GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. R. 68 **1 February 2013**

MEDICINES AND RELATED SUBSTANCES ACT (101 of 1965) REGULATIONS RELATING TO A TRANSPARENT PRICING SYSTEM FOR MEDICINES AND SCHEDULED SUBSTANCES:

PUBLICATION OF THE GUIDELINES FOR PHARMACOECONOMIC SUBMISSIONS

I, Ms MP MATSOSO, Director-General for Health, have determined in accordance with Regulation 14 (5) of the Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances published in Government Gazette number 28214 of 11 November 2005 that information relating to cost-effectiveness of a medicine or scheduled substance relative to that of other medicines or scheduled substances in the same therapeutic class should be compiled in a manner consistent with the guidelines appended to this Notice which shall be reviewed from time to time.

Pharmacoeconomic submissions shall be on a voluntary basis until such time as communicated otherwise by Notice in the Government Gazette as determined by the Director-General from time to time. Implementation of these guidelines shall be effective as of 1 April 2013.

MS MP MATSOSO
DIRECTOR-GENERAL: HEALTH
DATE: 18/1/2013

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

GUIDELINES FOR PHARMACOECONOMIC SUBMISSIONS

December 2012

Contents

Acronyms

ATC	Anatomic, Therapeutic, Chemical
D-G	Director-General
DoH	Department of Health
DPEE	Directorate Pharmaceutical Economic Evaluations
EDL	Essential Drug List
ICH	International Council for Harmonisation
INN	International Non-proprietary Name
ITT	Intention-to-treat
MCC	Medicines Control Council
MOH	Minister of Health
MRA	Medicines Regulatory Authority
MRU	Medicines Resource Utilisation
NDoH	National Department of Health
NDP	National Drug Policy
PC	Pricing Committee
PESC	Pharmacoeconomic Sub-committee
PMB	Prescribed Minimum Benefit
RCT	Randomised controlled trial
SEP	Single Exit Price
SORT	Strength of Recommendation Taxonomy

Part A: Process for Submission

1. Introduction

It is generally accepted that new medicines have the potential to improve health outcomes but the costs are often too high, which impacts access to treatment and affordability. This is an issue that is confronting healthcare programmes internationally. In order to inform healthcare decision-making that is objective, a transparent and formal process of economic evaluation is required.

The purpose of pharmacoeconomic evaluations is to establish whether a medicine represents fair value for money. In terms of encouraging transparency, guidelines needed to be developed for the South African context. The objectives of these guidelines for pharmacoeconomic evaluation of new and existing medicines in the South African private healthcare sector are to:

(a) Create a standard for conducting economic evaluation;
(b) Describe a process of compiling a submission;
(c) Describe the process to be followed when submitting an application;
(d) Provide an overview of the principles and methods to be applied;
(e) Promote transparency regarding the value of medicines;
(f) Create a forum which provides an objective review of the value of medicines;
(g) Ensure 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 in accordance with the *Medicines and Related Substances Control Act* 101 of 1965 (as amended) as well as the accompanying regulations, to make recommendations to the Minister for Health on medicine prices. The role of the Committee is to promote a transparent pricing system for medicines in South Africa. Part of this process requires the Pricing Committee to consider cost-effectiveness of a medicine.

Relevant sections consulted in compiling these guidelines included Section 22B(2), and Section 22G(2)(a) of the Medicines Act and, Regulation 14(5), Regulation 17, Regulation 19(7) and Regulation 21(1)(a) of the Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances (as amended). Pharmacoeconomic evaluations will be conducted in accordance with the conditions of registration as determined by the Medicines Control Council (MCC). All medicines that are found to be unreasonably priced will be listed on the National Department of Health's (NDoH) website in the prescribed manner.

2.1. Pharmacoeconomic Evaluations Sub-committee

The Pricing Committee will establish the terms of reference for a Sub-committee to assess pharmacoeconomic submissions. The details of the terms of reference for this Sub-committee will be available on the NDoH website.

2.2. Secretariat to the Sub-committee

The Sub-committee is administratively supported by the Secretariat of the Directorate: Pharmaceutical Economic Evaluations (DPEE) of the National Department of Health. All queries and interactions with stakeholders will be handled by the Secretariat. All correspondences should be in writing and addressed to:

The Chairperson: 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
Corner Andries and Struben Streets
Pretoria
0001

3. Criteria for Medicines Requiring Pharmacoeconomic Submissions

Medicines that may require pharmacoeconomic submissions include, amongst others:

(a) New chemical entities;
(b) New clinical indications for an existing medicine;
(c) Where it is the opinion of the Minister, Pricing Committee or the Director-General (D-G) that a pharmacoeconomic submission is necessary/required for a particular medicine.

Prior to developing any model for a pharmacoeconomic submission, pre-approval should be obtained from the DPEE as per Part B section 8.1.

4. Assessment Process Followed by the Sub-committee

All submissions will be subjected to a sequential assessment procedure:

Step 1: Administrative screening in accordance with a checklist;
Step 2: Review of the clinical evidence used in support of the submission;
Step 3: Review of the qualifying pharmacoeconomic submission;
Step 4: Request for comment from the applicant on the preliminary findings;
Step 5: Presentation to the Pricing Committee for approval of the pharmacoeconomic assessment report;
Step 6: Recommendation to the Minister;
Step 7: Notice period; and
Step 8: Publication of the findings in a prescribed manner.

5. Recommendations on Therapeutic Value

The Pricing Committee may recommend that a medicine does not offer therapeutic value relative to the single exit price set by the manufacturer or is unreasonably priced in accordance with regulations 21(1) (a) and regulation 22(1) to 22(3) of the

Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances.

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

Recommendations are based on information available at the time of submission. In the event that additional information becomes available that would have a material impact on a recommendation, see Section 6.4.

6. Procedures for Submissions

6.1. Source of Submissions

The Sub-committee will consider submissions for products from applicants who are the licence holders as per the registration certificate issued by MCC.

6.2. Timing of Submissions

As this is a voluntary process, only products which hold a registration certificate in accordance with the Medicines and Related Substances Control Act 101 of 1965, will be considered for evaluation.

All applicants will receive a response within a maximum of 180 days as per the "stop the clock provision" (see section 6.6 for explanation).

6.3. Summary Report on the Recommendations to the Pricing Committee

The Sub-committee will submit a summary report of the evaluation to the Pricing Committee regarding their findings. Before the summary report is submitted to the Pricing Committee the applicant will be given an opportunity to comment on the findings within 30 working days.

6.4. Resubmissions

New information that is considered to materially change a previous recommendation by the Sub-committee requires a new submission be made.

6.5. Appeals

As this is a voluntary process, the findings of the assessment are not binding and no provision has been made for the appeals process in this version of the guidelines.

6.6. Evaluation of the Work of the Sub-committee

The work of the Sub-committee will be assessed in terms of working days using a "stop the clock provision", i.e. if any queries or clarifications are sent to the applicant, the clock will be stopped until the applicant has responded satisfactorily.

7. Requirements for a Submission

The purposes of these guidelines are to:

(a) Specify the information and format required for a submission and
(b) To provide guidance on how to conduct pharmacoeconomic evaluations.

All submissions to the Pricing Committee for pharmacoeconomic evaluation shall comply with the prescribed format (See Appendix A: Sample Template for Submission Format) and failure to do so will result in administrative rejections. The current approved template can be obtained from the NDoH website or directly from the DPEE.

A complete submission shall comprise both a hard copy and electronic versions. The application should be in both Microsoft Word and Pdf format. Note that these documents should be accessible to the reviewer and if protected, a password should be provided as part of the submission. Supporting documentation could be presented either as Microsoft Word or Pdf format. For dispute resolution purposes, the signed

hard copy shall serve as a point of reference. Pharmacoeconomic models must be explicit and full details should be available to the reviewer. Where a software programme/package has been used to develop a model, this should be converted to Microsoft Excel for review.

7.1. Checklist of Material to be submitted

The applicant checklist (Appendix B: Checklist for Submission Documents) should accompany all applications submitted as a final check before a submission is lodged with the DPEE.

Four (4) suitably bound copies of the Application for Submission containing:

(a) Signed covering letter for the submission;
(b) Signed official pharmacoeconomic evaluation application form;
(c) The completed document with a title "Answers to Key Questions" to determine the acceptability of the submission. See section 7.3, Appendix C: Key Questions;
(d) The executive summary of the submission which should ideally be limited to 10 pages;
(e) The MCC approved clinical package insert;
(f) Appendices and references;
(g) Computer disc/s with electronic versions accompanied by passwords if protected;
(h) Full copy of the investigator's brochure compliant with International Council for Harmonisation (ICH) regulations;
(i) 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:

(a) Be suitably bound;
(b) Have a clear and adequate index;
(c) Have dividers that are consistent with the index and the prescribed format;

(d) Have sequential pagination throughout;

(e) Have attachments containing full copies of the key clinical trials, which must be:

(i) either the published paper or the applicant's summary for unpublished trials with adequate details of the trial methods and of any results used in the economic evaluation(s); and

(ii) in English. For translated documents, a form of verification should be made available.

(f) The main body of the submission should follow the guidelines as in the remainder of this document as far as possible. To facilitate its evaluation, it should also use the headings of each section in the layout as suggested in Appendix A: Sample Template for Submission Format;

(g) All costs should be presented in ZAR (South African Rand).

7.2. Key Questions to Determine Acceptability of Submission

The following questions should be answered concisely. This will assist the DPEE determine the acceptability of the submission. See Appendix C: Key Questions:

(a) Are the indication(s) for pharmacoeconomic evaluation consistent with the conditions of registration as determined by MCC?

(b) Is the comparator justified in accordance with the criteria provided in Part B, Section 3.5?

(c) Has a thorough search for relevant randomised controlled trials been conducted?

(d) Does the key clinical evidence in the submission support the proposed main clinical indication?

(e) Have the measures taken to minimise bias in the key clinical trial been assessed?

(f) Are the clinical outcomes of the studies clearly defined, relevant and justified from a South African perspective?

(g) Has a meta-analysis been conducted?

(h) Has primary outcome data (as opposed to secondary or sub-group outcomes) been used as the main clinical inputs for the pharmacoeconomic submission?

(i) Have all the important and relevant costs been identified and measured? Have the sources of these costs been clearly identified?

(j) Has a clear description been given of the type of pharmacoeconomic study and the rationale for its selection?

(k) Has a third party payer perspective been used and only the relevant costs included?

(l) Has an appropriate time horizon been used and justified?

(m) Has an incremental analysis of costs and consequences of alternative treatments been performed? How was the cost-effectiveness ratio expressed?

(n) 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 ideally be no more than 10 pages.

The Executive Summary should clearly state the key aspects and issues presented in the main body of the submission. As a minimum, the executive summary must address each of the following key aspects:

(a) The South African approved brand name, INN, registration number, principal pharmacological action and indication(s) of the medicine;

(b) The formulation(s), strength(s), pack size(s) and single exit price (approved or proposed);

(c) Brief description of the clinical indication(s), which forms the focus of the pharmacoeconomic evaluation application;

(d) Brief description of patient group, e.g. age, gender, risk status and disease severity;

(e) The recommended duration of treatment;

(f) The main comparator(s);

(g) Whether the key clinical evidence in the submission comes from randomised head-to-head trials or from an analysis of two sets of randomised trials involving a common comparator (e.g. placebo or other active therapy);

(h) The main results of the key clinical evidence;

(i) The key costs;

(j) If a modelled economic evaluation has been undertaken:

  (i) The type of pharmacoeconomic evaluation;

  (ii) The main results of the analysis in the pharmacoeconomic evaluation; and

  (iii) The pivotal assumptions underlying the model (as tested in the sensitivity analysis in Part B, Section 8.7).

(k) The Executive Summary also needs to indicate whether the pharmacoeconomic evaluation submitted is an adaptation of an existing international model or whether it is an entirely new pharmacoeconomic evaluation.

Part B: Content of Submission

1. Executive Summary

Please ensure that the Executive Summary contains adequate cross-referencing (hyperlinks for electronic versions) to the main body of the submission and any other additional documents (see Part A, Section 7.3 for detail of content of Executive Summary).

2. Description of Disease/Clinical Condition

This section should describe the disease/clinical conditions intended for treatment and include South African information on the following:

(a) Demographics of patients suffering from this condition including target population for treatment;
(b) Epidemiological data;
(c) Burden of Disease;
(d) Current treatments;
(e) Challenges of current treatments; and
(f) Any existing Clinical Guidelines (local or international) for the condition.

Where there is no South African data available, international information may be presented, provided that a sound argument is led in support of its relevance locally.

3. Details of Medicine

3.1. Pharmacological Class and Action

Give the South African approved brand name, INN and ATC therapeutic class for the medicine. What is its principal pharmacological action? What pharmaceutical formulation(s) (i.e. ampoule, vial, or 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 and then state the indication/s covered by this submission.

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

(a) The clinical efficacy of the medicine in this group is determined on the basis of a RCT **and**
(b) Where this group has been defined *a priori* in the clinical trial protocol; **or**
(c) 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 specific patient group is within the South African approved indication/s (it may be narrower, for example, to identify the patient group likely to benefit most).

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, dosing interval and course of treatment recommended in the current approved product information. For the key clinical evidence, indicate whether the dosing is consistent with the above.

Indicate whether the medicine has to be administered using a specific health technology or whether it requires the results of specific diagnostic tests or requires specific monitoring.

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 treatment.

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 adverse drug reactions.

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 adverse drug reactions of current therapies if the medicine under review were to be used? List any therapies which are likely to be substituted by the medicine under review. Provide the details requested in Part B 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 such as those described in the Prescribed Minimum Benefits (PMB) and Essential Drugs List (EDL). 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 based on the Single Exit Price (SEP) that is available for the same indication.

The following will assist in selecting the main comparator:

(a) If the medicine is in a therapeutic class for which pharmacological alternatives are already registered, the main comparator will usually be the alternative;

(b) If the 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 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 medicine under review;

(c) If no registered medicine can be identified as a comparator then the main comparator will usually be the 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;

(d) 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:

(a) Active ingredients;
(b) Pharmacological action;
(c) Clinical indications;
(d) Dose, frequency and duration of therapy;
(e) Co-administered therapies; and
(f) Route of administration and any additional costs associated therein.

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

Describe and provide references for the main differences in the indications, contra-indications, cautions, warnings and adverse effects between the 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), include a concise description of the comparator treatment so as to justify its position as a comparator.

3.6. Expert Opinion

Where 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.), refer to Appendix E: Expert Opinion, which 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, then the review of the pharmacoeconomic analysis will not proceed. Insufficient clinical evidence includes:

(a) Lack of well-designed, robust clinical trials;
(b) Lack of clinically and statistically significant clinical outcomes, such as unplanned sub-group analyses.

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

(a) South African prevalence and incidence rates of the disease;
(b) Mortality rates and life expectancy, based on South African and/or international data;
(c) Adverse drug reactions and treatment thereof;
(d) Patient adherence to treatment; and

(e) Where relevant, information about impact on quality of life from a South African perspective.

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 medicine and the main comparator for the main indication. A comprehensive search strategy must be used to identify these trials. This should involve at least three approaches:

(a) A search of the published literature;
(b) A search of the Cochrane Controlled Trials Register; and
(c) A check with the manufacturer for additional and unpublished information.

The search strategy is pivotal to assessing the completeness of the information presented. Therefore the applicant is required to specify:

(a) The specific databases searched (including at least MEDLINE/EMBASE and the Cochrane Controlled Trials Register), as well as internal databases;
(b) The date the search was conducted;
(c) The time horizon for the search;
(d) The complete search strategy used, including the search terms (key words or MeSH terms) and the relationship (sets and Boolean logic) between the search terms and filters applied; and
(e) Any supplementary sources, such as manual checking of references in the retrieved papers.

4.2. List of all Comparative Trials

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

List citation details of all randomised trials that compare the medicine directly with the main comparator for the main indication ("head-to-head trials"). If there are no "head-to-head trials", list the citation details of all randomised trials comparing the medicine with other therapies, including placebo, for the main indication. If there are no randomised trials of either the medicine or the main comparator, state this and then list all non-randomised studies that are relevant to the main indicator.

For each citation, indicate 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 head-to-head, double-blinded, randomised controlled trials that directly compare the medicine with the main comparator where these are available.

Where no head-to-head trials are available, other forms of evidence may be considered. 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 need to be included.

It is recognised that randomised trials are not always available. However, without any evidence from randomised trials, it is often not possible to determine whether there is a clinical or economic difference between the medicine and the main comparator.

Clinical trial evidence will be considered based on the Strength of Recommendation Taxonomy (SORT) hierarchy of evidence 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.

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).

4.4. Exclusion of Clinical Trials

Against each excluded reference in the outcome of the literature search, indicate the reason for its exclusion. Not all references in the outcome of a literature search need be presented in Section 4.2, as there are many possible reasons for excluding references (see below).

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

(a) Uncontrolled studies;

(b) Case reports;
(c) Anecdotal evidence or key opinion leader reports or reviews;
(d) Animal or in vitro studies;
(e) Marketing or advertorial literature; or
(f) Trial with irrelevant comparator.

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 references with a brief comment (See Appendix H: Reasons for Exclusion of Clinical Trial):

(a) The trial has a methodological flaw in randomisation, follow-up or blinding;
(b) Trial participants are not representative of patients likely to receive the medicine;
(c) The trial uses a different dosage form or regimen;
(d) The trial has inadequate duration of follow-up; or
(e) The trial measures an outcome that is not relevant to the submission.

The Pricing Committee reserves the right to request the inclusion of any excluded studies that it might deem necessary for this analysis.

4.5. Evaluation of Clinical Trials for Inclusion in the Submission

As stated previously, the quality of the clinical evidence must be assured before an analysis of the pharmacoeconomic submission can proceed. Section **4**.5 seeks to assist the applicant in the rigorous assessment of the selected literature and data.

The main body of the submission should include summaries of the key randomised trials such as description, subject characteristics, intervention and outcome measures, primary outcomes, secondary outcomes and biochemistry, adverse drug reactions, methodological comments and general comments. Full trials should be submitted as attachments in the appendix. 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 such as Medicines Resource Utilisation (MRU) findings.

Where the primary source of evidence in the submission is a meta-analysis published in a peer-reviewed journal, this should be inclusive of all-important trials listed in this section. This should be presented in accordance with Appendix I: Use of meta-analysis. Justify the inclusion of any supplementary randomised trial data.

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.

Describe each Trial with respect to the following:

(a) Method of randomisation;
(b) Loss to follow-up; and
(c) Blinding.

For further details refer to Appendix J: Evaluation of the Measures taken by Clinical Trial Investigators to Minimise Bias.

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 K: Characteristics of Each Trial, 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 medicine and the main comparator (Relative Risk Reduction, Absolute Risk Reduction, Odds Ratio, Hazard Ratio etc.), as well as the 95% confidence intervals for these differences.
Appendix L: Analysis of the outcomes of each trial, 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 section **4**.2. For more information on Quality of Life outcomes see Section 8.**4**.1.

Appendix I: 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 explain the impact that each excluded trial 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 clinical outcomes of treatment and they contribute to the total cost of care. Avoidance of an adverse outcome typically associated with the 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 are experienced 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 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.

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 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 medicine with the main comparator by comparing one set of trials in which subjects were randomised to the 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 medicine with the main comparator, the comparability of the two sets of trials must be established. The trials in the two sets should be assessed for any important differences as per Appendix L: Analysis of the outcomes of each trial. 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.) where randomised trials are not available. However, it is generally accepted that such studies are subject to a range of biases that may lead to over-estimation of the true benefit of the treatment given to the intervention group.

Data from 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 M: Presenting non-randomised studies. Consequently, claims about comparative clinical outcomes that are based solely on data from these types of studies will not be given the same weight as a well-designed high quality randomised clinical trial.

Some criteria that should be used to assess the scientific rigour of non-randomised studies are provided in Appendix N: Measures taken by the investigators to minimise bias in non-randomised studies. The interpretation of the results of such studies is difficult and expert epidemiological guidance is recommended if data of this type are central to the submission.

Where data from non-randomised studies are included, follow the advice on how to present the methods and the results of the studies that are given in Appendix M: Presenting non-randomised studies. Attach a report of each study presented in the main body of the submission with clear cross-references.

As discussed here and Appendix N: 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 pivotal in a pharmacoeconomic analysis. If claimed clinical advantages for the medicine are not supported by robust, randomised clinical trials, they are unlikely to be accepted by the Pricing Committee as grounds to support a pharmacoeconomic analysis.

5. Perspective

The perspective of the pharmacoeconomic submission should be stated clearly with particular attention to the costs included in the evaluation.

Ordinarily, the Pricing Committee will only accept pharmacoeconomic submissions that adopt a third-party payer (i.e. a funder) perspective. Where a strong case can be made for adopting a broader perspective, the applicant must provide supporting argument, which at a minimum addresses the following:

(a) Justification for use of broader perspective;
(b) Rationale for additional costs to be included;
(c) Source of information to support additional costs and
(d) Impact of this perspective on the results of the analysis

6. Time Horizon

State and justify the time horizon applied 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 sufficient to capture all relevant 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 projected over time, explain the underlying assumptions and rationale. For instance, the number of relapses of a condition is unlikely to remain constant over successive time periods whilst 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. There are 4 main types of pharmacoeconomic analysis, namely:

(a) Cost-minimisation analysis;
(b) Cost-effectiveness analysis;
(c) Cost-utility analysis; and
(d) Cost-benefit analysis.

The evaluation should be based on the outcome measure(s) that most closely and validly estimates the final outcome (see Appendix O: Final Outcomes of Therapy and Appendix P: Relationship between surrogate and final outcomes). The choice of any outcome measure should be justified and 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

The Pricing Committee discourages the use of complex models where a simple model will adequately support the economic argument. Only models that are transparent, as determined by the Pricing Committee, will be considered. For the purposes of pharmacoeconomic evaluations, transparency will be considered to include the structure of the model as well as all the information required by the Pricing Committee to test the assumptions and inputs. Where models are not found to be sufficiently transparent, the submission will be rejected with reasons highlighting lack of transparency.

Models have three basic attributes, i.e.:

(a) Input variables;
(b) Structured arrangement to manipulate variables; and
(c) The outputs that form the results.

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).

Indicate which results from randomised trials are extrapolated. Explain how the model achieves the extrapolations.

8.1. Application for Use of a Model

Prior to the development of a model to support a pharmacoeconomic analysis, an application for the use of a model must be submitted in writing to the DPEE with the following information:

(a) South African approved brand name, INN and MCC registration number of the medicine;
(b) Key clinical trials intended for use in the model (e.g. extrapolation of survival data);
(c) Justification for use of that particular model;
(d) Type of model;
(e) Description of design of model including schematic diagrams;
(f) Main clinical outcome to be modelled;
(g) Time horizon for the model; and
(h) How the model intends to handle uncertainty (i.e. probabilistic sensitivity analysis).

Note: Acceptance of the use of the model does not imply approval of the submission.

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 Discrete Event Analysis. The choice of a model will be dependent on the nature of the disease, the treatment options, time horizon and input variable. See Appendix Q: Modelling Considerations.

The Pricing Committee may accept international models that have been adapted to reflect the South African environment using local input variables under the following conditions:

(a) The full model in unlocked electronic format is made available;
(b) The model and its workings are clearly transparent; and
(c) The model is designed so that the Sub-committee 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.

Provide an attachment to the submission to give details of calculations as well as the electronic copy of any computer model used. Ensure that clear cross-references are provided as appropriate between the attachment and the relevant item in the main body of the submission. Where a software programme/package has been used to develop a model, this should be converted to Microsoft Excel for review.

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. 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.

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 O: 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 P: 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 and at the end of the extrapolation).

If clinical data have been transformed in any way (e.g. 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.

8.4.1. Quality of Life Measures and Utilities

For many medicines, an important outcome of therapy is to improve quality of life and/or survival. Where information is available regarding quality of life and survival these may be expressed as quality-adjusted life-years (QALYs). In practice few trials have measured the impact of medicine therapy on quality of life and it may be possible to transform clinical outcomes 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.

8.4.1.1. Use of Quality of Life Instruments:

A measure of quality of life should be considered where a change in quality of life is the principal intended final outcome (Appendix O: Final Outcomes of Therapy).

Where a quality of life instrument is used, details should be provided on the instrument. Currently, there is no golden standard for quality of life instruments and therefore, detailed information should be provided on 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 as well as to changes in health states over time experienced by any one individual;
(d) The clinical importance of any differences detected by the instrument; and
(e) Validity of the tool in the South African context.

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

8.4.1.2. Use of Quality-Adjusted Life-Years (QALYs)

If utilities have been measured or derived for the purposes of adjusting survival to estimate QALYs, provide details of the methods used. Comment on the perspective of the utility measured (e.g. patient, care-giver, taxpayer etc.) and on the applicability of any of the utilities estimated to the South African population. 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

Systematically identify, measure, and value resources that are relevant to the study perspective (Appendix R: Identifying and defining economic inputs and outcomes).

As a minimum, provide a table clearly identifying:

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

Where necessary ensure that:

(a) 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 and
(b) Future costs 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.

In general, resource use should be based on South African practice. Where data on resource utilisation are from international clinical trials and peer-reviewed scientific publications, 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, etc.) from which the values are derived.

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 as an attachment containing the detailed calculations. Provide clear cross-references between these calculations and the main body of the submission.

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 may also be calculated. This means that where health outcomes are anticipated over a number of time periods (beyond 1 year) these may be discounted. Discounting should be at the discretion of the applicant. However, if discounting is performed then the impact of discounting must still be included in a sensitivity analysis. Undiscounted outcomes should always be reported. If discounting is performed, a baseline annual discount rate of **5%** for costs and benefits is proposed with a sensitivity analysis measuring the impact of a discount rate from 0% to 10% (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.) that needs to be justified and supported by evidence. This should be presented in tabular form.

A two-way sensitivity analyses could be conducted on all variables shown to be sensitive in the one-way analyses. Where complex models have been approved, serious consideration should be given to a probabilistic sensitivity analysis.

8.8. Presenting the Results of the Evaluation

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

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.

1. Title Page
2. Contacts Page
3. Disclosure of relationships and conflicts of interest
4. Contents
5. List of Tables
6. List of Figures
7. Abbreviations
8. Executive Summary (refer to section 7.3)
9. Introduction
   - 9.1 Description of disease or condition
   - 9.2 Overview of treatment options for the disease or clinical condition
   - 9.3 Overview of medicine under review
   - 9.4 Objective of study and motivation for the submission
10. Product description (see section 3)
11. Comparators (see section 3.5)
12. Co-administered therapies (see section 3.4)
13. Review of Clinical Trials
    - 13.1. Description of search strategy
    - 13.2. Selection of comparative trials used in the submission
    - 13.3. Exclusion of clinical trials
    - 13.4. Evaluation of clinical trials included in submission
14. Methods
    - 14.1. Study Design (i.e. Type of pharmacoeconomic analysis used)
    - 14.2. Description of model (if approved)
    - 14.3. Patient population
    - 14.4. Perspective
    - 14.5. Time Horizon
    - 14.6. Clinical Inputs (see section 8.4)

14.7. Costs and Resource Use Inputs (see section 8.5)
14.8. List of Assumptions
15. Results and Analysis
16. Sensitivity Analysis
17. Discussion
17.1. Including review of other relevant health economic evaluations and outcomes
17.2. Limitations of the analysis
17.3. Generalisability and transferability of data in the submission
18. Conclusion
19. References
20. Appendices

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

Appendix B: Checklist for Submission Documents

Items	Y/N
1. Signed covering letter for the submission	
2. Signed official pharmacoeconomic application form	
3. The completed document entitled " Key Questions" to determine the acceptability of the submission. See section 7.3 and Appendix C	
4. The executive summary of the submission	
5. The MCC approved clinical package insert of the medicine being evaluated and its main comparator.	
6. All appendices and references	
7. Computer compact disc/s (with any spreadsheet and word document compatible with Microsoft Excel and Microsoft Word) accompanied by passwords for any protected documents	
8. Full copy of the investigator's brochure compliant with ICH regulations	
9. The submission is suitably bound	
10. There is a clear and adequate index	
11. The submission has sequential pagination throughout	
12. Dividers that are consistent with the index and prescribed format	
13. Attachments of key clinical trials; either the published paper or the applicant's summary of unpublished trials with adequate details	
14. All cost calculations are in ZAR	
15. All documentation is in English	
16. 4 hard copies of the submission	
17. Electronic list of all excluded clinical trials/studies	

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 consistent with the conditions of registration as determined by MCC?		
2. Is the comparator justified according to the criteria given in Part B, Section 3.5?		
3. Has a thorough search for relevant randomised controlled trials been conducted?		
4. Does the key clinical evidence in the submission support the proposed main clinical indication?		
5. Have the measures taken to minimise bias in the key clinical trial been assessed?		
6. Are the clinical outcomes of the studies clearly defined, justified and relevant from a South African perspective?		
7. Has a summary table been included which compares the clinical trials in terms of indication studied, study design, sample size, comparators, results, and conclusions		
8. Has primary outcome data (as opposed to secondary or sub-group outcomes) been used as the main clinical inputs for the pharmacoeconomic submission?		
9. Was the link between the surrogate and final outcomes justified?		
10. Have all the important and relevant cost components been identified and measured accurately. Are the sources of these costs clearly identified and have these costs been inflation adjusted for the specified period.		
11. Was a setting (e.g. hospital) and place in therapy for use of the drug presented?		
12. Were safety issues considered? Was the impact of adverse drug events on expenditure discussed?		
13. Have all the assumptions for the model been stated and justified?		
14. Has a clear description been given of the type of pharmacoeconomic study and the rationale for its selection?		
15. Has an incremental analysis of costs and consequences of alternative treatments been performed?		
16. Has a third-party payer perspective been used and only the relevant costs included?		
17. Has an appropriate time horizon been used and justified?		
18. Have the main sources of uncertainty been identified and has a sensitivity analysis been carried out to assess the uncertainty of the variables in the evaluation?		
19. Has the level of evidence for each study indicated in accordance with the criteria provided in Part B, section 4.3		

Appendix D: Additional information required for fixed combinations of medicines

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 combination medicines such as fixed dose combination (FDC) formulations or co-packaged medicines. These guidelines do not relate to combinations of medicines and diagnostic entities.

Submissions of FDCs and co-packaged medicines must comply with all other provisions in these guidelines. Prices of these combination medicines should not be 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.

Conditions required for consideration of a combination medicine:

(a) The medicine should be approved by the MCC;

(b) The combination of the medicines should offer a clear clinical advantage;

(c) The combination should not promote or contribute toward the irrational use of medicine relative to each individual component;

(d) The clinical evidence should demonstrate efficacy of the fixed combination under trial conditions and not only the individual components;

(e) 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;

(f) Where improved adherence is used as an argument for enhanced clinical outcomes, data should be provided.

Appendix E: Expert Opinion

REFER: Part B, Sections 3.6,

1. Uses of expert opinion

Expert opinion is not a substitute for sound scientific evidence. However, expert opinion has been found to be useful in some aspects of preparing submissions to the committee:

(a) To help set the context of the economic evaluation by defining the place of the medicine in treatment (the main indication and the main comparator, see Sections 3.**2** and 3.5 respectively);
(b) To help modify the patterns of resource use and
(c) To help predict which resources will be used and how often each will be used to manage outcomes reported.

2. Presenting expert opinion

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

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

3. Describing the collection and collation of expert opinion

The following details should be provided:

(a) The criteria for selecting the experts;
(b) The number of experts approached;
(c) The number of experts who participated and their educational qualifications;
(d) The number of experts who declined to participate;
(e) Whether a declaration of potential conflict(s) of interest was sought from all experts or medical specialty groups whose opinions were sought;
(f) A copy of the informed consent form provided to the experts at the time of collecting their opinion;
(g) The method used to collect the opinions;
(h) The medium used to collect the opinions;
(i) The questions asked or the tool used to gain the opinion from the experts;
(j) Whether iteration was used in the collation of opinions and, if so, how it was used;
(k) The number of responses received for each question;
(l) Whether all experts agreed with each response, and, if not, what approach was used to finalise the estimates and
(m) 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 reference 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. Each reference should be categorised according to the following format:

Ref No	Citation	Selected	Excluded
Sec 1.	Head-to-head randomised trials		
Sec 2.	Indirect comparative trials		
Sec 3.	Non-randomised trials		

Appendix G: SORT Hierarchy of levels of evidence

Refer: Part B, Section 4.3.

The full details of the SORT levels of evidence are available in the reference above. The table below outlines the 3 levels of evidence and how to determine whether results are consistent or not.

In general, only key recommendations for readers require a grade of the "Strength of Recommendation." Recommendations should be based on the highest quality evidence available. For example, vitamin E was found in some cohort studies (level 2 study quality) to have a benefit for cardiovascular protection, but good-quality randomized trials (level 1) have not confirmed this effect. Therefore, it is preferable to base clinical recommendations in a manuscript on the level 1 studies

Strength of recommendation	*Definition*
A	Recommendation based on consistent and good-quality patient-oriented evidence *
B	Recommendation based on inconsistent or limited-quality patient-oriented evidence *
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,* or case series for studies of diagnosis, treatment, prevention, or screening.

Use the following table to determine whether a study measuring patient-oriented outcomes is of good or limited quality, and whether the results are consistent or inconsistent between studies

Study quality	*Diagnosis*	*Treatment/prevention/screening*	*Prognosis*
Level 1—good-quality patient-oriented evidence	Validated clinical decision rule SR/meta-analysis of high-quality studies High-quality diagnostic cohort study†	SR/meta-analysis of RCTs with consistent findings High-quality individual RCT‡ All-or-none study§	SR/meta-analysis of good-quality cohort studies Prospective cohort study with good follow-up
Level 2—limited-quality patient-oriented evidence	Unvalidated clinical decision rule SR/meta-analysis of lower-quality studies or studies with inconsistent findings Lower-quality diagnostic cohort study or diagnostic case-control study§	SR/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings Lower-quality clinical trial‡ Cohort study Case-control study	SR/meta-analysis of lower-quality cohort studies or with inconsistent results Retrospective cohort study or prospective cohort study with poor follow-up Case-control study Case series
Level 3—other evidence	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening		

Consistency across studies	
Consistent	Most studies found similar or at least coherent conclusions (coherence means that differences are explainable) or If high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation
Inconsistent	Considerable variation among study findings and lack of coherence or If high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

*—*Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).*

†—*High-quality diagnostic cohort study: cohort design, adequate size, adequate spectrum of patients, blinding, and a consistent, well-defined reference standard.*

‡—*High-quality RCT: allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80 percent).*

§—*In an all-or-none study, the treatment causes a dramatic change in outcomes, such as antibiotics for meningitis or surgery for appendicitis, which precludes study in a controlled trial.*

Ebell M, Siwek J, Weiss B et al. 2004. Strength of Recommendation Taxonomy (SORT): A Patient-Centred 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 I: 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.

I.1. Conducting 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) and
(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. 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.

I.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) 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 J: Evaluation of the Measures taken by Clinical Trial Investigators to minimise bias

Refer: Part B; Section 4.5.1.

The following information is required 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.

For each of the following methods, 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 in the format below:

Trial	Randomisation*	Adequacy of Follow-up*	Blinding**

*Choose A, B or C below in sections J.1 and J.2
**Choose A or B in section J.3

J.1. Randomisation

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/un-blinded trial; treatment assignment kept in consecutive "sealed" envelopes and open/un-blinded 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 toil-free telephone number or by the pharmacy department after the decision has been made to enter the subject in the trial).

J.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 dropouts with no assessment of trial outcome(s) in the subjects who dropped-out and dropout rates differed between treated and control groups.
B. There were some dropouts with no assessment of trial outcome(s) in the subjects who dropped-out, and dropout 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.

J.3. Supplementary information

For each comparison group, summarise the number randomised to treatment, the number of dropouts and the number of participants who were lost to follow-up.

Take Note: a drop-out is a participant who 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.

J.4. 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 "un-blinding", 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 trial personnel and participants, 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 trial personnel and participants 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).

Take Note: To maintain, "Full blinding", it is usually necessary to blind all people directly involved in the care of the trial participants and the trial participants themselves (i.e. double-blinding) to prevent the potential of bias.

J.5. Purpose of these assessments

The intention of these assessments is to provide the applicant and the Sub-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 medicine works. The Pricing Committee will consider 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.

Appendix K: Characteristics of Each Trial

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.

Question No.	Question
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 participants included in the trial compare with patients who are likely to receive the 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 Package Insert?
e.	What was the median (and range) duration of follow-up of the trial?

Notes:

FOR (a)**:** if the submission includes one or more crossover 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 points:

(a) How do the trial participants 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?

(b) 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. (See Section 8.7).

(c) Is the data transferable to the South African setting?

(d) Is the trial setting relevant to that of the SA environment?

FOR (d): The trial should use the correct doses of the 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 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 dropouts should be excluded from the calculations.

Appendix L: Analysis of the outcomes of each trial

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? $^{\alpha}$
4. If the trial measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.$^{\beta}$

Notes:

#: 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).

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

***: The respective p-value is an alternative, but is less preferred.

****: 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 dropouts and withdrawals, see the note for "adequacy of follow-up" in Appendix J: Evaluation of the Measures taken by Clinical Trial Investigators to minimise bias

*****: 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.

α: 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.

β: 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 M: Presenting non-randomised studies

REFER: Part B, Section 4.5.4.

Categorise the studies into the study type(s) defined in **Appendix N: 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 N**, 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 L: Analysis of the outcomes of each trial** , 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 N: Measures taken by the investigators to minimise bias in non-randomised studies

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

The following information is required 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.

Categorise the studies into the study type(s). If the submission includes a number of studies of the same type, tabulate the responses.

As for the assessment of randomised trials in **Appendix J: Evaluation of the Measures taken by Clinical Trial Investigators to minimise bias** 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. 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 non-randomised studies which may affect the results of such studies and their comparability with different studies of the same type. These aspects should be identified and explanation provided of how they are dealt with.

The submission should consider the following biases inherent in these study designs:

(a) Possibility of confounding;
(b) Adequacy of follow-up;
(c) Blinding of outcomes assessment;
(d) Selection of cases;
(e) Selection of controls and
(f) Possibility of measurement bias.

Appendix O: Final Outcomes of Therapy

Refer: Part B, Section 8.4.

Applicants are required to define principle intended final outcomes and 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 along with a valid outcome.

Appendix P: Relationship between surrogate and final outcomes

Surrogate outcomes may only be considered where adequate evidence to support the relationship to final outcomes has been provided.

Applicants should generally consider the final intended effects of the medicine 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, impaired quality of life or a myocardial infarction.

In a few instances, relationships have been established between surrogate and final outcomes. 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 Q: Modelling Considerations

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:

(a) The decision analysis diagram showing decision nodes, chance nodes and terminal nodes;
(b) 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 medicine and its main comparator;
(c) All assumptions need to be stated clearly with justification.

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:

(a) 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;
(b) Health states, which should be defined (e.g. temporary, absorbing). Justify the health states chosen (and those excluded to avoid excessive complexity);
(c) 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 medicine and its main comparator, respectively. Clearly link each patient-relevant outcome and resource item in the model to its relevant health state(s);
(d) Define the cycle length and the follow-up time and comment as necessary;

(e) 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;

(f) State whether a half-cycle correction has been included or justify its exclusion;

(g) Describe how the model is calculated (e.g. hypothetical cohort or Monte Carlo simulation) and

(h) Indicate implicit assumptions, where relevant.

Appendix R: Identifying and defining economic inputs and outcomes

REFER: Part B, Sections 8.5.

1. Direct medical resources

Identify and list the resource items for which there will be a change in use or new use associated with substituting the 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.

2. 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.

3. 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.

4. 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.

5. Definition of types of costs

Identify where costs are recurrent, capital, fixed or variable. These costs are defined as follows:

5.1. **Recurrent costs**: resources that are *used up within one year* or costs that are incurred on an annual basis (e.g. staff time, supplies including medicines and diagnostic tests, general operating costs);

5.2. **Capital costs**: refer to inputs (or resources) that *last for more than one year* e.g. buildings, equipment, vehicles, and staff training;

5.3. **Fixed costs**: the costs associated with operating a particular programme or intervention that *does not vary with the scale of provision* (in the short term) such as the rent, building maintenance, administration costs;

5.4. **Variable costs**: the cost associated with a programme or intervention that *varies with the size of the programme* or the number of patients treated.

Economic costs should be included where applicable. Economic costs include the estimated value of goods and services for which there were no financial transactions (i.e. additional items such as donated goods and services, e.g. equipment, condoms, and volunteer labor).

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