



Healthcare  
Improvement  
Scotland

**SMC**  
Advice on new  
medicines

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

December 2022

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## General guidance notes

### i. SMC remit

The remit of the Scottish Medicines Consortium (SMC) is to provide 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 make its recommendations as soon as is practical after a new medicine becomes available for use. The SMC remit is confined to Prescription Only Medicines (PoMs); it does not assess vaccines for public health purposes, generic medicines, blood products (with the exception of anti-bradykinin and C1 inhibitor therapies) and medicines used in diagnosis. Devices containing medicines will be reviewed only if they have a marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)

The New Product Assessment Form (NPAF) provides a template for the evidence required by the Scottish Medicines Consortium (SMC) to make recommendations to NHS Boards and Area Drug and Therapeutics Committees. This form should be used for all full submissions. In some circumstances an abbreviated submission may be appropriate – more guidance is available on the *Making a submission* section of our website.

The guidance notes relate to each section within the submission form. These include a description of the type of information expected to be submitted within each section of the form, an indication, where appropriate, of the expected source of the information and how the information should be presented.

Since the Scottish Government's review into access to new medicines in 2013, SMC applies a more flexible approach in the evaluation of medicines used at the end of life or in the treatment of very rare conditions. This process includes the option of input from a Patient and Clinician Engagement (PACE) meeting).

Further changes were implemented following a more recent review into access to new medicines (2016).

Separate guidance supplements are available for the following:

- Submissions for medicines for extremely rare conditions (ultra-orphan medicines)
- Supplement for medicines eligible for the interim acceptance decision option (medicines with Great Britain (GB) conditional marketing authorisation, included in the MHRA Innovative Licensing and Access Pathway (ILAP) and/or have a positive MHRA Early Access to Medicines Scheme (EAMS) scientific opinion.
- Submissions for medicines where the comparator is available through a confidential PAS (*via the Making a submission* section of our website, on the '*Patient Access Schemes*' page).
- Resubmissions where the only change is a new or improved simple Patient Access scheme (*via the Making a submission* section of our website).

General points regarding completion of the submission are detailed below:

## **ii. Deadlines for submission**

Deadlines for receipt of company submissions to the SMC secretariat, are provided on a month-by-month basis on the SMC website. This is the deadline for receipt of the entire submission, including all elements described in the checklist for completion of the NPAF. Failure to provide any of these elements, including a full set of electronic references, will be classified as failure to meet the deadline. No amendments can be made to the NPAF after it has been submitted.

## **iii. Size of submission**

The quantity of evidence to be submitted will vary depending on the product under consideration. A succinct and relevant review of the available evidence is required. Submissions should be concise, but also complete and comprehensive. The submission should focus on information related to the indication or positioning for which approval is sought, rather than all available data for the medicine. The required information is stated for each section of the document and applicants should focus on these requirements and not include any information that is not directly relevant to the information under review. If a submission is extensive because of the inclusion of irrelevant or unnecessary information, it will not be considered by SMC and will be returned to the submitting company for editing. This is likely to result in SMC advice for the medicine being delayed. Submitting companies should therefore ensure that only relevant information is included in submissions.

As far as possible, submitting companies should limit the electronic size of the document since it may have to be distributed across servers with varying limits to file size. For guidance, most submissions have a file size of around 5 megabytes.

## **iv. Appendices**

The submission should be a stand-alone document. Appendices may be used for information that exceeds the level of detail requested in this guidance but only when considered essential and not to present core information. For example it is not sufficient to attach a key study as an appendix and to complete the efficacy section with 'see Appendix X.' In some cases it will be more appropriate to include data as a supporting document, referenced in the text, than as an appendix.

## **v. Formatting**

The boxes in the NPAF will expand with the text. When completing the submission submitting companies should use the style embedded in the template i.e. 12 point Calibri, black font. Page numbering will also alter with the text and the page-numbering format within the template. For example, splitting the document into sections other than those inherent in the template may disrupt page numbering, causing problems for assessors. Please do not alter the template format.

In resubmissions text added or altered since the most recent submission should be shaded grey in order to identify changes. This approach should be taken when changes are relatively few and may be required only in selected sections of a resubmission, e.g. when limited new clinical evidence is available but a substantially new economic case is being presented.

## **vi. Commercial-in-confidence (CIC) or academic-in-confidence (AIC) data**

SMC is committed to transparency in its decision making in relation to each health technology appraisal. SMC and the ABPI acknowledge that while it is in the interests of patients generally for all relevant information about products being appraised to be put into the public domain the rights of the owners of the data must also be respected. Confidential information should be kept to a minimum. Marking the whole submission or whole sections of the submission as confidential is unacceptable. Only data that are genuinely confidential such as actual numbers may be marked as confidential. The Checklist of Confidential information within the NPAF should be completed, and all confidential information should be underlined and shaded in the NPAF (blue shading for commercial in confidence and pink shading for academic in confidence) (see section viii. c.). Information that is CIC or AIC will be removed from the version of the Detailed Advice Document (DAD) that is shared with public observers and company participants at SMC meetings and omitted from the version of the DAD available to the public. SMC will respect confidentiality, but reserves the right to include data that are already in the public domain e.g. as a published abstract or conference poster. In such cases, SMC will not exceed the level of detail in the published source and the submitting company will have an opportunity to review the DAD as part of the routine consultation process. It should be noted that SMC's critique of the clinical and economic evidence as summarised in the DAD is owned by SMC and may not be marked as confidential (excluding information that is genuinely confidential as described above). SMC is committed to adhering to the guidelines agreed with ABPI that appear on the SMC website.

## **vii. References**

All evidence cited should be referenced appropriately throughout the form, and references should be numbered in the order in which they first appear in the text. At the end of the submission a list of all references should be provided in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text. Author/date styles of referencing should not be used.

References should be provided in a RIS formatted file with a copy of all references (pdfs) provided either via email and contained in zipped files or uploaded to the Egress Secure Workspace, to be received no later than the monthly deadline for receipt of company submissions.

Full versions of in-house clinical study reports and/or drafts for publication should be provided where these have been used as data sources. These are required not only in order for assessors to make factual checks but also for them to gain a comprehensive understanding of relevant study methodology, conduct and results, therefore synopses and selective extracts are not sufficient. On request from the submitting company, SMC will

treat data from these sources (that are not otherwise in the public domain) as CIC/AIC. CIC information will not be disclosed in any form to persons or organisations out with the SMC and NDC committees, SMC clinical and economic assessors and secretarial staff; AIC information may be shared in confidence with participants in a PACE meeting. These data will be annotated to indicate that they are CIC/AIC in paperwork provided to the SMC and NDC committees, and will be removed from the SMC Detailed Advice Documents that are issued to the NHS and posted on the SMC website.

While SMC encourages full referencing of the evidence presented to it, please avoid the inclusion of unnecessary references such as those that are not directly relevant to a point being made and/or that duplicate evidence provided by more robust sources.

Further guidance on referencing, including the use of abstracts and posters as sources of information, is provided under 'Guidance on types of studies to be included and sources.'

## **viii. Completion of NPAF**

### **a. Front page**

The NPAF should be given a title that includes the approved and proprietary name of the product, the indication under review and the name of the company making the submission.

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 point 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.

### **b. Patient groups**

Understanding the experiences of patients, their families and carers is a key element in the SMC decision making process. Patients, family members and their carers provide unique knowledge about what it's like to live with a condition. They can give their perspective on the advantages and disadvantages of medicines and other treatments that may not be available in the published literature or reflected within quality of life measures.

SMC works in partnership with patient groups to gather this information through patient group submissions. It is important that submitting patient groups fully understand how a new medicine works, as this helps to ensure the information they submit is accurate and informed.

Companies must provide a Summary Information for Submitting Patient Groups as part of the submission to SMC, see section 8. SMC worked in partnership with The Association for British Pharmaceutical Industry (APBI) in producing this form, and it is compliant with the Prescription Medicines Code of Practice.

The completed form will be provided to submitting patient groups to assist them in the preparation of their submission.

**c. Checklist of Confidential Information**

The Checklist of Confidential Information should be completed for all CIC and AIC data, including the reasons why the data are CIC/AIC and the timescale within which they will remain confidential. All confidential information should be underlined and shaded in the NPAF (blue shading for CIC; pink shading for AIC). If the medicine is subject to a confidential Patient Access Scheme (PAS), SMC preference is to publish the with-PAS incremental cost-effectiveness ratio (ICER). If you do not agree to public disclosure of the with-PAS ICERs, the reasons should be detailed in the Checklist of Confidential Information. (If a comparator medicine has a Patient Access Scheme in place, please refer to the supplement for submissions for medicines where the comparator is available through a confidential PAS (via the *Making a submission* section of our website, on the 'Patient Access Schemes' page).

**d. Freedom of Information (FoI)**

The Freedom of Information (Scotland) Act 2002 came into force in 2005, and enables any person to obtain information from Scottish public authorities, giving legal right of access including all types of recorded information of any date held by Scottish public authorities.

As such all information received may be subject to disclosure under the Freedom of Information (Scotland) Act 2002.

On receipt of a request for information, the SMC secretariat will contact your designated company representative to confirm that information being released is not deemed as commercial in confidence.

**e. Checklist for completion of New Product Assessment Form**

Before submitting the New Product Assessment Form (NPAF) please ensure the following checklist is complete:

<b>All sections of NPAF completed</b>	
<b>Signed electronic copy of full NPAF and appendices enclosed</b>	
<b>Electronic summary of product characteristics (SPC) and patient information leaflet (PIL) enclosed</b>	
<b>References provided in a RIS formatted file with a copy of all references (pdfs) provided either via email and contained in zipped files or uploaded to the Egress Secure Workspace.</b>	



**Guidance notes:**

The above checklist should be completed before the NPAF is submitted to SMC. Failure to complete any of these may delay processing of the submission.

**f. Submitting the NPAF to the secretariat**

The secretariat will accept the electronic version of the NPAF as the master document, provided that the person responsible for compiling the submission has entered a scanned signature on the front page.

**ix. Patient and Clinician Engagement (PACE)**

When making a submission for the following categories of medicines, the company will have the opportunity to request a PACE meeting and/or to submit a new or revised PAS in the event of NDC preliminary 'not recommended' advice.

- End of life medicine
- Orphan or orphan equivalent medicine
- Ultra-orphan medicine following evidence generation through the ultra-orphan pathway

The company will have the option to submit a brief statement for consideration at the PACE meeting at the same time as the post NDC company comments. The template for the company PACE statement can be found on the SMC website. The company PACE statement should focus on additional information covering factors that may not be fully captured within conventional clinical and economic assessment, such as:

- Unmet need
- Severity of condition
- Added value of the medicine for the patients and family/carers
- Place in therapy, and
- Details of any sub-groups whom the medicine may specifically benefit.

It should not contain any commercial in confidence information.

The Summary Information for Submitting Patient Groups (see Section 8) is the vehicle for the submitting company to support patient groups in their preparation for PACE

The output from the PACE meeting will be an important factor in the SMC decision, see section 6.14 PACE and decision modifiers.

**x. Patient Access Schemes**

For submission of a PAS, refer to section 6.15 Patient Access Schemes.

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## 1. Registration details

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

**Guidance notes:**

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, the submitting company is required to model cost effectiveness using a range of potential discounts for the other medicine between 5% and 95% in 5% increments. Please refer to the guidance supplement on submissions where the comparator is available through a confidential PAS.

- b) If the submission positions the medicine for use in a sub-population of the licensed indication, please state clearly 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 (i.e. selective by indication) or to a sub-group of the population eligible under the marketing authorisation (selective by population).

- (i) 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.
- (ii) Where a submission proposes the use of a medicine when positioned for use in a sub-group 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 sub-group of the population covered by the marketing authorisation. The focus of the submission must be clear and refer to a single population i.e. either the full licensed population or a sub-population. This must match the clinical and economic case presented.**

In the Efficacy section under 3b), the clinical evidence base to support the use of the medicine in the proposed population should be presented. This should preferably be

from a pivotal study, with evidence from a subgroup of the primary analysis or from a secondary outcome measure with the subgroup / outcome being pre-specified in the study protocol. If the evidence base comes from a less robust dataset this should also be described in full.

In Clinical effectiveness (section 5), any limitations of the evidence base to support use of the medicine in the proposed target population should be discussed. Any difference/discrepancy in the evidence presented in the clinical section from that used in the economic analysis must be identified and justified.

The economic and budget impact analyses presented in sections six and seven of the submission should always relate specifically to the target population that is the focus of the company submission and SMC advice will relate only to this. The SMC advice box will make clear the elements of the marketing authorisation covered by the advice.

- c) State any other indication(s) for the product which fall within the remit of SMC. If these have not been reviewed by SMC, provide details of timelines for provision of submissions.

**Guidance notes:**

If the product is licensed for other indication(s) that fall within the remit of SMC, please state this and specify the indication(s). If these have not been reviewed by SMC, please provide details of timelines for provision of submissions to SMC for the indication(s).

A separate NPAF for each indication is preferred and facilitates the development of a coherent case for each indication. However this may not be appropriate when indications are closely related e.g. a product licensed for different grades of severity of the same disease.

- d) Provide details of the licence status of the product for the indication(s) detailed in the submission, including dates of granted or expected marketing approval, and if this is a conditional marketing authorisation.
- e) In the event of New Drugs Committee preliminary 'not recommended' advice, eligible medicines have the option of a Patient and Clinician Engagement (PACE) meeting and a new or revised Patient Access Scheme (PAS) post NDC.

If you wish SMC to assess eligibility for a PACE meeting please answer Yes or No to each of the following:

Is this submission for:

- i. an end of life medicine: a medicine used to treat a condition at a stage that usually leads to death within three years with currently available treatments?

YES/NO

- ii. a medicine with GB orphan marketing authorisation (i.e. conditions affecting fewer than 2,500 people in a population of 5 million) or a medicine to treat an equivalent size of population irrespective of whether it has designated orphan status.

YES/NO

Supporting evidence and rationale for end of life and orphan status must be included in section 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 sub-population of the licensed indication. The definition of end of life medicine may be based on a sub-population of the licensed indication where the submission is positioned for use in this subgroup and the submitting company provides adequate justification.

- f) Has the product received a positive MHRA Early Access to Medicines Scheme (EAMS) scientific opinion for the indication(s) detailed in the submission? If YES, please include the EAMS number and the date on which this occurred.
- g) Does the product have an 'Innovation Passport' allowing entry into the MHRA Innovative Licensing and Access Pathway (ILAP)? If YES, please provide the date that the IP was granted.
- h) Has the product been designated a biosimilar medicine for the indication(s) detailed in the submission?

**Guidance notes:**

Biosimilar medicines are those that are similar to an approved biological reference product and have undergone an abbreviated licensing process whereby they are compared to the reference product with respect to quality, safety and efficacy. SMC requires a full submission for biosimilar medicines where the reference product is not recommended by SMC/HIS for the same indication(s). Please refer to the SMC policy statement on biosimilar medicines on our website.

Provide a statement to indicate whether the medicine has been designated a biosimilar medicine for the indication(s) detailed in the submission and when appropriate include the date on which this occurred.

- i) Does the product require a diagnostic test (e.g. 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 (e.g. somatic, germline or biomarker test) should be completed.*

- j) Provide details of the confirmed or estimated 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 (i.e. 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 GB 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.

- k) 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).

- l) Has a Patient Access Scheme (PAS) been included within this submission YES/NO

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

- m) Provide details of any relevant active comparator(s) for the product in the indication(s) (with respect to any selective indication or selective population, if relevant) detailed in the submission and indicate whether any of these comparators are available under a PAS.

**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 a key comparator medicine in the economic case is available under a PAS, the submitting company is required to model the cost effectiveness of their product using a range of potential discounts for the comparator between 5% and 95% in 5% increments. Please refer to the guidance supplement on submissions where the comparator is available through a confidential PAS.

- n) Provide details of any scheduled or ongoing health technology assessment of this product in the UK.

**Guidance notes:**

Provide details of any other health technology assessments, such as those performed by the National Institute for Health and Clinical Excellence (NICE) 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).

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## 2. Overview and positioning

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

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

### Guidance notes:

The summary should include:

- Brief overview of the condition and target population.
- For end of life medicines this should include an estimate of median overall survival with currently available treatments for the relevant population.
- 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 GB orphan medicines provide the designation number and the date of designation.
- Brief overview of current treatment options within Scotland, which may include treatment options other than medicines.
- 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.
- 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.

SMC will consider the submitting company's case and confirm eligibility for consideration as an end of life or orphan / orphan equivalent. All supporting data should be fully referenced. The submitting company may be asked to provide further justification.

If the proposed end of life and/or orphan / orphan equivalent status is not accepted after a validation process, the submitting company may appeal the validation decision. This should be done within two weeks of being notified of the validation decision by submitting a short statement explaining the basis of the disagreement with the validation decision. No new data can be submitted as part of the appeal.

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### 3. Direct evidence

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#### Efficacy

- a) Give 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 on types of studies to be included and sources:**

The efficacy 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, 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. Placebo-controlled and uncontrolled studies can also be included if they provide evidence of relevant clinical benefits not demonstrated in active-controlled studies.

Details of these studies should be taken from complete published reports or publications produced by regulatory authorities, i.e. the EPAR produced by the EMA and medical reviews produced by the American food and Drug Administration (FDA). 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.

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)



**Guidance notes on the 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, e.g. 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.

For example 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 (e.g. "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 this 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 (e.g. 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 (e.g. analyses in a subgroup within which the medicine is licensed) or analyses of relevant secondary outcomes (e.g. 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.

**Guidance notes on the description of the study outcomes:** 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.

**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.

**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. 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.

**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 sub-analysis 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 may be included if they provide relevant evidence.

- c) Provide details of ongoing studies that should provide additional evidence on the medicine in the indication(s) under review and when this further data is expected (i.e. within up to 5 years).

**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.

- d) If the medicine has a GB 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 approval, 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.

- e) 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

- f) 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 in section 3.
- 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.

- g) Provide details of any additional safety issues for the medicine in the indication(s) under review compared to 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 to 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, e.g. 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 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.	<p>What type of indirect comparison has been performed? Describe and justify the methods used.</p> <p><b>Guidance note</b> 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.</p>	
2.	<p>What are the comparators? Give the rationale for selecting these comparators, with reference to the clinical and economic case</p>	
3.	<p>Have the results of this indirect comparison been used in the economic analysis? (base case / sensitivity analysis).</p>	
4.	<p>Describe the target population, this should match the clinical and economic case.</p>	
5.	<p>Provide details of the data sources used and the search strategies employed.</p> <p><b>Guidance note</b> See 4 b) below for further information.</p>	
6.	<p>Provide a PRISMA diagram showing studies included and excluded from the indirect comparison (i.e. studies which were eligible for inclusion in the systematic review and were excluded from the analysis)</p>	

	<p><b>Guidance note</b></p> <p>Details of the number of results returned, assessed, and included/excluded from the search results should be presented in accordance with the PRISMA flow diagram which can be downloaded <a href="#">here</a>.</p>	
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 PICOS.	
9.	<p>Which individual studies (and not records) have been used in the indirect comparison?</p> <p><b>Guidance note</b></p> <p>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'.</p>	
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.	<p>Provide a quality assessment of included studies indicating which tool has been used.</p> <p><b>Guidance note</b></p> <p>A quality assessment of the studies included should be provided and the tool used should be specified (for example, the <a href="#">Cochrane Risk of Bias Tool</a> or the <a href="#">Newcastle Ottawa Scale</a>). 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.</p>	
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.	



	<p>Include details of any statistical or clinical assumptions made.</p> <p><b>Guidance notes</b></p> <p>For example, are proportional hazards assumed in the analyses or are methods used to account for non-proportional hazards.</p>	
14.	<p>Include evidence to support choice of fixed or random effects model (for example goodness of fit statistics, DIC).</p>	
15.	<p>What clinical and safety outcomes have been assessed in the indirect comparison? Provide adequate justification.</p>	
16.	<p>Provide tabulated details for each treatment group of each study included in the indirect comparison including:</p> <ul style="list-style-type: none"> <li>• number of patients in each treatment group or relevant subgroup</li> <li>• patient characteristics</li> <li>• baseline severity of condition</li> <li>• previous treatments</li> <li>• interventions and any additional medication used</li> <li>• length of follow-up and/or data maturity</li> <li>• primary outcome (with definition)</li> </ul>	
17.	<p>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.</p> <p><b>Guidance note</b></p> <p>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.</p>	

18.	<p>If a simulated treatment comparison has been undertaken, please outline the baseline characteristics identified and include the degree of systematic error for the analysis.</p> <p><b>Guidance note</b> 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.</p>	
19.	<p>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.</p>	
20.	<p>Comment on any differences between the included studies in terms of:</p> <ul style="list-style-type: none"> <li>• study methods</li> <li>• patient or disease characteristics</li> <li>• previous treatments</li> <li>• interventions and assessment time-points</li> <li>• outcomes or durations of follow-up</li> <li>• common comparator used</li> <li>• results in common comparator groups</li> <li>• statistical analysis</li> </ul>	
21.	<p>Provide the results of the indirect comparison in terms of the relative treatment effect of the medicine under review versus the selected comparators.</p> <p><b>Guidance note</b> This should include the relative treatment effect (hazard ratio, difference, odds ratio [with justification for choice]) and the 95% confidence or credible interval around this. In addition, ranking of treatments should be reported.</p>	
22.	<p>Where relevant, describe any evidence of inconsistency between direct and indirect results.</p>	

23.	<p>Report any measures or assessment of heterogeneity.</p> <p><b>Guidance note</b></p> <p>Further information can be found here: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from <a href="http://www.training.cochrane.org/handbook">www.training.cochrane.org/handbook</a>.</p>	
24.	<p>Provide details of any sensitivity analyses performed to explore uncertainty, including justification and relevance to the economic analysis.</p>	
25.	<p>Conclusions of the indirect comparison.</p>	

- 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 (Population, Intervention, Comparison, Outcome, Study) 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.

<b>Section</b>	<b>Details</b>	<b>Reported on page number</b>
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	<ul style="list-style-type: none"> <li>- PICOS</li> <li>- Date limits</li> <li>- Language limits</li> <li>- Publication or study type limits</li> <li>- Human/animal limits applied</li> </ul>	
Information sources	List all information sources, including: <ul style="list-style-type: none"> <li>- platform used (e.g. OVID, Dialog),</li> <li>- databases searched and years of coverage,</li> <li>- date search was conducted,</li> <li>- details of any personal communications</li> </ul>	
Search	Present full electronic search strategies for all databases, including any limits applied (please include origin/name of filters used, e.g. McMaster, SIGN etc.) and the number of results retrieved.	
Study selection	Provide details of the process for selecting studies, including: <ul style="list-style-type: none"> <li>- number of studies identified through searches</li> <li>- number of studies screened</li> <li>- number assessed for eligibility</li> <li>- number included in the review with reasons for all exclusions at each stage</li> </ul>	
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% confidence 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.

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## 5. Clinical effectiveness

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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 sub-group of the eligible patient population, any limitations to the evidence base to support this positioning should be discussed, including any 'mis-match' 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 and adverse effects expected in practice and how the medicine would be expected to address any areas of unmet need.

**Guidance notes:**

Provide 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 markers have been measured e.g. reduction in blood pressure. Provide details of any association between surrogate markers and health benefits or disadvantages to patients.

For medicines designated as orphan medicinal products for the indication(s) under review, provide a detailed explanation of the relevance of surrogate markers and the theoretical basis for this selection. This should also be related to quality of life data.

Provide relevant details from guidance, such as that from regulatory authorities or professional bodies, on preferred outcome measures for the condition under review.

- 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 to 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 GB 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 the MHRA 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 health boards in NHSScotland. Recommendation of the treatment in national clinical guidelines may also be relevant.

- 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 (e.g. 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 recommendation 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 to 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:**

These would include, but are not limited to, differences in terms of:

- 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 contra-indicated 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 to 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 to usual clinical practice with the relevant comparator(s). For example, increase or reduction in healthcare facilities.



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). These would include, but not be limited to, differences in terms of (a) patient populations; (b) baseline severity of conditions; (c) interventions; (d) any additional treatments used; (e) outcomes measured; (f) methodology; (g) length of study; (h) results and (i) study limitations.

**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:

- (a) patient populations, by comparing inclusion/exclusion criteria, baseline demographics, including defining relevant variables such as disease severity and previous or additional treatments;
- (b) medicine treatments, by comparing dosing schedules of study medicines and concomitant study medications that were allowed and disallowed;
- (c) 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;
- (d) length of study, by detailing any differences
- (e) results, by listing study results highlighting any inconsistent findings;
- (f) 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 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

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## 6. Pharmaco-economic evaluation

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This section should be completed by reporting the design, methods and results of the economic evaluation. Detailed guidance is provided on all of the relevant aspects. It can either be pasted in to this section or attached as an appendix to the submission. In either case, the checklist contained in this section must be completed to denote where in the submission each of the aspects has been covered.

### 6.1 Summary

- It is the responsibility of the submitting company to clearly demonstrate the case for the cost effectiveness of medicines submitted to the SMC. If the submitting company does not submit economic evidence according to the principles and standards outlined in the guide the SMC will be unable to recommend the medicine for use in NHSScotland.
- The perspective adopted on costs should be that of the NHS in Scotland and social work.
- The evidence submitted must be assembled systematically and synthesised in a transparent and reproducible way.
- All data used to estimate clinical and cost effectiveness must be presented clearly in tabular form and include details of data sources.
- Clinical and cost effectiveness needs to be considered over an appropriate time horizon relevant to Scottish practice and patients. All relevant treatment options for the specific patient groups should be compared.
- In general, cost-utility analysis is the preferred form of economic evaluation, with health effects expressed in terms of quality-adjusted life-years (QALYs).
- The SMC considers modelling a relevant framework within which available evidence can be synthesised and estimates of clinical and cost effectiveness generated.
- The annual discount rate recommended for both costs and benefits is 3.5%.
- Sensitivity analysis testing the uncertainty surrounding the estimates of cost effectiveness needs to be included.

#### 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.	
<b>Data collection</b>		
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.	
<b>Analysis and interpretation of results</b>		
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.	

Authors may enter N/A for items 7, 9, 12 and 17.

Detailed guidance is provided on the following design requirements for economic evaluations:

- approaches for synthesis of the evidence
- valuing health effects
- evidence on cost
- discounting
- modelling methodology
- presentation of data and results
- SMC approach to orphan medicines

To help pharmaceutical companies meet the SMC's requirements, the guidance includes specific advice supported by additional guidance in italics.

Where the medicine is an ultra-orphan; please see the guidance supplement for medicines for extremely rare conditions on the *Making a submission* section of our website.

## 6.2 Guidance development

This guidance was developed by health technology assessment experts from the SMC, the pharmaceutical industry and research centres. The principles and content of the guidance were agreed following extensive discussions and consultations. The guidance will be reviewed and updated as required.

## 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. One of the requirements for an abbreviated submission is that the medicine is expected to have minimal impact on the NHSScotland medicines budget, thus no economic evidence is required.

## 6.4 Responsibility of the submitting company

SMC makes recommendations 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 to 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.

While SMC requires pharmaceutical companies to comply with the SMC Guide, it has not defined a single reference case which must be submitted. Should companies wish to use a reference case approach, then SMC recommends that set out by NICE (see Annex 1).

## 6.5 Consistency of requirements across the UK

SMC recognises that the pharmaceutical industry engages with a growing number of organisations performing similar roles, notably the National Institute for Health and Care Excellence (NICE) and the All-Wales Medicines Strategy Group (AWMSG). A key theme in developing this SMC Guide was consistency with existing, authoritative guidance; in the UK context this means the NICE document, [Guide to the Methods of Technology Appraisal](#) (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.

## 6.6 Guiding principles

### 6.6.1 Clinical and cost effectiveness

In order to inform the SMC’s decision makers, the analytical framework within which evidence is synthesised to estimate clinical and cost effectiveness needs to include a number of important features.

- Consistency between the methods used in submissions is needed to assist the SMC in making consistent appraisals of different medicines and over time.
- All relevant comparators for the medicine being appraised need to be included in the analysis.
- All relevant evidence needs to be assembled systematically and synthesised in a transparent and reproducible manner.
- The costs that are most relevant are those of the NHS in Scotland and local government social work departments.
- Measures of health-related benefits used should be comparable to promote consistency between appraisals and to allow comparison with the benefits from other medicines that may be displaced if new medicines are adopted.
- The time horizon should be sufficient to reflect important cost and benefit differences between the medicines being compared.
- The uncertainty surrounding the estimates of cost effectiveness needs to be explored.

### 6.6.2 Synthesis and modelling

The process of assembling evidence needs to be systematic. Evidence must be identified, quality-assessed and, where appropriate, pooled using explicit criteria and justifiable and reproducible methods. These principles apply to all categories of evidence that are used to estimate clinical and cost effectiveness, including evidence typically drawn from a number of different sources such as:

- cohort studies for parameters relating to the natural history of the condition
- randomised studies for relative treatment effects,
- cross-sectional surveys for resource use and costs

It is necessary that clinical and cost effectiveness are considered over an appropriate time horizon relevant to Scottish practice and patients and that all relevant treatment options for the specific patient groups are compared. It will be necessary to provide an analytical framework within which the available evidence to estimate clinical and cost effectiveness relevant to the decision making context can be synthesised. Modelling provides a relevant framework based on decision analytic models using aggregated data or statistical models using patient-level data.

### **6.6.3 Requirements for evidence**

The requirements for evidence of effectiveness include the quantification of the effect of the medicines on the course of the disease, the effect of the medicines on patients' health related quality of life (HRQoL) and the valuation of those effects in a way that reflects the preferences of the general population.

Data are required to quantify the effect of the medicines on use of resources in terms of physical units (for example, days in hospital and visits to a GP) and valuing those effects in monetary terms using appropriate prices and unit costs.

Despite limitations or deficiencies in the evidence base, decisions still have to be made concerning the use of medicines. For example, small sample sizes may result in some parameters being estimated with a low degree of precision or evidence on effectiveness might come from outside the UK healthcare system or relate to subgroups of patients other than those of principal interest for the appraisal. Therefore, analyses should use the best evidence available, be explicit about data limitations and any attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis.

### **6.6.4 Analysis of uncertainty**

It is important for the SMC to understand the uncertainty associated with the clinical and cost effectiveness information. This requires the appropriate use of rigorous methods to quantify the implications of parameter and methodological uncertainty for the results of an analysis. This assessment of decision uncertainty enables the SMC to make consider implications for further research.

**Guidance notes:**

The SMC recognises that estimating cost effectiveness of a medicine at launch is not easy, but its advice will commit scarce NHS resources so an economics submission is essential. This applies to all medicines, including those with orphan status. If evidence is only available for part of the indication then any positive advice will be restricted accordingly. Where there is uncertainty around the value of parameters this should be addressed within the text and through sensitivity analysis.

A key aim of SMC is to keep its process efficient so that advice is issued as close as possible to product availability. Pharmaceutical companies can help by being concise: experience suggests a typical economic case can be summarised in around thirty pages, provided it is clearly referenced and supported by appendices and accompanied by electronic versions of the original articles that provide the evidence base. Reviewers can request more detail if necessary.

The SMC does not routinely require the submitting company to submit an electronic copy of a model or spreadsheet of calculations. When further analysis is required the economics reviewer will ask the submitting company to carry this out. However, the SMC assumes the model or spreadsheet is readily available and may ask to see a copy at any point.

## 6.7 Design of the economic evaluation

The design of the evaluation is one of the crucial aspects and pharmaceutical companies must give it very careful attention. If the design of the economic analysis submitted does not meet the basic points set out in this section then the submission has little chance of success.

### 6.7.1 Defining the decision problem

Estimating clinical and cost effectiveness should begin with 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. An SMC recommendation will then necessarily be limited to the element of the indication for which evidence is submitted. Patient groups/indications for which there is no economic evaluation will be explicitly excluded from SMC recommendations.

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 will make clear the elements of the marketing authorisation covered by the advice if a selective submission has been made.



## 6.7.2 Comparator

Comparator medicines must be specified as precisely as the medicine being appraised. There are frequently several potential comparator medicines as, for example, practice is not necessarily consistent across Scotland or the UK and between the UK and elsewhere. All relevant comparators must be identified, although a full comparison will not always be appropriate for every one of these comparators.

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. 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.

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 Health Boards in NHSScotland. Recommendation of the treatment in national clinical guidelines may also be relevant.

The relevant comparator may be different to the comparator in the clinical studies programme for the medicine; if so the submitting company must carry out an indirect comparison. The service replaced might also involve no active treatment of the condition.

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 six months at the time of the submission, SMC would expect the company to include this comparator in the analysis.

If the key comparator medicine is available under a Patient Access Scheme (PAS) then please refer to the guidance supplement on submissions for medicines where the comparator is available through a confidential PAS.

Flow diagrams can be helpful to show how patients were managed before the medicine became available and the proposed patient pathway if the medicine is accepted by SMC.

### **Guidance notes:**

The SMC's recommendations to NHSScotland are based in part on the likely additional costs (or savings) and health benefits of using the medicine in question. For this reason, the appropriate comparator is the medicine or care that will be replaced by the new medicine.

This aspect of the design is critically important: cost effectiveness is a relative concept so if the comparator is inappropriate, then the resultant net costs and benefits will be unsuitable for decision-making purposes and lead to the SMC failing to recommend a medicine.

Some potential difficulties include:

- the current treatment involves the use of a medicine that is unlicensed or has a licence but this does not cover the specific indication in question (“off-label” use). In this case, the submitting company must make a judgement about what is the most appropriate comparator. In some cases it may be possible to seek a view in writing from the SMC Executive Team on appropriate comparators. 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 also 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.
- current practice is highly variable - in this case, the SMC preference would be for the comparator to be based on Scottish treatment or audit data. Information on the volume of prescriptions by general practice is available at the Prescribing and Medicines section of the Information Services Division website ([www.isdscotland.org](http://www.isdscotland.org)). 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.
- current practice is not "best practice", for example, where SMC or NICE guidance has been issued but not implemented. If data on prescribing trends suggest the SMC/NICE recommended medicine is likely to become standard practice in the near future (e.g. next twelve 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 as comparator.
- where a submission includes an off-label or unlicensed medicine as a comparator that is recommended in national clinical guidelines, the SMC preference is for guidelines that include a cost effectiveness assessment.

If advice on the choice of comparator is sought please refer to Section 1.4 of “Working with SMC – A Guide for Manufacturers” which is located in the *Making a submission* section of our website.

### 6.7.3 Perspective

The perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS in Scotland and social work (referred to as Personal Social

Services (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.

This is consistent with an objective of maximising health gain from available resources. Some features of healthcare delivery that are often referred to as ‘process characteristics’ may ultimately have health consequences – for example, the length of waiting lists for elective surgery. When there are significant characteristics of healthcare medicine that have a value to individuals that is independent of any direct effect on health, these should be noted. These characteristics include the convenience with which healthcare is provided and the level of information available for patients.

#### **6.7.4 Type of economic evaluation**

In general, cost-utility analysis is the appropriate form of economic evaluation, with health effects expressed in terms of quality adjusted life years (QALYs). Cost-minimisation analysis 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. Therapeutic equivalence may be established on the basis of final patient outcomes, preferably, but evidence from surrogate endpoints e.g. blood pressure, may also be acceptable. Cost minimisation analysis 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). Where a cost-utility analysis 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 cost-minimisation analysis approach (i.e. no differences in QALYs).

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 in 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 in 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).

- Where cost-minimisation analysis using non-QALY outcome measures can be demonstrated to be appropriate.
- Where the medicine is an ultra-orphan; please see the guidance supplement on the *Making a submission* section of our website.

Submitting companies are urged to think carefully before deciding not to use QALYs as the SMC regards this methodology to be the most appropriate to make comparisons of value across health care interventions. If submitting companies present other methods (e.g. willingness to pay studies or a discrete choice experiment) these must be fully described and the uncertainty in results fully explored.

**Guidance notes:**

It should be emphasised that the SMC’s decision making process focuses on patient outcomes. Thus whilst the SMC is interested in claims such as reduced toxicity or greater patient convenience, the key factor is what impact these will have on patient outcomes in terms of reduced illness or higher concordance. The preferred economic evaluation is therefore cost utility analysis.

The focus on cost effectiveness analysis is justified by the more extensive use and publication of these methods compared with cost-benefit analysis and the focus of the SMC on maximising health gains from a fixed NHS/PSS budget. Given its widespread use, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and HRQoL effects. It is recognised that alternative measures exist (for example, the healthy-year equivalent) but few economic evaluations have used these methods and their strengths and weaknesses are not fully understood. If the assumptions underlying QALYs (for example, constant proportional trade-off and additive independence between health states) are considered inappropriate in a particular case, then evidence to this effect should be produced and analyses using alternative measures may be presented as a non-reference case analysis.

Submitting companies should note that failure to collect data to measure and value QALY gain in the clinical study programme is NOT an adequate reason for not using QALYs. Similarly, disease-specific outcomes are not helpful since they do not give comparability of the cost effectiveness of a medicine against other common health services.

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 supplement on the *Making a submission* section of our website for more details.

**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 e.g. at end of study follow-up, at five years follow-up and at five-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.

### 6.7.6 Incremental cost effectiveness

The incremental cost effectiveness ratio – typically a net cost per QALY gained - is a summary statistic for the economics evidence. Its appeal is that it is concise and allows comparisons with other health services. Its two main drawbacks are:

- (i) it gives an impression of precision when an indication of the extent of uncertainty might be more appropriate  
and
- (ii) it needs to be set in the context of other factors relevant to decision-making.

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

In making its decisions SMC notes sections 6.3.2 to 6.3.5 from the NICE guidance, as follows:

#### **NICE guidance:**

6.3.2 Below a most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of 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 presented are less than £20,000 per QALY gained and the Committee judges that particular interventions should **not** be provided by the NHS, the recommendations will make specific reference to the Committee's view on the plausibility of the inputs to the economic modelling and/or the certainty around the estimated ICER. This might be affected, for example, by sensitivity analysis or limitations to the generalisability of findings regarding effectiveness.

6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:

- The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.
- Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.
- The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.
- The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'
- Aspects that relate to non-health objectives of the NHS.

6.3.4 As the ICER of an intervention increases in the range of £20,000 to £30,000 per QALY gained, the Committee's judgement about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed in section 6.3.3.

6.3.5 Above a most plausible ICER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, with regard to the factors listed in section 6.3.3.

#### **Guidance notes:**

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). SMC conventional modifiers may be applied to all new medicines assessed, if appropriate. See also guidance supplement for ultra-orphan medicines.

## **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. 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 section 5 for details on advice for conducting and reporting of indirect treatment comparisons. Note that for the purposes of the economic analysis, the value 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 insufficient to provide values for relevant variables, and such values can be obtained from expert opinion, then SMC will consider this as a valid source of evidence. The impact of this evidence will be greater if the submission is transparent on the process used, for example on the selection criteria used to approach potential experts and the range of values provided by the experts. Variables elicited from expert opinion should be tested in the sensitivity analysis.

## **6.9 Valuing health effects**

In order to make clear comparisons of the value of new medicines, the SMC has a preference for cost-utility analyses using QALYs as the primary outcome measure. This should include gains in length of life and quality of life, as well as adverse effects such as toxicity, which should be included as negative impacts on quality of life.

The SMC guidance regarding the use of QALYs has largely adopted the NICE guidance (section 5.3 of the NICE Methods of Technology Appraisal Guide to Manufacturers) but specifies this in terms of a preference (rather than a requirement) for utility estimates from a validated generic utility instrument such as the EQ 5D. SMC also allow submitting companies to use alternative well-designed methods of utility measurement if generic utility data are not available or to use non-QALY outcome measures if this is shown to be appropriate and the value of the medicine to NHS in Scotland can be demonstrated. This is reflected in the full SMC guidance for valuing health effects presented below.

To calculate QALYs for any medicine, it is necessary to use a classification system to describe patients' HRQoL over time. To allow comparisons across interventions, the SMC prefers that health states should be measured in patients using a generic and validated classification system for which reliable and appropriate population preference values, elicited using a choice-based method such as the time trade-off or standard gamble (but not rating scale), are available. Ideally, these data will be generated through randomised controlled studies of the medicine, although utilities derived from observational studies of patients would be acceptable as long as it can be shown that the patients and health states adequately match those in the clinical studies used in the submitted economic evaluation.

It is recognised that different classification systems do not give consistent utility values to the same health states and hence results from the use of different systems cannot always be compared. Given the comparative nature of the SMC's work and the need for consistency across appraisals, the SMC would ideally wish that all appraisals used the same system. Currently, the most appropriate choice in the UK appears to be the EQ-5D. Whilst it is widely used and simple to incorporate into studies, the EQ-5D may not be appropriate in all circumstances. Given the evolving nature of this methodology, the SMC believe it would be inappropriate to require the use of the EQ-5D to the exclusion of any other valid generic utility measures. Those submitting data should provide reasons for their choice of instrument. Submitting companies should also indicate whether they have any evidence



that will help the SMC to understand to what extent, and for what reason, their choice of instrument will have impacted on the valuation of the QALYs gained.

If utility data from generic validated instruments is not available, the SMC will, in general, accept utilities from three other sources:

- (i) Utilities mapped from a disease specific quality of life measure included in a clinical study: the SMC will want to see well designed and explicit methods of mapping from the disease-specific measure to a generic measure and from there to utilities. The SMC User Group Forum considered the issue of good practice in mapping of utility values and produced a short summary report on the topic, which is presented in annexe 3 of this guide.
- (ii) Specific surveys for direct measurement of utilities for appropriate disease/condition health states. This should use time trade off (TTO) or standard gamble (SG) methods of utility elicitation. SMC will accept values from either public members or patients and places more store by the perceived validity of the utility values when put in the context of utilities for other health states. The SMC need a description of the vignettes of health states used for the valuation and a clear explanation of how the health states were derived.
- (iii) Values taken from previous studies reported in published literature. However, the submission must report all of the utility values reported in the literature and the literature selection process, in order that the SMC can see that the submitting company has not been selective. The submission must also show that the health state valued in the literature reflects the health states in the submitted economic evaluation. For example, if the new medicine is for advanced prostate cancer it is not sufficient to use literature values that are reported for the state "prostate cancer" with no further description.

Use of any other approaches to measuring QALYs will require clear justification in the submission. If appropriate data on utilities/QALYs for carers or other groups other than the patients affected is provided as additional evidence this will need to be presented separately from the primary QALY analysis as it is outside the perspective adopted by the SMC.

**Guidance notes:**

Where survival is a factor, [life-table data from the Office for National Statistics website](#) are acceptable.

## 6.10 Evidence on costs

### 6.10.1 NHS and social work costs

Costs should relate to resources that are under the control of the NHS in Scotland and social work (equivalent to Personal Social Services in England) where differential effects on costs between the medicines under comparison are possible. These resources should be valued using costs relevant to the NHS in Scotland and social work. Where the actual price paid for a resource may differ from the public list price, the public list price should be used. Sensitivity analysis should assess the implications of variations from this price. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

Where cost 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.

Staffing costs should include all costs incurred by the NHS as an employer, not just the salary. Choice of staff costs taken from the Unit Costs of Community Care document produced by Personal Social Services Research Unit (available from [www.pssru.ac.uk/](http://www.pssru.ac.uk/)) should be justified by the submitting company. The standard approach to cost staff time would be to use estimates that include annuitised capital and education costs as in the long term all costs are variable and therefore have an alternative use and subsequent opportunity cost. However, in some cases SMC may wish to see additional analysis which excludes capital and training/education costs. This may arise where a shorter term perspective is relevant and short term efficiency savings are released from the use of a medicine. An example of this type of costing approach is given in annexe 2.

Capital costs should be annuitised and included in all types of costs where relevant, unless a specific short term perspective is required and only resources that can be released within this timeframe considered. All costs should be updated to the current year using a UK health service price index. Resource use (in physical units) and costs should be reported separately so that SMC can assess each part of the calculation.

Medicine costs should be based on unit prices listed in the BNF or MIMS. Where a Patient Access Scheme (PAS) is proposed for the medicine under review, both the list price and the PAS price should be used for calculating the base case results and all sensitivity analyses. For the comparator medicine cost, the product most likely to be replaced should be selected. If a volume-weighted average based on Scottish practice is used, a comparison with the cheapest medicine should be included in a sensitivity analysis. (If the company believes the generic version is less effective and is therefore not an appropriate comparator this argument and supporting evidence should be set out). If it is known at the time the submission is being prepared that the comparator medicine will soon become available as a generic product, a sensitivity analysis should be provided showing the impact of using the applicable or estimated generic price within an estimated weighted average cost of the generic and branded products and also as a worst case scenario analysis using only the lowest generic price for the comparator medicine. SMC will base its final decision on the

relevant medicine prices prevailing on the day of the SMC meeting when the medicine is assessed. Where the comparator medicine has a PAS, please see the supplement on submissions where the comparator is available through a confidential PAS for further guidance on how the cost of the medicine should be dealt with.

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 (e.g. by demonstrating that treatment patterns are similar between the country in question and Scotland) and included in a sensitivity analysis.

Value added tax (VAT) should be excluded from all economic evaluations but included in budget impact calculations at the appropriate rate (currently 20%) when the resources in question are liable for this tax.

### 6.10.2 Non-NHS and non-social work costs

There will be occasions where non-NHS/social work costs will be differentially affected by the medicines under comparison. In these situations, the SMC needs to be made aware of the implications of taking a broader perspective on costs for the decision about cost effectiveness. When sensitivity analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/social work costs.

#### Guidance notes:

In terms of the costs to value resource use, a first point of reference in identifying such costs and prices should be any current official listing published by the Scottish Government Health Department, National Services Division, the Department of Health 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 NHS Services Scotland's [Information Services Division website](#).

NHS Reference Costs from the [Department of Health in England](#) are acceptable.

Primary care and community costs from the Unit Costs of Health Care publication by Personal Social Services Research Unit, University of Kent, are also acceptable ([www.ukc.ac.uk/PSSRU/](http://www.ukc.ac.uk/PSSRU/)). As social service costs are hard to find for Scotland, English data (e.g. from PSSRU) are acceptable. Other sources of cost data should be clearly explained.

## 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. Situations where modelling is likely to be required include those where:

- patients participating in studies do not match the typical patients likely to use the medicine within the NHS
- intermediate outcome measures are used rather than effect on HRQoL and survival
- relevant comparators have not been used or trials do not include evidence on relevant subgroups are important
- the long-term costs and benefits of the medicines extend beyond study follow-up.

Providing an all-embracing definition of what constitutes a high-quality model is not possible, however some guidelines are available. In general, all structural assumptions and data inputs should 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 should be reported in order to compare the implications of different assumptions for the results. Scenarios might include that treatment benefit in the extrapolated phase is:

- (i) nil
- (ii) the same as during the treatment phase and continues at the same level  
or
- (iii) diminished in the long term.

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 must be included in a sensitivity analysis.

### **Guidance notes:**

The SMC welcomes the use of models to support the economic case for a medicine. However, modelling is also open to bias and the submitting company should make efforts to ensure the approach used is transparent in terms of the structure, workings and validity of their model.

Schematic representations of models are helpful. Two areas of weakness in submissions to date have been:

- (i) Being clear about where the data inputs come from. If they come from Section 3 of the submission, it is helpful to give a clear reference to a table and preferably a column and/or row and details of any calculations required to move from the clinical data to the model data, e.g. moving from annual transitional probabilities to monthly values. If the data estimate comes from the literature the key question for the SMC is whether the context from which it was taken is compatible with the context it is being used in. For example, if a heart disease model to represent the use of a medicine in a Scottish

population were being put forward, then including a piece of data on disease progression from a Japanese population would raise questions of generalisability. The company thus needs to provide a brief summary of the context for each data estimate from the literature.

- (ii) Reporting outputs from the model as opposed to net cost per QALY gained figures. For example, if the submitting company uses a Markov model then they must include a table that shows the number of patients in each state of the model at the end of study follow-up, at five years follow-up and at five yearly intervals thereafter. This gives reviewers a better feel for the model and gives the SMC some evidence to judge whether the model behaves in a realistic manner.

## 6.13 Presentation of data and results

### 6.13.1 Presenting data

All data used to estimate clinical and cost effectiveness must be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses and measures of precision should be detailed for all variables

Consideration should be given to the graphical representation of clinical and cost effectiveness data to support its effective communication and interpretation.

#### Guidance notes:

NICE emphasises the use of tables but the SMC also finds well-designed graphs to be especially helpful and would urge submitting companies to give more thought to this aspect of presentation.

### 6.13.2 Presenting expected cost effectiveness results

The expected value of each component of cost and expected total costs should be presented; expected QALYs for each option compared in the analysis should also be detailed. Incremental cost effectiveness ratios should be calculated as appropriate.

Standard decision rules should be followed in combining costs and QALYs. These should reflect any situation where dominance or extended dominance exists. Incremental cost effectiveness ratios (ICERs) reported must be the ratio of expected cost to expected QALY.

### 6.13.3 Dealing with parameter uncertainty in cost effectiveness analysis

Sensitivity analysis should be used to deal with sources of uncertainty. This includes uncertainty about the clinical and cost effectiveness estimates, choice of studies to include in a meta-analysis, and the structural assumptions made in a model.

The analysis of the uncertainty in all parameters for decision uncertainty assumes that factors such as a model's structure and data inputs are considered to be appropriate. However, these characteristics of the model are also subject to uncertainty, which should be formally examined using sensitivity analysis.

Common examples of this type of sensitivity would be:

- where there are doubts about the quality or relevance of a particular study in a meta-analysis, in which case the analysis could be re-run excluding this study
- where there is uncertainty about the most appropriate assumption to use for extrapolation of costs and outcomes beyond study follow-up
- where there is variability between hospitals in the cost of a particular resource or service, or the acquisition price of a particular medicine.

Uncertainty about the appropriateness of the methods used can also be dealt with using sensitivity analysis, but these analyses must be presented separately.

Analyses using alternative methods other than those prescribed in the SMC Guide should be presented separately from those relating to structure and data.

If the submitting company presents a base case analysis which includes some differences which were not statistically significant, within the sensitivity analysis they should include such an analysis with the non-significant differences removed.

#### **6.13.4 Uncertainty in ICERs**

The SMC require the submitting company to demonstrate, through the use of sensitivity analyses:

- The robustness of the ICERs.
- Under which circumstances the ICER exceeds £20,000 and £30,000.

#### **6.13.5 Presenting sensitivity analyses**

Consideration should be given to one and two-way sensitivity analyses, supported by graphical representation including threshold values. Each alternative analysis should present separate results.

Probabilistic sensitivity analyses may be submitted in support of the application, but are not considered mandatory.

Appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the cost effectiveness plane and cost effectiveness acceptability curves.

#### **Guidance notes:**

NICE require probabilistic sensitivity analysis to address parameter uncertainty. The SMC recognises the potential benefits of this approach and welcomes research in the area. However, the SMC recognise that the robust, well-evidenced data required to inform probability values for each parameter may not be available until the medicine has been in use for some time.

Hence the SMC do not require probability sensitivity analysis but require robust one-way and scenario-based sensitivity analyses, which explore a range of plausible values for the

parameters of interest. The rationale behind the range of estimates explored should be provided.

In addition the SMC require the submitting company to show under what circumstances the net ICER exceeds £20,000 and £30,000.

### **6.13.6 Presenting analysis of clinical and cost effectiveness for patient sub-groups**

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 sub-group and the expectation of a differential effect. Ad hoc "data-mining" in search of significant sub-group effects should be avoided. Care should be taken to specify how sub-group analyses were undertaken, including the choice of scale on which effect modification is defined. The precision of all sub-group estimates should be reflected in the analysis of parameter uncertainty. The characteristics of the patients associated with the sub-groups presented should be clearly specified to allow the SMC to judge the appropriateness of the analysis with regard to the decision problem.

### **6.13.7 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 socio-demographic details, or their pre- or post-treatment level of health. This position reflects the absence of consensus regarding whether these or other characteristics of individuals should result in differential weights being attached to QALYs gained.

#### **Guidance notes:**

It can be difficult to include equity considerations within an economic evaluation. They can certainly be included in a discussion of the main findings, and the submitting company may consider summarising these in Section 2 of the submission as well.

## **6.14 PACE and decision modifiers**

In assessing the relative clinical and cost effectiveness of new medicines, SMC requires a robust clinical and economic case to be made and for the medicine to demonstrate value for money. For the following categories of medicines, the submitting company may request a PACE meeting if the preliminary NDC advice is not recommended:

- End of life medicine
- Orphan or orphan equivalent medicine
- Ultra-orphan medicine following evidence generation through the ultra-orphan pathway

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 Quality Adjusted Life Year (QALY). The additional factors include (but are not limited to) the following:

## Where more uncertainty in the economic case may be accepted

### Orphan medicines

SMC has a remit to assess the clinical and cost effectiveness of new medicines including those designated as orphans. The GB criteria for orphan medicines are set out on the MHRA website. In terms of the rarity of the disease, an orphan medicine is defined as one for which the frequency of the disease is less than 5 per 10,000 of the British population.

SMC requires that all submissions are comprehensive and that all sections of the product assessment form are completed. This requirement also exists for orphan medicines, for which a meaningful attempt needs to be made to present robust clinical and economic data. SMC recognises that orphan medicines may have a smaller clinical trials programme and, therefore, that less information than usual may be available for some sections (e.g. on efficacy and safety). On the other hand, other parts of the submission may require more detail, e.g. on the relevance of surrogate markers and the theoretical basis for their selection, which should then be related to quality of life data.

As with all products, the managed introduction and subsequent monitoring of orphan medicines needs to be a joint responsibility between the submitting company and the NHS. If there is a significant lack of data on long-term outcomes with an orphan medicine, this monitoring may include specific clinical audit and, where relevant, a patient register.

The assessment process for orphan medicine submissions is the same as for all other medicine submissions. However, recognising the limited data on efficacy, SMC will accept a greater level of uncertainty in the economic case. Additional factors, such as whether the medicine: treats a life threatening disease; substantially increases life expectancy and/or quality of life; can reverse, rather than stabilise, the condition; or bridges a gap to a “definitive” therapy, will also be considered in assessing both the level of uncertainty and cost per QALY which is acceptable.

Where orphan designation has been granted by MHRA, SMC will consider the cost effectiveness estimate of the medicine with reference to these factors. Should a submitting company wish to have their product’s cost effectiveness viewed in light of these factors it can be helpful to make reference to this in section 6 (discussion) of the NPAF, using appropriate supporting references where possible.



## Where a higher cost per QALY may be accepted

SMC does not have a formal threshold cost per QALY below which cost effectiveness would be considered shown and above which cost effectiveness would be considered not to have been demonstrated. The cost per QALY is only part of a wider judgment of the value of a new medicine. Where the cost per QALY is relatively high, other factors also play a role in SMC's assessment and may modify the final decision. These modifiers include, but are not limited to:

- Evidence of a substantial improvement in life expectancy (with sufficient quality of life to make the extra survival desirable). Substantial improvement in life expectancy would normally be a median gain of three months, but the SMC assesses the particular clinical context in reaching its decision;
- Evidence of a substantial improvement in quality of life (with or without survival benefit);
- Evidence that a sub-group of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this sub-group;
- Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS;
- Possible bridging to another definitive therapy (e.g. bone marrow transplantation or curative surgery) in a defined proportion of patients;
- Emergence of a licensed alternative to an unlicensed therapy which is established in clinical practice in NHSScotland as the only therapeutic option for a specific indication.

SMC also looks at any other special issues which may have been highlighted by the submitting company, by clinical experts and/or by Patient Interest Groups. These special issues are usually very specific to the medicine or disease under consideration and are thus not readily categorised.

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.

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

SMC takes account of these modifiers in respect of any medicine being assessed under its end of life / orphan medicines processes, in addition to considering the PACE meeting output, where applicable.

## 6.15 Patient Access Schemes

Patient access schemes (PAS) are schemes proposed by pharmaceutical companies to improve the cost effectiveness of medicines, thereby facilitating patient access. Patient access schemes 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.

It is recognised that while such schemes can facilitate access to new medicines on cost-effective terms, there will be implications for NHSScotland in implementing them effectively. In order to ensure this is manageable, these schemes should be the exception rather than the rule. It is reasonable for NHSScotland to prioritise schemes that deliver most benefit to patients e.g. for medicines that address a previously unmet need.

The full costs to NHSScotland of operating such a scheme must be taken into account in the assessment process.

A Patient Access Scheme Assessment Group (PASAG) has been established to undertake an objective and independent assessment of PAS submitted by companies, and advise on their acceptability for implementation by Health Boards in NHSScotland. PASAG will have a national focus operating under the auspices of NHS National Services Scotland, functioning separately from the SMC. As at present, SMC will assess the clinical effectiveness and cost effectiveness of the product according to its standard process, taking into account the impact of PAS on the product's cost effectiveness.

Submitting companies should submit a PAS application pack at the same time as they are making their submission to SMC. Submitting companies also have a second opportunity to submit a new or revised PAS to the SMC Secretariat within a two week period following the issue of preliminary NDC advice. A new application pack should be completed when revising the previous PAS application. It is important to note that a submission at this stage may extend timelines for the SMC review of the medicine. For this reason, pharmaceutical companies are strongly encouraged to submit any proposed PAS at the first opportunity with the initial SMC submission. Refer to the PAS Guidance which is available from the PASAG secretariat [nss.np-pasag@nhs.scot](mailto:nss.np-pasag@nhs.scot)

If a company wishes to make a resubmission and the only change is a new or improved simple PAS, the company may submit using the fast-track process. To be considered for the fast-track submission process, the resubmission must be received within three months of the date that the original SMC decision was issued to the company and there must be no change to any other aspect of the submission. This will allow a resubmission to proceed directly to SMC i.e. there is no consideration by the New Drugs Committee (NDC). Please see the guidance supplement in the *Making a submission* section of our website for further information.

In terms of specific guidance to submitting companies on the content of sections six and seven of the NPAF, the following should be noted:

- Section 6 of the new product assessment form (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 (e.g. simple discount, responder- based scheme, fixed price per patient etc), 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 separate document describing the full details of the PAS, as per the PASAG submission requirements.
- The submitting company must provide cost effectiveness estimates both with and without the PAS. In terms of presentation, section 6 of the NPAF should present the base case estimates with and without the PAS.
- The submitting company must also provide full sensitivity analysis on the cost effectiveness estimates both with and without the PAS. If deterministic and probabilistic sensitivity analysis is provided for the base case without PAS analysis, this should be provided for the with PAS analysis too i.e. the same sensitivity analysis should be provided for both sets of analyses. 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. Only in circumstances where PASAG estimates these costs to be very high in comparison to the discount offered will SMC 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 detailed advice document (DAD) on the product will indicate that a PAS has been proposed and provide the ICERs used for decision-making where possible. 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 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 in the economic case is available under a PAS please refer to the guidance supplement on submissions for medicines where the comparator is available through a confidential PAS. This supplement also provides guidance on the situation where the medicine under review is given as part of a combination regimen with another medicine which is marketed by a different company and available under a PAS.
- In terms of budget impact, the company must provide budget impact estimates both with and without the PAS, in section 7 of the NPAF. As noted above, budget impact estimates are completed through the use of an excel spreadsheet template, with the summary table from the spreadsheet inserted into section 7 of the NPAF to indicate the results. In the case of submissions with a PAS, budget impact templates and summary results tables must be completed for both the with and without PAS scenarios. Both sets of summary results tables should be inserted into section 7 of the NPAF and both budget impact templates should be sent to the SMC secretariat when the submission is made. Where a comparator medicine has a PAS, there is no

need to take account of this in the budget impact calculation; list price should be used for the comparator.

## 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 Patient Access Scheme (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 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:

- A table of results, which clearly shows the impact of the new/revised PAS on the base case incremental cost-effectiveness ratio (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 (i.e. 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 provide a revised budget impact template to take account of the new/revised PAS.

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

### 6.16 Diagnostic Testing (e.g. somatic, germline or biomarker)

If the medicine under review requires a diagnostic test (e.g. 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, Appendix A 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.

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## 7. Resource implications

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The purpose of this section of the submission is to provide an estimate of the potential budget impact in a way that an NHS board could identify, for example, how much money they might have to find if the new treatment replaces existing therapy in the population proposed in the economic evaluation. Budget impact information is not taken into account in the SMC decision on whether or not to accept a medicine. This section should include acquisition costs of the new treatment, and any direct effect on the use of other resources e.g. on changing from parenteral to oral therapy. However, a full economic analysis is not required here, since cost effectiveness is considered in the economics section.

Where data are not readily available, estimates in this section may have to be based on assumptions.

SMC has prepared a template for completion of the budget impact calculations. This is a Microsoft Excel workbook which can be accessed from the *Making a submission* section of the SMC website, and which should be downloaded each time a new submission is made. The budget impact template Excel workbook contains full explanatory notes and instructions for completion.

Where SMC issues 'accepted for use/restricted use', or 'accepted on interim basis for use/restricted use' advice on a medicine, the full budget impact template for the medicine will be distributed to NHS Boards together with the SMC advice on the product. This is to allow each Board to have access to a tool to assist with working out the implications of implementation of the product at a local level. If the advice on a product is 'not recommended' then the template will not be distributed to NHS Boards.

Submitting companies should complete the Excel workbook and the completed summary table showing the net total budget impact contained on the worksheet entitled "Summary" should be copied and pasted into section 7 of the New Product Assessment Form. The completed Excel workbook must also be sent as a separate Excel file to SMC at the same time the New Product Assessment Form is sent to the SMC Secretariat. Failure to do so may result in a delay to scheduling of the submission.

While the template provides full instructions for completion, it is worth highlighting several important issues for clarity;

- Where a Patient Access Scheme (PAS) submission has been made, a budget impact template must be completed for the with PAS scenario and the without PAS scenario. Comparator medicines should be included at list price, i.e. there is no requirement to incorporate any PAS applicable to comparators.
- Where a new/revised PAS is submitted after NDC, the following should be provided:
  - A copy of the summary table on budget impact for the new/revised with-PAS scenario
  - A revised budget impact template to take account of the new/revised PAS.
- In the event that SMC accepts the medicine with restrictions on its use such that the patient numbers originally presented in the New Product Assessment Form and

budget impact template no longer apply, the submitting company will be contacted by the SMC Secretariat and asked to re-work the budget impact template to reflect the reduced patient numbers. A timely response to such requests will be necessary in order to be able to provide the appropriate budget impact template to NHS Boards alongside the SMC advice on the product.

- For the majority of SMC submissions a single estimate of budget impact should be provided to represent the submitting company best estimate of resource implications following introduction of a new medicine. In the event that a submitting company wishes to present a range of alternative estimates in addition to a base case estimate of budget impact, separate Excel workbooks will need to be completed and returned to SMC with the submission.

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## 8. Summary information for submitting patient groups

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### 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, and encourages and provides support to them 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.

For this reason 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.

Representatives of those groups may also wish to obtain information from the submitting company about the treatment(s) under consideration.

Completion of the template has been added to the submission checklist. The template prompts companies to answer questions that are designed to help provide the type of information that patient groups have indicated would be of interest. Companies should avoid duplicating detailed clinical trial information provided in the SMC submission or replicating the Patient Information Leaflet.

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 end-points 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. 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, but 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” template. 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 health technology assessments 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 sympathetic 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, but also 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**

### **Front page**

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 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.

### **8.1 What condition is this medicine to be used for?**

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 sub group of the licensed indication, explain the relevant sub group and why it has been selected.

### **8.2 How is this condition currently managed in Scotland?**

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?**

Please don't use overly technical language, but 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?**

Please detail any unmet need and how the medicine addresses this. Try to summarise the clinical trial 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 to current treatment(s)? As mentioned in section 2, 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?**

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?**

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?**

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 to current treatment(s)? This might include secondary trial 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?**

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 trial 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 trial centres and early access programmes. Are there patient information materials and websites that may be helpful?

# ANNEXES

## Annex 1 The concept of the reference case

The SMC requires companies to submit economic evaluations consistent with its guidance. The SMC has not specified a reference case which must be adopted as a base case. This reflects the emphasis SMC places on receiving submissions as close as possible to the time of launch: such timing may preclude submitting companies from presenting all the data required for a pre-specified reference case.

However, to assist submitting companies, the SMC has judged that the reference case set out in section 5.1 of the NICE Guide is appropriate for use in a submission to the SMC. The key elements of the analysis in the NICE reference case are summarised in Table 1.

<b>Table 1</b>	
<b>Element of Health Medicine Assessment</b>	<b>Reference Case</b>
Comparator	Alternative therapies routinely used in the NHS in Scotland
Perspective on costs	NHS in Scotland and social work
Perspective on outcomes	All health effects on individuals
Type of economic evaluation	Cost-utility analysis
Synthesis of evidence on outcomes	Based on a systematic review
Measure of health benefits	Quality-adjusted life years (QALYs)
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument
Method of preference elicitation for health state	Choice-based method, for example, time trade-off

## Annex 2: Example of calculating hourly staff costs for use in economic evaluations

The following example is taken from Section 12.1 of the PSSRU Unit Costs of Health and Social Care 2009 document, page 157 ([www.pssru.ac.uk](http://www.pssru.ac.uk))

In the PSSRU estimate the numerator is as follows:

Salary	£35,900
On-costs	£8,926
Qualifications	£4,686
Overheads	£3,097
Capital	£2,510
Total	£55,119

Alternative denominators are as follows:

Weeks	41.3	per year
Hours	37.5	per week
	1,549	hours per year
Proportion face-to-face with patient	45%	
	697	face-to-face hours per year

This gives £36 per hour based on a working week or £79 per hour based on hours of face-to-face contact with patients. Excluding qualifications costs gives a total of £50,433 (after excluding £4,686). The hourly figures then become £33 and £72. All of these results are as per PSSRU.

In order to calculate staff costs for use in economic models, SMC ask for salary plus on-costs divided by the full working week. Using the PSSRU costs as an example:

Salary	£35,900
Oncosts	£8,926
Qualifications	£0
Overheads	£0
Capital	£0
Total	£44,826

Weeks	41.3	per year
Hours	37.5	per week

1,549 hours per year

This gives a figure of £28.94 per hour. The SMC's presumption is that this is the appropriate value for such resources that NHSScotland wishes to see in economic analyses. Submitting companies can make the case for an alternative figure but the set of circumstances would have to be unusual and appropriate justification given for not using these principles in the base case analysis.

## Annex 3: Conversion from condition-specific measures into preference-based outcomes (QALY-weights) for use in economic evaluation – current best practice

### Background

The SMC User Group Forum (UGF) discussed the issue of best practice methodology for converting condition-specific measures into preference-based outcomes (or ‘QALY weights’) for use in cost-utility analysis. This is a process otherwise known as ‘mapping’.

A particularly useful paper discussing this issue is Petrillo & Cairns 2008<sup>1</sup> which describes the methodology that should be undertaken when undertaking a mapping exercise. It lists four main steps:

- Examining the relationship between instruments
- Data collection
- Statistical analysis for algorithm development
- Testing model performance

*It should be noted that this paper is not intended to be fully prescriptive, but more to outline best practice. This methodology itself will not necessarily need to be followed in every case, but it should be a useful prompt whereby if practices have not been followed, justification may need to be provided.*

### Relationship between instruments

There must be a certain degree of comparability or overlap between domains of the condition-specific measure and the generic target (e.g. from the asthma quality of life questionnaire across to EQ-5D). Petrillo & Cairns suggest that the best instruments are HRQoL measures with a condition-specific focus as these support the face validity of the mapping. In addition they suggest that factor analysis should be conducted to demonstrate convergent validity. (Convergent validity is useful to conduct in addition to a face validity test, as it provides empirical support for the mapping.)

### Data collection

“Data for mapping studies are usually collected using both the condition-specific and generic instruments simultaneously.” The authors suggest that retrospective studies with large patient samples and an even distribution of severities feature health states actually experienced by patients. They suggest that the full range of severities increases the probability that the mapped instrument will discriminate across the entire scale, and also that stable patients allow reproducibility and factor analysis testing. Data can be collected from both patients and the general public, though the authors suggest that data collection is

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<sup>1</sup> Petrillo J, Cairns J. Converting condition-specific measures into preference-based outcomes for use in economic evaluation. Expert rev Pharmacoeconomics Outcomes Res 2008; 8: 453-461

normally restricted to patients. A large dataset and a sample of representative patients are key requirements.

#### Statistical analyses

No suggested preferred analyses are given, though the authors state that most studies have used multiple regression models or correlation tests.

#### Model performance / validation

The model must be tested in terms of reliability and validity. The authors state, “Reliability involves examining the reproducibility of results, while validity testing refers to the degree to which the model can accurately predict the scores in terms of the generic measure that will be associated with patients in different condition-specific health states.” One approach is to split the original sample, and estimate the model for part of the data, and then to use the estimated coefficients to predict health-state values for the other part of the data. An alternative is to test the predictions of the model on a completely different set of data (but this is a more demanding test given that the datasets may contain differences).

Another useful paper on the matter is that by Mortimer & Segal 2008<sup>2</sup> which looks at the strengths and weaknesses of the use of different algorithms to convert descriptive measures in QALY weights. Further examples of studies utilising mapping techniques are also listed for information.<sup>345</sup>

#### Overall comment

It should be noted that mapping is not always an ‘easy fix’ and some quarters suggest that the only robust method is to incorporate both the disease-specific and generic instrument in an observational study utilising patients with the specific condition. However, in the world where it is understood that data for health economic modelling may not always be available directly from clinical trials, mapping appears to be a pragmatic approach that, if carried out robustly, should be acceptable to health technology decision makers.

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<sup>2</sup> Mortimer D, Segal L. Comparing the incomparable? A systematic review of competing techniques for converting descriptive measures of health status into QALY-weights. *Med Decis Making* 2008; 28: 66-89

<sup>3</sup> Wu EQ, Mulani P, Farrell MH, Sleep D. Mapping FACT-P and EORTC QLQ-C30 to patient health status measured by EQ5D in metastatic hormone-refractory prostate cancer patients. *Value in Health* 2007; 5: 408-414

<sup>4</sup> McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. *Value in Health* 2009; 12: 167-171

<sup>5</sup> Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQ C-30 to the preference-based EQ-5D, SF-6D, and 15-D instruments. *Value in Health*; 2009; 12:1151-1157