GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. R. 1265 **31 December 2010**

MEDICINES AND RELATED SUBSTANCES ACT, 1965

REGULATIONS RELATING TO A TRANSPARENT PRICING SYSTEM FOR MEDICINES AND SCHEDULED SUBSTANCES:

(DRAFT GUIDELINES FOR PHARMACOECONOMIC SUBMISSIONS)

The Director-General, on the recommendation of the Pricing Committee, in terms of Regulation 21 of the Regulation Relating to a Transparent System for Medicine and Related Substances as published in Government Gazette Number 28 of 11 November 2005, intends to make the Guidelines for Pharmacoeconomic Evaluations of Medicines and Scheduled Substances in the Schedule.

Interested persons are invited to submit any substantiated comments or representation in writing on a compact disc and a hard copy, on the proposed Guidelines within three months of publication of this notice addressed and hand delivered to: The Director: Pharmaceutical Economic Evaluations: Room 2611: Civitas building: Corner Struben and Andries street: Pretoria

SCHEDULE

THE GUIDELINES FOR PHARMACOECONOMIC EVALUATIONS OF MEDICINES AND SCHEDULED SUBSTANCES

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DIRECTOR-GENERAL: NATIONAL DEPARTMENT OF HEALTH

DECEMBER 2010

Contents

Acronyms

ATC	Anatomical Therapeutic Chemical classification
DG	Director General
DoH	Department of Health
DPEE	Directorate Pharmaceutical Economic Evaluations
INN	International Non-Proprietary Name
ITT	Intention to Treat
MCC	Medicines Control Council
MOH	Minister of Health
MRA	Medicines Regulatory Authority
NDoH	National Department of Health
NDP	National Drug Policy
PETT	Pharmacoeconomics Task Team
RCT	Randomised Controlled Trial
SEP	Single Exit Pricing

Part A: Process for Submission

1. Introduction

There is no doubt that new medicines have the potential to greatly improve health outcomes but at what cost? This is the issue that is facing healthcare programmes across the globe and in order to conduct clinical decision-making with credibility a transparent, consistent and formal process of cost-effectiveness evaluation is required.

The objectives, therefore, of the Pricing Committee in establishing a Guideline for Pharmacoeconomic Evaluation of new and existing medicines, are to:

- Describe the process to be followed by applicants when submitting an application
- Describe the criteria for medicines which require a submission for pharmacoeconomic evaluation.
- Provide an overview of the principles and methods of assessment at each stage of the appraisal process
- To promote access to information regarding the value of medicines
- To create a forum which provides independent and objective review of the value of medicines
- To expedite the review process by ensuring a common understanding of the criteria and information that is required

2. Role and Responsibilities of the Pricing Committee

The Pricing committee was established in 2003 under the *Medicines and Related Substances Control Act* 101 of 1965 to make recommendations to the Minister for Health on medicine prices. The role of the committee was to assist in bringing about a more transparent pricing system for medicines in South Africa. To this end, the Committee is required to consider the cost-effectiveness, of a medicine compared to other therapies.

Medicines must be registered with the Medicines Control Council (MCC) before being brought to the Pricing Committee for an economic evaluation. Registration of medicines is based on an assessment of quality, safety and efficacy, a process that often involves the Medicines Regulatory Authority (MRA) and the Medicines Control Council. The Pricing Committee accepts that products registered by the MCC have reasonable safety and efficacy adequate to allow marketing in South Africa.

The role of the Pricing Committee is to make recommendations to the Minister of Health on the value for money that a medicine offers in South Africa. These recommendations are dealt with in further detail in Part A, Section 5. It may, therefore, consider the cost-effectiveness of a product compared with other products already registered for the same, or similar, indications. Where there is no listed alternative, the Committee considers cost-effectiveness, compared with standard medical care or the benefits for patients that the new product will provide compared to the cost of achieving those benefits.

The payers of medicines e.g. the medical schemes will determine the re-imbursement criteria for such medicines as deemed appropriate by their individual benefit design. The latter will determine who may prescribe the medicines (e.g. GP or specialists) and under which conditions the medicine will be re-imbursed (e.g. acute, chronic and / or first or second line). A policy for restrictions to the indications may be applied. When recommending cost-effectiveness of a particular medicine, the Committee may also provide recommendations to healthcare funders, prescribers, dispensers and patients regarding comparison with alternatives or their cost-effectiveness ("value for money").

All medicines that are considered cost-effective will be listed on the Department of Health website.

2.1. Pharmacoeconomic Task Team

The Pricing Committee may establish task teams, to assist it in performing its functions. In 2007/8, the Pharmacoeconomic Task Team (PETT) was appointed. The PETT

comprises a Chair, Vice Chair and Reviewers. The Task Team is made up of ordinary Pricing Committee members and experts co-opted to assist on the Task Team. This subcommittee will provide recommendations on cost-effectiveness to the Pricing Committee. The PETT will review the submissions and compile a report to be presented to the Pricing Committee.

In formulating its conclusions, the PETT may seek expert opinion from relevant professional bodies and/or appropriate subject specialists and may meet with representatives of relevant medical professional Institutions.

2.2. Pricing Committee Secretariat

The Pricing Committee and its Task Teams are serviced by the secretariat of the Directorate: Pharmaceutical Economic Evaluations (DPEE), which are part of the National Department of Health. They are also the first point of contact concerning pricing committee discussions and decisions.

All queries and interactions with the manufacturers will be handled by the Secretariat. Queries about the procedure for submission will be dealt with by the pricing committee secretariat.

All correspondence should be in writing.

All correspondence should be addressed to:

The Chair: Pricing Committee

c/o The Director: Pharmaceutical Economic Evaluations

Private Bag X 828

Pretoria 0001

Submissions should be delivered to:

The Director: Pharmaceutical Economic Evaluations

Room S2611 Civitas Building

Cnr Andries and Struben Streets

Pretoria

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3. General Guidelines Followed By The Pricing Committee

The cost-effectiveness of a medicine will be the primary consideration. The role of a medicine in meeting the health needs of the South African community will also be considered.

All submissions will be evaluated in a step-wise process;

Step 1: Is the submission complete? If yes, go to Step 2

Step 2: Is the clinical evidence sufficient to warrant a pharmacoeconomic evaluation? If yes, go to Step 3: Does the pharmacoeconomic evaluation prove cost-effectiveness?

A document will be made available on the DoH website regarding the full details of the steps followed in the evaluation process from the first communication with the DPEE to the final recommendation by the Pricing Committee.

Only medicines recommended as cost-effective by the Minister of Health will be listed on the Department of Health website. Recommendations of cost-effectiveness will be

based on a number of criteria as determined by the Pricing Committee and each submission will be assessed on a case-by-case basis

Decisions regarding funding for medicines (i.e. whether a medicine is re-imbursed or not and under what conditions) will remain with the medical schemes. However, the Pricing Committee may recommend an applicant consider a reduced SEP for the medicine under review based on their evaluation of the pharmacoeconomic submission.

4. Criteria for Medicines Requiring Pharmacoeconomic Submissions

Medicines that will **require** a pharmacoeconomic evaluation include, amongst others;

- New chemical entities
- New clinical indications for an existing medicine
- Where it is the opinion of the Pricing Committee that a pharmacoeconomic evaluation is necessary/required for a particular medicine

Submissions which **do not require an economic evaluation** include;

- Where the price of a new formulation (or strength) is less or equal to the price of a currently listed medicine of the same ingredient or strength.
- Any generic equivalent (or new brand) of the same formulation of a medicine with an existing SEP provided it is less or equal to the price of the currently listed medicine

If there is any doubt as to whether a product will require a submission, please send a short request (no more than 400 words) including the name, active ingredient and clinical indication of the medicine for clarification from the Directorate PEE Secretariat.

5. Recommendations of Cost-Effectiveness

The Pricing Committee **may recommend** a medical entity as cost-effective if:

1. It is at least as effective and safe as a medicine already listed for the same indications and is of acceptable or better cost-effectiveness; or
2. It is more effective, less toxic (or both) than a medicine already listed for the same indications and is of acceptable cost-effectiveness; or
3. It is needed for the prevention or treatment of significant medical conditions where alternative treatments are not available and is of acceptable cost-effectiveness;

A **recommendation** of cost-effectiveness may be withdrawn if new material or evidence is shown to render the medicine no longer cost-effective.

The Pricing Committee may make a recommendation with regards to the use of the medicine in specific patient groups, or prescribing by general practitioners or specialist groups or under specific circumstances.

Recommendations are based on information submitted at a point in time. See Section 6.4 regarding re-submissions

6. Procedures for Submissions

6.1. Source of Submissions

The Committee will consider submissions from the manufacturers of the medicine under review. The onus is on the applicant to supply all the necessary data and information, e.g. clinical trials, costing data and health economic models to the pricing committee for evaluation.

6.2. Timing of Submissions

The Committee is conscious of the need to avoid unnecessary delays between marketing approval and recommendation of cost-effectiveness.

Submissions should be completed according to the criteria as specified in this document. Timing will work on a "stop the clock system", i.e. if any queries or clarifications are sent to the applicant, the clock will be stopped until the applicant has satisfactorily responded. The clock will not start until a complete submission has been received.

All applicants will receive a response from the Pricing Committee within 180 working days of receipt of their completed submission

6.3. Summary Report of Recommendation to Pricing Committee

A summary report will be submitted by the PETT to the Pricing Committee stating their intention to recommend a particular decision. Before the summary report is submitted to the Pricing Committee the applicant will be given an opportunity to comment on the report within 30 days.

Submissions from other stakeholders such as healthcare providers, funders, patient groups and specialist groups will be considered at this stage.

6.4. Re-Submission

The Pricing Committee may be requested to consider a re-submission under the following circumstances;

- Introduction of new data, scientific evidence or randomised controlled clinical trials
- Modification of a previously requested indication
- Change of comparator based on new evidence supporting consideration of a different comparator.
- Substantial amendment of the health economics model and input data (e.g. costs)

The information in the re-submission must provide a substantial motivation for a change to the Committee's earlier decision.

The re-submission must highlight the following aspects:

- The main matters of concern to the Pricing Committee and/or the matters that the Committee has requested be addressed in a re-submission and how the re-submission addresses them;
- All new data, new circumstances, new arguments or new approaches included in the re-submission should be identified.

An executive summary should be submitted which addresses all the new information and queries that the re-submission focuses on. Simply submitting a new clinical trial or publication will not suffice. The executive summary should detail the new supporting evidence.

A re-submission will be processed in the same manner as an original submission, i.e. it will not take priority over existing submission in the queue, a response will be given within 180 working days of receipt of re-submission and a “stop the clock” rule will apply.

All re-submissions will be reviewed by the PETT before a decision is made whether to forward this on to the Pricing Committee agenda with a recommendation. Once the Pricing Committee has made a decision on the re-submission, this decision is final.

7. General Recommendations on Preparing a Submission

These guidelines are designed to assist in identifying and formatting the information needed by the Pricing Committee and to provide guidance on the most appropriate form of economic evaluation required.

While all attempts should be made to adhere to the suggested layout (See **Appendix A: Sample Template for Submission** Format), this will not always be the most appropriate so deviations, which may be necessary for some medicines, are permitted. It should be clearly stated where submissions deviate from the required format with an explanation for the deviation. Please note the template in Appendix A is a sample – please consult the Department of Health website for the most recent format template in full detail.

The submission should be as succinct and informative as possible. The Pricing Committee is most likely to be influenced by arguments based on scientifically rigorous data rather than opinions. Use suitable scientific language, but avoid jargon.

The executive summary is the document from the submission, which is included in both the PETT and the Pricing Committee agenda papers. The main body of the submission should be a separate bound document including reports of the key trials.

It is vital therefore that the submission provides frequent and accurate cross-references between the executive summary and the main body of the submission, and between the main body of the submission and reports of the key trials, attachments, technical documents and computer discs. This will assist those who have to evaluate and consider the submission.

Submissions must be made in both hard-copy and electronic copy. Documentation should be presented in Microsoft Word or pdf. Spreadsheets will be accepted in Microsoft Excel. If a software programme/package has been used to develop a model, this should be converted to Microsoft Excel for review. In addition to this, a copy of the software licence should be made available to the PE TT in order for them to complete a comprehensive review of the model.

7.1. Checklist of Material to be Submitted

Use the following checklist as a final check before lodging a submission with the Directorate Pharmaceutical Economic Evaluations. See **Appendix B: Checklist for Submission Documents** for a complete checklist. The checklist is designed to ensure that each submission lodged is sufficient for a complete assessment while not unnecessarily requiring the submission to be referred back to the applicant.

Ten (10) suitably bound copies of the Application for Submission containing:

- Signed covering letter for the submission
- Signed official application form for the medicine, formulation or strength and stating the current SEP and clinical indication
- The completed document entitled "Answers to Key Questions" to determine the acceptability of the submission. See section 7.3 and **Appendix C: Key Questions**
- The executive summary of the submission; this should be limited to no more than 10 pages

- The letter of MCC registration with details of marketing approval and registration and
- The official package insert

Five (5) suitably bound copies of the Full Submission containing:

- Main body of the submission
- Appendices and References

Additional documentation that may be required;

- Any technical documents as necessary (in addition to the main body of the submission and which must be separately bound); and
- Any computer disc/s as necessary (with any spreadsheet and word document compatible with Microsoft excel and Microsoft word).
- Full copy of the MCC's investigator's brochure compliant with ICH regulations
- If a registration application has been considered more than once by the MCC, documentation relating to all MCC considerations should be supplied.

Each copy must:

- Be suitably bound;
- Have a clear and adequate index;
- Have consistent pagination throughout;
- Have attachments containing full copies of the key clinical trials, which must be:
    - either the published paper and/or the investigator's summary of unpublished trials and adequate details of the trial methods and of any results used in the economic evaluation(s); legible; and
    - in English or be accompanied by a reputable translation.
- The main body of the submission should follow the guidelines in the remainder of this document as far as possible. To facilitate its evaluation, it should also use the headings of each Section in layout as suggested in **Appendix A: Sample Template for Submission** Format

Applicants are encouraged to send a copy of the submission in electronic format (with any word processed document compatible with Microsoft Word). The electronic version would supplement, not replace, the associated paper-based submission.

7.2. Key Questions to Determine Acceptability of Submission

The following questions should be answered concisely. This will help the Directorate Pharmaceutical Economic Evaluations determine the acceptability of the submission. See **Appendix C: Key Questions** .

- Are the indication(s) for pharmacoeconomic evaluation within the MCC-approved indications?
- When was the medicine registered by the MCC?
- Is the comparator justified according to the criteria given in Part B, Section 3.5.? Give the page number of the submission where the choice of comparator is justified.
- Has a thorough search for relevant comparative randomised trials been conducted? Give the page number of the submission where the search strategy is presented.
- Does the key clinical evidence in the submission relate to the proposed main clinical indication?
- Have the measures taken by the investigators to minimise bias in the key clinical evidence been assessed? Give the page number of the submission where the assessments are presented.
- Have the clinical outcomes of the studies been clearly defined? Give the page numbers of the submission where these outcomes are presented.
- Has a meta-analysis been conducted? Give the page number of the submission where the methods and results of the meta-analysis are presented.
- Has primary outcome data (as opposed to secondary or sub-group outcomes) been used as the main clinical inputs for the health economics submission?
- Have all the important and relevant costs been identified and measured. Are the sources of these costs clearly identified and have these costs been adjusted for

differential timing. Give the page number of the submission where this information is presented

- Has a clear description been given of the type of health economics model and an explanation for its use?
- Has a payer perspective been used and the only the relevant costs included?
- Has an appropriate time horizon been used and justified? Give the page number of the submission where this information is presented
- Has an incremental analysis of costs and consequences of alternative treatments been performed? How was the cost-effectiveness ratio expressed?
- Has a sensitivity analysis been carried out to assess the uncertainty of the variables in the evaluation?

7.3. Recommendation on preparing the Executive Summary

The Executive Summary should be no more than 10 pages. This will be included in the meeting pack of information for agenda papers for the Pricing Committee meeting so it should be regarded as the applicant's primary vehicle for communicating with each committee member.

The executive summary should therefore clearly state the key aspects and issues presented in the main body of the submission, which is forwarded to each task team member along with the agenda. As a minimum, the executive summary must provide the details to address each of the following key aspects;

- The South African approved brand name, INN, registration number, principal pharmacological action and indication(s) of the medicine.
- The formulation(s), strength(s), pack size(s) and single exit price
- Brief description of the clinical condition intended for treatment
- Brief description of patient eligibility for treatment, e.g. age, gender, risk status, disease severity
- The recommended duration of treatment.
- The main comparator(s).

- Whether the key clinical evidence in the submission comes from randomised head-to-head trials, from an analysis of two sets of randomised trials involving a common comparator (e.g. placebo or other active therapy), or from non-randomised studies.
- The main clinical results of the randomised trials
- If a modelled economic evaluation has been undertaken:
- The type of economic evaluation;
- The main results of the cost-effectiveness analysis in the economic evaluation based on the evidence from the randomised trials and the type of economic evaluation.
- The pivotal assumptions underlying the model (as tested in the sensitivity analysis in Part B, Section 8.7); and
- The relevance/importance of submitting this product for evaluation in patient health and clinical-decision making

Part B: Content of Submission

1. Executive Summary

See Part A, Section 7.3.

The Executive Summary also needs to indicate whether the pharmacoeconomic evaluation submitted is an adaptation of an existing international model (usually developed by the company's head office) or whether it is an entirely new pharmacoeconomic evaluation. In either instance, all the detailed clinical, costing and modelling information required in the sections below is still required.

Please ensure that the Executive Summary contains adequate cross-referencing to the main body of the submission and any other additional documents

2. Description of Disease/Clinical Condition

This section should describe the disease/clinical condition intended for treatment and includes information on the following:

- Demographics of patients suffering from this condition including target population for treatment
- Epidemiological data
- Burden of Disease
- Current treatments
- Challenges of current treatments
- Any existing Clinical Guidelines (local or international) for the condition

South African data should be included wherever possible

3. Details of Medicine

3.1. Pharmacological class and action

Give the South African approved brand name, INN and ATC therapeutic class for the proposed medicine. What is its principal pharmacological action? What pharmaceutical formulation(s) (ampoule, vial, sustained release tablet etc), strength(s) and pack size(s) are submitted for evaluation?

Appendix D: Additional information required for fixed combinations of products gives details of the information requirements of submissions containing fixed combination products.

3.2. Clinical Indication/s

State the indication/s approved by the MCC.

Then state the indication/s covered by the submission.

If the submission pertains to a specific sub-group of patients within the registered indication, a clear description of that sub-group must be provided. A submission will only be considered for this sub-group of patients if;

- The clinical efficacy of the medicine in this sub-group is determined on the basis of a RCT **and**
- Where this group has been defined *a priori* in the clinical trial protocol; **or**
- If the design of trial has allowed for stratification and is sufficiently powered to analyse the specified strata.

Sub-group analyses within a randomised controlled trial where the trial is powered to detect a difference within the general population of the trial will not be considered.

Ensure that any sub-group analysis is within the approved indication/s (it may be narrower, for example, to identify the patient group likely to benefit most).

Alternatively the applicant can submit an entirely new dossier for each main indication – particularly where the indication is in a different disease state or condition – e.g. different cancers or cancer vs rheumatoid arthritis)

3.3. Treatment Details

List the dose, frequency per day and length of course recommended in the current approved product information. Is this the same as used in the clinical trial data? If not, please give a clear explanation for the differences.

Indicate if the medicine has to be administered using specific health technologies or based on the results of any diagnostic tests

3.4. Co-administered Therapies

State what other therapies, if any, are likely to be prescribed with the medicine as part of a course of a treatment protocol?

List the therapies, particularly already registered medicines, which are likely to be prescribed for use in conjunction with the medicine, for each diagnosis/symptom area. This should include medicines, which are likely to be used to manage or prevent side effects of treatment.

Indicate, what therapies, if any, are likely to be prescribed *less* for the target patient population for the therapeutic indication or for the treatment of side effects of current therapies if the proposed medicine were to be used? List any therapies which are likely to be substituted by the proposed medicine. Provide the details requested in Section 3.1 and 3.3 for each medicine included in the economic evaluation.

3.5. Choice of Comparator Treatment

The main comparator is the therapy, which is deemed to be the standard of care for local practice. In some cases, comparisons with more than one comparator will be necessary. All possible comparators should be listed, then describe and justify the comparators that are chosen for the evaluation and give an explanation for those that are not chosen. The comparators should also include the lowest cost alternative that is available for the same indication.

The following will assist in selecting the main comparator;

- If the proposed medicine is in a therapeutic class for which pharmacological analogues are already registered, the main comparator will usually be the analogue.

- If the proposed medicine is in a new therapeutic class but will be used for an indication for which there are other medicines widely used to treat that indication, the main comparator will usually be the medicine which is prescribed to treat that indication for the largest number of patients. (Section 4.3. gives further advice if there is relevant evidence from a comparison of the proposed medicine with several medicines widely accepted as clinically equivalent to the main comparator or of the main comparator with several medicines widely accepted as clinically equivalent to the proposed medicine).

- If no registered medicine can be identified as a comparator then the main comparator will usually be standard medical management (this could include a surgical procedure or conservative management). This should be clearly and consistently defined in both the submission and the comparative randomised trials.

- If the medicine is supplied in a special formulation (e.g. sustained release tablets, oral pressurised inhalation), the main comparator selected according to the above criteria should be in a similar formulation, if available. If a similar formulation is not available then the value of using the special formulation at an additional cost should be clearly demonstrated.

Details of the comparators should also include;

- Active ingredients
- Pharmacological action
- Clinical indications
- Dose, frequency and duration of therapy
- Co-administered therapies
- Route of administration and any additional costs associated therein

The package insert registered with the MCC of the main comparator should be included in the submission.

Describe and provide reference for the main differences in the indications, contra-indications, cautions, warnings and adverse effects between the proposed medicine and the main comparator.

Where the comparator is not a medicine but rather a surgical treatment or alternative form of treatment (e.g. lifestyle, preventive care), please include a concise but detailed explanation of the comparator treatment so as to justify its position as a comparator.

Where the entry of future comparators is expected, including the anticipated entry of lower cost treatments (e.g. generics), these should be considered for analysis, particularly where there is already clinical evidence to support the use of these products.

3.6. Expert Opinion

If an expert panel, Delphi panel or survey has been used to help identify any of the input variables (e.g. the main indication, locally relevant comparator, resource utilisation etc), **Appendix E: Expert Opinion** gives further advice on the necessary background information.

4. Clinical Outcomes (Effectiveness)

The quality of the clinical evidence used in the pharmacoeconomic analysis is critical in determining whether further evaluation should be considered. If the clinical evidence submitted is considered to be insufficient to support the recommendation of the medicine regardless of the cost-effectiveness, then the evaluation of the pharmacoeconomic analysis will not continue.

Insufficient clinical evidence includes;

- Lack of well-designed, robust clinical trials
- Lack of clinically and statistically significant clinical outcomes

In addition to the clinical effectiveness of the proposed medicine, clinical inputs can also include the following information;

- Incidence rates of disease
- Mortality rates and life expectancy
- Adverse drug reactions and treatment thereof
- Patient compliance/adherence to treatment
- Uptake of treatment as well as discontinuation or withdrawal from treatment

4.1. Description of search strategies for relevant data

The selection of trials for analysis must start with a consideration of all relevant trials that enable a comparison between the proposed medicine and the main comparator for the main indication. An adequate search strategy must be used to locate these trials. This should involve at least three approaches: a search of the published literature; a search of the Cochrane Controlled Trials Register; and a check with the manufacturer's head office and other subsidiaries of the company for further trials (which may be unpublished).

The methodology used to search the literature is pivotal to assessing the completeness of the search. Therefore the applicant is required to specify:

- The specific databases searched (including at least MEDLINE/EMBASE and the Cochrane Controlled Trials Register), as well as databases internal to the cornpany;
- The date the search was conducted;
- The date span of the search (which should be up to date to the most recent database update);
- The complete search strategies used, including the search terms (key or MeSH words) and the relationship (sets and boolean) between the search terms; and
- Any supplementary searches, especially manual checking of references in the retrieved papers

4.2. Listing of all Comparative Trials

A list of the search results should be included in the Appendices of the submission. The listing of comparative trials retrieved by the search strategy must be complete. The Directorate PEE will run an independent literature search. If this search retrieves relevant trials that were not listed in the submission, processing of the submission will stop until the matter has been resolved.

List citation details of all randomised trials that compare the proposed medicine directly with the main comparator for the main indication ("head to head trials"). If there is none, state this and then list citation details of all randomised trials comparing the proposed medicine with other therapies, including placebo, for the main indication. Provide the same details for all randomised trials comparing the main comparator with the same reference treatments for the main indication. if there are no randomised trials of either the proposed medicine or the main comparator, state this and then list all non-randomised studies that are relevant to the main indicator.

Indicate for each citation whether it will be included or excluded in the clinical evaluation

See **Appendix F: Citation Details of Comparative Trials** for listing citation details.

4.3. Selection of Comparative Trials used in the Submission

The Pricing committee has a strong preference for economic evaluations that are based on so-called "head-to head" double-blinded, randomised controlled trials that directly compare the proposed medicine with the main comparator where these are available.

Where no head-to-head trials are available, other forms of evidence may be accepted and given full and proper consideration. An analysis of two sets of randomised trials involving a common reference represents a possible alternative (see Part B, Section 4.5.4. for further information), however a clear description of the analysis and potential biases needs to be included.

It is recognised that randomised trials are not always available (for example some medicines for cancer or rare diseases). However, without any evidence from randomised trials, it has often proved difficult to determine whether there is a clinical or economic difference between the proposed medicine and the main comparator.

Clinical trial evidence will be considered based on the SORT hierarchy of evidence (See **Appendix G: SORT Hierarchy of levels of evidence** for more details) as set out below;

This system contains three levels:

Level	***Description***	***Examples***
Level I	Good quality evidence	Systematic review including a meta-analysis of high quality RCTs with consistent findings High quality individual RCT

Level II	Limited quality patient orientated evidence	Systematic review including a meta-analysis of lower quality studies or studies with inconsistent findings Low quality clinical trial Cohort studies Case-control studies
Level III	Other	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series

For each study used in the submission, the level of evidence must be indicated.

To enable evidence of the highest scientific rigour to be considered, in some circumstances it may be reasonable to support the key head-to-head trials with evidence from additional randomised trials, for example, if only one under-powered head-to-head trial is available. Possible supportive information includes:

- An analysis of two sets of trials involving a common reference that is based on much larger subject numbers;
- A meta-analysis including all trials of the proposed medicine against several medicines widely accepted as equivalent to the main comparator in terms of effectiveness and safety as well as the head-to-head trials; or
- A meta-analysis including all trials of the main comparator against several medicines widely accepted as equivalent to the proposed medicine in terms of effectiveness and safety as well as the head-to-head trials.

Supportive randomised trials should be separately identified and included with any other references to the submission. This supportive information should be clearly labelled to distinguish it from the information from the key trial(s).

The clear preference for evidence from the most scientifically rigorous sources does not imply that a minimum standard must be met. The Pricing Committee has and will continue to consider all evidence, but will be most influenced by the results of the most rigorous randomised trials.

4.4. Exclusion of Clinical Trials

Against each excluded citation in the results of the literature search indicate the reason for its exclusion. Not all citations in the results of a literature search need be presented in Section 4.2. as there are many possible reasons for excluding citations that are unlikely to be disputed (see below).

Clinical studies that will **not** be considered for comparative evidence include;

- Uncontrolled studies
- Case reports
- Anecdotal evidence or key opinion leader reports or reviews
- Animal or in vitro studies
- Marketing or advertorial literature

However, if a trial is excluded for any of the following reasons, the exclusion may be disputed and therefore must be included in the list of citations with a brief comment on the exclusion (See **Appendix H: Reasons for Exclusion of Clinical Trial**);

- The trial has a methodological flaw in randomisation, follow-up or blinding

- Trial subjects do not overlap with patients likely to receive the proposed medicine
- The trial uses a different dosage regimen or form to that proposed for reimbursement
- The trial has inadequate duration of follow-up
- The trial measures an outcome that is not relevant to the submission

These exclusion criteria are optional. Depending on the data available, applying these exclusion criteria would not be appropriate if they exclude the most scientifically rigorous evidence available (e.g. it would not be appropriate to exclude a randomised trial if no more relevant randomised trial data is available). If there is uncertainty about whether to exclude a trial, it is recommended to rather include it.

4.5. Evaluation of Clinical Trials For Inclusion in the Submission

As stated previously, the quality of the clinical evidence must be assured before analysis of the pharmacoeconomic submission can proceed. Section 4.5. seeks to assist the applicant in a rigorous assessment of the selected literature and data.

The main body of the submission should include sufficient details of the key randomised trials as attachments or appendices. Where there is more than one report of a randomised trial (e.g. a published paper and the applicant's internal trial report held for regulatory purposes), provide both the published paper and key extracts from the applicant's trial report (see checklist at the beginning of this Part for details). The results may vary between the reports of the same trial. If so, justify the selection of the source of results extracted for the submission.

If the primary source of evidence in the submission is an independently-conducted meta-analysis published in a peer-reviewed journal and incorporating all important trials listed in this Section, then consult **Appendix J: Use of meta-analysis.**

Justify the inclusion of any supplementary randomised trial data. List the supplementary trials that are added for further reporting.

4.5.1. Assessment of measures taken to minimise bias in the comparative randomised trials

Provide information on the assessment of measures taken to minimise bias in each of the randomised trials listed in response to Section 4.2.

Appendix K: Measures taken by investigators to minimise bias in each trial listed in response to Section 4.2. Lists three sets of methodological topics (randomisation, loss to follow-up and blinding) that are to be used to describe each trial and a supplementary question that is also to be answered for each trial. This is a useful guide to help the committee and the applicant review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

4.5.2. Characteristics of the comparative randomised trials

Provide information on other characteristics of each of the randomised trials listed in response to Section 4.2.

Appendix L: Characteristics of each trial listed in response to section 4.2. lists a short series of questions that are to be answered for each trial.

4.5.3. Analysis of the comparative randomised trials

For each patient-relevant outcome listed, report differences between the proposed medicine and the main comparator, as well as the 95% confidence intervals for these differences.

Appendix M: Analysis of the outcomes of each trial listed in response to Section 4.2. lists a series of questions to help describe the type of information which should be presented for each trial. Only report Quality of Life outcomes in this section if they have been measured in the clinical trials selected in 4.2. For more information on Quality of Life outcomes see Section 8.4.1.

Appendix J: Use of meta-analysis provides suggestions on deciding whether a meta-analysis is appropriate and, if so, what methods may be appropriate. The method(s) of statistical pooling and statistical tests should be described and justified. If any of the trials are excluded from the meta-analysis, the reasons for doing so (e. g. on grounds of inadequately minimising bias) should be explained and the impact that each exclusion has on the overall meta-analysis should be examined.

It is important to take care when including information on adverse outcomes in the evaluation. Adverse outcomes have two main impacts on an economic evaluation - they affect the medical outcomes of medicine treatment and they contribute to the total cost of therapy. Avoidance of an adverse outcome typically associated with use of a class of medicine may be an important and intended outcome of therapy. Adverse outcomes may affect quality of life particularly if they have to be tolerated over long periods. Adverse outcomes may also lead to discontinuation of the medicine leading to substitution of another medicine or other medical intervention.

A comparative analysis of time to treatment cessation of the proposed medicine and the main comparator on the basis of "intention-to-treat" is useful in this situation. Adverse outcomes themselves can contribute to costs through unintended hospitalisation,

additional procedures and investigations. Take care to ensure that these factors are dealt with appropriately.

4.5.4. Indirect comparison of outcomes from randomised trials

In the case of an analysis of two sets of randomised trials involving a common reference, present the extent of any difference between the proposed medicine and the main comparator after adjusting for any differences in the trial populations and/or the results of the common reference.

This type of analysis indirectly compares the proposed medicine with the main comparator by comparing one set of trials in which subjects were randomised to the proposed medicine or to a common reference with another set of trials in which subjects were randomised to the main comparator or to the common reference. The common reference is often placebo, but may be a medicine from another therapeutic class. Before comparing the proposed medicine with the main comparator, the comparability of the two sets of trials must be established. The answers to (c) and (d) in **Appendix M: Analysis of the outcomes of each trial listed in response to Section 4.2.** for the trials in the two sets should be assessed for any important differences. The results for the common reference should also be assessed for any important differences.

4.5.5. Evaluation of non randomised clinical trials

The Committee will generally only consider primary clinical efficacy outcomes from high quality randomised controlled trials.

Classical community-based epidemiological designs, such as controlled cohort and case-control studies, can be used to estimate the secondary clinical performance of therapy (such as quality of life, adverse drug reactions, hospitalisation etc) if randomised

trials are not available. However, it has been repeatedly shown that such studies are subject to a range of biases that frequently lead to over-estimation of the true benefit of the treatment given to the intervention group.

Data from the other types of quasi-experimental non-randomised designs, for instance "before and after" studies, case series with historical controls; and comparisons of results of two or more single-arm studies are subject to major and (often) non-quantifiable biases. This topic is dealt with in **Appendix O: Measures taken by the investigators to minimise bias in non-randomised studies**. Consequently, claims about comparative clinical outcomes that are based solely on data from these types of analysis will be treated with scepticism.

Some criteria that should be used to assess the scientific rigour of non-randomised studies are provided in **Appendix O: Measures taken by the investigators to minimise bias in non-randomised studies**. However these are for general guidance only and may have to be adapted to particular situations. The interpretation of the results of such studies is difficult and expert epidemiological guidance will be helpful if data of this type are central to the submission.

Where data from non-randomised studies is included, follow the advice on how to present the methods and the results of the studies that is given in **Appendix N: Presenting non-randomised studies**. Present the studies in the main body of the submission and attach a report of each study presented to the main body of the submission. Provide clear cross-references between the presentation of the studies and the reports.

As discussed here and in **Appendix O: Measures taken by the investigators to minimise bias in non-randomised studies**, these results are likely to be biased, so their interpretation should be conservative.

The interpretation of the clinical data presented in the previous sections is crucial in determining the success of the submission. If claimed clinical advantages for the proposed medicine do not have a basis in the results of robust, randomised clinical trials, they are unlikely to be accepted by the Pricing Committee.

5. Perspective

The perspective of the pharmacoeconomic evaluation under submission should be stated clearly, particularly in terms of the costs included in the evaluation.

The default perspective for pharmacoeconomic evaluations for submission should be that of a third-party payer (i.e. funder). However, where a case is to be made for adopting a broader perspective, this should be explained clearly and include the following information;

- Justification for use of broader perspective
- Impact on clinical outcomes (if any)
- Description of additional costs to be included
- Impact of this perspective on the results of the analysis

6. Time Horizon

State and justify the time horizon used in the pharmacoeconomic submission. In general, the time horizon is based on the natural course of the condition and the likely impact that the treatment will have on it. It is important that the time horizon is long enough to capture all relevant differences in both clinical outcomes and future costs.

Depending on the type of intervention, it may be appropriate to present a short-term analysis based on the primary clinical data and then use a longer-term analysis based on extrapolated or modelled data if required..

Where outcomes have been quantified over time, explain the underlying assumptions and rationale. For instance, the number of relapses of peptic ulcer is unlikely to remain constant over successive time periods. In other diseases, assuming a linear relationship between outcomes and time may be clinically plausible.

7. Type of Pharmacoeconomic Analysis

The selection of the type of pharmacoeconomic analysis should be clearly stated with justification of use of that particular analysis. See **Appendix P: Types of Pharmacoeconomic Analyses**. There are 4 main types of pharmacoeconomic analysis, namely;

- Cost-minimisation analysis
- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis

The use of clinical inputs from the comparative clinical studies will be dependent on the type of analysis used. In some instances, such as the Cost-Utility analysis, the clinical outcomes will need to be adapted to reflect the required outcome of the pharmacoeconomic analysis.

The modelled evaluation should be based on the outcome measure(s) that most closely and validly estimates the final outcome (see **Appendix R: Final Outcomes of Therapy** and **Appendix S: Relationship between surrogate and final outcomes**). The choice of any outcome measure should be justified - more than one type of outcome measure may be needed in some models and/or to cover both desired and adverse outcomes.

It is preferred that, wherever possible, the outcomes presented include final outcomes such as deaths prevented, life-years gained, or quality-adjusted life-years gained.

8. Modelled Evaluations

Justify the decision as to whether or not to present a modelled economic evaluation.

Where the randomised trials available provide insufficient information on which to base a judgement about the full clinical and economic performance of the proposed medicine, a modelled economic evaluation may be useful.

All models have three basic attributes: input variables, a structured arrangement to manipulate those variables and the outputs that form the results. Sensitivity analyses are conducted to clarify those components of variables or structure that drive the model and thus to assess the robustness of its results and conclusions. This Section is intended to facilitate the transparent presentation of these three attributes of a model and its sensitivity analyses.

For each variable/input source, provide full citation details, including item number or page number as appropriate. It may be necessary to cite more than one source for

some variables (e.g. the quantity and unit cost of a resource item). For some variables, an assessment or justification should be provided as appropriate (e.g. if using data or opinion that differs from the evidence previously provided in Section 4.3).

Appendix T: Process for pre-approval of a model

An application for pre-approval of a model as part of a pharmacoeconomic evaluation must be submitted in writing to the Secretariat DPEE with the following information;

- Title: Application for pre-approval of a pharmacoeconomic model
- South African approved brand name, INN and MCC registration number of the medicine
- Key clinical trials intended for use in the model (e.g. extrapolation of survival data)
- Type of model (e.g. Markov chain)
- Description of design of model including schematic diagrams where appropriate
- Main clinical outcome to be modelled
- Time horizon for the model
- Justification for use of that particular model
- Indication why a simpler model cannot be used
- How the model intends to handle uncertainty (i.e. probabilistic sensitivity analysis)

Appendix U: Modelling Considerations contains advice on the circumstances where a modelled economic evaluation is likely to be informative.

The Pricing Committee discourages the use of more complex models where a simpler model will suffice. All efforts should be made to keep models as transparent as possible. Where a model is not fully transparent – the submission will be returned.

8.1. Pre-approval of a model

Where data is extrapolated, there is high degree of uncertainty or where numerous assumptions have been made, it is recommended that the applicant present the proposed model to the Pricing Committee for approval before their final submission. Approval of the model does not imply approval of the submission.

Pre-approval of a model must include certain information (See **Appendix T: Process for** pre-approval of a model

An application for pre-approval of a model as part of a pharmacoeconomic evaluation must be submitted in writing to the Secretariat DPEE with the following information;

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- Type of model (e.g. Markov chain)
- Description of design of model including schematic diagrams where appropriate
- Main clinical outcome to be modelled
- Time horizon for the model
- Justification for use of that particular model
- Indication why a simpler model cannot be used
- How the model intends to handle uncertainty (i.e. probabilistic sensitivity analysis)

Appendix U: Modelling Considerations) such as the key clinical trials, design of the proposed model, justification for why such a model is required, and any key inputs that would have relevance to the model.

8.2. Modelling Options

If approval is given for the use of the proposed model, please indicate as such in your submission. In addition, state your choice of model, justify its use and describe the model's structure.

Identify the options considered and justify the option chosen when designing the model. Consider implicit assumptions built into model structures and comment if appropriate. Indicate whether the modelled outcomes represent the final outcomes of treatment. Where appropriate, explain and justify the linking of measured short-term and/or surrogate outcomes to the modelled final outcomes, including a justification for how these are quantified over time.

The approaches to modelling an economic evaluation are varied and range from a simple spreadsheet table to a complex Monte Carlo simulation. The choice of model will be dependent on the nature of the disease, the treatment options, time horizon and input variable. Modelling options include;

- Spreadsheet analysis
- Decision analysis
- Markov models (chains and processes)
- Monte Carlo simulations

The Pricing Committee may accept international models that have already been developed by the manufacturer's head-office and are adapted to reflect the South African environment using local input variables under the following conditions;

- The full model in unlocked electronic format is made available
- The model and its workings are clearly transparent
- The model is designed so that the PETT and reviewers are able to change inputs and variables so as to determine the impact on the outcome

Adaptations need to be clearly stated and justified, as well as sources of local data.

In the case of a complex analysis, provide a technical document or an attachment to the submission to give details of calculations and an electronic copy of any computer model used. Ensure that clear cross-references are provided as appropriate between the technical document or attachment and the relevant item in the main body of the submission. Spreadsheet computer models should be formatted in the software used by the DPEE (Excel) or be in a format that can be read by this software. Where other software packages are used, a licence should be made available to the DPEE in order to access the full details of the model. Copies of the original sources of data or opinion used in the model should also be provided. These separate documents are assessed by the PETT during the evaluation, but are forwarded to a Pricing Committee member only at his or her request.

8.2.1. Decision Analysis Inputs

In addition to the general variables to be documented in Section 8.4 and 8.5, when a decision analysis is used, the following information is required;

- The decision analysis diagram showing decision nodes, chance nodes and terminal nodes
- Probabilities in each branch, paying particular attention to the probabilities that simulate a treatment effect by differing between the two decision models that represent the proposed medicine and its main comparator;
- All assumptions need to be stated clearly with justification

8.2.2. Markov Model Inputs

In addition to the general variables to be documented in Section 8.2 to 8.4., when a Markov model is used the following information is required;

- The transition diagram (or matrix), which must contain all the modelled health states and arrows reflecting the presence and direction of transitional paths between health states.
- Health states which should be defined (e.g. temporary, absorbing). Justify the health states chosen (and those excluded to avoid excessive complexity)
- Transition probabilities of the model. Transition probabilities are usually presented in a matrix. Indicate whether each transition probability is constant - a Markov chain, or varies over time - a Markov process. Pay particular attention to the transition probabilities that simulate a treatment effect by differing between the two Markov models that represent the proposed medicine and its main comparator, respectively. Clearly link each patient-relevant outcome and resource item in the model to its relevant health state(s).
- Define the cycle length and the follow-up time and comment as necessary
- Describe the population and number of people used in the model (e.g. cohort of 10 000) and justify the definition of the population in relation to both the target population in South Africa and the population in the clinical trials
- State whether a half-cycle correction has been included or justify its exclusion.
- Describe how the model is calculated (e.g. hypothetical cohort or Monte Carlo simulation).
- Indicate implicit assumptions, if appropriate. For example, it may be relevant to check the following Markov assumptions. Are there (non)-constant transition probabilities? Is the "memorylessness" assumption of the model valid in this case (i.e. is it correct to assume no memory for previous states?)

8.3. Population used in the modelled evaluation

State clearly the population that has been used as a basis for the calculation of costs and outcomes.

This may be a hypothetical population (e.g. 100 typical patients with angina; 1000 hypertensive males aged 40-60 years). If necessary, justify the definition of the

population in relation to both the target population in South Africa and the population in the trials.

8.4. Presenting Clinical Inputs

The clinical inputs are the result of the clinical outcome data selected from the trials (see Section 4.5.3.) that will form the basis of the incremental clinical benefit evaluation part of the health economic analysis. The clinical inputs should be tabulated with the point estimate, range of uncertainty and source (**Appendix R: Final Outcomes of Therapy**).

Identify and justify the outcome that best reflects the comparative clinical performance of the alternatives (e.g. the primary outcome and/or the final outcome; see also Appendix R: Final Outcomes of Therapy). Given the uncertainty of the relationship between surrogate outcomes and final outcomes, the use of surrogates in a pharmacoeconomic analysis should be avoided. Where a surrogate outcome is used, justification should include the robustness of the predictive relationship with the final outcome (**Appendix S: Relationship between surrogate and final outcomes**)

If extrapolations have been made to extend the time horizon, a description of the methodology must be included as well as the outcomes at the critical time points (i.e. at the end of the trial, at the end of the extrapolation)

If clinical data has been transformed in any way (for example, from probability of survival to life years gained, or from survival estimates to QALYs), a full description of the methodology and additional clinical inputs (e.g. utilities) as well as any formulae must be included.

Describe the extent to which the models have been modified to provide estimates which are relevant to the South African population and provide any data that would add to the

external validity of the model used. Consider providing a technical document or an attachment to the submission to give the details of the methods used.

Based on the results of the trials presented, state the category which best describes the proposed medicine.

- The proposed medicine has significant clinical advantages over the main comparator:
  - it is significantly more effective than the main comparator and has similar or less toxicity; OR
  - it has similar effectiveness to the main comparator, but has less toxicity;
  - it is significantly more effective than the main comparator, but has more toxicity.
- The proposed medicine is no worse than the main comparator in terms of effectiveness and toxicity
- The proposed medicine is less effective than the main comparator, but has less toxicity.

Categorising the proposed medicine as above helps determine the most appropriate form of economic evaluation.

8.4.1. Quality of Life Measures and Utilities

For most medicines the ultimate outcome of therapy is to improve quality of life and/or survival, and in theory all outcomes could be expressed as quality-adjusted life-years (QALYs). In practice few trials have measured the impact of medicine therapy on QALYs and in most cost-utility economic evaluations it will be necessary to transform clinical outcome indicators to QALYs.

All quality of life instruments should be validated using South African data. Where South African validation is not available, compelling justification should be made as to the relevance to the South African population

Use of quality of life instruments

For medicines which cure short-term illnesses (e.g. infections) quality of life is unlikely to be an issue. It may also be reasonable to assume that certain events which may themselves be serious do not greatly impair quality of life in the survivors (e.g. pneumonia). In these and other instances, quality of life does not need to be considered in the evaluation.

Where a change in quality of life is the principal intended final outcome (**Appendix R: Final Outcomes of Therapy**), a quality of life measure should be considered. This is true for some indications (e.g. relief of pain, treatment of depression, treatment of some cancers) in which improved quality of life is the principal aim of therapy. Alternatively, quality of life may actually be impaired by the proposed medicine or by the main comparator (or other intervention). Quality of life measures may supplement other clinical measures.

Quality of life instruments include global quality of life scales and disease-specific rating scales (e.g. for pain or depression), which may themselves be the surrogate outcome indicators used as the primary measure of outcome in the trials. Increasingly trials are collecting data using both types of quality of life instrument.

Where a quality of life instrument is used, details should be provided on the instrument. Because there is currently debate over which quality of life instruments are most acceptable, special attention should be given to the following parameters:

a) The validity of the instrument;
b) The reliability of the instrument;

c) The responsiveness of the instrument to differences in health states between individuals and to changes in health states over time experienced by any one individual; and

d) The clinical importance of any differences detected by the instrument.

e) South African validated tools

Where possible, provide any supportive data and references in a technical document or an attachment to the submission (provide clear cross-references between these data and the main body of the submission).

Use of quality-adjusted life-years (QALYs)

"Utilities" may be measured directly in a trial or derived and are different from quality of life measures. They are weights which are derived for specific health states which are used to adjust the estimated survival. At present it is not mandatory that outcomes are expressed in QALYs, but this form of analysis should be considered whenever it is appropriate to the proposed medicine.

If utilities have been measured or derived for the purposes of adjusting survival to estimate QALYs, provide details of the methods used. Comment on how the controversy of whose utility is measured (patient, care-giver, taxpayer etc) was addressed and on the likely applicability of any of the utilities estimated to the SA population.

Ideally quality of life measures are included in the clinical trial data used for the economic evaluation, however, where this is not the case supporting literature may be required. The availability of Utility measures in South Africa is limited and therefore international utility measures may be used. A thorough sensitivity analysis must be included to assess the impact of the uncertainty of these utility measures on the economic evaluation

8.5. Resource Use and Costing Inputs

Appendix V: Identifying and defining economic inputs and outcomes

Systematically identify measure and value resources that are relevant to the study perspective.

As a minimum, provide a table clearly identifying:

- Each type of resource included in the evaluation(s);
- Its natural unit of measurement;
- The unit cost used to value that resource in the evaluation(s); and
- The source/reference of the unit cost.

Where necessary please ensure that;

- Past costs are adjusted to reflect the costs in the year stated for the study with an explanation of the methodology used to adjust these costs; Future costs are valued at current prices. This is consistent with using constant prices in the evaluation. Accordingly, no allowance for future inflation should be included in these calculations.
- The present value of future costs should also be estimated. This means that where costs extend over a nurnber of time periods (beyond 1 year), these should be discounted (see Section 8.6). Discounting of future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%.

In general, resource use should be based on South African practice. Where resource data are from international sources, clinical trials, guidelines or other non-observational sources, these should be validated and adjusted for the South African setting.

Values (prices) of resource use must be based on South African data and include relevant tariffs and codes (e.g.NHRPL tariffs, nappi codes, CPT codes, DRGs etc) from which the values are derived.

More detail and precision should be given to resources that contribute most to the total and incremental costs. A sensitivity analysis must be carried out on total costs as well as individual costs which are likely to substantially impact the outcomes of the model.

Present the estimated costs in disaggregated form, i.e. separately for each type of resource provided. All steps taken to calculate costs should be clear during the evaluation. If a complete presentation is likely to make the main body of the submission too bulky, the calculations should be presented in a technical document and, if necessary, a computer disc should be provided containing the detailed calculations. Provide clear cross-references between these calculations and the main body of the submission. As advised in Part A, these documents and discs are assessed during the evaluation, but are not routinely forwarded on to Committee members.

8.5.1. Indirect Costs

In general, indirect costs should not be included in the submission

8.6. Discounting

The present value of future health outcomes measured from the trials or estimated from the model should also be calculated. This means that where health outcomes are anticipated over a number of time periods (beyond 1 year) these should also be discounted. Discounting of future costs and benefits is a standard feature of economic evaluation. Costs or benefits are discounted at an annual rate of 5%. If discounting is

used in an economic evaluation, this should be examined in sensitivity analyses using different discount rates (see Section 8.7.).

8.7. Dealing with Uncertainty and Sensitivity Analyses

One-way sensitivity analyses must be conducted on all variables using an appropriate range (confidence intervals, best-case/worst-case, etc) with the sources and justifications for these ranges. This should be presented in tabular form and as a tornado diagram.

The ranges used for each variable should be stated and referenced.

A two-way sensitivity analyses should be conducted on all variables shown to be sensitive in the one-way analyses. Present in tabular form and as graphs.

If the software allows it, a probabilistic sensitivity analysis is encouraged but not mandatory.

Compare any aspect of the model's results against any corresponding results obtained from the sensitivity analysis and comment on any differences. It may be helpful to examine the sensitivity of the model to any changes in assumptions concerning the structure of the modelled evaluation, which are important but debatable.

These analyses are important to determine how sensitive the evaluation is to changes in the variables that have been used in the evaluation. If discounting has been necessary, the robustness of the conclusions to different discount rates (including a zero discount

rate on non-monetary outcomes alone and on both costs and outcomes) should be tested.

8.8. Presenting the Results of the Modelled Evaluation

Present the results of the model firstly in disaggregated form, then in increasingly aggregated form. Present the appropriately aggregated and discounted results separately for outcomes and resources and separately for the proposed medicine and its main comparator. Finally, present the incremental cost of achieving each additional unit of outcome with the proposed medicine when substituted for the main comparator.

The final outcome of the model should be presented as an Incremental Cost-Effectiveness Ratio (ICER) based on the following formula;

$$ICER = (C_2 - C_1)/ (E_2 - E_1)$$

If the model estimates change over time, present key outputs (such as incremental costs, incremental outcomes and incremental cost-effectiveness) on a graph with time on the x-axis against the changing outputs on the y-axis.

Part C: Appendices

Appendix A: Sample Template for Submission Format

Refer: Part A, Section 7.

Title Page

Contacts Page

Disclosure of relationships

Contents

Abbreviations

Table Contents

Figure Contents

Executive Summary

Introduction

Description of disease or condition

Overview of treatment options for the disease or condition

Details of medicine under review

Co-administered therapies

Comparators

Objective of study

Type of pharmacoeconomic analysis used

Clinical Review

Description of search strategy

Selection of comparative trials used in the submission

Exclusion of clinical trials

Evaluation of clinical trials included in submission

Methodology

Study Design

Patient population

Perspective

Time Horizon

Clinical Inputs

Costs and Resource Use Inputs

List of Assumptions

Results and Analysis

Sensitivity Analysis

Discussion

Including review of other relevant health economic evaluations and outcomes

Conclusion

References

Appendices

See Department of Health website for most recent Template in full detail

Appendix B: Checklist for Submission Documents

Refer: Part A, Section 7.1.

To be inserted once complete

Appendix C: Key Questions

Refer: Part A, Section 7.1. and 7.2.

Key Question	Yes/No	Page No
1. Are the indication(s) for pharmacoeconomic evaluation within the MCC-approved indications?		
2. When was the medicine registered by the MCC?		
3. Is the comparator justified according to the criteria given in Part B, Section 3.5.? Give the page number of the submission where the choice of comparator is justified.		
4. Has a thorough search for relevant comparative randomised trials been conducted? Give the page number of the submission where the search strategy is presented.		
5. Does the key clinical evidence in the submission relate to the proposed main clinical indication?		
6. Have the measures taken by the investigators to minimise bias in the key clinical evidence been assessed? Give the page number of the submission where the assessments are presented.		
7. Have the clinical outcomes of the studies been clearly defined? Give the page numbers of the submission where these		

outcomes are presented.		
8. Has a meta-analysis been conducted? Give the page number of the submission where the methods and results of the meta-analysis are presented.		
9. Has primary outcome data (as opposed to secondary or sub-group outcomes) been used as the main clinical inputs for the health economics submission?		
10. Have all the important and relevant costs been identified and measured. Are the sources of these costs clearly identified and have these costs been adjusted for differential timing. Give the page number of the submission where this information is presented		
11. Has a clear description been given of the type of health economics model and an explanation for its use?		
12. Has a payer perspective been used and the only the relevant costs included?		
13. Has an appropriate time horizon been used and justified? Give the page number of the submission where this information is presented		
14. Has an incremental analysis of costs and consequences of alternative treatments been performed? How was the cost-effectiveness ratio expressed?		
15. Has a sensitivity analysis been carried out to assess the uncertainty of the variables in the evaluation?		

Appendix D: Additional information required for fixed combinations of products

REFER: Part B, Section 3.1.

These are the minimum requirements that combination products need to meet to be eligible for consideration.

This Appendix relates to fixed combination products either presented as combinations of medicines in a single dosage form or as individual dosage forms in composite packaging. It does NOT relate to medicines which for specific indications are almost invariably used together in fixed dose combinations for clinical reasons such as oral contraceptives, hormone replacement therapy and H. pylori eradication regimens.

Submissions must comply with the remainder of these Guidelines concerning clinical and economic data. Pricing of combination products will normally be no greater than the sum of the individual components (at the current single exit price). Where a higher price is requested, this must be supported by evidence of enhanced clinical outcomes and acceptable cost effectiveness. Where the combination product will substitute for two or more products, the single exit price should reflect the sum of the individual components as a function of the anticipated proportion of substitution.

Conditions required to be met for consideration of a combination product:

- the product should be approved by the MCC and meet all clinical criteria required by the MCC;
- Restrictions for the component products should be consistent with those proposed for the combination;
- The doses of the listed component products and the proposed combination should be consistent;
- There should be additive (not necessarily synergistic) beneficial effectiveness of the components;
- The combination should not encourage or result in an inappropriate increase in overall utilisation of the components, nor in inappropriate use of one or both components in specific patient groups; the combination product should not result in inappropriate dosing of either component, nor contain components which require

individual dose titration; the combination product should not result in unnecessary proliferation of products and/or dose forms. A demonstrated clinical outcome advantage with acceptable cost effectiveness will provide strong support for a recommendation

- The clinical evidence should demonstrate efficacy of the fixed combination under trial conditions and not only the individual components
- Where benefits in patient convenience or cost savings to the patient are claimed, these should be demonstrated and will be regarded as supportive but not necessarily an adequate basis for approval.
- Where improved compliance is used as an argument for enhanced clinical outcomes, data should be provided.

Appendix E: Expert Opinion

REFER: Part B, Sections 3.6,

Uses of expert opinion

Expert opinion is not a substitute for sound scientific evidence. Therefore it will only be considered if there are no data from randomised trials or non-randomised studies addressing the matter for which expert opinion has been sought. However, when these data are not available, or are unlikely to become available in the near future, expert opinion has been found to be useful in some aspects of preparing submissions to the committee:

- to help set the context of the economic evaluation by defining the place of the proposed medicine in treatment (the main indication and the main comparator, see Sections 3.2 and 3.5 respectively);
- to help modify the patterns of resource use and, very rarely, the clinical outcomes measured in randomised trials conducted in different settings, such as in other countries and

- to help predict which resources will be used and how often each will be used to manage outcomes reported

Presenting expert opinion

If expert opinion is used in a submission, this should be presented in a technical document or an attachment to the main submission that has clear cross-references with the main body of the submission. This explanation should include;

- Justification for the need for expert opinion
- Description of the methods used to obtain and collate the opinions including details of the persons from whom opinions were sought
- A summary of the opinions obtained together with the extent of any variability in the opinions
- Indication of how the opinions have been used in the main body of the submission
- Justification of the approach used in the sensitivity analysis (see Part B, Section 8.7) to reflect any variability in the opinions obtained.

Describing the collection and collation of expert opinion

The following details should be provided:

- the criteria for selecting the experts;
- the number of experts approached;
- the number of experts who participated;
- whether a declaration of potential conflict(s) of interest was sought from all experts or medical specialty groups whose opinions were sought;
- the background information provided and its consistency with the totality of the evidence provided in the submission;
- the method used to collect the opinions;
- the medium used to collect the opinions;
- the questions asked;
- whether iteration was used in the collation of opinions and, if so, how it was used;
- the number of responses received for each question;

- whether all experts agreed with each response, and, if not what approach was used to finalise the estimates; and
- the approach used to present the variability in the opinions.

Appendix F: Citation Details of Comparative Trials

Refer: Part B, Section 4.2.

The citation format should be based on the **Harvard Referencing Style.**

A description of this style of referencing can be accessed at http://www.lib.uct.ac.za/infolit/bibharvard.htm . The most common instance that would be referenced would be a published clinical trial which should adhere to following convention - Author. Year. Title of article. *Title of journal*, volume of journal (number of issue): page reference, date of issue.

Ref No	Citation	Selected/Excluded
Sec 1.	Head-to-head randomised trials	
Sec 2.	Indirect comparative trials	
Sec	Non-randomised trials	

3.		

Appendix G: SORT Hierarchy of levels of evidence

Refer: Part B, Section 4.3.

Additional information on SORT to be inserted

Ebell M, Siwek J, Weiss B et al . 2004. Strength of Recommendation Taxonomy (SORT): A Patient-Centered Approach to Grading Evidence in the Medical Literature. Am Fam Physician ;69:548-56

Appendix H: Reasons for Exclusion of Clinical Trial

Refer: Part B, Section 4.4.

Ref No	Citation	Brief description of reasons for exclusion

Appendix J: Use of meta-analysis

REFER: Part B, Sections 4.5.

In some cases a meta-analysis of a number of randomised comparative trials will be useful in an economic evaluation. Meta-analysis may increase the precision of the estimates of differences between the proposed medicine and the main comparator. It is useful when there are conflicting results from trials of similar scientific rigour. It can also highlight advantages of a proposed medicine which are too small to be detected reliably in individual randomised trials, but might be clinically important for a medicine which will be used widely.

J.1. Presenting a meta-analysis

If the trial results are available as dichotomous data, the following approach should be adopted;

a) Tabulate the results (point estimates and 95% confidence intervals) of the individual trials.
b) Plot the results (point estimates and 95% confidence intervals) of the individual trials, both as relative risk reductions and absolute risk reductions.
c) Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate the trial results are heterogeneous, try to provide an explanation for the heterogeneity
d) Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all)
e) Select one estimate from the four options in (d) for use in the economic evaluation. Justify the selection.

A similar approach to the above should be attempted if the trial results are available as continuous, ordinal, categorical or time-to-event data. Expert biostatistical advice will be helpful in such circumstances. The approach used in the statistical combination of the results (e.g. pooled hazard ratios) should be justified and explained in a short technical document or attachment to the submission.

J.2.Assessing a published meta-analysis

If a published meta-analysis is the principal source of clinical evidence, it should include the following:

a) A description of the trials and trial subjects;
b) a description of the patient-relevant outcomes measured in the included trials;
c) some assessment of the scientific rigour of the included trials;
d) a tabulated and/or graphical display of the individual and combined results;
e) an adequate description of the methods of statistical combination; and
f) a discussion or explanation of any heterogeneity observed in the results.

Appendix K: Measures taken by investigators to minimise bias in each trial listed in response to Section 4.2.

Refer: Part B; Section 4.5.1.

This appendix is designed as a useful guide to help the committee and the applicant to review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

For each of the following methodological topics, choose the description that best fits each trial and answer the supplementary question for each trial. If there is more than one trial, tabulate the responses.

K.1. Randomisation

In an adequately randomised clinical trial it is important that clinical staff are unable to predict which treatment a patient will receive prior to a final decision being made regarding entry to the trial.

Which of the following best describes the randomisation technique used?

a. No details of randomisation were reported, or the method used was inadequate (e.g. randomisation according to the day of the week, even/odd medical record numbers).
b. An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open/unblinded trial; treatment assignment kept in consecutive "sealed" envelopes and open/unblinded trial).
c. A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care (e.g. randomisation performed at a separate site available through a toll-free telephone number or by the pharmacy department after the decision has been made to enter the subject in the trial).

K.2. Adequacy of follow-up

It is important that an attempt is made to summarise the trial outcomes for **all** subjects who were included in the trial. A full "intention-to-treat" (ITT) analysis is the preferred basis for an economic evaluation that attempts to model the likely impact of the medicine in the community.

Which of the following best describes the adequacy of follow-up?

a. There were significant numbers of drop-outs with no assessment of trial outcome(s) in the subjects who dropped-out and drop-out rates differed between treated and control groups.
b. There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped-out, and drop-out rates were (approximately) equivalent in treated and control groups.
c. Trial outcome(s) were assessed in all treated and control subjects who did not withdraw from the trial.

Supplementary information: summarise for each comparison group the number randomised to treatment, the number of drop-outs and the number of subjects who were lost to follow-up.

Notes: a drop-out stops the trial medication for a medical reason or a protocol violation but can and, particularly for an economic evaluation, should still be followed-up, whereas a subject who unilaterally elects to withdraw from the trial is deemed to be lost to follow-up.

K.3. Blinding of Outcomes Assessment

It is important that where the comparator is not indistinguishable by visual inspection or taste, or where there is a high chance of "unblinding", that the observer responsible for measuring the trial outcome remains unaware of the treatment assignment.

Which of the following best describes the blinding of the outcomes assessment?

a. There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer, measurement of vertebral height on an X-ray, quality of life instrument)

b. The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival).

Notes: the observer may be a trial investigator and/or a subject. To maintain "full blinding", it is usually necessary to blind all people directly involved in the care of the trial subjects and the trial subjects themselves (i.e. double-blinding) to prevent "unblinding" of the observer.

Purpose of these assessments

The intention of these assessments is to provide the applicant and the committee with a clear idea of which trials are of the highest scientific rigour and which are therefore likely to give the most accurate estimate of how well the proposed medicine works. There is no minimum standard, but the Pricing Committee is most likely to be persuaded by the data from the trials of the highest scientific rigour.

Give a brief description of the randomisation, loss to follow-up and blinding of each trial. Include for each comparator the number of patients randomised, dropped-out or who were lost to follow-up.

Trial	Randomisation	Loss to Follow-up	Blinding

Appendix L: Characteristics of each trial listed in response to section 4.2.

REFER: Part B; Section 4.5.2.

Answer each of the following questions for each trial. If there is more than one trial, tabulate the responses.

a. Was the design parallel-group or cross-over
b. Was the trial conducted in South Africa (or were one or more centres of the multi-national trial located in South Africa)?
c. How do the subjects included in the trial compare with patients who are likely to receive the proposed medicine? Consider factors known to affect outcomes in the main indication such as demographics, epidemiology, disease severity and setting.
d. What dosage regimens were used in the trial - are they within those recommended in the current MCC-approved product information?
e. What was the median (and range) duration of follow-up of the trial?

Notes:

FOR (a) If the submission includes one or more cross-over trials, indicate for each such trial whether a carry-over effect is likely.

FOR (b) This may be particularly useful in assessing the extent to which there is a change in the patterns of resource provision. For several reasons (such as different incentives), patterns of resource provision may differ between health care systems more than patient responses to a medicine across different health care systems.

FOR (c) This forms the basis of the consideration of the following three points.

- Firstly, how do the trial subjects compare with typical South African patients suffering from the relevant condition(s), for example in terms of age and sex distribution or of the natural history of the condition(s)? Are any differences likely to matter?
- Secondly, how do the trial subjects compare with South African patients in terms of disease severity? This can be important. A new medicine may be cost-effective

when use is confined to patients with severe disease but not when it is used to treat patients with milder disease who may respond to less effective and less expensive therapies. It may be possible to estimate the likely impact of this by performing sensitivity analyses in a modelled evaluation (see Section 8.7).

- Thirdly, is the trial setting relevant to that of the SA environment?

FOR (d) The trial should use the correct doses of the proposed medicine and the main comparator (and a suitable duration of therapy where this is relevant). Doses and duration should be those recommended in the product information as optimal for the relevant indication. These may differ from those shown by market research to be actually used in the community. However prescribing of higher than recommended doses (at higher cost) of a comparator medicine is unlikely to be accepted as an argument for a higher price for the proposed medicine.

FOR (e) The duration of follow-up for a trial subject is the length of time between randomisation and the end of blinded follow-up of that subject. The duration of non-blinded follow-up of drop-outs should be excluded from the calculations.

Appendix M: Analysis of the outcomes of each trial listed in response to Section 4.2.

Refer: Part B, Section 4.5.3.

Answer each of the following questions for each trial. If there is more than one trial, tabulate the responses.

1. Define the patient-relevant outcomes measured. Specify enough details of the measurement for the committee to assess its importance (e.g. supine/erect blood pressure).
2. For each outcome at 1:
   a. describe the natural unit of measurement;
   b. report the size of the effect;

c. provide a 95% confidence interval;

d. state whether "intention-to-treat" was used for the analysis - if not, can this form of analysis be conducted from the data available from the trial? Explain how data from drop-outs and withdrawals were incorporated into the analysis; and

e. discuss definitions of any clinically important differences.

3. If the trial was "negative" (failed to detect a difference), was the power of the trial calculated? If so, what was the result?

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

Notes:

FOR1. Examples of patient-relevant outcomes include:
a) primary clinical outcomes;
b) quality of life or utility measures; and
c) economic inputs and outcomes (See Section 8 for further assistance)

FOR 2.a) It is an advantage in an economic evaluation if trial outcomes can be expressed as the time to a particular event (examples of relevant events are death - as in a survival analysis, or cessation of the medicine). In such instances, differences in outcomes can be measured as the integral between the curves in time-to-event plots for the two therapies. If not available, the number of successes or failures of treatment (e.g. number of patients surviving; number of patients achieving target blood pressure; number of patients achieving a specified level of airways control; number of patients achieving a target Hamilton rating score for depression etc) are preferable to a mean change in the physiological variables. An exception could be in the case of a cost-minimisation analysis, where the mean change to a physiological variable may be sufficiently responsive to detect small but clinically important differences.

FOR 2.b) for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic.

FOR 2.c) the respective p-value is an alternative, but is less preferred.

FOR 2.d) for all important outcomes (both resources provided and health benefits) the trials should be analysed on the basis of "intention-to-treat". This form of analysis is the most appropriate for estimating the likely benefits of general use of a medicine in the community. For a definition of drop-outs and withdrawals, see the note for "adequacy of follow-up" in **Appendix K: Measures taken by investigators to minimise bias in each trial listed in response to Section 4.2.**

FOR 2.e) this is particularly important in the case of continuous variables where large trials may detect statistically significant but clinically unimportant differences between treated and control groups. It is helpful if a clinically important difference can be specified.

FOR 3. In the case of "negative" trials, it is helpful if an estimate can be provided of the power of the trial to detect a clinically important difference between the treated and control groups. This can be important in the interpretation of the results of cost-minimisation analyses where the two medicines are claimed to have equivalent effects.

FOR 4. Trials often target many outcomes at a variety of different times resulting in a large number of hypotheses to be tested. If not adjusted for multiple comparisons, the odds will be high that through chance alone a statistically significant difference will emerge in one of these comparisons.

Appendix N: Presenting non-randomised studies

REFER: Part B, Section 4.5.4.

Categorise the studies into the study type(s) defined in Appendix O: Measures taken by the investigators to minimise bias in non-randomised studies. Then, for each methodological topic listed for the relevant study type in Appendix O, choose the description that best fits each study. If the submission includes a number of studies of the same type, tabulate the responses.

Present the following characteristics of each study (tabulate the responses if more than one study):

a) Description of possibility of confounding
b) Adequacy of follow-up
c) Steps to minimise bias through blinding
d) The comparability of the study subjects with patients who are likely to receive the medicine;
e) The dosage regimens of the medicines; and
f) The definition of the patient-relevant outcomes measured and their natural units of measurement.

Present the results of all patient-relevant outcomes measured (see (a) in Appendix M: Analysis of the outcomes of each trial listed in response to Section 4.2.), together with their respective 95% confidence intervals. In general, the results will be in the form of a proportion, a difference in proportions, an odds ratio, a relative risk, or a hazard ratio. Occasionally the results will be in the form of a difference in some other response variable (e.g. forced expiratory volume).

Appendix O: Measures taken by the investigators to minimise bias in non-randomised studies

Refer: Part B, Section 4.5.5. Appendices N and M

This appendix is designed as a useful guide to help the committee and the applicant review the scientific rigour of the evidence by assessing the measures taken by the investigators to minimise bias. It is not intended to discourage the presentation of data.

Categorise the studies into the study type(s) defined below. Then, for each methodological topic listed for the relevant study type, choose the description that best fits each study. If the submission includes a number of studies of the same type, tabulate the responses.

As for the assessment of randomised trials in Appendix K: Measures taken by investigators to minimise bias in each trial listed in response to Section 4.2., the purpose of these assessments is to provide the applicant and the committee with a clear idea of which studies are of greater scientific rigour. There is no minimum standard, but the committee is most likely to be persuaded by the data of the highest scientific rigour. Submissions should therefore be particularly careful to justify using the results of studies with less scientific rigour in an economic evaluation in place of trials with greater scientific rigour.

There may be other aspects of particular non-randomised studies which may affect the results of such studies and their comparability with different studies of the same type. If these aspects are likely to be important, they should also be identified.

O.1. Classical observational designs

O.1.1. Controlled cohort studies

In this study type, assignment of the groups of individuals to treatment is not random. However, individuals receiving the proposed medicine and control individuals are followed forward in time from first exposure. Cohort studies can be concurrent or historical. In the former, the study is planned and conducted prospectively. In the latter, existing records are used to define treatment status and determine the outcomes.

O.1.1.1. Possibility of confounding: it is important that there are no substantial differences at baseline between treated and control subjects in respect of factors that could influence the outcome(s) being studied. Which of the following best describes the differences in baseline factors?

1. There were significant differences in baseline factors between treated and control subjects that have been shown to influence the study outcome(s), and these were not adjusted for in the main analysis.
2. There were significant differences in baseline factors between treated and control subjects that might have influenced the study outcome(s), and these were not adjusted for in the main analysis.
3. There were no differences in baseline factors between treated and control subjects that might have influenced the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O.1.1.2. Adequacy of follow-up: it is important that an attempt is made to summarise the study outcomes for all subjects who were included in the study. Which of the following best describes the adequacy of follow-up in the study?

1. There were significant numbers of drop-outs with no assessment of study outcome(s) in the subjects who dropped out, and drop-out rates differed between treated and control groups.
2. There were some drop-outs with no assessment of study outcome(s) in the subjects who dropped-out, and drop-out rates were (approximately) equivalent in treated and control groups.
3. Study outcome(s) were assessed in all or nearly all treated and control subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O1.1.3. Blinding of outcomes assessment: it is important that the observer responsible for measuring the study outcome is unaware of whether the subject belongs to the treated or control group. Which of the following best describes the blinding of outcomes assessment?

1. There was no attempt to blind the observer(s) to the treatment or control status of the study subjects, or any attempt made was inadequate to keep the observer(s) fully blind to the treatment or control status of the study subjects.
2. The observer(s) were kept fully blinded to the treatment or control status of the study subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O1.2. Case-control studies

In this study type, subjects are defined by the presence (cases) or absence (controls) of the study outcome, and their prior use of the proposed medicine is compared.

O.1.2.1. Selection of cases: it is most important that cases are selected independently of their treatment status. Which of the following best describes the selection of cases?

1. The process of referral and selection of cases was likely to have been influenced by the subjects' prior use of the medicine and knowledge of the association between use of the medicine and study outcome (e.g. a woman of child-bearing age with a painful swollen leg is more likely to be referred for investigation if she has been using an oral contraceptive).
2. The process of referral or selection of cases was not influenced by the subjects' prior use of the medicine or knowledge of the association between use of the medicine and study outcome.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O.1.2.2. Selection of controls: the purpose of the control group is to provide an estimate of the odds of exposure in subjects who are free of the disease in question in the source population. Which of the following best describes the selection of controls?

1. The controls were not drawn from the same source population as the cases.
2. The controls were drawn from the same source population as the cases (community controls).

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O1.2.3. Possibility of confounding: it is important that there are no substantial differences between cases and controls in respect of factors that could influence the outcome being studied other than the risk of exposure to the medicine. Which of the following best describes the comparability of cases and controls?

1. There were significant differences in factors between cases and controls that have been shown to influence the study outcome, and these were not adjusted for in the main analysis.

2. There were differences in factors between cases and controls that might have influenced the study outcome, and these were not adjusted for in the main analysis.
3. There were no differences in factors between cases and controls that might have influenced the study outcome, or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O.1.2.4. Possibility of measurement bias: it is important that assessment of treatment status (or exposure) is made in an unbiased way. Which of the following best describes the assessment of treatment status?

1. The measurement of prior medicine use (or exposure) was made using an unstructured interview or questionnaire by an observer who was aware of the case/control status of the subject.
2. The measurement of prior medicine use (or exposure) was made using a structured interview or questionnaire by an observer who was aware of the case/control status of the subject.
3. The measurement of prior medicine use (or exposure) was made using a structured interview or questionnaire by an observer who was unaware of the case/control status of the subject, or the definition of exposure preceded the outcome (e.g. based on a computerised prescription record, as in a case-control study "nested" in a larger cohort).

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O.2. Quasi-experimental designs

"Before and after" studies

In this type of study, subjects are observed before and after an intervention (e.g. a new medicine) is introduced. It is really only possible to use this design if the manifestations of the illness being treated are both chronic and reversible. Typically this will be an opportunistic study, rather than planned. In addition to the sources of bias that affect the previously mentioned observational designs, this study type has particular problems related to time (or order) effects, resulting from the subjects being observed over a period, and the lack of a contemporaneous control group. There may be changes in disease severity or symptomatology or resource use that are occurring independently of any treatment, and it is impossible to assess these properly without a contemporaneous control group. It is highly likely that subjects will be switched to the new therapy because they have not been doing well on the old therapy, and thus their symptoms will tend to be most severe at the time of switching. Regression to the mean will make the new medicine seem better than the old one, both in terms of apparent treatment responses and resource provision.

O2.1. Selection of subjects:

1. The subjects were selected retrospectively from case-notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.
2. The study was planned, and prospective data collection was undertaken in both study periods, and selection of the subjects was made without knowledge of the treatment responses.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O.2.2. Possibility of confounding:

1. There were within subject differences in factors between the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.
2. There were no within subject differences in factors between the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O2.3. Adequacy of follow-up:

1. Drop-out rates differed between the "before" and "after" study periods with no assessment of study outcome(s) in the subjects who dropped-out.
2. There were no drop-outs in either study period (this implies prospective data collection in both periods), or study outcome(s) were assessed in all subjects who were commenced on treatment.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O2.4.Blinding of outcomes assessment:

1. The observer(s) responsible for outcome assessment were aware of which treatment the study subjects had been receiving.
2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O3. Case series with historical controls

Typically this type of study is carried out by a clinical department that has introduced a new management procedure and wishes to compare the results with those of patients treated previously in the department using the old management procedure. Thus, this type of study shares the same problems of order effects as "before and after" studies but does not involve the same individuals in both arms.

O3.1. Selection of subjects:

1. The subjects were selected retrospectively from case-notes, and the investigators were probably aware of the responses to the old treatment at the time of selection.
2. The study was planned, and prospective data collection was undertaken in both study periods, and selection of the subjects was made without knowledge of the treatment responses.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O3.2. Possibility of confounding:

1. There were differences in factors between subjects in the two study periods that were likely to influence the study outcome(s), and these were not adjusted for in the main analysis.
2. There were no differences in factors between subjects in the two study periods that were likely to influence the study outcome(s), or any differences were adjusted for in the main analysis.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O3.3. Adequacy of follow-up:

1. Drop-out rates differed between the two study periods with no assessment of study outcome(s) in the subjects who dropped-out.
2. There were no drop-outs in either study period, or study outcome(s) were assessed in all subjects who were commenced on treatment.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O3.4. Blinding of outcomes assessment:

1. The observer(s) responsible for outcome assessment were aware of which treatment the study subjects had been receiving.
2. The observer(s) responsible for outcome assessment were kept fully blinded to the treatment being received by the study subjects.

NOTES: if there is insufficient information available to classify the study, assign it to the first category.

O4. Comparison of the results of two or more single-arm studies

In addition to all the problems noted earlier with "before and after" studies or case series with historical controls, this approach has the added disadvantage that the outcome assessments were made by different investigators in different settings. It is not possible to compare the results of such studies with any confidence.

Appendix P: Types of Pharmacoeconomic Analyses

Refer: Part B, Section 8.1.

Cost-minimisation

This is the simplest form of pharmacoeconomic analysis. The proposed medicine is demonstrated to have the same therapeutic outcome compared to other medicines at the same or a lower price. Assuming the committee accepts the alternative therapies as providing acceptable outcomes for their cost, a new treatment which offers these outcomes at a lower cost is preferable.

Cost-effectiveness

The proposed medicine is demonstrated to offer more of a given outcome. This goes beyond cost-minimisation. For example, a medicine may have a higher requested price but achieve an improved clinical outcome (e.g. the desired clinical outcome in a higher proportion of patients) than the alternative therapy. The outcome indicators reported from the randomised trials may need to be adapted in a modelled cost-effectiveness analysis, and where this is done the choice of outcome should be justified.

The summary measure of a cost-effectiveness analysis is the incremental cost per additional unit outcome achieved.

Cost-utility

The ultimate benefit of restored health is the restoration of opportunities to undertake activities of daily living. Economists have attempted to identify the value placed by patients, professionals and general public on different activities restored. The basis for this valuation is that each activity gives some satisfaction (termed "utility" by economists) which is the ultimate outcome of life.

A cost-utility analysis presents the outcomes in terms of an extension of life and a utility value of that extension. For example, quality-adjusted life-years (QALY) have been used to compare the benefits of renal transplantation and hip replacement. The latter does

not extend life but improves the quality of the years of life left to a patient. A quality weighting, based on the activities restored by the operation, can be used to convert two different lengths of survival and sets of utilities activities to a common parameter, the QALY.

A cost-utility analysis should report the changes in activities of daily living or other methods used to project the weighted outcomes.

Cost-benefit

In contrast to other forms of analysis, cost-benefit analysis (CBA) expresses all outcomes in monetary rather than physical units. This requires a monetary valuation of these outcomes and CBA often relies heavily on calculations of indirect costs and benefits, principally changes in production capacity. Such analyses are not likely to be helpful to the committee in its deliberations and are not encouraged.

Appendix R: Final Outcomes of Therapy

Refer: Part B, Section 8.4.

Section 8.4. Asks for a definition of the principal intended final outcomes which are expected to change with therapy. In general terms, this is the improvement in health which will result from the therapy. For instance this may be "prevention of death and suffering from stroke" in the case of a new anti-hypertensive medication, not the reduction in blood pressure which is a "surrogate" outcome indicator (see below). Another, more simple, example of a "final" outcome might be "cure of an uncomplicated urinary tract infection", in the case of an antibacterial agent.

Applicants are encouraged to consider which outcome indicators are most appropriate, and most feasible, given the data available to them. The clinical relevance of the outcome indicators should be established and if necessary supported with data. Where

possible the results of randomised trials should be analysed as the proportions achieving specified targets (e.g. target blood pressure, target Hamilton depression rating scale) rather than the mean change in the variable for the group. This may necessitate some re-analysis but generally the data will be available to the applicant. When models are used their origins should be specified, e.g. longitudinal population studies.

For many medicines the intended final outcome is the improvement in quality of life through alleviation of distress. Where the final outcome of the medicine therapy is a change in quality of life, a quality of life measure should be considered. The main therapeutic benefit being measured with a quality of life measure is a change in the health state. Thus return to normal daily functioning through relief of symptoms is a valid outcome. However, return to normal productive capacity with the associated "economic" gains should not be regarded as a final outcome.

Appendix S: Relationship between surrogate and final outcomes

Outcome indicators used in randomised trials

Appendix M asks for a definition of the outcome indicators used in the randomised trials. These are often "surrogate" outcome indicators (see below). Arguably, the closer a surrogate outcome indicator is to the final outcome (see table below), the more useful it is, but generally the more difficult it is to measure accurately.

Use of surrogate outcome indicators to estimate final outcome indicators

Applicants should generally consider the final intended effects of the medicine under review in terms of the ultimate change in health state brought about by therapy. For instance the ultimate aim of lowering moderately elevated blood pressure is to prevent death and impaired quality of life from a stroke or possibly a myocardial infarction. The

ultimate aim of treating a patient with severe asthma is to prevent death, to prevent hospitalisation and to return the patient to a normal level of functioning.

While the number of registration trials with large enough sample sizes and sufficient follow-up time to measure changes in final outcomes is increasing, in some instances only relatively small trials will be available at the time a medicine is considered for marketing approval. The response measures used in these trials will usually be readily measured physiological variables. For the two examples given above this would be blood pressure and spirometry. These are "surrogate" outcome indicators.

In a few instances, relationships have been established, or have been proposed, between surrogate and final outcome indicators. Examples include left ventricular ejection fraction and survival after myocardial infarction; or liver function tests and cure of viral hepatitis. The form of the relationships which have been established between these variables may vary according to whether the data were derived from longitudinal studies or randomised trials. For a very few risk factors (e.g. blood pressure and blood cholesterol), predictive models are available which estimate events, including deaths, prevented by specified reductions in these variables.

Appendix T: Process for pre-approval of a model

An application for pre-approval of a model as part of a pharmacoeconomic evaluation must be submitted in writing to the Secretariat DPEE with the following information;

- Title: Application for pre-approval of a pharmacoeconomic model
- South African approved brand name, INN and MCC registration number of the medicine
- Key clinical trials intended for use in the model (e.g. extrapolation of survival data)
- Type of model (e.g. Markov chain)
- Description of design of model including schematic diagrams where appropriate

- Main clinical outcome to be modelled
- Time horizon for the model
- Justification for use of that particular model
- Indication why a simpler model cannot be used
- How the model intends to handle uncertainty (i.e. probabilistic sensitivity analysis)

Appendix U: Modelling Considerations

Refer: Part B, Section 8

Modelling may be needed to address limitations of the preliminary economic evaluation based on the evidence from the randomised trials presented in Section 4. The following list of uses of models is intended to help an applicant decide whether a model is needed in the context of each submission;

- To link the surrogate outcomes measured in the trials to final outcomes and to extend the range of outcomes (for instance the number of patients with unhealed peptic ulcers who eventually need surgery). In such cases the trial results may be supplemented by estimates obtained from non-randomised studies, epidemiological data, market research data or an expert consensus. In particular, epidemiologically acceptable extrapolations of clinical differences demonstrated in the trials to more appropriate final outcomes are potentially helpful. Whatever the source, provide information regarding the validity of these estimates.
- To extrapolate the outcomes measured beyond the duration of the trials and duration of therapy within the trials to the likely duration of use. This overlaps the first reason to model listed above. In many submissions, it has been implicitly assumed that the outcomes measured in the trials are maintained in the longer term. Such assumptions should be considered explicitly.
- To examine the impact of differences between subjects enrolled in the trials and patients who would be likely to obtain the medicine in South Africa and between the settings of the trials and the community setting in South Africa. Both affect the generalisability of the trials in the South African context. There may also be important

differences in the mix of patients who will receive the medicine. Two concerns of the committee here are that there may be patients in the community who have disease which is less severe than that of subjects who participated in the randomised trials. There also may be patients in the community for whom the main comparator can be expected to perform better than in the trials. Both could diminish the difference in effectiveness between the proposed medicine and main comparator and, therefore, increase the incremental cost-effectiveness ratio. Factors relating to the setting include extrapolating results of trials conducted in hospitals to use outside the hospital and the effect of more rigorous follow-up, which may swamp important differences in the convenience and acceptability of the medicine compared with alternative treatments, with resulting effects on patient compliance and thence response to treatment.

- To modify resource use patterns measured in the trials to reflect more closely those in South Africa (and/or to add likely changes in resource use patterns not measured in the trials). Randomised trials performed overseas are an acceptable basis for an economic evaluation relevant to South African practice. Although the overall estimate of the change in a final or surrogate outcome may be transferable to South Africa, estimates of the costs of resources provided (medicines or other interventions e.g. investigations, procedures or operations) are often not readily transferable. It is easily apparent that the unit costs are usually quite different. Less apparent, but also important, the frequency or patterns of use of resources may not be relevant to South Africa because of major differences in medical practice or different incentives in different economies and health care systems. Sometimes assumptions will have to be made during the adaptation of overseas randomised trials to create a modelled economic evaluation which is relevant to the South African context. This is particularly important when the main comparator is a non-pharmacological therapy.
- To include any relevant differences in resource provision not measured in the trials and to exclude "protocol-derived" resource provision. On the one hand, the trials may not measure provision of all relevant resources and these may need to be added in a model. On the other hand, the trials may require more resources to be provided than would be typical in normal management of the condition (such as extra blood tests to demonstrate safety or effectiveness) and only resources provided or saved in actual practice need be included in a model. If any "protocol-derived"

resource provision is to be excluded in a model, consideration should be given to the extent to which these additional resources may have impacted on the results of the trials (e.g. high intensity screening for deep vein thromboses in trials being associated with lower rates of pulmonary embolism than in usual care).

Use of data from non-randomised studies to modify or extrapolate beyond the evidence from randomised trials in a modelled economic evaluation (see Section 8.2.,)

- Although the estimation of comparative clinical performance from non-randomised studies is a questionable exercise, it is accepted that data from non-randomised studies must sometimes be used in order to extrapolate beyond the results of a randomised trial. This is because the trial may have been of insufficient size or duration to capture the full impact of therapy on the outcomes of the disease, and/or the typical resource provision measured in an overseas trial may need adjustment to reflect patterns of use observed in SA (this is particularly important for resource estimates where the main comparator is a non-pharmacological therapy). Given that the data from non-randomised studies are subject to bias, assumptions based on these data made during a modelling exercise should be conservative.

- If data from non-randomised studies are used in a modelled economic evaluation to modify or extrapolate beyond the evidence from randomised trials, follow the advice on how to present the methods and the results of the studies in Appendix N: Presenting non-randomised studies. Present the studies in a technical document or an attachment to the submission. Provide clear cross-references between the presentation of the studies and the main body of the submission. If a technical document is used, attach a report of each study to this document. If an attachment is used, provide the report of each study separately, along with any other supplementary references.

- As requested in Section 8.2., indicate which results from the evidence from randomised trials are being modified or extrapolated. Explain how the modifications and extrapolations are achieved by the model. In particular, if non-comparative data

are used, it is necessary to make an assumption about how the comparator arm will change. The usual practice, in the absence of empirical evidence to the contrary, is to assume that the comparator arm will change so that the relative rate between the two arms measured in the randomised trial(s) will remain constant. Justify the use of this (or any other) assumption in the model presented in the submission.

Appendix V: Identifying and defining economic inputs and outcomes

REFER: Part B, Sections 8.5.

Definition of direct medical resources

Identify and list the resource items for which there will be a change in use associated with substituting the proposed medicine for the main comparator. Sometimes only changes in medicine use will need to be identified. The following should be considered where appropriate:

a. medicines (direct costs of treatment and of medicines used to treat side effects);
b. medical services including procedures;
c. hospital services;
d. diagnostic and investigational services;
e. community-based services; and
f. any other direct medical costs.

Definition of direct non-medical resources

Occasionally because of the condition under treatment or the age of the patients, consideration of direct non-medical costs such as social services (home help, day care, , nursing and physiotherapy services etc) may be relevant.

Definition of natural units of direct resources

Define the natural units (such as number of GP consultations) used to measure the change in the amount of resources provided.

Definition of economic outcomes to be excluded

Limit costs to those associated with the disease under treatment. In these evaluations do not attempt to include outcomes of other diseases which, in the fullness of time , are likely to afflict patients who live longer as a result of effective treatment which they receive now.

Glossary to Accompany the Guidelines for the Pharmaceutical Industry on the Preparation of Submissions to the Pricing Committee

Absolute risk (rate) (compare with relative risk)
The observed or calculated risk (rate) of an event in a defined population over a specified time period.

Absolute risk (rate) difference
Over a specified time period, the difference of the risk (rate) of an outcome in the exposed group (e.g. those provided with therapy involving the proposed medicine) and the risk (rate) of the outcome in the control group.

Accuracy (see also validity)
The extent to which a measurement, or an estimate based on measurements, represents the true value of the variable being measured.

Adverse outcome
An adverse event measured in a trial;/study; or an adverse event for which no assessment has been made of whether it was caused by a given therapy (e.g. involving the proposed medicine).

Adverse reaction
An adverse event reported in the approved product information of a medicine; or an

adverse event for which some assessment has been made of whether it was caused by a given therapy (e.g. involving the proposed medicine).

Association (see also causality)
A statistical dependence between two or more events, characteristics or variables. An association exists when the value of one predicts the value of the other(s) more often than could occur by chance, but this does not necessarily imply a causal relationship.

Attributable risk or attributable fraction
With a specified outcome, exposure factor (e.g. therapy involving the proposed medicine), time period and population, the rate of an outcome that can be attributed to the in factor the population (i.e. net of background risk). The population should be specified as either the exposed or total population.

Base case
The results of an economic evaluation using the projected most likely values against which the results of sensitivity analyses are compared.

"Before and after" study A quasi-experimental study in which subjects are observed before and after a therapy (e.g. involving the proposed medicine) is introduced.

Benefit
An advantage or improvement caused by a therapy or the desired of using outcome a therapy. Also, a medicine listed in the Schedule of Pharmaceutical Benefits.

Bias
Systematic variation; the deviation of results or inferences from the truth, or processes leading to such deviation (whether intended or not); an alternative explanation for an apparent treatment effect.

Blind/Blinding
The procedure or process of keeping subjects and/or those responsible for the care of subjects and/or observers responsible for measuring the trial/study outcomes ignorant of the intervention group to which the subjects belong.

Cardinal data
Ordinal data in which the difference between two equi-distant estimates on the ranked scale has the same value irrespective of where the estimates lie on the scale (e.g. 0.9-0.8 = 0.2-0.1).

Case series with historical controls A quasi-experimental study in which the outcomes measured in a group of subjects with a specified indication who are managed with a new therapy (e.g. involving the proposed medicine) are compared with outcomes measured in a similar group of subjects (usually seen previously in the same setting) who are managed with previous therapy (e.g. involving the main comparator).

Case-control study An observational study in which the past history of exposure to a suspected risk factor (e.g. therapy involving the proposed medicine) is compared proposed medicine between cases (who have the outcome or disease) and controls (who resemble the cases but do not have the or outcome disease).

Causality (see also association)
The relating of factors to the effects they produce. Hill (a clinical epidemiologist) proposed eight criteria (not all essential) of a causal association between a factor and an outcome **CBA**
cost-benefit analysis

CEA
cost-effectiveness analysis

Chance
Random variation; an explanation of the distribution of variables; an alternative explanation for an apparent treatment effect.

Clinical
Pertaining to health outcomes rather than economic outcomes, e.g. clinical performance or clinical comparison; of or by clinicians, e.g. clinical department, clinical use.

Clinically important
The extent to which a treatment effect is considered worth having.

CMA

cost-minimisation analysis

Co-payment

A payment made by the user at the time of service as part of the total payment for that service and any associated product.

Cohort study An observational study in which two or more sub-sets of defined populations are identified by the presence of a common factor or factors (e.g. non-randomly assigned to therapy involving the proposed medicine or to therapy involving the main comparator(s)) and then followed in time to investigate the influence of the factors on the probability of occurrence of an outcome or outcomes.

Common reference

A medicine or therapy to which a proposed medicine and its main comparator(s) have been compared in separate comparative randomised trials.

Confidence interval

The computed interval with a specified probability (by convention, usually 95%) that the true value of a population parameter is contained within the interval.

Confounding

The distortion of a measure of the effect of an exposure (e.g. to therapy involving the proposed medicine) on the risk of an outcome under investigation brought about by the association of the exposure with other factor(s) that can influence the outcome.

Consequence (see outcome)

Control group

A group of subjects who are observed but who do not receive therapy involving the proposed medicine. They may receive alternative therapy, no therapy or placebo. They provide data on the streams of outcomes (clinical and economic) for comparison with the streams of outcomes observed for subjects who take therapy involving the proposed medicine.

Correlation (see association)

Cost analysis

A partial economic evaluation that only compares the costs in monetary units of therapy involving the proposed medicine with therapy involving its main comparator(s).

Cost, financial

The monetary value of providing a resource accounted for in the budget of the provider.

Cost, economic or opportunity

The value of the best alternative use of a resource that is foregone as a result of its current use.

Cost-benefit analysis An economic evaluation that compares therapy involving the proposed medicine with therapy involving its main comparator(s) in which both costs and benefits are measured in monetary terms to compute a net monetary gain/loss or benefit gain/loss.

Cost-effective

A proposed medicine is considered cost-effective by the committee if the Committee considers that, for a specified main indication, the incremental benefits of therapy involving the proposed medicine over therapy involving its main comparator(s) justify its incremental costs and harms.

Cost-effectiveness analysis (An economic evaluation that compares therapy involving the proposed medicine with therapy involving its main comparator(s) having common clinical outcome(s) in which costs are measured in monetary terms and outcomes are measured in natural units.

Cost-efficacy analysis

A cost-effectiveness analysis using the most internally valid data available (i.e. from adequate randomised trials); if required, a preliminary step to inferring a more externally valid modelled economic evaluation incorporating extrapolations and assumptions.

Cost-minimisation analysis An economic evaluation that finds the least costly alternative therapy after the proposed medicine has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and toxicity.

Cost-utility analysis An economic evaluation that compares therapy involving the proposed medicine with therapy involving its main comparator(s) in which costs are measured in monetary terms and outcomes are measured in terms of extension of life and the utility value of that extension (e.g. QALYs or HYEs).

Cross-over (compare with parallel group)
A method of comparing two alternative therapies in which the subjects, upon completion of the course of one therapy, are switched to the other therapy.

CUA
cost-utility analysis

Data
Measurements of variables of interest.

Decision tree
A graphical representation of the probable outcomes following the various decision options in a decision analysis.

Decision analysis
A technique that formally identifies the options in a decision-making process, quantifies the probable outcomes (and costs) of each, determines the option that best meets the objectives of the decision-maker and assesses the robustness of this conclusion.

Dichotomous data
Data that are classified into either one of two mutually exclusive values, e.g. 'yes' and 'no' or 'cured' and 'not cured'.

Direct cost
The monetary value of a resource provided to deliver medical or social services as part of the management of the disease or disorder under therapy.

Direct medical resource A resource provided as part of the medical management (including therapy) of a disease or disorder, e.g. medicine, medical service, hospital service, diagnostic and investigational service, community-based service.

Direct non-medical resource A resource required as result of the disease or disorder under therapy but not provided as part of the medical management of the disease or disorder, e.g. home help, day care, meals on wheels.

Discounting

The process by which the streams of future costs and/or benefits (beyond 12 months) are converted to equivalent present values.

Discount rate

The rate used in a discounting formula to convert future costs and/or benefits into equivalent present values.

Double-blind

A trial design in which both the subjects and observers responsible for measuring the trial outcomes are kept ignorant of the group to which subjects are assigned.

Economic analysis or economic appraisal

An umbrella term covering both economic evaluation and financial analysis.

Economic cost (see cost, economic or opportunity)

Economic evaluation

A comparative analysis of the costs and outcomes of therapy involving the proposed medicine and therapy involving its main comparator(s). An umbrella term covering CBA, CEA, CMA and CUA. The analysis involves identification, measurement and valuation of the differences in costs and outcomes caused by substituting therapy involving the proposed medicine for therapy involving its main comparator(s).

Effectiveness

The extent to which a therapy produces a benefit in a defined population in uncontrolled or routine circumstances.

Efficacy

The extent to which a therapy produces a benefit in a defined population in controlled or ideal circumstances.

Efficiency (see also allocative efficiency and technical efficiency)
The extent to which the maximum possible benefit is achieved out of the available resources.

Error, random (see chance)

Error, systematic (see bias)

Estimate
The value of a quantity which is known, believed or suspected of incorporating some amount of error.

Evidence
An umbrella term covering data and opinion.

External validity (see also transportability)
A trial has external validity if it is free of confounding and can produce unbiased inferences regarding a specified target population beyond the subjects in the trial.

Extrapolation
The prediction of the value of a variable outside the measured range or an inference of the value of a variable of a related outcome (e.g. the extrapolation of a reduction in the rate of progression to AIDS from a stabilisation or improvement in the CD4 count).

Factor
An event, characteristic or other definable entity (e.g. therapy involving the proposed medicine) that results in a change in outcome.

Final outcome
The ultimate outcome of a therapy or disease in terms of overall impact on both quality of life and life expectancy.

Financial analysis (see cost, financial cost)
A procedure for comparing only the financial costs and cost off-sets of competing options, rather than comparing their clinical and economic costs and benefits. Also called budgetary analysis.

Financial cost (see cost)

Fixed effects model (compare with random effects model)
The model used in meta-analysis based on the assumption that all trials are estimating the same treatment effect and that the difference in effect observed across trials is only due to chance.

Follow-up The observation over a period of time of study/trial subjects to measure changes in outcomes under investigation.

Generalisability (see external validity)

Head-to-head randomised trial A randomised trial directly comparing therapy involving the proposed medicine with therapy involving the main comparator(s).

Health outcome
A change (or lack of change) in health status caused by a therapy or factor when compared with a previously documented health status using disease-specific measures, general quality of life measures or utility measures.

Health status (compare with quality of life)
A measure of the extent to which an individual is able to function physically, emotionally and socially.

Healthy-year equivalent (compare with quality-adjusted life-year)
The hypothetical number of years spent in perfect health that could be considered equivalent to the actual number of years spent in a defined imperfect state of health.

HYE
healthy-year equivalent

Incidence (compare with prevalence)
The number of new events (e.g. new cases of a disease) in a defined population within a specified period of time.

Incremental analysis
A measure of how much extra a proposed therapy costs to produce an extra unit of

outcome compared to an available alternative therapy (or management without a therapy) for a specified indication. It is calculated by dividing the difference in the net costs for the two alternatives by the difference in their net outcomes.

Incremental benefit
The absolute difference between the benefits of alternative management strategies of the same disease or disorder.

Incremental cost
The absolute difference between the costs of alternative management strategies of the same disease or disorder.

Indication
The disease or disorder which is the reason for commencing therapy. The indication can be restricted to a defined sub-group of patients with the disease or disorder.

Input (see also resource)
A resource provided as part of managing a disease or disorder.

Instrument
A tool used to measure a variable, including any defined administrative procedures in its use and scoring instructions in its interpretation.

Intention-to-treat A principle of analysis which includes data from all subjects allocated to a specified therapy arm as representing that arm irrespective of whether they received or completed the prescribed regimen or whether they were followed for the full duration of the study/trial. This involves following-up subjects to contribute data and/or predetermining procedures to deal with missing data.

Intermediate outcome (see also surrogate outcome)
A variable that occurs in a causal pathway from a therapy or factor to the final outcome.

Internal validity (see also external validity, treatment effect)
A trial has internal validity if, apart from possible sampling error, the measured difference in outcomes can be attributed only to the different therapies assigned.

Interval data (see cardinal data)

ITT
intention-to-treat

Life-year
An outcome measure computed by multiplying the number of affected individuals by the number of years each individual is expected to live.

Lump (compare with pool)
An inappropriate statistical combination of data from several trials, e.g. taking the simple average of the means or of the proportions.

Main comparator The therapy which most prescribers will replace with the proposed medicine.

Main indication The indication likely to account for the largest proportion of patients treated with the proposed medicine.

Marginal analysis
An analytical technique that examines the extra costs and outcomes caused by producing and providing one extra unit of a resource.

Marginal benefit (utility)
The extra benefit (utility) caused by providing one extra unit of a resource.

Marginal cost
The extra cost of producing one extra unit of a resource.

Marginal value
The maximum amount that an individual is willing to pay for one extra unit of a resource or for the extra outcome(s) resulting from its provision.

Markov chain process
An iterative decision analysis model that represents the changes in the proportions of individuals who are in different discrete health states based on constant probabilities of

remaining in each state or transiting to another state at the end of each successive time period.

Mask/masking (see blind/blinding)

Mean
A measure of central tendency. The arithmetic average which is computed by adding all the individual values in the group and dividing by the number of values in the group.

Measurement
The procedure of applying a standard scale to a variable or a set of values.

Median A measure of central tendency. The exact midpoint of a distribution of data that is ordered from highest to the lowest value.

Meta-analysis The systematic, organised, and structured evaluation of a problem of interest using information from all relevant independent randomised trials. It includes a qualitative component (application of predetermined criteria of scientific rigour, e.g. Appendix B) and a quantitative component (statistical combination of the data which can be pooled).

Modelled economic evaluation
Economic evaluation using modelling when trial data are insufficient.

Modelling
An analytical technique using simulated processes to explain the impact of one or more factors on a number of outcomes.

Monte Carlo simulation
Computer experiments of complex relationships that simulate and analyse sequences of events using random numbers controlled by a specified distribution function.

Multiple comparisons
The simultaneous comparison of more than two sets of results from one trial. The statistical analysis should be adjusted to account for the increasing chance that a result will have a p-value less than 0.05.

Net benefit

In a cost-benefit analysis, the total benefit (valued in monetary units) minus the total cost.

Net cost

In an incremental analysis, the monetary value of any increase in resource use minus any cost off-sets, e.g. those resulting from an improvement in outcome.

NNT

number needed to treat

Nominal data

Data which have been classified into unordered qualitative categories.

Number needed to treat

The number of patients with a specified indication who must be provided with the specified therapy in order to achieve the desired outcome or to prevent the adverse outcome in one patient in a specified time period. The reciprocal of the absolute risk reduction.

Observational study A non-randomised study that observes the characteristics and outcomes over time of subjects who do and do not take a particular therapy. An umbrella term for cohort and case-control studies.

Observer bias

The systematic difference between the true value and that actually observed due to observer variation.

Odds ratio (compare with relative risk)

The ratio of two odds. Usually the ratio of the odds in favour of exposure (to e.g. therapy involving the proposed medicine) among the cases of the disease or outcome(s) of interest to the odds in favour of exposure among those without the disease or outcome of interest. In a "rare" disease, the odds ratio is an approximation of the relative risk.

Opinion

The view of one or more individuals which is not based on direct measurement.

Opportunity cost (see cost, economic or opportunity)

Ordinal data

Data that are classified into ordered (i.e. one category is higher or lower than another) qualitative (i.e. the numerical distance between their possible values is undefined or unknown) mutually exclusive categories.

Outcome or output (see also patient-relevant outcome)

An effect produced by or a result of a therapy or other factor(s) (may include a subsequent change in the provision of resources following commencement of a therapy).

Parallel group (compare with cross-over)

An experimental design where each group in a comparative trial receives only one therapy and does not cross-over to the other therapy.

Parameter

In epidemiology, a measurable characteristic of a population. In economics, a constant in a model or formula.

Patient-relevant outcome An umbrella term covering any health outcome that is meaningful to the patient (or, if necessary, the next best surrogate outcome), any resource provided as part of on-going therapy of the patient's disease or disorder, any indirect outcome or any intangible outcome. Common examples of patient-relevant outcomes include: primary clinical outcomes, quality of life or utility measures and economic outcomes.

Perspective

The viewpoint from which an economic analysis is conducted (e.g. society, government, individual) which defines which costs and outcomes will be examined.

Pool (compare with lump) An appropriate statistical combination of data from several trials e.g. using the fixed effects model for dichotomous data.

Power

The ability of a trial to demonstrate a treatment effect if one exists.

Precision

A measure of the variability or random variation in a set of data. The inverse of the variance.

Present value

The value of a future cost or benefit after adjusting for time preferences by discounting.

Prevalence (compare with incidence)

The number of events (e.g. cases of a disease) in a defined population at a specified point in time divided by the number of people in that population.

Price

The exchange value of a good or service, most commonly expressed as the amount of money an individual or organisation is prepared to pay to buy a unit of that good or service. For an economic evaluation submitted the dispensed price is used for the proposed medicine and any other medicine/s.

Price premium

The increase in price of a medicine over its main comparator(s).

Proposed medicine

The medicine which is the subject of a submission to the pricing committee.

Prospective data

QALY

quality-adjusted life-year

Quality of life (see also health status)

The extent to which an individual perceives himself or herself able to function physically, psychologically and socially.

Quality-adjusted life-year (see also healthy-year equivalent)

The number of years of life weighted by a utility value of the relative quality of life experienced.

Quasi-experimental study A non-randomised study in which the investigator lacks full control over the allocation and/or the timing of the therapy, but otherwise conducts the study as a randomised trial. An umbrella term for "before and after" studies, case series with historical controls and comparison of the results of single-arm studies.

Random effects model (compare with fixed effects model)
The model used in meta-analysis based on the assumption that the treatment effect truly differs across trials and that the goal is to determine the average of the different effects.

Random variation (see chance)

Randomisation
The process by which subjects are allocated to one of two or more therapy groups by chance and thus minimise selection bias. Other than chance variation, the resulting groups are also likely to be similar to one another at the start of the trial. Randomisation involves application of a predetermined plan to ensure that chance alone determines allocation to therapy groups.

Range
The difference between the largest and the smallest values in a distribution.

Relative
A method of comparison involving the ratio of one variable to another.

Relative risk (rate) (compare with absolute risk difference and odds ratio)
The ratio of the risk (rate) of an outcome in the exposed group (e.g. to therapy involving the proposed medicine) to the risk (rate) of the outcome in the control group in a specified time period.

Relative risk (rate) reduction
One minus the relative risk (rate); can be computed only when therapy involving the proposed medicine is more effective than therapy involving its main comparator(s).

Reliability, reproducibility, repeatability
The extent to which the results obtained by a measurement procedure or instrument can be replicated under identical conditions.

Resource
A factor of production, an input or a produced good.

Responsiveness
The ability of an instrument to measure differences in health states between individuals and also to measure changes in health states over time experienced by any one individual.

Retrospective data
Data collected before the study was started.

Risk (rate) difference (see absolute risk reduction)

Robustness (see also sensitivity analysis)
The extent to which the conclusion of an economic analysis is likely to remain unchanged even if key variables, assumptions or even a model's structure are changed in the analysis to reflect remaining uncertainties.

Safety
The inverse of toxicity.

Selection bias
Error due to systematic differences in characteristics between those who are selected for study and those who are not.

Sensitivity analysis An analytical process by which the results and conclusions of an economic analysis are assessed for robustness.

Side effect (see adverse reaction)

Significant (see statistically significant)

Single-arm study

A group of subjects with a specified indication and managed with a specified therapy (e.g. involving the proposed medicine are systematically observed to measure outcomes of interest. A quasi-experimental study can be generated by comparing the results of one or more single-arm studies of therapy involving the proposed medicine with the results of one or more similar studies (usually by different investigators in different settings) of therapy involving its main comparator(s).

Statistic

A measurement of a variable of interest which is subject to random variation.

Statistically significant

The probability that the association between the factor and the outcome is due to chance is less than a specified level (by convention, $p < 0.05$).

Study (see also trial)

An investigation of the health and/or economic impact of one or more therapies in humans which may or may not involve a randomisation step. If a randomisation step is involved, the preferred term is trial.

Surrogate outcome

A variable that is suspected, but not necessarily demonstrated to occur on the causal pathway from a therapy or factor to the final outcome.

Survival data (see time-to-event data)

Systematic variation (see bias)

Technical efficiency

The production of the greatest amount or quality of outcome for any specified level of resources.

Therapy

The management and care of an individual for the purpose of combating (e.g. preventing, curing, ameliorating) a disease or disorder; all resources provided in this management or care.

Time preference
The perceived advantage of receiving a benefit earlier and/or incurring a cost or harm later.

Time-to-event data
Data that incorporates a measure of the time lapse before an event occurs, e.g. time to relapse, time to death or time to treatment cessation.

Toxicity (see also adverse outcome, adverse reaction, safety)
The harm to health caused by a therapy (e.g. involving the proposed medicine) considering the entire adverse reaction profile.

Transferability (see external validity and transportability)

Transportability (see also external validity)
A trial, study or model has transportability if it can produce unbiased inferences to another specified health care system.

Treatment effect (see also internal validity)
A difference in outcomes following provision of different therapies that remains after excluding random and systematic variation as alternative explanations.

Trial (see also study)
An investigation of the health and/or economic impact of one or more therapies in humans which does involve a randomisation step.

Uncertainty
The reduction of confidence in a conclusion when more than one estimate is available for a variable or more than one structure is available for a model. Statistical uncertainty arises when a variable includes a range of estimates within which the true value is likely to be found. Inferential uncertainty arises when there are alternative explanations for a measured difference or when extrapolations are made from an estimate. Structural uncertainty arises in a model when all the relationships between the various components are not fully demonstrated.

Utility

The numerical value assigned by an individual to a preference for, or a desirability of, a specific level of health status or a specific health outcome. By convention, utility is measured on a cardinal scale with 0 = death and 1 = full health.

Utility analysis

A method of measuring outcomes in terms of the preferences individuals express for specific health states or health outcomes; it provides a common unit that can be used to compare different types of outcomes under conditions of uncertainty.

Validity (trial or study - see also internal validity and external validity)

The extent to which an inference drawn from a trial/study is justifiable when account is taken of the methods of the trial/study, the representativeness of the sample investigated and the nature of the population from which the sample is drawn.

Validity (see measurement)

The extent to which a measurement measures what it purports to measure.

Valuation

The process of quantifying the desirability of an outcome in utility or monetary terms or of quantifying the cost of a resource or individual's productivity in monetary terms.

Value

In economics, a quantitative measure of the desirability of an outcome. This may be measured in monetary terms e.g. the maximum amount that an individual is willing to pay for a good or a service; for a defined benefit; or to avoid a defined harm. In science, the magnitude of a measurement.

Value for money (see cost-effective)

Variable

Any attribute, phenomenon or event that can have different values.

Variance (see also precision)

A measure of the variability or random variation in a set of data computed as the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of data.

Willingness to pay

The maximum amount of money that an individual is prepared to give up to ensure that therapy involving a proposed medicine is substituted for therapy involving its main comparator(s) based on valuing the resulting difference(s) in outcomes.

WTP

willingness to pay