impact on the population of Scotland whereas the health economic analysis considers the impact on an individual.

Only including direct consequences

- Only direct consequences of implementing individual SMC guidance are included. Direct consequences are the changes in practice that will result from implementation.
- Indirect consequences cannot be considered in the budget impact assessment. As an example, a person who has an intervention that prevents them from dying could later develop other diseases that are costly to treat. The person could develop any disease unrelated to the guidance recommendation for their original condition. This would be an indirect consequence.

Only including what is in scope of SMC advice

- Budget impact only covers changes funded by the NHS Health and Social Care system. This includes the funding of services provided by the public, private, third party and charity sectors.
- VAT is included within a budget impact assessment when payable by the NHS (for medicines provided in secondary care). The option to include VAT is available in the budget impact template.
- Homecare service costs are included when payable by the NHS.
- Costs are not discounted over time.
- The main focus of the budget impact is the impact of the new treatment on the medicines budget.

Matching time periods for costs and savings

- Costs and savings relate to the same time period, usually a financial year. Differences may arise if costs are incurred earlier on that will result in savings in the future. It is not acceptable to combine costs and savings to produce a net cost or saving if time periods do not match.

Providing detailed information

- The budget impact template identifies the resource impact for the remainder of the current financial year and each of the next 2 financial years.

- National estimates should be provided.

Quality

- Data used are accurate and credible with referenced sources.
- The best available datasets are used and supplemented with expert opinion.

7.4 Completing the budget impact template

7.4.1 Background

To complete the budget impact template, the submitting company should identify:

- the population affected by the SMC advice, which may be smaller than the patient population covered by the licensed indication if a positioning is being sought
- the predicted net treated patient numbers following implementation of the SMC advice, including predicted uptake rate and discontinuation rate over time
- the dose, unit cost, relative dose intensity and duration of treatment associated with the new medicine
- the dose, unit cost, relative dose intensity and duration of treatment associated with the comparator medicine(s), which should reflect the comparator(s) included in the health economic evaluation
- the administration type and costs associated with the new medicine and comparator(s).

7.4.2 Population sources

Resident populations by NHS board are sourced from the latest population estimates from the National Records of Scotland (Year 2022).

7.4.3 Incidence and prevalence data

Incidence and prevalence measure different aspects of disease or care need in a population, although they are related. The incidence rate is the rate at which new events occur in a population. The prevalence of a condition is the number of people in a given group or population who are reported to have the condition at a given time.

It is important to understand the basis on which data on incidence and prevalence are gathered and presented.

Examples of incidence and prevalence types include:

- annual incidence is the number of people who will develop a disease or have a care need over the course of a year; this is the most common way of expressing incidence
- point prevalence is the burden of disease or care need in a population at a particular point in time; this is the most common way of expressing prevalence.

Incidence or prevalence data may be used in budget impact estimates. For example:

- the prevalence of a chronic condition lasting many years may determine its budget impact, but
- the annual incidence would be more appropriate to calculate the impact of a technology used to treat, for example, newly diagnosed cancer.

Both prevalence and incidence data may need to be considered within a single budget impact template, so that the budget impact of different medicine types can be calculated accurately.

The budget impact template is based on the population of Scotland. However, NHS boards can amend the template to their local population to estimate the local resource impact.

7.4.4 Data sources to establish current practice

Data used to establish current practice vary depending on the topic. In some cases, multiple sources may be needed.

Commonly used types of data and sources used to establish a baseline may include:

- [Care and Outcomes Research Centre \(formerly Personal Social Services Research Unit\)](#)
- [Public Services Delivery Scotland](#)
- hospital data, such as [Hospital Episode Statistics](#)
- primary care data
- prescribing data.

In some situations, current activity may be particularly difficult to define. When this is the case, assumptions may be required which should be clearly explained and justified.

7.4.5 Data sources to establish future practice

Predicting future practice after implementing SMC advice is challenging. Predictions of future uptake should rely on more than one source, when possible.

Assumptions should be documented, fully referenced and checked with clinical experts.

Sources used for estimating future practice include:

- previous uptake of similar medicines
- information used to inform related economic models
- relevant clinical experts.

7.4.6 Prices used in the budget impact template

For some medicines, PASAG and the company agree that if accepted by SMC the medicine will be made available to NHSScotland with a discount or PAS. The size of the PAS discount is CIC. Any PASAG-approved PAS for the submitting medicine should be used in the budget impact template, along with the list price, to allow both the 'with PAS' and list price budget impact estimates to be calculated.

For comparator medicines available with a PAS, the list price should be used. However, NHS boards will have access to the confidential comparator PAS discount level to allow this to be factored into the overall budget impact estimates in confidence.

8 Summary information for submitting patient groups

General guidance

i. Patient groups

SMC is committed to working in partnership with patient groups to capture patient and carer experiences and use these to inform decision making.

Understanding the experiences of patients, their families and carers is a core part of the SMC decision-making process and helps SMC members to fully understand how a new medicine impacts the quality of life of patients and carers. Patients, members of their families and carers can provide information about what it's like to live with a condition and a real-life view of the potential impact of a new medicine.

SMC works in partnership with patient groups to gather this information through our patient group submission process.

The SMC Public Involvement Team identifies patient groups for each appraisal. Patient groups are encouraged and supported by the team to provide a patient group submission. For medicines that are designated as orphan, ultra-orphan, or for end-of-life, the patient group(s) may also be invited to participate in a Patient and Clinician Engagement (PACE) meeting to capture their input in greater detail. Therefore, it is important that relevant patient groups have an informed and appropriate understanding of the medicine under review.

To support understanding, companies are required to provide a patient/public friendly version of their submission by completing section 8 of the NPAF together with the SPC and Patient Information Leaflet (PIL). The SMC Public Involvement Team will forward these to any patient group making a patient group submission in connection with a new product submission.

Patient group representatives may also wish to obtain information from the submitting company about the treatment(s) under consideration.

Completion of the Summary Information for Submitting Patient Groups form in section 8 of the template is essential and a prompt to include the SPC and PIL has been added to the submission checklist. The form prompts companies to answer questions that are designed to provide the type of information that patient groups have indicated would be of interest. Companies should avoid duplicating detailed clinical study information provided in the SMC submission or replicating the PIL.

Where relevant, information should focus on the impact and implications for patients such as:

- severity of the condition

- need for the medicine, including level of unmet need and how medicine addresses it
- added value of medicine for patient and patient's carer/family including secondary trial endpoints including those related to quality of life
- Key side effects and the impact on quality of life.

General points regarding completion of the submission are detailed below.

ii. Association of the British Pharmaceutical Industry (ABPI) Code of Practice

The ABPI Code of Practice for the Pharmaceutical Industry sets standards for the pharmaceutical industry including requirements for the provision of information to patients and the public as well as relationships with patient groups. The Code reflects and extends beyond UK and European law.

Individual companies will have their own compliance procedures relating to the Code, noting Clause 26 prohibits the advertising of prescription only medicines to the public. Clause 26.2 and its supplementary information is of particular relevance to the completion of the Summary Information for Submitting Patient Groups form. It notes that information about prescription only medicines which is made available to the public either directly or indirectly must be factual and presented in a balanced way. It should represent fairly the current body of evidence relating to a medicine and its benefit/risk profile. The quality standards in Clause 7 of the Code apply to information to the public including the need to be able to substantiate information.

Clause 26 Supplementary Information also notes the following:

Clause 26.2 Health Technology Assessments

Companies may supply information to relevant patient organisations, the public or patients in relation to forthcoming HTAs by public national organisations such as NICE, AWMSG or SMC, provided the information is accurate, not misleading, not promotional in nature and otherwise complies with Clause 26.2.

Clause 1.2 includes that information supplied by pharmaceutical companies to national public organisations, such as NICE, AWMSG and SMC is exempt from the Code provided the information is factual, accurate and not misleading.

iii. Size of submission

The quantity of information provided in section 8 of the NPAF should be proportionate to the fact that many patient groups have limited resources and may only comprise a few individuals, who are not used to reviewing information relating to a product submission. Succinct and relevant information is required with questions answered using plain English rather than being overly technical. Information should be concise, complete and comprehensive. The submission would not be expected to be more than 5-10 pages including any references.

iv. Completion of section 8 of the NPAF

Guidance notes:

This section should include the approved and proprietary name of the product, the submission date for the NPAF and the name of the company making the submission.

Please include the name and position of the person who is the main contact for patient groups. This may be different to the contact details provided for the rest of the NPAF but should be the appropriate person responsible for liaising with patient groups. It does not need to be someone who can directly answer enquiries, but the contact person should have sufficient knowledge to be able to relay enquiries to the appropriate person within the company.

8.1 What condition is this medicine to be used for?

Guidance notes:

Give a brief overview of the condition and the target population, focusing on the submitted indication. Whilst this can include the exact wording of the licence, an explanation in plain English would also be helpful. It may be relevant to use the wording from the PIL.

If the submission positions the medicine for use in a subgroup of the licensed indication, explain the relevant subgroup and why it has been selected.

8.2 How is this condition currently managed in Scotland?

Guidance notes:

Please give an outline of the current patient pathway and in particular the current treatment(s) likely to be displaced by the medicine under review, which may include non-medicine treatment options. Consider the severity of the condition and the implications for patients.

8.3 How does the medicine work?

Guidance notes:

Please don't use overly technical language. If appropriate include how the medicine might be different and why this might be relevant to the way patients are managed.

8.4 How effective is this medicine and is it different from other medicines currently available to treat this condition?

Guidance notes:

Please detail any unmet need and how the medicine addresses this. Try to summarise the clinical study results as briefly and simply as possible, rather than giving too much detail. Highlight the outcomes that are likely to be most important to the patient. What are the advantages and any disadvantages from a patient perspective compared with current treatment(s)? Information should be factual and presented in a balanced way. It should represent fairly the current body of evidence relating to a medicine and its benefit/risk profile. Submitting companies should be mindful of not appearing disparaging of other treatments.

8.5 How is the medicine administered and how will this affect patients and carers?

Guidance notes:

Please include details such as: form, frequency, handling and self-administration/or otherwise. Consider the impact on patient care, such as avoiding the need for hospital visit.

8.6 What are the side effects of this medicine and how are they managed?

Guidance notes:

Include the main side effects that are likely to be experienced. Use this question to explain the implications for patients and how they are managed. For a full list of side effects, reference can be made to the PIL instead of listing them here.

8.7 What is the quality-of-life impact of this medicine on patients and their carers?

Guidance notes:

Focus on what is likely to be most important for the patient and patient's carer/family. What is the added value of the medicine for patients and carers compared with current treatment(s)? This might include secondary study end points including those related to quality of life. However, secondary endpoints should be set in the context of primary endpoints.

8.8 Are there any potential equality issues that should be taken into account when considering this condition and medicine?

Guidance notes:

Focus on any potential equality issues that affect groups of people, such as people who share the protected characteristics of age, disability, gender reassignment, marriage and

civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation, or people with the condition who have difficulties using currently available treatments, or people with the condition who may have difficulties using the new medicine, or people who may be affected by health inequalities.

There is space to provide signposting to further online information about this medicine which patient groups may find useful.

This might include reference points, resources or published clinical study data. There may be other publicly available regulatory documents regarding this medicine, including the Public Assessment Report and a Risk Minimisation Document (where relevant). Patient groups may also find it useful to know what experience there has been of the medicine in Scotland and the rest of the UK. For example, local clinical study centres and early access programmes. Are there patient information materials and websites that may be helpful?

Appendix A Diagnostic Testing (e.g. somatic, germline or biomarker testing)

Please complete the following summary table if the medicine under review requires a diagnostic test in order to identify the patients eligible for treatment within the marketing authorisation / target population and this **represents a change in clinical practice**.

Please note that the information below should be based on the data used in the economic and budget impact models.

SMC will share this information in confidence with the Scottish Genomic Test Advisory Group (SG-TAG) or Scottish Pathology Network (SPaN), as appropriate, who will advise SMC on the diagnostic testing aspects of the economic case.

Approved name of medicinal product:	
Brand name:	
Indication:	
Company:	
1. Test strategy	
a) Describe the test / test sequence included in the economic analysis.	
b) Is this a patented test?	
c) Does the Summary of Products Characteristics (SPC) for the medicine require this specific test to be used?	
2. Patient numbers	
a) How many patients will require to be tested for this somatic/germline/biomarker across Scotland?	
b) What is the estimated prevalence of this diagnostic test in those who would be tested?	
c) What proportion of samples is likely to be of insufficient size and quality to support the diagnostic test? Please provide further details	
3. Accuracy of test	
a) What is the accuracy of the test / test sequence (i.e. sensitivity, specificity, positive and negative predictive values)?	

4. Costs	
a) What is the cost per test used in the economic model? Please provide a breakdown of the total cost including staffing, consumables and equipment.	
b) What is the cost per patient included in the economic model (i.e. cost per patient identified with this diagnostic test)?	
5. Service issues	
a) Are there likely to be any specific service issues associated with the introduction of the test in NHSScotland? If so, please describe (e.g. additional biopsies etc.)	
b) Are these service issues included in the budget impact templates submitted to SMC?	

Appendix B PRO EDI participant characteristics table 22/3/2024

Item	Mandatory or depends on review?	Explanation
Age	Mandatory	How to complete this item: We suggest ideally mean or median years together with an indication of spread such as range or standard deviation.
Sex	Mandatory	How to complete this item: We suggest using Male, Female and Intersex. Other descriptions of intersex might be found and if so, they should be reported as reported by study authors. If authors have asked a question about trans history, this information should also be extracted.
Gender	Mandatory	How to complete this item: We suggest using man and woman together with any other gender identities as reported by the included study. If authors have asked a question about trans history, this information should also be extracted. If no other gender identities than 'man' and 'woman' are reported, review authors should report this.
Sexual identity	Depends on review	How to complete this item: We suggest using bisexual, gay, lesbian, heterosexual together with any other sexual identities as reported by the included study.
Race, ethnicity and ancestry	Mandatory	How to complete this item: We suggest using the categories reported by study authors.
Socio-economic status (SES)	Mandatory	How to complete this item: We suggest using the categories used by study authors.
Level of education	Depends on review	How to complete this item:

Item	Mandatory or depends on review?	Explanation
		We suggest ideally mean or median years together with an indication of spread such as range or standard deviation. Alternatively, categories of grades completed as a number and percentage.
Disability	Depends on review	How to complete this item: This depends on the review but type of disability and severity would be examples of what could be extracted.
Location (country/countries of data collection and site coordination)	Mandatory	How to complete this item: We suggest reporting country or countries where study participants were recruited, together with the country or countries of study coordination sites. The additional of rural/urban is helpful if provided.
Other factors relevant to the review	Depends on review	How to complete this item: Depends on the item.

<https://www.trialforge.org/trial-diversity/pro-edi-improving-how-equity-diversity-and-inclusion-is-handled-in-evidence-synthesis/> [7 October 2026]

Appendix C Example scenarios for the handling of comparator/combination/subsequent treatment PAS or national contract prices as part of the economic evaluation

Scenario 1: new medicine with simple PAS, single key comparator with simple PAS	
Medicine being submitted for assessment	Simple PAS proposed.
Comparator medicine	With simple PAS.
Submission requirements: base case	ICER presented using PAS price for new medicine and list price for comparator treatment.
Submission requirements: sensitivity analysis	Sensitivity analysis presented using PAS price for new medicine and list price for comparator treatment. The provision of an economic model that facilitates the input of the PAS discount for the comparator medicine. If this is not possible then, (1) For the base case ICER, the list price for the comparator medicine should be varied through a discount range of 5% to 95% at 5% increments. (2) The base case ICER above should be tested using conventional sensitivity analysis. In addition, for the key variables identified, the results should also be presented to show the impact of assuming the 5% to 95% discounts for the comparator.
Submission requirements: budget impact templates	Single template with optional PAS selection for new medicine. Use only the list price for the comparator.
Reporting of results in final SMC advice	No ICERs would be presented. Statement added to explain this is due to CIC concerns.

Scenario 2: new medicine without a PAS, single key comparator with simple PAS	
Medicine being submitted for assessment	No PAS proposed.
Comparator medicine	With simple PAS.
Submission requirements: base case	ICER presented using list price for new medicine and list price for comparator treatment.
Submission requirements: sensitivity analysis	Sensitivity analysis presented using list price for new medicine and list price for comparator treatment. The provision of an economic model that facilitates the input of the PAS discount for the comparator medicine. If this is not possible then, (1) For the base case ICER, the list price for the comparator medicine should be varied through a discount range of 5% to 95% at 5% increments. (2) The base case ICER above should be tested using conventional sensitivity analysis. In addition, for the key variables identified, the results should also be presented to show the impact of assuming the 5% to 95% discounts for the comparator.
Submission requirements: budget impact templates	Template using list price for new medicine and list price for the comparator.
Reporting of results in final SMC advice	No ICERs would be presented. Statement added to explain this is due to CIC concerns.

Scenario 3: new medicine with a PAS, multiple key comparators with simple PAS	
Medicine being submitted for assessment	Simple PAS proposed.
Comparator medicine	More than one of the key comparators has a simple PAS.
Submission requirements: base case	ICER presented using PAS price for new medicine and list price for comparator treatments, using pairwise comparisons.
Submission requirements: sensitivity analysis	Sensitivity analysis presented using PAS price for new medicine and list price for comparator treatments, using pairwise comparisons. The provision of an economic model that facilitates the input of the PAS discounts for the comparator medicines. If this is not possible then, (1) For the base case ICER, the list price for each of the comparator medicines should be varied through a discount range of 5% to 95% at 5% increments. (2) The base case ICERs above against each comparator should be tested using conventional sensitivity analysis. In addition, for the key variables identified, the results should also be presented to show the impact of assuming the 5% to 95% discounts for each of the comparators.
Submission requirements: budget impact templates	Single template with optional PAS selection for new medicine. Use only the list price for the comparators.
Reporting of results in final SMC advice	No ICERs would be presented. Statement added to explain this is due to CIC concerns.

Scenario 4: new medicine with a complex PAS, single comparator with simple PAS	
Medicine being submitted for assessment	Complex PAS proposed.
Comparator medicine	With simple PAS.
Submission requirements: base case	ICER presented using equivalent simple PAS for new medicine and list price for comparator treatment.
Submission requirements: sensitivity analysis	ICER presented using equivalent simple PAS for new medicine and list price for comparator treatment. The provision of an economic model that facilitates the input of the PAS discount for the comparator medicine. If this is not possible then, (1) For the base case ICER using the equivalent simple PAS for the new medicine, the list price for the comparator medicine should be varied through a discount range of 5% to 95% at 5% increments. (2) The base case ICER above should be tested using conventional sensitivity analysis. In addition, for the key variables identified, the results should also be presented to show the impact of assuming the 5% to 95% discounts for the comparator. This analysis should also be provided assuming the equivalent simple PAS applies for the new medicine.
Submission requirements: budget impact templates	Single template with optional PAS selection for new medicine. Use only the list price for the comparators.
Reporting of results in final SMC advice	No ICERs would be presented. Statement added to explain this is due to CIC concerns.

Scenario 5: new medicine with a simple PAS and this medicine is used in combination with another medicine marketed by a different company with a simple PAS, comparator has no PAS.	
Medicine being submitted for assessment	Simple PAS proposed, but is used in combination with a medicine from a different company that has a PAS.
Comparator medicine	No PAS.
Submission requirements: base case	ICER presented using PAS for the new medicine and list price for the medicine it is used in combination with.
Submission requirements: sensitivity analysis	Sensitivity analysis presented using PAS for the new medicine and list price for the medicine it is used in combination with. The provision of an economic model that facilitates the input of the PAS discount for the combination medicine. If this is not possible then, (1) For the base case ICER, the list price for the other medicine used in the combination should be varied through a discount range of 5% to 95% at 5% increments. (2) The base case ICER above should be tested using conventional sensitivity analysis. In addition, for the key variables identified, the results should also be presented to show the impact of assuming the 5% to 95% discounts for the other medicine used in the combination.
Submission requirements: budget impact templates	Single template with optional PAS selection for new medicine. Use only the list price for other medicine used in the combination.
Reporting of results in final SMC advice	No ICERs would be presented. Statement added to explain this is due to CIC concerns.

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