HEALTH TECHNOLOGY ASSESSMENT METHODS GUIDE

TO INFORM THE SELECTION OF MEDICINES TO THE SOUTH AFRICAN NATIONAL ESSENTIAL MEDICINES LIST

14 June 2021

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TEMPLATES

A major benefit of a Health Technology Assessment (HTA) Methods Guide is consistency and comparability of reporting and gathering information. The application of this Guide involves the use of the relevant template depending on the required analysis type or function being performed. The relevant templates and tools that should be used in the Essential Drugs Programme HTA Process are as follows:

1. Health Technology Motivation Template
2. Health Technology Scope Template
3. Technical Review Report Template
4. Cost-comparison Analysis Template
5. Rapid Review of Economic Evaluations Template
6. Cost-Effectiveness Analysis Template
7. Budget Impact Analysis Template
8. Pricing Analysis Template

FOREWORD

The purpose of the *Health Technology Assessment Methods Guide to inform the selection of medicines to the South African National Essential Medicines List* (the Guide) is to inform the methods for the development and interpretation of clinical, economic and other evidence to guide decision-making related to the selection of medicines on South Africa's Essential Medicines List (EML). The Guide is the first attempt to formalise the methods for health technology assessment (HTA) for decision-making related to South Africa's public sector and is designed to be used within the existing decision-making context and in future structures under National Health Insurance.

The Guide provides detailed guidance on the processes and methods to follow when developing a scope for a technology assessment, assessing and appraising a medicine or group of medicines, development of a standardised Technical Review Report for all medicines prioritised and selected for assessment, plus methods on how to conduct additional analysis if needed.

The specific objectives of the Guide are to:

- Provide clear guidance on the methods for gathering and producing evidence on clinical efficacy, safety, effectiveness and affordability, as well as factors like equity, feasibility and cost-effectiveness.
- Ensure consistency of methods for analysis and reporting, leading to more consistent and transparent decision-making

The Guide can be used by anyone involved in preparing the technology assessment, including staff of the Essential Drugs Programme (EDP), Expert Review Committee (ERC) members, members of the National Essential Medicines Committee (NEMLC), National Department of Health (NDoH) partner organisations, provincial Pharmaceutical and Therapeutics Committee (PTC) members, pharmaceutical or medical device companies, and Contracted External Reviewers (CER) or academic units.

The EDP unit coordinates the assessment of all technologies that fall within the scope of the Standard Treatment Guidelines (STGs), the Essential Medicines List (EML) and the Tertiary and Quaternary Hospital Level Essential Medicines Recommendations (T&Q EMR) utilising internal staff secretariat and Ministerial-appointed advisory committees. The scope of this Guide applies to medicine technologies only in the form of an individual medicine or a class of medicines to be listed on the EML. Medicines are defined in line with the definition of the South African Health Products Regulatory Authority (SAHPRA) definition of an "orthodox medicine" (1). Future iterations and additional guidance may extend methodologies to other technology types in coordination with relevant departments or NDoH programmes. Some of the approaches and principles described in this Guide may be applicable to the assessment of vaccines and medical devices, so can be used if considered appropriate for that particular topic.

This is a first version of the Guide. HTA methods guides are not intended to be static documents and this Guide should be routinely and systematically updated to incorporate the changing use of HTA in the South African environment and under the proposed National Health Insurance. This version is intended to be used as a baseline on which to build further methods specification in consultation with a wider stakeholder group, and facilitate application and trial of HTA methods using current analytical and technical secretariat capacity of the EDP and contributors.

ACKNOWLEDGEMENTS AND AUTHORSHIP

This Guide was drafted under the Better Health Program South Africa by Tommy Wilkinson and Maryke Wilkinson in consultation with the staff of the Essential Dugs Program, National Department of Health. Background contextual information for the Guide was developed with assistance from Kim MacQuilkan.

The development of this Guide builds on global best practice in HTA but is firmly anchored in the existing experience of the EDP programme, including the processes and methods that have been put into place in the review of the EML and STGs.

In particular, this guide builds on the following existing documentation produced by the South African Department of Health:

- Essential Drugs Program Reviewer's manual (2)
- Methods guide for rapid reviews for COVID-19 medicine reviews (3)
- Existing medicine reviews and economic analyses (4)
- Guidelines for Pharmacoeconomic Submissions in South Africa (5)

In addition, the development of the Guide included a review of methods and processes of multiple HTA agencies and research organisations globally, and incorporates concepts and approaches appropriate for the South African setting. Organisations reviewed include:

- National Institute for Health and Care Excellence (NICE), England and Wales https://www.nice.org.uk
- Canadian Agency for Drugs and Technologies in Health (CADTH), Canada https://www.cadth.ca
- The International Decision Support Initiative Reference Case for Economic Evaluation, https://idsihealth.org/resource-items/idsi-reference-case-for-economic-evaluation/
- Scottish Medicines Consortium (SMC), Scotland https://www.scottishmedicines.org.uk
- Pharmaceutical Management Agency (PHARMAC), New Zealand https://pharmac.govt.nz
- All Wales Medicines Strategy Group (AWMSG), Wales https://awmsg.nhs.wales
- Republic of the Philippines Health Technology Assessment, Philippines https://hta.doh.gov.ph
- National Centre for Pharmacoeconomics (NCPE Ireland), Ireland http://www.ncpe.ie
- European network for Health Technology Assessment (EUnetHTA), Europe https://eunethta.eu
- International Network of Agencies for Health Technology Assessment (INAHTA), International https://www.inahta.org
- Health Intervention and Technology Assessment Program (HITAP), Thailand https://www.hitap.net
- Cochrane Training, International https://training.cochrane.org

1. INTRODUCTION

1.1 Health technology assessment in South Africa's public health system

The EDP was established under the National Drug Policy (1996) (6), and aims to ensure that affordable, good quality essential medicines are available at all times, in adequate amounts, in appropriate dosage forms, to all South African citizens. The South African public health sector operates in a resource-limited environment, where the health care demands are continually growing. Whilst new health technologies entering the South African market hold the potential for improved health outcomes, they may also introduce an additional cost to the health system, meaning their availability introduces challenges for priority setting, resource allocation, and patient care choices. Funders and administrators in the public health system need to choose between alternative interventions for a given disease, treating a disease or preventing it in the first place, and/or treating one disease as opposed to another. In order to make these complex choices, the EDP aims to utilise the best available evidence using an approach that is systematic, unbiased, and transparent.

The process of determining which medicines are selected to the EML is described below.

The EML is a list of medicines that should be available to all South African citizens when they access the health system at a particular level of care. The selection/deselection of essential medicines on the EML takes place after an assessment of the available evidence (considering efficacy, safety and affordability), and forms part of the broader STG Review process. The STGs are the implementation mechanisms for the EML and provide guidance to health care professionals on the rational use of the essential medicines at a particular level of care. The T&Q EMR is a list of recommendations supporting or advising against the use of specialist treatments for conditions managed at the tertiary and quaternary levels of care.

Expert Review Committees (ERCs) are convened through the EDP to support the creation and maintenance of South Africa's EML, STGs and T&Q EMR. The ERCs are technical advisory committees that make recommendations to the National Essential Medicines List Committee (NEMLC) in regard to a specific technology after an assessment of the available clinical and cost-effectiveness evidence. NEMLC reviews the recommendations and evidence produced by the ERCs and make the decision to approve an update to the EML, STG or Tertiary and Quaternary Hospital Level recommendation, or not. The decision made by NEMLC is sent to stakeholders for comment, with the relevant technology assessment documents published on the National Department of Health (NDoH) website. Any comments received are reviewed and addressed by the relevant ERC, after which the final recommendation is sent to NEMLC for ratification.

There are three ERCs - one for each of the following settings:

1. Primary Health Care and Adult Hospital (PHC and AH ERC);
2. Paediatric Hospital (PH ERC);
3. Tertiary and Quaternary Hospital Level (T&Q ERC).

The EDP HTA process convened by the EDP is summarised in the 5-step approach outlined in Figure 1, with the relevant reference documents and templates for the different stages presented.

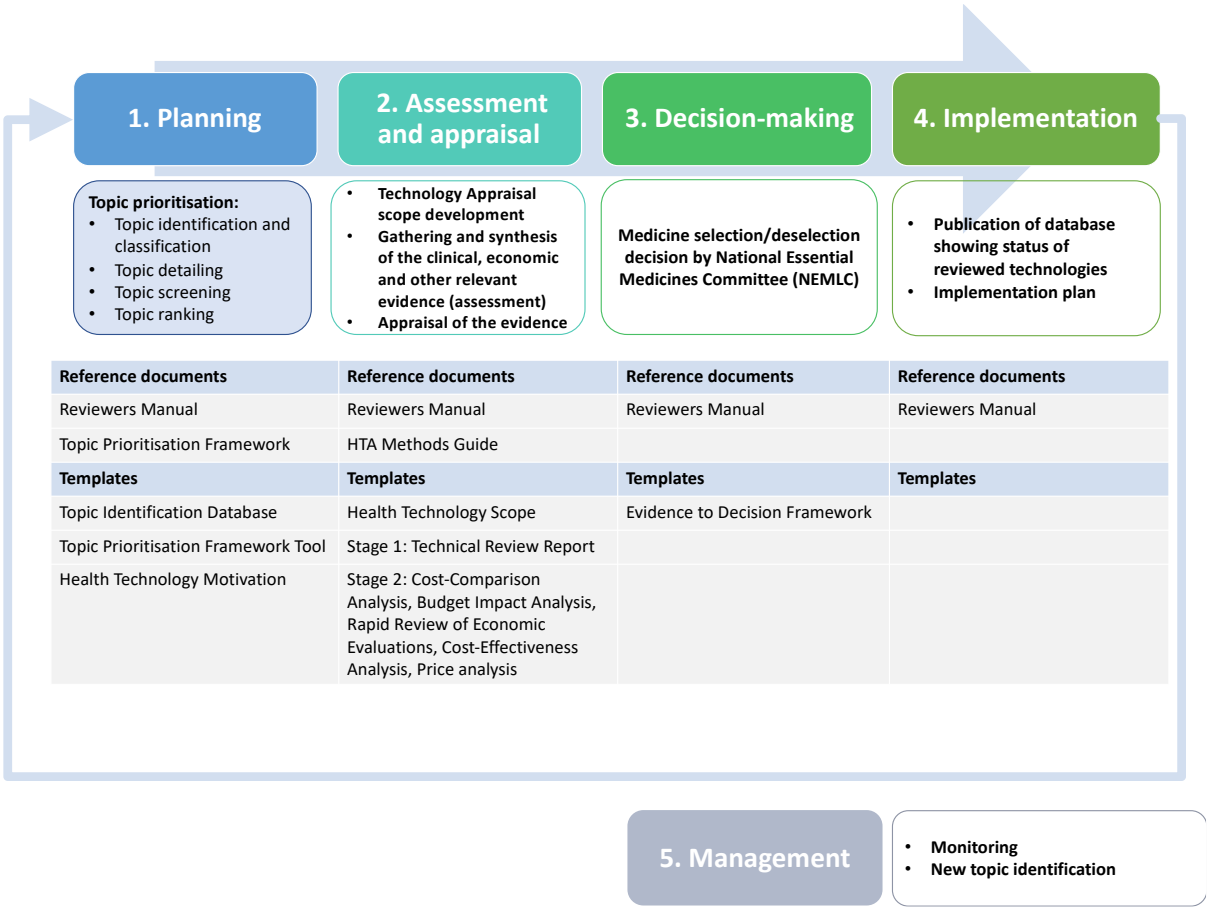

Figure 1. The Essential Drugs Programme health technology assessment process

1.1.1 GUIDING PRINCIPLES FOR HTA IN SOUTH AFRICA

This Guide focusses on the methods for the production and use of evidence for medicines and is nested in the context of South Africa's developing health technology assessment (HTA) system. HTA goes beyond a technical exercise and incorporates a series of social and scientific value judgements to inform an accountable approach to determining what health technologies are funded in the public health system. It is therefore important to note the general principles under which this Guide was developed and should be interpreted.

1. HTA in South Africa is anchored in the ideals of Universal Health Coverage (UHC).
2. HTA is both a technical and political process, involving a range of stakeholders, systems, disciplines and viewpoints. It is imperative that any HTA processes developed in South Africa effectively incorporate the views and experiences of a broad range of stakeholders, across income quintiles and sectors, and seeks to develop a sense of ownership.
3. The measurement of whether HTA is successful or not is the extent to which it contributes to defined policy objectives such as achieving value for money and improving health outcomes, and addressing inequalities and access to health technologies.
4. Although general standards of good HTA practice exist internationally and will inform the approach in South Africa, there is no internationally accepted standard for how to practically design HTA. The structure of the HTA system in South Africa will necessarily be unique to policy needs, health system design and funding structures, nature and availability of evidence and existing approaches to decision-making.
5. The design of the HTA system in South Africa should be sustainable and country led. Funding and technical contribution from development partners in support to the HTA system development is

welcomed. However, all support should be in line with the overall objectives and vision as defined by National Department of Health and National Treasury.

6. The "HTA journey" of South Africa will be highly instructive to other countries moving towards UHC. Participation in and contribution to regional and global networks will be a central component of the development of HTA in South Africa in order to build collaborations and efficiencies in HTA activities.
7. The development of an HTA system should not focus on immediate decision requirements only but incorporate assessment of longer-term outcomes and health system performance, acknowledging that decision-making is an iterative process.
8. Leadership is recognised as a critical requirement of a successful HTA system. HTA processes in South Africa should incorporate the governance, sustainable funding and capacity strengthening components required to develop and support leadership.
9. Stakeholders are engaged throughout the HTA process through regular consultations and feedback mechanisms.

1.2 Stakeholder engagement

Stakeholder engagement is a fundamental part of any inclusive and responsive HTA process.

Currently, there is a limited stakeholder engagement process following the review through the ERCs and the decision by NEMLC, with the relevant documents published on the NDoH website. This process seeks inputs and views of stakeholders. It is proposed that a structured stakeholder engagement strategy and process is established as part of a broader HTA Process Guide to accompany this Guide (which focusses on the analytical methods of HTA).

Relevant stakeholders in South Africa include clinical experts, healthcare professional organisations (councils, associations), clinical academic units, patients, patient or carer organisations, manufacturers of the assessed technologies (intervention and comparators), provincial pharmaceutical and therapeutics committees, and research units.

1.3 Topic prioritisation process

Topic prioritisation is the process of choosing which technologies should be considered within the HTA process. It is an essential component of any HTA process because the demand for technologies to be evaluated will always exceed the capacity to evaluate. The topic prioritisation process is made up of multiple components, including (a) topic identification and classification, (b) topic detailing, (c) topic screening, (d) topic ranking, and (e) topic selection. An overview of the EDP topic prioritisation approach is provided below.

The EDP unit coordinates the assessment of all technologies that fall within the scope of the STGs, the EML and the T&Q EMR. Topics are **identified t**hrough many established routes, including motivation forms submitted by stakeholders, ABC analysis of utilisation data, planned amendments to national guidelines, and new clinical or cost data.

Due to the EDP's wide remit, topics identified can include requests for guidance on a variety of intervention types. For this reason, identified topics are classified into the following broad categories:

- Medicines
- Medical device
- Diagnostic / diagnostic technique
- Screening tool / screening technique
- Medical procedure
- Vaccine
- Public health programme

Figure 3 presents the decision-flow when classifying topics for EDP reviews. The determination of technology topics as either requiring an assessment of one technology for one indication (Single Technology Topic), or multiple technologies in the same class for one indication (Multiple Technologies Topic) is needed to support allocation of limited analytical capacity, as a review of multiple technologies from will require more intensive analysis. Topic areas that include multiple interventions and/or multiple indications (e.g. therapeutic reviews) require tailored prioritisation processes to ensure topics are prioritised and selected based on criteria relevant to that programme of work.

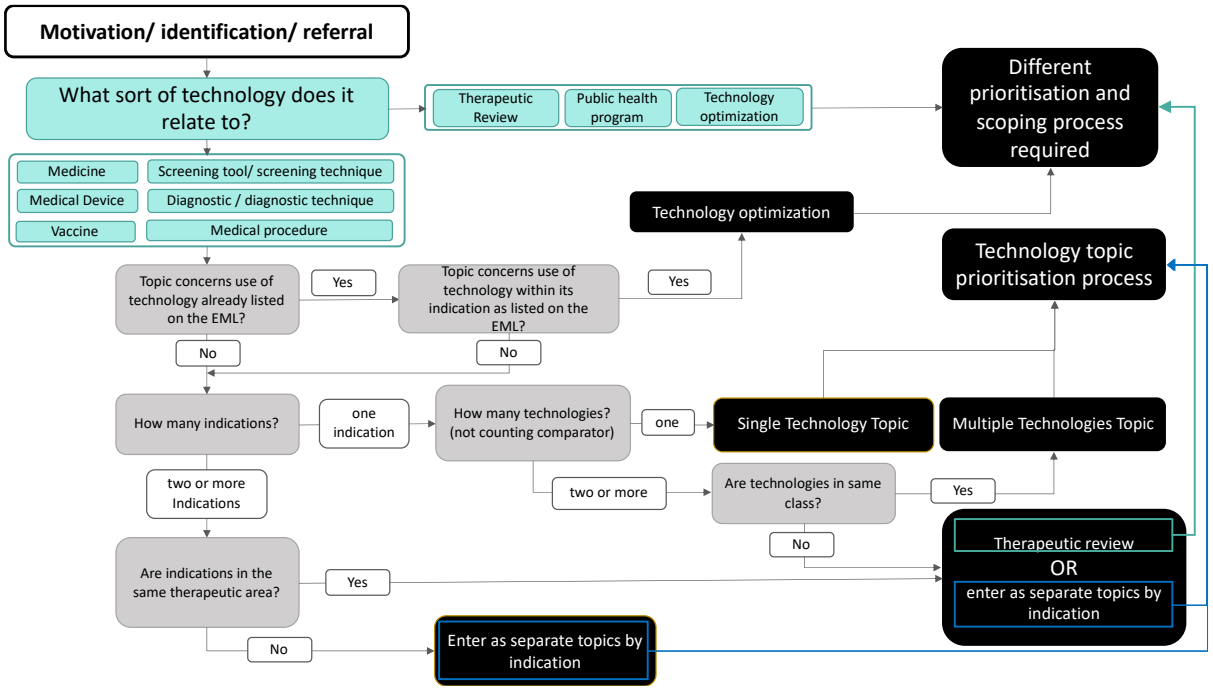

Figure 2. Classification of Essential Drugs Programme assessments

EML – Essential Medicines List

Following identification and classification of technology topics, more **detailed** information relating to the topics are required to enable screening and prioritisation. As it is unknown at this point in the process what the priority of the topic will be or whether the topic will be considered further in the process, minimal information on the topic will be gained at the detailing stage. This will include the name of the technology or technology class, a clear description of the indication for which the EML listing is sought, and the relevant comparator(s) in the South African context.

Before technology topics are prioritised for assessment, they are **screened**[1] to ensure they are eligible and suitable for the EDP HTA process. Specific topic screening criteria are used to assess a proposed topic in terms of (1) its applicability to the EDP HTA process, (2) the importance of the assessment to patient care, (3) the technology's availability in South Africa, (4) relevant recommendations issued about the technology by other HTA agencies, (5) the implementability of the technology in South Africa, and (6) potential for duplication of effort. Although technologies that do not meet the screening criteria can be advanced to the topic prioritisation stage on exception, the EDP HTA process needs to focus its limited resources on technologies that are available and implementable, likely to

[1] Approach adapted from the screening criteria used by the Canadian Agency for Drugs and Technologies in Health (CADTH)(40) and the National Institute for Health and Care Excellence (NICE)(41) in their topic identification and prioritisation processes.

make a significant contribution to patient care, and have a reasonable chance of being cost-effective in the South African context.

Technology topics considered suitable for inclusion to the EDP workplan after the initial screening will be ranked for assessment order. Topic **ranking** is a formal process whereby suitable topics are placed in a values/benefits matrix such that their positioning for assessment is created by an explicit and visible process. The topic ranking criteria for South Africa have been selected based on substantive consultation with EDP staff, NEMLC and Expert Review Committee members, and previous implicit prioritisation practice. The criteria also draw on international best practice examples with consideration with its relevance to the South African context. The criteria takes into account the technology's expected: (1) clinical benefit compared to existing treatments, (2) population impact, (3) economic impact, (4) variations in clinical practice across country, (5) equity in health for marginalised groups, and (6) ease of implementation. Topics will receive a score for each the prioritisation domains and are then ranked in order of priority.

The prioritised list of technology topics will be presented to NEMLC for review and **selection decision**. Once a technology is selected for assessment, a draft Scope for the Technology Assessment (TA) will be developed by the EDP secretariat and it will be **referred** to the relevant ERC.

1.4 Tiers of assessment

The EDP will coordinate the TA workplan in a manner that takes into account the urgency of the decision, the level of uncertainty and the available resources. A TA will therefore consist of two stages: Stage 1 and Stage 2.

STAGE 1: TECHNICAL REVIEW

A Technical Review Report will be compiled for all TAs, and it is expected that in most cases the information presented in this report will be sufficient to inform a decision regarding the inclusion or exclusion of a technology to the EML or T&Q EMR. The Technical Review Report will contain technology details, a description of the review question/s, a review of the clinical evidence, pharmaceutical costs, a summary of other HTA agency decisions (if relevant), equity considerations, social value considerations, and feasibility considerations. The evidence presented in the Technical Review Report will be obtained from the information provided in the Health Technology Motivation Form (when available), information gathered as part of the Topic Prioritisation process, and data collected by the reviewer.

Depending on the urgency and potential impact of the decision, a Brief Technical Review Report may be compiled (completed by one reviewer [full-time] in 1-2 weeks), or a Standard Technical Review Report (completed by two or more reviewers [part-time] over 3-4 weeks). A Standard Technical Review is the preferred approach unless there is certainty that a Brief Technical Review would be sufficient.

STAGE 2: ADDITIONAL ANALYSIS

Some technology topics will however require different or more complex analytical assessment of clinical and economic data than that provided in the Technical Review Report. For these topics, trade-offs between certainty of evidence, urgency and available resources will need to be made. A request for additional or higher levels of clinical and economic analysis can be made (if needed) after appraisal of the Technical Review Report by the ERC. In select cases with sufficient motivation, additional analyses might be assigned and conducted at the same time as the Technical Review.

Figure 3 summarises some of the considerations when determining the appropriate Stage 2 analysis for a TA. The different types of additional analysis are described in more detail below, classified as clinical, economic or bespoke analysis.

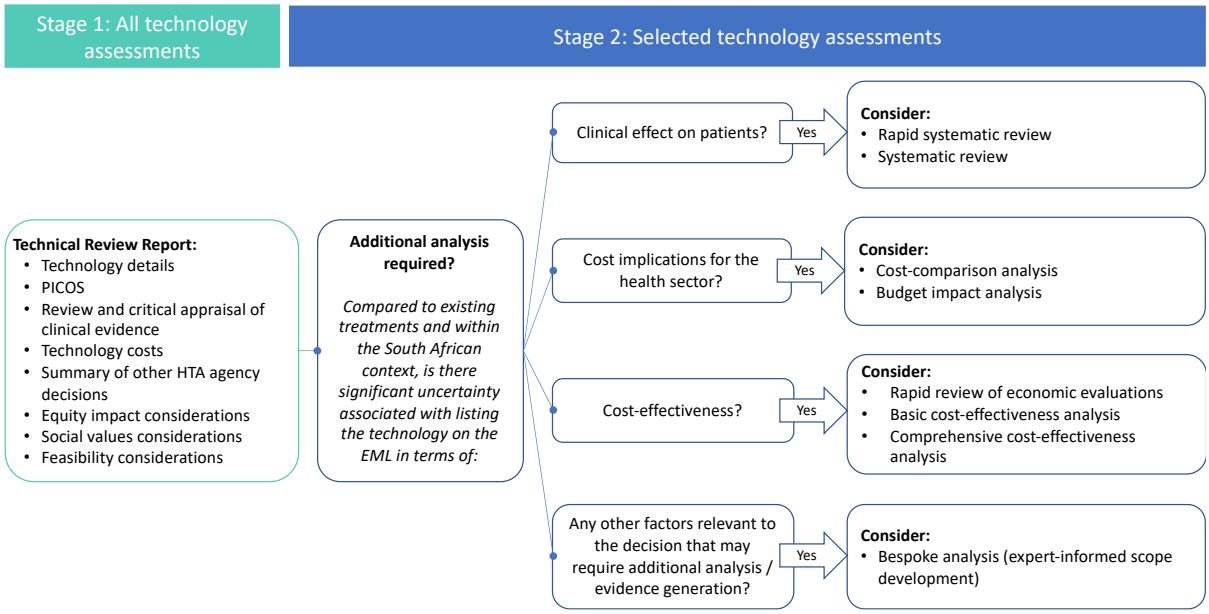

Figure 3. Determining analysis required for a technology assessment

EML – Essential Medicines List, PICOS – population, intervention, comparator(s), outcome(s), study design(s)

A brief outline of each type of Stage 2 analysis is given in Table 1, with a detailed description of the methods involved provided later in the document.

Table 1. Stage 2 Additional analysis

Type		Description	Resource requirements	Estimation of lead time required~
Clinical	Rapid Systematic Review	A form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting specific methods to produce evidence for stakeholders in a resource-efficient manner (7).	**Medium**	**3-6 months**
	Systematic Review	Attempts to identify, appraise and synthesise all the empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. Researchers use explicit, systematic methods that are selected with a view aimed at minimising bias to produce more reliable findings to inform decision-making (8).	**High**	**12 months +**
Cost or economic evaluation	Cost-comparison Analysis	Comparing cost of two regiments or formulations. Analysts consider aspects like costs of treatments and human resources, and clearly state the assumptions they made when conducting the analysis.	**Low**	**1-2 weeks**
	Rapid review of economic evaluations (RREE)	Review of economic evaluations conducted by HTA agencies or published in peer reviewed journals.	**Low**	**1-2 weeks**
	Basic cost-effectiveness analysis	Used to compare costs and effects of treatment alternatives using a common outcome measure e.g., cost per hospitalisations averted or exacerbations treated. Generates a summary measurement of efficiency (a cost-effectiveness ratio).	**Medium to High**	**3-6 months**
	Comprehensive cost-effectiveness analysis	Used to compare costs and effects of treatment alternatives using a common outcome measure e.g., cost per hospitalisations averted or exacerbations treated. Can also use generalized outcome measure e.g. Quality Adjusted Life Year (QALY) to produce a cost-utility analysis. Generates a summary measurement of efficiency (a cost-effectiveness ratio).	**High**	**6 months +**
	Budget impact analysis (BIA)	Used to assess the potential financial consequences due to the introduction of the intervention / health technology in a particular level of care	**Low**	**1-2 weeks**
	Pricing Analysis	Comparison of prices for a specific treatment and formulation in selected countries and locally.	**Low**	**1 week**
Bespoke	Variable	Clearly specify what is needed and how the additional analysis will assist the decision problem e.g., WHO EML list information, regulatory status in other countries, scoping review to assess availability of evidence	Dependent on analysis required	Dependent on analysis required

HTA – Health Technology Assessment, WHO EML – World Health Organisation Essential Medicines List

~Estimation of lead time is based on the assumption that the Technical Review Report has been completed and is available to the analysts, and that the analyses might require input from more than one analyst at different stages/ time points.

Clinical Assessment

A clinical review of the evidence includes the explicit review of a technology's clinical benefits and safety. In many settings, systematic reviews underpin policy and practice decisions, but they can be demanding, resource-intensive and time-consuming, which limits their routine use in the current South African context.

A higher-level assessment of the clinical evidence than the clinical assessment conducted for a Technical Review may be required if, compared to existing treatments, there is significant uncertainty associated with the clinical effect of a technology, especially if it might have a high budget impact if implemented (due to high acquisition/ monitoring costs and/or high penetration). In these cases, a request for a **rapid systematic review** or **standard systematic review** might be warranted. A rapid or standard systematic review might also be required if a cost-effectiveness analysis (Stage 2 economic analysis) is required, and the clinical data identified in the Technical Review will not provide the required inputs for the analysis.

Scheduling of rapid or standard systematic reviews and the commissioning thereof need to be part of a considered workplan with due consideration of the potential time and resource challenges.

Costing analysis and economic evaluation

If there is significant uncertainty about the cost-effectiveness of a technology, it is advisable to first conduct a detailed review of published economic analysis and other evidence that informed other HTA agency decisions, to determine if conducting an additional cost-effectiveness analysis (CEA) for the South African context is warranted.

This Guide details the specifications for a Basic CEA and a Comprehensive CEA. Due to limited analytical resources available, it is expected that a Comprehensive CEA will be conducted for a limited number of technologies per year. These "analytical slots" should only be allocated to technologies where there is confidence that there is superior clinical effectiveness compared to the comparator, but for which the cost-effectiveness in the South African context is uncertain. Undertaking a resource-intensive CEA when not entirely necessary limits the analytical capacity to undertake other analyses. If the clinical effectiveness of a technology is shown to be non-inferior or equivalent to the comparator, a detailed cost-comparison should be sufficient to answer an economic review question. The outputs of a cost-comparison are also required as inputs to a CEA, so in many cases it might be preferable to first conduct a cost-comparison before a CEA is undertaken.

A budget impact analysis can be requested as an additional analysis in isolation but should always be included if a cost-effectiveness analysis was conducted to ensure that both the 'value for money' and 'affordability' (in terms of expected impact on local budgets) of a technology is considered.

Technologies with indications for rare conditions are less likely to undergo a high level of economic analysis due to unavailability of data.

A pricing analysis should be requested if there is significant concern that the pricing of the technology in SA is (or will be) higher than other countries and the price is likely to have a significant impact on the cost-effectiveness results.

Bespoke analysis

If the ERC or NEMLC determine that another type of analysis (not listed in Table 1) should be conducted to address the review question, the remit of the analysis must be clearly described. Examples of additional analyses include: WHO EML list information, regulatory status in other countries, or a scoping review to assess availability of evidence.

2. TECHNOLOGY ASSESSMENT SCOPE DEVELOPMENT

A clear and well-defined Technology Assessment (TA) Scope will provide a framework for gathering and analysing the clinical evidence by defining what the TA will and will not examine. This will ensure that the findings presented to the relevant committees for appraisal (ERC) and decision-making (NEMLC) will be fit for purpose.

A draft TA Scope is developed by the EDP for all technology topics approved by NEMLC. The information gathered as part of the topic prioritisation process provide a basis for the development of the draft TA Scope.

The TA Scope will provide the framework for Stage 1 of the TA, which involves the production of the Technical Review Report. The TA Scope will include a clear statement about why the analysis is required, accompanied by the review question/s which can be adapted from the following statement:

To assess the [effectiveness/ safety/ cost/ cost-effectiveness/ other] of the use of [technology x] compared to [technology b] for [patient population and disease/condition] in [health care setting]

The TA Scope will also provide detailed information about the relevant population, intervention (technology being assessed), comparator(s), outcomes and study design (PICOS) that will be considered in the assessment. See Table 2 for a description of the PICOS strategy.

In addition, any other issues identified relating to equity, implementation or the acceptability of the technology that should be considered as part of the TA must be clearly described.

The TA Scope should be drafted with input from relevant clinical and methodological experts. The findings presented in the Technical Review Report and interpretation of the evidence will form the basis for any additional analyses requested for Stage 2 of the TA (if any).

The Lead Reviewer/s assigned to the TA is responsible for finalising the TA Scope in consultation with EDP staff, before it is sent to NEMLC for final approval. It is advisable to gain input from relevant stakeholders as part of the finalisation of the TA Scope to ensure all relevant review questions are included and will be addressed by the TA. The final TA Scope will frame the focus and content of the Technical Review Report, and any additional analyses that may be required.

Once the TA Scope has been approved by NEMLC, the Lead Reviewer and the EDP agrees the anticipated time frame for completing the TA.

Table 2. PICOS approach to technology appraisal scope development

Criteria	Details
Population	• Patient population who will be eligible to receive the health technology being assessed. Include specifics on condition/disease, age, sex, comorbidities, and subgroups.
Intervention	• Technology being assessed and its place in the current care pathway • Will it replace current treatment or be an add-on therapy? • Include specifics of dose, duration, delivery mode, co-intervention/s, setting (e.g. inpatient/ outpatient)
Comparison	• Current standard of care and currently available for use in South African public health sector • Should be the treatment most clinicians will replace with the technology being assessed, or the treatment most prescribed currently for the management of the disease/condition. • Can be active treatment or placebo • Include specifics of dose, duration, mode of delivery
Outcomes	• Identify principal measures for clinical effectiveness for population of interest and with consideration of place in care pathway/stage of disease. • Include both clinical and safety outcomes • Specify primary and secondary outcomes (including survival, disease progression and health-related quality of life) • Define time horizon – time it takes to demonstrate the identified outcomes (may vary for clinical and economic outcomes). • If applicable, identify feasibility, acceptability, and cost-effectiveness outcome data
Likely study designs or data sources to be included	• Systematic reviews • Clinical practice guidelines and health technology assessments • Primary studies (order of preference: randomised controlled trials, observational studies, case series)

3. ASSESSMENT

This Guide can be used to conduct a TA for (a) a single technology with a single indication, or (b) a group of technologies in the same class assessed for use in a single indication. Lead Reviewer/s appointed by the relevant ERC will be responsible for overseeing the TA. The Lead Reviewer might conduct the analysis themselves or coordinate the evidence production (or parts thereof) commissioned from Contracted External Reviewer/s (CER/s).

It is essential that the evidence utilised to inform health technology recommendations are transparent, relevant and of the highest standard. This section sets out the methods of evidence syntheses to assess the clinical and economic impact of a technology, as well as the relevant equity, feasibility, and social value considerations. These formal methods aim to standardise the approach to TAs and ensure a rigorous product is used to inform healthcare decisions in the best interests of people in South Africa.

Stage 1 of the assessment stage involves the production of the Technical Review Report. A Technical Review will be conducted for all TAs and will in most cases be sufficient to inform a decision regarding the inclusion or exclusion of the medicine to the EML. If the Technical Review is not sufficient, additional analysis should be considered (Stage 2). In some instances, additional analysis may not reduce the uncertainty associated with the decision to list the medicine on the EML, so careful consideration should be given to the value of any additional analysis conducted.

3.1 Stage 1: Technical Review Report

The TA Scope will specify the population, intervention, comparators, outcomes, and study designs that will be used to guide the conduct of the TA and production of the Technical Review Report.

The Technical Review Report will contain technology details, a description of the review question/s, a review and appraisal of the clinical evidence, pharmaceutical costs, a summary of other HTA agency decisions (if relevant), equity considerations, social values considerations, and feasibility considerations.

This section aims to provide a standardised approach to the production of the Technical Review Report. Reporting should be aligned to the Technical Review Report template.

3.1.1 CLINICAL EVIDENCE

The objective of the clinical evidence assessment is to identify and synthesise clinical evidence (benefits and harms) relevant to the PICOS review question. The proposed methods has been adapted from guidance issued by the Cochrane Rapid Review Methods Group (7).

The clinical evidence presented in the Technical Review Report will build on existing evidence syntheses whenever possible, with data from primary studies only selected for appraisal and reporting if high quality, recent SRs are not available. Depending on the urgency of the decision, the Technical Review Report may be compiled as a Brief or Standard Report. The two report types have different timelines and resource requirements for production. It is estimated that the Brief Technical Review will require one reviewer [full-time] over 1-2 weeks, while the Standard Technical Review will require two or more reviewers [part-time] over 3-4 weeks. The main differences in the Brief and Standard Technical Reviews are presented in Table 3.

3.1.1.1 Search strategy

A systematic search of scientific databases should be conducted to identify all relevant literature that should be included in the clinical assessment of the technology. In addition, grey literature searches should be conducted to identify any relevant CPGs, HTA and policies.

Systematic literature search

The TA Scope should be used to inform an explicit search strategy. An information specialist or experienced reviewer should be involved in determining the search strategy to ensure it meets acceptable methodological standards (for Brief Technical Reports, only if time and resources allow). The *PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement* includes a checklist that can be used to guide and evaluate electronic search strategies (9).

The search strategy should be as comprehensive as possible and consist of the following elements:

- Search terms (derived from population and intervention components of the review question)
- Limits applied to the search
  - Time period covered by the search - with a clinical or methodological justification for any restriction (for brief reports, consider applying more restrictive date limitations based on the breath of literature)
  - Study design (stepwise approach to study design inclusion: SRs (and CPGs for Standard Technical Reviews) ⇨ controlled trials ⇨ observational studies
  - Language (English language only)
- Databases searched
  - Rapid assessments: only search Medline (via PubMed) and Epistemonikos
  - Standard assessments: Medline (via PubMed), Cochrane CENTRAL, Embase (if available access), Epistemonikos and other topic-specific databases (e.g. PsycInfo, CINAHL) identified by an information specialist or experienced reviewer.

Table 3. Methods for producing Brief versus Standard Technical Reports

	Brief Technical Review	Standard Technical Review
Timeframe	1-2 weeks (1 x full-time reviewer)	3-4 weeks (2/more part-time reviewers)
Study design eligibility	• Emphasis on SRs • Stepwise approach to study design inclusion: SR ⇨controlled trials ⇨ observational studies	• Emphasis on SRs • Stepwise approach to study design inclusion: SR ⇨controlled trials ⇨ observational studies • Clinical Practice Guidelines (CPGs)
Search strategy	• Use explicit search strategy • Search strategy determined by Lead Reviewer • Restrictive date limitations (with a clinical or methodological justification) • Limited number of databases searched • English language only	• Use explicit search strategy • Involve information specialist when developing search strategy • No/less restrictive date limitations (with a clinical or methodological justification provided if restrictions applied) • More sources (more databases, wider search of grey literature) • English language only
Selection of evidence for inclusion	• Title and abstract screening – single (duplicate if possible) • Full text screening – single (duplicate if possible)	• Title and abstract screening – duplicate • Full text screening – duplicate
Data extraction	• This may be done by one reviewer, checked by a second reviewer	• This may be done by one reviewer, checked by a second reviewer
Appraisal of clinical evidence presented	• Critical appraisal (SRs only)	• Critical appraisal (SRs and CPGs only)
Evidence synthesis	• Synthesise evidence from systematic reviews narratively, if available. • If no high quality, recent SR available, summarise controlled clinical trials narratively.	• Synthesise evidence from systematic reviews narratively, if available. • If no high quality, recent SR available, summarise controlled clinical trials narratively. • Extract relevant information from published clinical practice guidelines and summarise narratively.
Key findings and recommendations	• Cautious interpretation required • Draft key findings and recommendations	• Cautious interpretation required • Draft key findings and recommendations

CPG – clinical practice guideline, SR – systematic review

<u>Grey literature search</u>

A grey literature search should be conducted as part of a Standard Technical Review to identify CPGs or other guidance documents. Sources searched should include websites of organisations that produce and/or publish CPGs and health product regulatory bodies. See a list of potential sources listed in Table 4.

There is currently no central repository for South African CPGs, so local guidelines and policies need to be identified through the use of search engines like 'Google' and through searches of governmental and professional society websites.

Table 4. Official websites to include in grey literature search

Name	Country	Website
CLINICAL PRACTICE GUIDELINES		
World Health Organization (WHO)	Multinational	www.who.int/publications/guidelines/en/
Guidelines International Network (GIN)	Multinational	www.g-i-n.net
National Institute for Health Care Excellence (NICE)	England and Wales	www.nice.org.uk/guidance
Scottish Intercollegiate Guidelines Network (SIGN)	Scotland	www.sign.ac.uk
National Guideline Clearinghouse	United States of America	www.guideline.gov
Irish National Clinical Guidelines (supported by National Patient Safety Office)	Ireland	http://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/
Clinical Practice Guidelines Portal	Australia	www.clinicalguidelines.gov.au/portal
HEALTH PRODUCT REGULATORY BODIES		
European Medicines Agency (EMA)	European Union	https://www.ema.europa.eu/en
European Commission	European Union	https://ec.europa.eu/health/home_en
US Food and Drug Administration (FDA)	United States of America	https://www.fda.gov

3.1.1.2 Selection of evidence

Each study or guidance document must be assessed against pre-specified eligibility criteria.

For database searches, follow a stepwise approach to study design inclusion:

1. SRs of trials (plus CPGs for Standard Technical Reviews)
2. Where SR not available, seek randomised controlled trials (RCT) in patients
3. Where RCTs not available, seek non-randomised controlled studies
4. Where none of the above are available, single arm cohorts, case series may be reported

The results of database searches should be presented graphically in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (10). Title and abstract, as well as full-text screening of retrieved records should be done in duplicate for Standard Technical Reviews, and for Brief Technical Reviews whenever possible (otherwise a single reviewer).

For grey literature searches (as part of a Standard Technical Review): Relevant CPGs are identified through the assessment of individual recommendations made in a CPG and comparing its eligibility to the TA's PICOS. The identification and selection of HTAs and CPGs can be conducted by a single reviewer.

3.1.1.3 Data extraction

One reviewer can extract the relevant data from the selected publications and/ CPGs, after which the accuracy and completeness of the extracted data should be checked by a second reviewer.

Data fields to extract from SRs (and primary studies if no appropriate SR is identified) include the following:

- Study design (including methods, location, sites, groups)
- Participant characteristics (specify any relevant subgroups)
- Intervention characteristics (specify details including healthcare setting / level of care)

- Comparator characteristics
- Outcomes assessed
- Analysis conducted
- Numerical data for outcomes of interest (should include if it is non-inferior or superior to the comparator, the effect size, confidence intervals and statistical p-value).

For a Standard Technical Review Report, any useful information (e.g. recommendations on the use of the technology) must be extracted from the selected CPGs.

3.1.1.4 Appraisal of evidence

Only SRs and CPGs should be critically appraised. A single reviewer can rate the risk of bias for the included evidence, with full confirmation of all judgements (and support statements) by a second reviewer.

- For systematic reviews: Use the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) checklist (11), which can be found at https://amstar.ca/Amstar_Checklist.php
- For CPGs: Use the Appraisal of Guidelines and Research and Evaluation (AGREE) II tool (12), which can be found at https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf .

If no appropriate SR is found, the findings from primary studies will be summarised narratively in the Technical Review Report. A critical appraisal of primary studies will be subject to available resources and time limitations. If primary studies are appraised, relevant tools should be used:

- For randomised controlled trials: Assess risk of bias using the standard Cochrane risk of bias assessment tool 2.0 (13), which considers random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias (https://training.cochrane.org/handbook/current/chapter-08), or another standard tool. Where possible, develop graphic representations of potential bias within and across studies using RevMan 5.3.5 or other software.
- For non-randomised studies: Use relevant tools, e.g. CEBM Oxford appraisal tools (14) (https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools), or report narratively.

3.1.1.5 Evidence syntheses

Systematic reviews: The results of included SRs will be presented as a narrative synthesis. Outcomes measured and the measures of effect (with p-values and confidence intervals) should be compared across studies and presented in summary tables along with a description of the methodological quality of the study.

Primary studies: If no acceptable SRs are available, primary studies will be summarised narratively. If time and resources allow, a narrative synthesis and critical appraisal may be undertaken. If the included studies are sufficiently homogeneous in terms of design, population, interventions and comparators, and reporting the same outcome measures, the reviewer may choose to undertake a meta-analysis, but this is not required for Stage 1 analysis. The results for clinically homogeneous studies will be meta-analysed using RevMan (Review Manager). Meta-analyses should be conducted using the inverse variance method. A random effect model should be used. Separate meta-analyses can be presented for specific populations or interventions if statistically significant heterogeneity is explained by some of these, or if a convincing subgroup effect is found.

Clinical practice guidelines (for Standard Technical Reviews only): Relevant recommendations in selected CPGs will be summarised narratively with all the relevant recommendations from the CPGs presented in a table. If a systematic review was conducted as part of the CPG development process, and detailed methods and results of the SR are available, it should be noted under the CPG section with the SR results presented alongside other included SRs. These SRs should be included in the PRISMA diagram under 'additional record identified through other sources'.

Information on adverse drug reactions listed in the medicine's Prescribing Information (PI) approved by South African Health Products Regulatory Agency (SAHPRA) (15) should be reviewed and included if not assessed adequately in the included clinical evidence.

3.1.1.6 Interpretation of clinical effectiveness and safety evidence

The Lead reviewer and the review team should present the conclusions supporting clinical superiority, similarity, non-inferiority or equivalence of the technology compared to the comparator/s assessed. They should then draft recommendations for the use of the technology indicating the strength of evidence that underpin the recommendations. Currently, NEMLC has endorsed the adoption of the Strength of Recommendation Taxonomy [SORT] system (16) to describe the strength of the evidence used. Related evidence grading systems, such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) may also be used (17).

3.1.2 ECONOMIC EVIDENCE

3.1.2.1 Pharmaceutical costs

A comparison of the pharmaceutical costs of the intervention and comparator/s is presented in the Technical Review Report. These costs reflect the cost to the pharmaceutical budget; if further analysis is required related to non-pharmaceutical costs, additional analysis can be commissioned as part of Stage 2 of the TA. If significant additional costs are expected (e.g. for companion diagnostics), this should be noted to inform commissioning of Additional Analysis (Stage Two).

Pharmaceutical prices for intervention, comparator, and co-administered technologies must be sourced from the latest Master Health Product List with the contract number and item number referenced for each technology. If a medicine is not listed in the Master Health Product List but a Single Exit Price (SEP) is available for the medicine (private sector price) then the SEP hould be used to represent the price of the medicine, even though a reduction in price may be possible with public sector tenders and exemption from the SEP regulations. If the SEP is used, the medicine's National Pharmaceutical Product Index (NAPPI) code as well as the SEP publication year should be referenced for each medicine. The Medicine Price Registry (MPR) details the SEPs and can be found at https://medicineprices.org.za. A consistent year of analysis should be used. If a medicine is not currently available in any market in South Africa, a Pricing Analysis (Stage 2 analysis) could be requested if there is significant uncertainty about the price range that might be expected in the South African public sector.

The average dose of medicines should be based on the recommended dose from the SAHPRA approved Prescribing Information (PI). When dosing is not uniform (e.g. it is based on weight, severity of disease), appropriate averages and/or ranges must be obtained from a literature search. Real-world drug use information can be used if available (e.g. drug utilisation data). Drug wastage (e.g. vial that cannot be stored once it has been opened) should be accounted for in the calculations.

Medicine costs should be presented as an average cost per patient per day. In addition, costs for the chronic management of conditions (e.g. diabetes) should be represented over the course of a year, while costs for acute (e.g. antibiotics) or short-term changes in treatment (e.g. due to pregnancy) presented for the average length of a course of treatment. If treatment regimens vary over time (e.g.

tuberculosis or antiretroviral treatment), the disaggregated costs for the relevant time periods should be presented.

Table 5 can be adapted to report the drug acquisition costs. If the technology being assessed is co-administered with another pharmaceutical, the prices for the individual medicines as well as for the treatment regime should be calculated and reported. For each input the source should also be reported.

Table 5. Acquisition costs of the intervention and comparator technologies

	Intervention	Source	Comparator	Source
Pharmaceutical formulation	*e.g. Tablet*	*SAHPRA PI*		
Method of administration	*e.g. Oral*	*SAHPRA PI*		
Average dose/s and dosing schedule/s	*e.g. 10mg tablet once a day*			
Average daily dose	*e.g. 10mg*			
Dose adjustments	*n/a*			
Acquisition cost for smallest available pack size	*e.g. R25 for 30 x 10mg tablets*	*Master Health Product List **		
Cost of one dosing unit	*e.g. R25÷30=R0.83*			
Cost of treatment for one day	*R0.83*			
Average length of a course of treatment	*One year (chronic treatment)*			
Cost of a course of treatment	*R300*			
(Anticipated) average interval between courses of treatment	*n/a*			
(Anticipated) number of repeat courses of treatment	*n/a*			

Table adapted from the NICE cost-comparison submission template (15)

* Source from the latest Master Health Product List, with the contract number and item number referenced for each medicine.

3.1.2.2 Summary of Health Technology Assessment (HTA) agency decisions

Technology use and/or reimbursement recommendations based on published technology appraisals by reputed HTA agencies should be summarised narratively with an overview of the recommendations presented in a table. It is not necessary at this stage to provide a full description of the analytical approach taken by different HTA agencies, but a simple tabulation of decisions made by HTA agencies internationally will help avoid duplication and inform statements regarding a technology's expected cost-effectiveness. A list of HTA agencies that publish their HTA decisions are listed in Table 6.

Table 6. Official websites of recommended HTA agencies

Name	Country	Website
National Institute for Health Care Excellence (NICE)	England and Wales	https://www.nice.org.uk/guidance/published?type=ta
Canadian Agency for Drugs and Technologies in Health (CADTH)	Canada	https://www.cadth.ca/reimbursement-review-reports
Scottish Medicines Consortium (SMC)	Scotland	https://www.scottishmedicines.org.uk/medicines-advice/
Australian Government Department of Health	Australia	https://www1.health.gov.au/internet/hta/publishing.nsf/Content/home-1
Health Intervention and Technology Assessment Program (HITAP)	Thailand	https://www.hitap.net
European network for Health Technology Assessment (EUnetHTA)	Europe	https://eunethta.eu/rapid-reas/
International HTA Database	Multinational	https://database.inahta.org/

3.1.3 EQUITY CONSIDERATIONS

An equity impact statement must be included in the Technical Review Report. The statement should indicate the potential impact on equity in health for marginalised groups as a result of listing the technology on the EML.

The Guidance for Priority Setting in Health Care (GPS-Health) framework (18), initiated by the World Health Organisation (WHO), provides a map of equity criteria relevant to healthcare allocation decisions, and can be used as a guide when considering the potential equity impact of an intervention. GPS-Health includes equity considerations related to the disease and intervention, characteristics of the intervention population, other social and financial effects. See Table 7 for an overview of the criteria and relevant equity questions.

Table 7. Equity criteria to be considered when making healthcare allocation decisions

Criteria		Questions
Disease and intervention criteria	Severity of condition or disease	Have you considered whether the intervention has special value because of the severity of the health condition (present and future health gap) that the intervention targets?
	Realisation of potential	Have you considered whether the intervention has more value than the effect size alone suggests on the grounds that it does the best possible for a patient group for whom restoration to full health is not possible?
	Populations with past health loss	Have you considered whether the intervention has special value because it targets a group that has suffered significant past health loss (e.g. chronic disability)?
Criteria related to characteristics of social groups	Socioeconomic status	Have you considered whether the intervention has special value because it can reduce disparities in health associated with unfair inequalities in wealth, income or level of education?
	Geographical disparities	Have you considered whether the intervention has special value because it can reduce disparities in health associated with area of living?
	Age and gender	Have you considered whether the intervention will reduce disparities in health associated with age or gender?
	Race, ethnicity, religion and sexual orientation	Have you considered whether the intervention may disproportionally affect groups characterized by race, ethnicity, religion, and sexual orientation?
Criteria related to protection against the social and financial effects of ill health	Economic productivity	Have you considered whether the intervention has special value because it enhances welfare to the individual and society by protecting the target population's productivity?
	Care for others	Have you considered whether the intervention has special value because it enhances welfare by protecting the target population's ability to take care of others?
	Catastrophic health expenditures	Have you considered whether the intervention has special value because it reduces catastrophic health expenditures for the target population?

Norheim et al (18)

The equity impact statements can be supported by expert opinion when published research evidence is missing or inadequate. Experts include clinicians, patients, patient group representatives, economists, or others who may have contextual information or insight on the health condition or technology of interest.

The equity considerations can be analysed in a matrix to assess the potential impact of implementing or not implementing a technology (see Table 8).

Table 8. Equity considerations matrix

Equity criteria	Benefits when proceeding with implementation	Adverse consequences when proceeding	Benefits when refraining from implementation	Adverse consequences when refraining
Severity of condition or disease				
Realisation of potential				
Populations with past health loss				
Socioeconomic status				
Geographical disparities				
Age and gender				
Race, ethnicity, religion and sexual orientation				
Economic productivity				
Care for others				
Catastrophic health expenditures				

3.1.4 SOCIAL VALUE CONSIDERATIONS

A description of stakeholder preferences and value considerations should be presented in the Technical Review Report. Social, cultural, religious and other factors will affect a stakeholder's views and the likelihood that they will find the technology acceptable.

The reviewer should consider the relative importance of the intervention and other issues identified to all or most stakeholders (including how much variability there are amongst stakeholders). An overview of some of the potential considerations are presented Table 9. Questions listed in Table 9 and Table 11 were informed by sections in the EUnetHTA HTA Core Model 3.0 (19).

Table 9. Social value considerations

Type of consideration	Description	Questions
Relevance	An assessment of whether – and how well – a technology is addressing an unmet need.	• What expectations and wishes do patients have with regard to the technology and what do they expect to gain from the technology? • Are there groups of patients who currently don't have good access to available therapies? • Is there important uncertainty or variability about how much people value the treatment options for this disease/condition?
Cultural and social considerations	An assessment of how acceptable the intervention will be to key stakeholders. Will be based on the risks and benefits posed to the different groups, as well as their specific values, expectations and preferences	• What are the benefits and harms of the technology for patients? • Is the technology likely to have any hidden or unintended consequences for patients? • What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.? • Any specific burden on caregivers? • Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles? • Does the implementation or use of the technology affect human dignity, or the patient's moral, religious or cultural integrity? • Are there factors that could prevent a group or person from gaining access to the technology (e.g. access to a certain type of facility)?

Some questions adapted from EUnetHTA HTA Core Model 3.0 (19)

The social value statements can be supported by expect opinion when published research evidence is missing or inadequate. Experts include clinicians, patients, patient group representatives, health care administrators or others who may have contextual information or insight on the health condition and health system operations.

The social value considerations can be analysed in a matrix to assess the potential impact of implementing or not implementing a technology across all relevant stakeholder (see Table 10). This will help identify the areas where values might differ between stakeholders.

Table 10. Social value considerations matrix by stakeholder group

Stakeholder	Benefits when proceeding with implementation	Adverse consequences when proceeding	Benefits when refraining from implementation	Adverse consequences when refraining
Patient				
Family and important others				
Health care providers				
Heads of Pharmaceutical Services (HOPS)				
Pharmaceutical and Therapeutics Committees				
National Programmes				
Society				
Others				

3.1.5 FEASIBILITY CONSIDERATIONS

A description of feasibility considerations should be presented in the Technical Review Report. An overview of some of the potential considerations are presented Table 11.

Table 11. Feasibility considerations

Type of consideration	Description	Questions
Economic considerations	An assessment of the viability of a technology	Are there significant pharmaceutical and/or health system budget impacts associated with implementing the technology, e.g. set-up costs?
Operational feasibility	Consider the ways in which different kinds of resources need to be mobilised and organised when implementing a technology and the consequences this may produce in the organisation and the health care system as a whole. Also consider the availability of resources and expertise to implement and maintain use of the technology.	How does implementation or withdrawal of the technology affect the distribution and use of health care resources? How will this technology affect health care staff capacity? Does implementation of the technology require a higher level of expertise than current treatments? Training requirements for staff implementing the intervention? Does use of this technology modify the need for other technology? Any other interventions/equipment required to deliver the intervention? What patient/participant flow is associated with the new technology? How will the technology affect the current work processes? Will it be easy to incorporate into current processes? How long will it take to incorporate the technology into the care process? Are there special supply chain considerations for the technology? Is the monitoring system of the technology organised to ensure it is adopted into practice in an appropriate and efficient manner? In what way is the quality assurance of the technology organised?
Legal feasibility	Assessment of how well the solution can be implemented within existing legal and contractual obligations.	Are there any regulatory concerns regarding the technology? Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations? Does the implementation or use of the technology affect the realisation of basic human rights?

Adapted from EUnetHTA HTA Core Model 3.0 (19)

The feasibility statements can be supported by expect opinion when published research evidence is missing or inadequate. Experts include clinicians, patients, patient group representatives, health care administrators or others who may have contextual information or insight on the health condition and health system operations.

The feasibility considerations can be analysed in a matrix to assess the potential impact of implementing or not implementing a technology (see Table 12).

Table 12. Feasibility considerations matrix

	Benefits when proceeding with implementation	**Adverse consequences when proceeding**	**Benefits when refraining from implementation**	**Adverse consequences when refraining**
Economic considerations				
Operational feasibility				
Legal feasibility				

3.1.6 RECOMMENDATIONS

The Lead reviewer and the review team should draft the key findings and recommendations based on the evidence presented in the Technical Review Report.

Technical Reviews should be reported using the Technical Review Report template, with draft recommendations presented in the Evidence to Decision Framework (EtDF).

The Technical Review Report will be appraised by the relevant ERC, after which the ERC will adjust the EtDF to reflect their deliberations and present the Technical Review Report with final recommendations for approval by NEMLC.

3.2 Stage 2: Additional analysis

3.2.1 SYSTEMATIC REVIEW

Some clinical research questions are best addressed through an up-to-date, systematic review (SR) of published, peer reviewed literature. A well-conducted SR can be a time-consuming and resource-intensive process due to the rigorous methods applied to ensure bias is minimised, but it is considered the most trustworthy and objective view of the available literature in a particular topic area and the best estimate of an intervention's effects.

If a formal SR of the clinical evidence for a technology is required, it should be commissioned from reputable research unit with researchers experienced in conducting systematic reviews. Standards for conducting and reporting SRs have been published by multiple research organisations, including the Cochrane Collaboration (20) and the Center for Reviews and Dissemination (CRD) (21).

Rapid reviews (RRs) are used frequently to quickly collate and present relevant evidence to inform healthcare decisions. The Cochrane Rapid Reviews Methods Group (RRMG) has been established to help inform rapid review methodology, and has produced an evidence-informed guidance document for conducting rapid reviews (7). The approach to identifying, assessing and synthesising clinical data for the EDP Technical Reviews (described in the previous section) is based on this guidance. In cases where the clinical assessment presented in a Technical Review Report is not sufficient, but a SR is considered excessive, a RR (conducted according to the Cochrane guidance for rapid reviews) can be commissioned from reputable research unit with researchers experienced in conducting rapid or systematic reviews.

The general comparison by Kangura et al (21) of the differences between SRs and RRs are presented in Table 13.

Table 13. General comparison of rapid review versus systematic review approaches

	Rapid Review	**Systematic Review**
Timeframe	<5 weeks	6 months to 2 years
Question	Question specified a priori (may include broad PICOS)	Often a focused clinical question (focused PICOS)
Sources and searches	Sources may be limited but sources/strategies made explicit	Comprehensive sources searched and explicit strategies
Selection	Criterion-based; uniformly applied	Criterion-based
Appraisal	Rigorous; critical appraisal (SRs only)	Rigorous; critical appraisal
Synthesis	Descriptive summary/categorization of the data	Qualitative summary +/- meta-analysis
Inferences	Limited/cautious interpretation of the findings	Evidence-based

Kangura et al (21)

PICOS – population, intervention, comparator, outcomes, study designs

Guidance documents by Cochrane and CRD can be used for methods for conducting SRs (20,21) or RRs (7). Methods should be transparent with limitations clearly noted.

3.2.2 COST-COMPARISON ANALYSIS

This section describes the approach to conducting a cost-comparison analysis as one element of Stage 2 analysis within the EDP HTA process[2].

A cost-comparison analysis is an analytical technique that details the per-patient net difference in costs between intervention(s) and comparator(s) associated with implementation in the local health system. A cost-comparison analysis can be conducted with reasonably limited analytical resources and is commonly used when there is reasonable certainty that intervention(s) offer a similar or greater health benefit than the comparator.

Cost-comparison analysis has many similar components as cost-effectiveness analysis (CEA) and budget impact analysis (BIA). A critical difference between cost-comparison analysis and CEA is that cost-comparison analysis does not incorporate any health outcomes as it reports differences in costs only. If there is significant uncertainty about the differences in clinical outcomes between the intervention and its comparator, a Basic or Comprehensive CEA (see cost-effectiveness analysis section) should be chosen for Stage 2 analysis rather than a cost-comparison analysis.

The difference between a cost-comparison analysis and a BIA is that a BIA represents a summative total cost to the health budget (and other budget perspectives such as the pharmaceutical budget) over various implementation scenarios, while cost-comparison will generally represent the expected per patient difference in costs. See BIA section for further guidance on the specifications on the conduct of a BIA.

This section describes an approach to conducting a cost-comparison analysis, and includes guidance on how to identify, estimate and interpret the healthcare costs associated with an intervention. The approach to estimating pharmaceutical costs are described in the methods for developing the Technical Review Report and not repeated here. It is critically important that the principles of conducting a cost-comparison is aligned to the principles used when producing the Technical Review Report, or conducing a CEA or a BIA, within the EDP HTA process.

3.2.2.1 Considerations for conducting cost-comparison analysis

Table 14 provides an overview of factors that needs to be considered when conducting a cost-comparison analysis to allow appropriate quantification of resource use of a technology and its comparators.

[2] The concept of cost-comparison analysis presented here builds on recent methodological developments to advance pragmatic analytical approaches at HTA Agencies globally, in particular at the National Institute for Health and Care Excellence, (NICE), UK.

Table 14. Considerations for conducting cost-comparison analysis

Component	Methods requirement
Comparator	Existing practice within the South African public health sector (can be multiple where variation in practice exist). (ensure chosen comparator(s) aligns with Technical Review)
Costs represented	Drug acquisition costs Drug administration and monitoring costs Costs of additional associated interventions (such as companion diagnostics) Cost of healthcare appointments Costs of management of adverse events
Time horizon	Must be sufficient to capture clinically significant cost differences between the intervention and comparator (including cost of treatment and cost of managing adverse events). A lifetime time horizon is required if the technology has an impact on overall survival or provide clinically meaningful benefits to patients for the rest of their lives**.**
Uncertainty	One-way sensitivity analysis with representation of a "extreme" clinically relevant scenario and a "conservative" clinically relevant scenario
Perspective	Health system perspective. Technologies listed on the EML is provided to patients without cost.
Health outcomes	Not required

3.2.2.2 Identifying and estimating costs

Only direct healthcare costs should be included in the cost-comparison analysis. This includes:

1. Acquisition cost of pharmaceutical treatment and additional associated interventions (e.g. companion diagnostics)
2. Healthcare resource use and associated costs (e.g. drug administration and monitoring costs)
3. Costs of management of adverse events
4. Cost or cost savings incurred to the public health sector budget not captured elsewhere

Sources for all costs should be reported and justified. The total cost of each type of resource is calculated by multiplying the quantity of resources by their unit cost. The quantity of resource use should be calculated based on the technology's approved SAHPRA indication, and with consideration of the setting in which it will be implemented. The STGs or other NDoH clinical guidelines (if available) should be used to determine normative utilisation estimates for parameters such as frequency of administration and duration of treatment. If the quantity of resources used needs to be sourced from published literature or expert opinion, the methods used to identify and select the evidence should be reported.

Cost data should be obtained from most recent validated official South African data sources wherever possible (see Table 15). If costs need to be sourced from published literature, the methods used to identify and select those publications should be described. Costs from previous years or reported for a different country should be adjusted to reflect the costs in the year of assessment and South Africa, with an explanation of the methods used to adjust the costs provided.

The different types of costs must be presented in disaggregated form, with all steps taken to calculate the overall costs clearly described. This includes estimating the quantity of the inputs, criteria for allocating shared costs, and any costs excluded.

The quantity and cost of resources should be presented for: one day of treatment, a course/cycle of treatment, and for the specified time horizon. The course length of a year should be used for

technologies that manage chronic conditions (e.g. diabetes), and the average length of a course of treatment for acute treatment (e.g. antibiotics) or short-term changes in treatment (e.g. due to pregnancy). If resource use varies over time (e.g. tuberculosis or antiretroviral treatment), the disaggregated costs for the relevant time periods should be presented.

Table 15. Data sources for cost-comparison analysis

Type of cost	Source	Weblink
Price of the technology	Master Health Product List – include contract number and item number in reference	http://www.health.gov.za/tenders/
	Single Exit Price (SEP)* – include NAPPI code as well as SEP publication year in reference	https://medicineprices.org.za
Laboratory tests and investigations	National Health Laboratory Service (NHLS)	NHLS price list for most recent year should be requested from the EDP secretariat.
Health care utilisation	District Health Barometer	https://www.hst.org.za/publications/Pages/HSTDistrictHealthBarometer.aspx
	Standard Treatment Guidelines	https://www.idealhealthfacility.org.za
	National Department of Health Programme Guidelines	http://www.health.gov.za

*Use only if the technology is a medicine that is not listed in the Master Health Product List.

a) Acquisition cost of the technology

The approach to comparing acquisition costs for the intervention/s and comparator/s is presented in the pharmaceutical costs section in the Technical Review Report. This reflects the cost to the pharmaceutical budget, but not the wider health sector costs. The cost for a course of treatment will be presented in the Technical Review Report, but for the cost-comparison analysis, the costs over the assessment time horizon should also be calculated and reported. The acquisition costs should be updated if more than 3 months after Technical Review Report date, or if the cost-comparison analysis is conducted in a new calendar year.

b) Healthcare resource use and associated costs

The healthcare resource costs associated with administering and monitoring the technology should be reported separately and be compared between the intervention and comparator technologies. Relevant healthcare resources to report include:

- Any specific/additional health technologies required to administer the technology under review
  - The lifespan of the additional technologies (e.g. delivery devices) should be taken into account when calculating the quantity of the resource required.
  - e.g. diagnostic tests, drug delivery devices like insulin pens, nebulisers, tests determining the drug dose.
- Health professional resource (type and duration) required to administer the technology under review
  - Take into account the level of care
  - e.g. infusions require physicians and/or non-physicians time in inpatient/outpatient setting
- Any specific monitoring tests or investigations required associated with the technology under review
  - e.g. INR when warfarin is used
- Health professional resource (type and duration) required to monitor the technology under review
  - e.g. more regular clinic check-ups required to monitor response to medicines

Only differences in cost incurred as a result of implementation of a particular technology should be reported. Resource use and costs associated with the routine management of the condition/disease should not be reported unless if it changes based on the technology administered.

The total cost of healthcare resource costs should be calculated per day, per course of treatment for the full time horizon. Table 16 can be adapted to present the healthcare resources associated with the intervention and comparator technologies.

Table 16. Healthcare resource costs of the intervention and comparator technologies

	Intervention	Source and justification	Comparator	Source and justification
Resource 1				
Unit cost				
Number of units per course of treatment				
Total cost of Resource 1:				
Per day				
Per course of treatment				
Over full time horizon				
Resource 2				
Unit cost				
Units per course of treatment				
Total cost of Resource 2:				
Per day				
Per course of treatment				
Over full time horizon				
Add more rows, as needed				

Adapted from the NICE cost-comparison submission template (15)

c) Costs of management of adverse events

The resource use and costs associated with the management of adverse reactions to the technologies should be compared between the intervention and comparator technologies.

For each type of adverse event, the costs associated with its management (e.g. medicines used, clinic/hospital appointments, inpatient care) should be reported separately, with each input clearly referenced. The total cost of each adverse reaction per course of treatment should then be calculated for each technology, as well as the total cost of adverse reactions over the full time horizon.

Table 17 can be adapted to present the healthcare resources associated with the intervention and comparator technologies.

Table 17. Adverse events resource costs of the intervention and comparator technologies

	Intervention	Source and justification	Comparator	Source and justification
ADVERSE EVENT 1				
Resource 1				
Unit cost				
Number of units per course of treatment				
Total cost of Resource 1:				
Per day				
Per course of treatment				
Over full time horizon				
Resource 2				
Unit cost				
Units per course of treatment				
Total cost of Resource 2:				
Per day				
Per course of treatment				
Over full time horizon				
Add more rows, as needed				

Adapted from the NICE cost-comparison submission template (15)

d) Cost or cost savings not captured elsewhere

Any other costs or savings to the health system not captured elsewhere should be tabulated in a similar format suggested above. This can include significant changes in infrastructure required to implement a technology, such as cost savings resulting from changes to the clinical care pathway.

3.2.2.3 Summary of costs

An overview of the costs should be reported using Table 18 and aligned to the Cost-comparison Analysis Template. If possible, clinical experts assigned by the EDP should assess the cost and healthcare resource use values reported prior to appraisal by the ERC.

Table 18. Total costs associated with the intervention and comparator technologies *[insert time period over which costs are represented]*

	Intervention	Comparator	Add more rows/columns, as needed
Acquisition costs			
Health resource costs			
Adverse event costs			
Other costs			
Total costs			
State the time horizon			

3.2.2.4 Sensitivity analysis

Any uncertainties in the resource quantity and cost inputs should be presented. The impact of these inputs should then be tested by varying the inputs in an “extreme” clinically relevant scenario and a “conservative” clinically relevant scenario.

3.2.2.5 Subgroup analysis

A subgroup analysis should be conducted if specified in TA Scope and supported by the relevant clinical evidence.

3.2.2.6 Interpretation of the cost-comparison analysis

The general interpretation of the cost-comparison analysis is that if the net costs for the intervention are greater than the costs associated with the comparator, the intervention is unlikely to represent good value for money in the public health sector, as limited additional clinical benefit has already been established. If the net costs of the intervention are less than the comparator then the intervention is likely to be cost saving and may represent a good investment.

3.2.3 BUDGET IMPACT ANALYSIS

A budget impact analysis (BIA) provides information about the estimated financial consequences of introducing a new technology to the health system. It reflects an estimated cost for the eligible population over a specified time period, for both the existing context (status quo scenario) and the new proposed scenarios (implementation scenarios), as well as the incremental cost between the status quo scenario and each implementation scenario. The analysis differs from CEA as it is principally concerned with financial implications over time, while a CEA measures costs relative to effects (incorporating quality of life and mortality effects). The information provided by a BIA is complementary to CEA results, as the budget impact of the proposed new technology is a vital consideration for decision-makers in addition to cost-effectiveness. In addition, BIA results are likely to be an useful aid to implementation and post-decision budget planning and preparation purposes.

3.2.3.1 Analytical framework

A critical consideration for the use of BIA in decision-making is that the methodology used is consistent and in a form that can be easily interpreted by decision-makers. The analytical framework detailed below draws on existing BIA methods used internationally (22–25) and provides clear directions on how a BIA should be conducted and reported when estimating the financial impact of selection (or deselection) of technologies on South Africa's EML. This framework underpins the approach and calculations in the EDP HTA process which is flexible and expandable based on the particular analytical needs. The BIA should be conducted within the Budget Impact Analysis Template.

a) Perspective

The BIA should be conducted from the national public sector payer perspective and should represent two different budget constraints: the pharmaceutical budget and the larger public health system budget. The majority of public healthcare spending in South Africa is currently distributed to providers at provincial level, however EML technology selection decisions require a national perspective to determine relevance for the country as a whole.

b) Intervention

The analyst must consider the following information (described in the Technical Review Report) regarding the new technology under assessment:

- Licenced treatment indication
- Route of administration and dosage
- Population of interest including sub-populations
- Setting of administration
- Related diagnostic tools
- Additional training or equipment required to use the technology.

c) Comparators

The comparators listed in the Health Technology Scope must be used for calculation of the budget impact. The same information categories outlined above for the new technology must be described, and relevant data collected by the analyst.

d) Eligible Population

Determining the eligible population over the specified period of analysis (annual and 5-year) is a vital component of the analysis requiring several data points outlined further below. Factors to be considered are population accessing public sector services, age groups and gender, and how much of the population would be affected by the condition of interest.

To determine the eligible population, the analyst must first collect the mid-year population estimates for SA (available from http://www.statssa.gov.za) and project over the specified period. In estimating the eligible patient population, prevalence and incidence data as well as mortality data should be collected. Lastly, any specific sub-groups identified can be separated (if appropriate) as well as the proportion of population relying on public sector healthcare. The analyst should also consider the likelihood that patients will receive the new medicine in the public sector, as well as discontinuation rates, when determining the number of eligible patients estimated to be treated each year.

e) Status quo and implementation scenarios

Description of scenarios

The analyst must clearly define and describe the status quo and implementation scenarios.

The status quo makes an estimation of the current cost of treating the indication for which the technology is being considered across South Africa in terms of costs to the public pharmaceutical budget and the broader public health system. It will be necessary to make assumptions about proportion of patients currently accessing treatment relative to prevalence estimates, in addition to representing known and unknown national variation in care. However, it is important to have a reasonable estimate of current expenditure for the indication in order to understand how the budget may change as a result of the introduction on the new technology.

The implementation scenarios that are required are:

- Rapid adoption of the new technology (1 year and 5-year estimates)
- Slow adoption of the new technology (1-year and 5-year estimates)

The rapid adoption scenario should represent a phased approach under an assumption that there are little or no delays in supply and eligible patients will access the new technology where indicated. This may change based on the type of access; for example, a medicine used in primary care clinics may be more rapidly adopted than a medication that requires access to specialist at a tertiary hospital.

The slow adoption scenario should represent a scenario whereby the prescribing and uptake of the new technology or indication is constrained. This may be due to, for example, required training of health care professionals, complex supply chain arrangements, additional equipment required for implementation or known limitations with access to health care providers.

The development of the rapid adoption and slow adoption scenarios should be done in consultation with clinical experts and should consider major health system elements that may impact on the implementation of the new technology should it be approved. It is important that all assumptions made in developing the different scenarios are clearly detailed.

Market share

The status quo represents a scenario whereby the existing market share of the comparators are not affected by the introduction of a new technology. For both the rapid and slow adoption scenarios, the analysis should describe how the market share may change over the specified period of analysis (i.e. Year 1 to Year 5) for all technologies (new and current). Estimated market share of the new technologies and each comparator must be outlined for each year of analysis (1 to 5 years), totalling 100% each year.

Resources and costs

Calculating the technology acquisition costs, as well as health care resource unit costs, must be consistent with the costing approach used in the cost-comparison analysis and the CEA. Procurement costs must include VAT.

Unless otherwise indicated, costs are presented on a per annum basis. Full year costs should be calculated, even if the new technology will only be implemented part way through the year.

f) Time Horizon

BIA should be conducted over a one- and five-year-time horizon, with the five-year time horizon presented in annual increments, without discounting of costs.

g) Uncertainty methods and scenario choices

The analysis should utilise deterministic sensitivity analysis in terms of alternate scenarios to account for any uncertainty in individual parameters or scenario structure. Where upper and lower levels for specific parameters are not available from literature a standard +/- 50% on the point estimate can be used. A number of scenarios can be included the analysis, and should include as minimum the following scenarios:

- Variation in the price of the new technology under evaluation
- Variation in the uptake of the new technology in both the rapid and slow scenarios
- Variation in the assumptions underpinning eligible population

3.2.3.2 Interpreting results of the budget impact analysis

A BIA demonstrates the estimated net financial costs incorporating potential savings and expenditure due to the implementation of the new technology. A BIA does not represent the full economic consequences (such as loss of productivity or health impacts) nor the non-health related costs (such as other public department costs for instance social development in the case of substance abuse) of a potential investment. The financial costs are representative of those incurred at a national level in the public sector only (pharmaceutical and the healthcare budget), over an annual period and five-year period.

The estimated impact on the pharmaceutical budget should be interpreted in the context of medicines spending only. The health system budget impact gives an indication of the affordability across the health system and results can be used to aid budgeting and planning following the decision. It is important to consider that the larger the expected impact, the more increasingly certain the decision-makers would want to be about the clinical benefits of the new technology.

3.2.4 RAPID REVIEW OF ECONOMIC EVALUATIONS

The global market dynamics influencing the timing of the introduction of new technologies typically results in the South African public health sector receiving motivations for technologies after implementation in many other high-income countries and regions including North America, Japan, UK and Europe and Australia and New Zealand. Many middle-income countries with developing and established HTA systems such as Thailand, India, China, Mexico and Brazil may also be considering introduction of technologies before or at a similar time to South Africa. In addition, global institutions and development partners frequently conduct economic evaluations on technologies that have specific relevance for low and middle-income country context, such as the WHO-CHOICE program (26) at the World Health Organization. There is also a growing number of research units in South Africa that are conducting and publishing economic evaluations that may be of relevance to a decision within the TA process.

This means that there will commonly be an extensive body of economic evaluations in published peer-reviewed literature and in grey literature published on institutional websites relating to technologies under consideration in the EDP TA process. A rapid review of published economic evaluations and HTA agency reports can provide important information for the TA process, including sources of evidence, modelling parameters, structure and approach to analysis, and key factors influencing decisions and areas of uncertainty. The approach to the rapid review builds on existing processes in the EDP program and is informed by approaches to Rapid Review of Economic Evaluation (RREE) in other contexts (27).

3.2.4.1 Objectives of the Rapid Review of Economic Evaluations (RREE)

As part of the screening and prioritisation of technologies, analysts will have checked the approval and/or funding status of technologies at major HTA agencies. In addition to a simple representation of the final outcome of the HTA process in other agencies, the RREE aims to present the approach and content of the analysis in addition to the results and final determination.

The objective of the RREE is to:

- Gain an understanding of the clinical and economic evidence for the technologies under consideration
- Identify additional parameters and determine potential sources of information to inform analysis
- Avoid duplication of analysis and evidence synthesis that may be applicable to South Africa and relevant to the decision-making process
- Identify decision analytic model structures used to assess cost-effectiveness in other contexts
- Identify current gaps in the economic evaluation literature, which may motivate for de novo analysis to be conducted in the South African setting
- Identify ethical, legal and other social issues that were relevant for assessment of the technologies in other contexts

3.2.4.2 Steps in the RREE process

The steps in the RREE are to 1) identify relevant economic evaluations, 2) critically appraise them, 3) assess their applicability to the South African context, and 4) summarise and present the findings (Figure 5). Assessing applicability has been explicitly separated from critical appraisal to allow dedicated assessment of these two components and alignment with existing critical appraisal and applicability assessment tools.

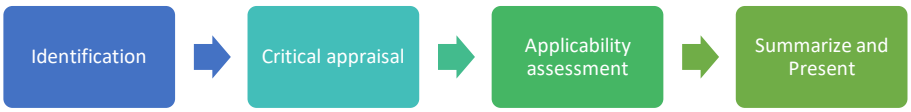

Figure 4. Steps in the rapid review of economic evaluations process

Step 1: Identification of economic evaluations

There are a series of global initiatives that facilitate the collection and organisation of economic evaluation and HTA evidence to enable countries to more rapidly identify and assess evidence that may be useful to local HTA processes. The RREE iterative search should start with databases for published economic evaluations and HTA Agency reports (Table 19) in addition to HTA Agencies that publish detailed technology assessments (Table 6).

Table 19. Literature databases that include economic evaluations and HTA reports

Source	Content	Website
INAHTA HTA Database -	Summaries and bibliographic information of published and ongoing HTA reports	https://database.inahta.org
Center for the Evaluation of Value and Risk in Health at Tufts Medical Center	Registries summarising published cost-utility analyses	https://cevr.tuftsmedicalcenter.org/databases
National Health Service Economic Evaluation Database (NHS EED)	Reviews of published economic evaluations~	https://www.crd.york.ac.uk/crdweb/Homepage.asp
WHO-CHOICE program	List of generalised cost-effectiveness analysis	https://www.who.int/choice/cost-effectiveness/en/
EconLit	Search engine specialised in economic journal literature	https://www.aeaweb.org/econlit/

HTA – Health Technology Assessment, INAHTA – International Network of Agencies for Health Technology Assessment, WHO-CHOICE – World Health Organisation CHOosing Interventions that are Cost-Effective
~ Additions to database ceased 31 March 2018

Analysts should include cost-effectiveness analysis and HTA reports that assess the technology or one of the technologies under consideration within the indication or therapeutic area as defined in the TA Scope. Costing analyses that have not been conducted in the South African setting should be excluded unless it is considered that inclusion will provide additional information to inform the decision. A list of included studies should be developed for inclusion.

As the objective of the RREE is to provide generalized information about approaches to the assessment of the technologies rather than a meta-analysis of final results, it is acceptable for the analyst to apply judgement and exclude economic evaluations in Step 1 where it is expected that inclusion will not add further insight onto the economic evaluation of the technologies in the South African context. A PRISMA diagram should be developed, with studies excluded at Steps 1, 2 and 3 reported.

Step 2: Conduct critical appraisal of included economic evaluations

A critical appraisal assesses the quality of an economic evaluation and can be used to exclude studies or highlight limitations of studies where the methodological approach, evidence used or reporting limits confidence in the analytical findings and use in the TA process. In the RREE it is not necessary to

critically appraise HTA reports from HTA agencies that apply established high-quality economic evaluation methods [3].

The included economic evaluations should be appraised using the Critical Appraisal checklist as proposed by Drummond et al (28) and as listed in Appendix 1. The checklist identifies 10 methods components with sub-questions requiring a yes/no answer to systematically assess the quality of an economic evaluation. The number of sub-questions within a component that are answered "yes" will facilitate judgement as to whether the study achieves an overall "yes" for a particular component.

Although there is no explicit exclusion cut-off based on critical appraisal score, studies that receive a "no" for four or more components should be considered for exclusion, where exclusion should be confirmed by an independent analyst or NEMLC member. Included economic evaluations should progress to Step 3: Applicability assessment.

Step 3: Applicability assessment

The applicability to the South African context is an important consideration when interpreting the findings and recommendations of an economic evaluation or HTA report. An economic evaluation conducted in the context of a high-income country health system might have substantial differences in cost structures (in terms of technologies, staffing and facilities), pathways of care and patient management, and clinical outcomes when compared to the South African setting. In addition, economic evaluations that do not apply a similar methodological approach to a reference case analysis recommend for CEA in the EDP TA process (Table 25) may also have limited applicability. For example, an economic evaluation that utilised a different approach to identify the comparator or incorporated costs from a different perspective than a public sector payer may produce findings that are different than an analysis that was conducted for the EDP TA process.

Assessing context and methodological applicability of economic evaluations and HTA reports enables determination of the extent to which the approach and findings can inform the TA process. This RREE does not provide a comprehensive assessment of transferability (29) but offers a limited number of applicability questions to aid in interpretation.

The applicability checklists (Table 20 and 21) should be applied to all economic evaluations or HTA reports considered for inclusion. Each "yes" awarded is allocated one point, which enables each economic evaluation to receive a Context applicability score and Methods Applicability score out of six. The applicability scoring system is a simple approach to quantifying the judgements made in applying the checklist to aid in communicating findings to NEMLC members. The applicability scoring should not be used to quantitatively adjust results or findings of economic evaluations or HTA reports.

Assessing applicability to the South African setting (context applicability) is not a measure of analytical quality, and it is possible that a high-quality economic evaluation could have very low applicability to the South African setting and have limited use in informing the EDP TA process. However, as the purpose of the RREE is not only to identify analytical results but to gain understanding on evidence sources and analytical approaches, it may be that economic evaluations and HTA reports that have limited applicability to the South African setting can still provide useful information for the EDP TA Process. The context and methods applicability checklists are presented in Table 20 and Table 21 respectively.

[3] HTA reports will commonly follow a standardised methodology of the HTA agency. A list of HTA agencies that follow methods of sufficient quality will be developed to enable inclusion of HTA reports from identified HTA agencies.

Table 20. Context applicability checklist

	Yes/No/Unsure	Score *("yes" = 1 point)*
Is the population similar to South African patients?		
Is the technology administered in a similar way as in the South African public sector?		
Is the comparator similar to the comparator defined in the Technical Review?		
Is the clinical management of patients indicated for the technology being assessed similar to the South African public sector?		
Is the health system context similar to the South African public sector?		
Are there significant differences in costs and costs structures compared to the South African public sector?		
	Total score	/6

Adapted from Drummond et al (29)

The methodological applicability checklist[4] (Table 21) seeks applicability to the methods for the Comprehensive CEA reference case analysis. Where an answer of "no" or "unsure" is entered in the applicability checklist, then the analysis should describe the relevant aspect of the economic evaluation or HTA report and the extent to which it influences interpretation of the analysis.

Table 21. Methodological applicability checklist

	Yes/No/Unsure	Score *("yes" = 1 point)*
Is the type of economic evaluation a cost-utility analysis?		
Are health effects reported direct health effects experienced by patients and health effects on informal caregivers?		
Is the value of health effects expressed in terms of Quality Adjusted Life years?		
Is the analysis over a time horizon that captures all relevant differences in costs and effects between the intervention and comparator?		
Are costs reported from the perspective of a 3rd-party payer (e.g. public sector)?		
Are costs and effects discounted at an annual rate of 5%?		
	Total score	/6

Adapted from NICE Guidelines Manual (30)

Step 4: Summarise and present

The final step of the RREE is to present the included economic evaluations and HTA reports from other HTA agencies transparently and consistently. HTA reports and published economic evaluations should be reported separately following the fields of the Table 22 and Table 23 below and utilising the Rapid Review of Economic Evaluations Template. Summary or explanatory notes should be recorded under the tables if additional information is required.

[4] Informed by the Methodology Checklist: economic evaluations (Appendix G) of the NICE Guidelines Manual (30)

Table 22. Summary Table: HTA reports

	HTA report 1	HTA report 2	Add more columns if needed
Country + HTA agency			
Year			
Indication			
Intervention			
Comparator			
Modelling approach			
Results			
Major areas of uncertainty			
Ethical, social, legal issues			
Recommendation			
Context applicability score /6			
Methods applicability score /6			

Table 23. Summary Table: Published economic evaluations

	Economic evaluation 1	Economic evaluation 2	Add more columns if needed
Author			
Year			
Context (country and health system)			
Indication			
Intervention			
Comparator			
Economic evaluation type			
Modelling approach			
Results			
Major areas of uncertainty			
Critical appraisal score /10			
Context applicability score /6			
Methods applicability score /6			

3.2.5 COST-EFFECTIVENESS ANALYSIS

This section describes the required methodological approach for conducting a cost-effectiveness analysis (CEA) to inform decisions about the selection of technologies to the National Essential Medicines list (EML). The CEA approaches defined below will generate a stand-alone CEA report that will form part of the Stage 2 analysis requested under the EDP HTA process.

3.2.5.1 The role and use of cost-effectiveness analysis in informing decision making within the Essential Drugs Program (EDP)

Economic evaluation is the broad term for the comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes and effects) (28). There are many types of economic evaluation that can be applied to decision-making in health, and major types are listed in Table 24 below. While there are many similarities between the different types of economic evaluation, each type applies implicit judgements about aggregation and representation of costs and consequences including opportunity cost, and have specific use cases depending on the nature and context of the decision problem and requirements of the decision-maker. In addition, methodological choices made when conducting any form of economic evaluation (such as how a comparator is chosen or timeframe for the analysis) will also reflect the context, decision problem and the needs of the decision-maker.

Table 24. Types of economic evaluation

Type	Description
Cost-Consequence Analysis	An analysis where the costs and consequence are identified and represented in disaggregated form without substantive synthesis or aggregation.
Cost-Effectiveness Analysis	An analysis used to compare costs and effects of treatment alternatives using a common outcome measure e.g. cost per hospitalisations averted or exacerbations treated. Generates a summary measurement of efficiency (a cost-effectiveness ratio).
Cost-Utility Analysis	A form of cost-effectiveness analysis used to compare treatment alternatives that differ in their therapeutic or clinical outcome by calculating a generalised outcome measure (QALY or DALY). By using a summary measurement of efficiency (a cost-effectiveness ratio) alternative treatment options with different costs and outcomes can be fairly compared along a level playing field against all potential investments available to the health system.
Cost-Benefit Analysis	An analysis where all outcomes (health and non-health) are expressed in monetary units and commonly adopting a wide societal perspective.

DALY – Disability-Adjusted Life Year, QALY – Quality-Adjusted Life Year

The approach required to inform decision-making within the EDP TA process is cost-effectiveness analysis (CEA). CEA is used within an HTA process primarily to generate evidence about the efficiency of an intervention (or set of interventions) relative to an alternative course of action, and to give an indication of the opportunity cost of investing in the intervention rather than investing in other parts of the health sector. CEA results are commonly reported in terms of an incremental cost-effectiveness ratio (ICER), which is the ratio of the difference in costs and the difference in effects between the intervention and its comparator.

$$\frac{Cost_{intervention} - Cost_{comparator}}{Effect_{intervention} - Effect_{comparator}}$$

Reporting CEA results in the form of a ratio of the amount of spending required to achieve a unit of health (relative to existing practice in the local health system) provides useful information to decision-makers where there is uncertainty about intervention efficiency and the opportunity cost of the

investment decision in the local context. As a HTA process utilizes multiple types of information to inform a decision, CEA does not provide all the evidence required to definitively determine whether a health intervention should be used in the public sector, however it does provide a basis on which to manage the trade-offs when incorporating considerations beyond efficiency in the decision-making process, such as prioritizing investment for previously disadvantaged populations.

This section describes the method and approach for two particular forms of CEA to be used within the EDP HTA process:

1. **Basic CEA** which is performed when there is limited analytical resources available and the use of natural units as outcome measures (such as disease-specific outcomes or lives saved) are considered acceptable in the context of the decision problem; and
2. **Comprehensive CEA** where there is greater analytical time, evidence and resources available, and there is significant uncertainty associated with the opportunity cost of the use of the technology in the South African public health sector.

Given constraints on analytical resources and evidence available, the specification of a basic and comprehensive form of CEA allows the prioritisation of analytical resources to decisions for where there is greatest uncertainly. Regardless of resources and time available however, it is important that the methods and approach for conducting CEA for the EDP HTA process are consistent and adhere to basic analytical principles to allow those using the analysis to make coherent and procedurally sound decisions.

3.2.5.2 The South African Essential Drugs Program Reference Case

The methodological specifications for Basic CEA and Comprehensive CEA are detailed in the Table 25 in the form of a reference case, which is a standard set of methods to be applied consistently when planning, conducting and reporting analysis. The EDP HTA reference case builds on the practice of many HTA agencies internationally that specify a common set of methods to generate economic evidence to inform national decision-making, and guidance from the International Decision Support Initiative (iDSI) that proposed a principle-based approach to the development of locally relevant economic evaluation methods in low and middle-income countries (31). The EDP HTA reference case also incorporates some elements of the existing South African Pharmacoeconomic Guidelines (5) that were issued by the NDoH in 2012 to inform appropriate regulation of pharmaceutical pricing in South Africa's private sector.

Table 25. Recommended guidance for EDP Reference Case Analysis

Component	Description	
Analytical question	Clear and unambiguous description of: • the intervention • the intervention against which it is being compared • the indication for which it is used • the population that would receive it • the platform in which it would be applied	
Comparators	• The intervention in the South African public health system that is most likely to be replaced if the intervention was to be funded • Additional analysis should compare to minimal supportive care	
Perspective on outcomes	Direct health outcomes on treated population	
Perspective on costs	Costs related to the public health system	
Type of economic evaluation	***Basic***	***Comprehensive***
	Cost-effectiveness analysis	Cost-utility analysis
Time horizon	Between 1-5 years (lifetime projection based on simple assumptions)	Lifetime or sufficient to capture all relevant differences in costs and effects between the intervention and comparator
Health effects source	Technical Review Report, existing literature (e.g. published systematic review or primary studies)	Technical Review Report, existing literature (e.g. published systematic review or primary studies), de novo systematic review
Representing health effects	Natural units and life-years saved (QALYs where significant QoL differences between the interventions and comparator are expected)	QALYs; life-years saved
Valuing health effects – life years saved and quality of life	• Life years saved calculated by average expected age of death in treatment population multiplied by expected life-years remaining • HRQoL transferred from other setting with applicability checklist applied	• Life years saved – as for Basic CEA • HRQoL measurement from South African patients and/or carers using validated HRQoL instrument, valuation of HRQoL from established value set, *or* HRQoL transferred from other setting with applicability checklist applied.
Weighting of effects	None. It is proposed that health effects are reported without any weighting to reflect social value judgements such equity.	
Representing costs and resource use	South African data sets and basic cost synthesis	South African data sets and basic cost synthesis and primary data collection where necessary
Parameterisation (general)	Parameters sourced from published, peer-reviewed sources preferred. Use of expert opinion and opportunistic data where necessary.	Parameters sourced from published, peer-reviewed sources. Limited use of expert opinion and opportunistic data.
Discounting	5% annual discount rate for costs and health effects (sensitivity analysis at 0% and 10%)	
Sub-groups	Representation of costs and effects on identified sub-groups and populations	
Uncertainty	Description of major areas of uncertainty in analysis. Parameter uncertainty represented by deterministic univariate and threshold sensitivity analysis. Structural uncertainty represented by scenario analyses	As for basic CEA but with more extensive use of sensitivity analysis including probabilistic sensitivity analysis where feasible

a) Analytical question

Defining the analytical question that the analysis seeks to answer is a fundamental initial step in any analysis and is imperative to ensure transparency and coherence. The analysis should directly align to the specification of the decision problem as defined in the TA Scope and Technical Review Report and should incorporate the following:

- the intervention
- the intervention against which it is being compared
- the indication for which it is used
- the population that would receive it
- the platform in which it would be applied

As the substantive detail of the intervention and comparator characteristics and use will be defined in the Technical Review Report, it is sufficient for the CEA Report to simply list the items in the list above and refer to the existing Technical Review Report. If the CEA and Technical Review are being conducted simultaneously, it is imperative that there is coherence and coordination between the analysis.

b) Comparators

As cost-effectiveness analysis is a comparative analysis, the comparator against which the intervention is assessed will be a major determinant of the analytical results. A reference case analysis should choose a comparator that represents current existing practice within the South African public sector, as this is the intervention that is most likely to be displaced by the introduction of the new intervention. Where the current practice in the South African public sector is not considered to represent ideal, effective, or efficient care, additional analysis should be conducted that compares the intervention to best supportive (or minimal) care.

Depending on the indication, current practice may represent another medicine, a non-pharmaceutical intervention such as lifestyle advice or a surgical intervention of commonly no treatment. In cases where the medicine is to be used as an adjuvant treatment to existing therapies, the comparator would be existing therapies, where the new intervention would not displace existing therapies, but be added to existing therapy.

The approach to selecting the comparator should be done transparently and in consultation with NEMLC, aligning to the comparator identified in the TA Scope and Technical Review. In the first instance, the analyst should identify the normative comparator which is the current treatment recommended in the existing STGs or other NDoH programme guidance. Where there is significant uncertainty as to whether the recommendations in the STGs represent current practice, the analyst should seek expert input from NEMLC to identify the predominant or most common intervention offered for the technology's's intervention. Where there is significant geographical variation in treatments available for the same indication, for example where treatment varies depending on proximity to tertiary hospital, it may be necessary to represent two separate analysis to reflect treatments are different levels of care.

c) Perspective on outcomes and costs

The perspective refers to which costs and outcomes should be incorporated in the analysis. Common perspectives that can be reflected within an economic evaluation are: 1) Public sector payer; 2) Private payers; 3) Broader public sector payer; and 4) Societal. Although a full economic evaluation will seek to accurately reflect all costs and effects no matter to whom they fall, it is imperative to present analysis in a way that is coherent, symmetrical and consistent, and reflects the realities of the opportunity cost of spending from the perspective of the funder. In the South African public sector,

for the majority of patients, care is offered free at the point of use under the larger policy aim of Universal Health Care (UHC). In this context, the public sector is the purchaser of health care and means that health spending in one area will have a direct implication for ability of the public sector to purchase health care in another area. It is therefore imperative for an analysis to represent a scenario that reflects the impact of public sector spending in isolation to other costs that may be associated with accessing care. Therefore, a reference case analysis requires that the perspective on costs is that of the public health sector. This does not mean that non-public sector costs, such as those incurred by households and indirect costs such as lost productivity are unimportant or cannot be reflected. In instances where it is expected that there will be significant non-health sector costs associated with a technology, a non-reference case analysis should be conducted.

Within a reference case analysis, costs that fall on donor or non-government organization (NGO) budgets should be incorporated within the perspective of public sector payer. This is because it is considered that donors and NGOs are providing services and interventions that complement and support the public sector and the opportunity costs incurred by donors and NGOs are expected to have a comparable impact on the health of South Africans. This is a simplifying assumption as there is limited empirical evidence to support the fungibility of donor and NGO funding in the South African public sector. Where a technology investment decision is expected to have significant impact on donor and NGO budgets, these costs can be reflected separately in scenario analysis.

Health outcomes included in a reference case analysis should reflect direct health effects experienced by patients and health effects on informal caregivers where relevant. This means that the health impact as observed in the clinical evidence base for those receiving treatment would be incorporated in addition to any health impact on informal carers. It is important that a similar standard of evidence generation and synthesis is used to identify and represent informal carer health impact.

The types of health outcomes and costs that should be incorporated in a reference case and non-reference case analysis differentiated by perspective are detailed in Table 26 below, and is informed by the methods used in the Canadian Agency for Drugs and Technologies in Health (CADTH). While perspectives other than the public sector can be conducted and considered within the HTA process, these are conducted as non-reference case analysis.

Further detail on the approach to measurement and representation of costs is detailed in the Cost-Comparison section of this Guide.

Table 26. Health outcomes and costs in reference case and non-reference case analysis

	Reference case analysis	***Non-reference case analysis***			
Perspectives:	*Public sector payer*	*Private payers*	*Broader Government payer*	*Societal*	*Examples*
Types of costs					
Costs to the public sector	✓		✓	✓	• Medicines, medical devices, procedures • Equipment, facilities, overhead • Health care providers • Hospital services • Diagnostic, investigational, and screening services • Informal caregivers' health care costs • Rehabilitation in a facility • Community-health worker costs • Long-term care in nursing homes
Costs to other government departments			✓	✓	• Criminal justice system • Affordable housing • Education
Costs to donors and NGOs	✓		✓	✓	• Medicines, medical devices, procedures • Staffing and facilities • Public health messaging
Costs to medical aid schemes		✓		✓	• Medicines, medical devices, diagnostics • Aids and appliances • Alternative care (e.g. traditional healer) • Rehabilitation in a facility or at home • Community-based services, such as home care, social support • Long-term care in nursing homes
Costs to patients and informal caregivers				✓	• Out of pocket payments (e.g. co-payments for drugs, dental, assistive devices) • Cost of travel, paid caregivers • Medical aid premiums • Patient's time spent for travel and receiving treatment
Productivity costs				✓	• Lost productivity due to reduced working capacity, or short-term or long-term absence from work • Lost time at unpaid work (e.g., housework) by patient and family caring for the patient • Costs to employer to hire and train replacement worker
Types of outcomes					
Health effects relevant to patients and informal caregivers	✓	✓	✓	✓	• Health-related quality of life • Life-years gained • Clinical morbidity
Non-health effects relevant to patients and informal caregivers			✓	✓	• Information available to patients • Reduction in criminal behaviour • Better educational achievements

Adapted from CADTH methods Manual, 4th Edition (32)

d) Time horizon and discounting

The time horizon chosen for the analysis can have a significant impact on analytical results, particularly where there are important differences in the timing of costs and effects between the intervention and comparator. In addition, where there are significant mortality differences between the intervention and comparator and a generalised measure of outcome is being used, applying a short time frame will limit the benefits for those who have had their life extended by a particular intervention. Therefore, a reference case analysis for a comprehensive CEA should be long enough to incorporate all significant differences in terms of costs and effects; commonly this will mean a life-time time horizon.

When conducting a Basic CEA, analysts can apply a shorter timeframe of between 1-5 years in consultation with NEMLC. The analyst should ensure that the chosen timeframe in a Basic CEA is long enough to capture the major differences in costs and effects, and may project costs and effects over a longer time horizon using simple assumptions.

Discounting is an analytical technique used to represent future costs and effects at present value. A reference case analysis should apply an annual discount rate of 5% for both costs and effects, with sensitivity analysis at 0% and 10%. This is higher than the rate applied commonly in high-income country contexts but aligns to the recommendations of the South African Pharmacoeconomic Guidelines (2012) and is expected to be more closely aligned to South Africa' context (33). In future iteration of this guide, empirical evidence based on South Africa's rate of inflation, government borrowing costs, risk of catastrophic events and time preference for health will inform a discount rate however the above rates should be applied routinely whether a basic of comprehensive analysis is conducted.

e) Sourcing, representing and valuing health effects

The conduct of the CEA should be done in coordination with the clinical analysis of the EDP HTA. The approach to sourcing and generating clinical evidence is detailed in the clinical evidence section of this Guide. The sourcing of clinical effects represents a significant proportion of the analytical time in conducting a CEA and the approach can be adjusted depending on whether a basic or comprehensive CEA is being conducted.

A Rapid Review of Economic Evaluations (RREE) may be conducted under the EDP HTA process as a Stage 2 analysis. A RREE will be a useful source of evidence for informing the parameterisation of the analysis and any decision analytic modelling structure, and analysts should refer to the RREE section for details on the methodological approach.

Within a Basic CEA, sufficient evidence on clinical effects is likely to have been sourced as part of the Technical Review. Where additional clinical information is required beyond that provided in the Technical Review Report, analysts should identify evidence from published systematic reviews, primary studies and the RREE, adhering to clinical sourcing approach in the EDP HTA process. Comprehensive CEA should also incorporate clinical findings from the Technical Review Report and RREE, in addition to conducting *de novo* searches of the literature for additional systematic reviews and primary studies, with *de novo* systematic review conducted if there are available resources.

f) Representing health effects

The approach to representing health effects within an economic evaluation is a major factor determining how the results can be used and interpreted. Health effects represented in a basic form, such as "alive or dead", "sick or well", "infected or not infected" or as directly reported from a clinical trial are commonly called natural units. Natural units have advantages as an intuitive measure of health impact, and can be easily interpretated in cost-effectiveness analysis with ratios such as "cost per lives saved" or "cost per percentage reduction in pain score". This enables useful comparison of

the cost-effectiveness of competing interventions within a similar therapeutic area and can identify which interventions are more technically efficient. However, there are significant limitations to only using natural units of health in economic evaluation. Many medicines and other health interventions have positive and negative direct health impacts, particularly related to unwanted effects of treatment. Using a health impact measure that only incorporates positive health impacts can bias towards interventions that have a less favorable unwanted effect profile. In addition, a major consideration in measuring health is not only whether a person is alive or dead, but the quality of life in which that life is lived. Therefore, it is important to represent both morbidity and mortality in an outcome measure to avoid bias against interventions or disease states where these is substantial morbidity. This is increasingly important in South Africa where rising non-communicable disease requires consideration of morbidity in addition to impact on mortality.

The most significant consideration for representing health in an economic evaluation however is the context of the decision. The EDP HTA process is anchored in the objectives of UHC, which means decision-makers are interested in improving health across the whole population, not only within one specific patient group. Spending limited health resources in one area will have a direct impact on the ability for the health system to invest in other areas, meaning that all health spending will have an "opportunity cost" in terms of lost population health. In order to assess whether the health gains that may be achieved from the intervention under consideration is greater than the health "lost" from not investing the limited health budget in other areas, an economic evaluation needs to represent health impact in a "generalised" form, which means health can be compared across disease states and regardless of which populations are gaining or losing health.

The above considerations mean that in a Comprehensive CEA, health should be represented in a generalised form that takes into account morbidity and mortality and represents positive and negative impacts on health. There are various generalised measures of health, and the reference case analysis requires that a comprehensive CEA represents health in the form of a Quality Adjusted Life Year (QALY). The QALY is a composite measure of health effect where the number of years in a particular health state is multiplied by the health-related quality of life (HRQoL) in that state. Use of the QALY enables the effect of an intervention to be measured in a consistent and comparable manner, across diseases and intervention types, and critically can allow the estimation of lost population health elsewhere in the health system as a result of investment in a particular health intervention. The difference in the number of QALYs that are expected to be produced from an intervention relative to a comparator enables calculation of incremental QALYs, and when this is expressed as a ratio of the increment costs between the intervention and comparator, enables calculation of the incremental costs-effectiveness ratio (ICER), a summary metric of a cost-effectiveness analysis.

An alternative generalised health outcome measure in use in economic evaluations in South Africa is the Disability Adjusted Life Year (DALY). The DALY can be conceptualised as the inverse of the Quality Adjusted Life Year (QALY) where it measures the number of years in a particular health state multiplied by the burden (or morbidity) associated with that health state. In this way, a positive health impact of a health intervention is the extent to which it can reduce or "avert" DALYs. There are important differences however between the theoretical underpinnings, valuation and calculation of the QALY and DALY[5]. While the QALY remains the recommended outcome measure for a Comprehensive CEA, cost/DALY-averted analysis can be considered within the EDP HTA process if sufficient justification has been provided. In addition, studies that report cost/DALY-averted analysis should be included in the Rapid Review of Economic Evaluations (RREE).

[5] It is beyond the scope of this methods guide to provide comprehensive methodological detail on each of the outcome measures, and readers should refer to leading texts (28) for further details.

The development and synthesis of a cost/QALY analysis can be resource intensive and depending on underlaying evidence base, may introduce significant uncertainty to the decision process. Therefore, a Basic CEA should report in natural units, acknowledging the limitations that a non-generalised measure introduces for the interpretation of results.

g) Valuing health effects

Applying the QALY within a Comprehensive CEA requires a consistent and transparent approach to valuing and calculating the health-related quality of life (HRQoL). A Comprehensive CEA should ideally measure health impacts from a representative sample of the South African population using a validated instrument and the effects should be valued with a South African-based value set. While this recommendation should be the aim of all Comprehensive CEAs for the EDP HTA process, it is acknowledged that this approach is unlikely to be possible for the majority of analyses. In contrast to economic evaluation in many high-income country contexts, there is limited use of local HRQoL findings in economic evaluations based in South Africa. A review by Wilkinson et al (2020) of all economic evaluations reporting cost per QALY in the 20-year period since 1999 found 33 studies, predominantly in the HIV/AIDS and vaccination therapeutic areas. A range of valuation approaches for HRQoL were applied, but an important finding was that only 15% of HRQoL estimates were measured in the local South African population. In addition, there is currently no South African-based value set for qualifying measured health effects, which means it is currently not possible to create a QALY measured in the South African population and valued representing preferences of the South African population.

Therefore, it is likely that valuation of health effects may require use of a secondary HRQoL measure, which is an estimation of the value of a HRQoL state from the existing literature. Applying a secondary HRQoL estimate introduces significant uncertainty into the analysis and limits the consistency of approach. It is considered that use of secondary HRQoL measures are acceptable in the EDP HTA process as it allows the approximation of the QALY and consideration of the wider opportunity cost of decisions. However, analysts should apply the applicability checklist (wee Table 27) when any use of a secondary HRQoL is applied.

Table 27. Use of secondary HRQoL estimate: Applicability checklist

Component	
Cited use of HRQoL estimate	
Primary source of HRQoL estimate	
Country of HRQoL measurement	
Method of HRQoL measurement	
Method of valuation of HRQoL	

HRQoL – Health Related Quality of Life

There is limited synthesis or complex analysis involved in secondary valuation of health effects in a Basic CEA, and the main consideration is that there is transparent and coherent calculation of natural health units. Representing life years saved should be calculated by estimating the expected age of death for the patient population, multiplied by the life years remaining for the average South African within that age cohort using established life-tables.

If a QALY is represented in a Basic CEA, the HRQoL estimates can be obtained from secondary sources such as existing published economic evaluations or HRQoL studies, as detailed above[6].

[6] It is recommended that the global burden of disease estimate for the specific cause is used to assess consistency and validity

h) Weighting of effects

A reference case analysis should not weight any health outcomes based on additional preference or value considerations such as disease severity or deservedness of the population group. This enables the results of the economic evaluation to be presented as a reflection of costs and health effects only and the opportunity cost of the decision to be reflected consistently. Value judgements and considerations beyond efficiency should be incorporated in the EDP HTA process, however, can be considered at the point of decision-making rather than as a component of the analysis.

i) Parameterisation (general)

Conducting an economic evaluation will frequently involve incorporating evidence from a range of sources to inform analytical parameters beyond the immediate clinical effects and costs of the intervention and comparator. Parameters relating to progression of disease and underlying clinical effects, utilization rates and the broader health system context will often form essential elements of the analysis. The analytical time associated with identifying and validating parameters can often be significant and an important consideration where capacity is limited by the productivity of the EDP HTA process. Therefore, a distinction is made between approaches to parameterization within a Basic CEA and a Comprehensive CEA. While parameters sourced from published, peer-reviewed and locally validated sources are preferred, a Basic CEA may utilise opportunistic data and expert opinion in order to complete the analysis within the required timeframe. An overarching principle in parameterization however is that all sources are transparently reported, with assumptions and approximations clearly explained.

j) Sub-groups

Depending on the requirements of the decision, it may be necessary to assess the cost-effectiveness of the intervention in a sub-group of the population. This may be a clinically defined sub-group, such as a particular sub-classification of the clinical indication of the medicine, or geographical grouping to represent differences in prevalence or progression of disease. It may be appropriate to represent different sub-groups based on age or other population characteristics, but care should be taken when representing sub-groups to ensure and ethical issues are considered before the analysis is undertaken. Any sub-group analysis should be incorporated within the TA Scope and confirmed with NEMLC before analysis is undertaken.

k) Uncertainty

A fundamental aspect of an HTA process is that it facilitates decision-making under uncertainty. Uncertainty in an analysis can come in many forms, from uncertainty about the precision of parameters, to the structure of the analysis, the methods used and sources of evidence. While an extensive evidence base and sophisticated methodological approach can assist in improving precision in an analysis, the aim within an HTA process is not to present a single, highly precise result, but to ensure the uncertainty associated with a decision is represented and characterised appropriately to allow decision-makers to weigh the evidence and make an accountable decision based on available evidence. At no point should the analysis seek to obfuscate or mis-represent uncertainly; this is particularly important for the South African setting where resources available for generation and synthesis of local evidence is constrained and any analysis will naturally need to rely of a series of assumptions and techniques to represent available evidence in a way that most aids decision-making.

There are three major categories of uncertainty within economic evaluation:

- Parameter uncertainty is associated with the variation in the numerical data points in the analysis, such as clinical effect estimates or cost parameters. This is the most common understanding of uncertainty and is aided by the use of parameter distributions and confidence intervals to provide

decision-makers with a plausible range within which a parameter estimate can be expected to vary.

- Evidence Source uncertainty refers to uncertainty association with the origin of data and evidence. For example, whether costing information from a one hospital is reflective of hospital cost structures across the country.
- Structural uncertainty refers to the design or form of the analysis and arises when there is uncertainty about the pathway of care and how best to represent the clinical management and outcomes of a clinical condition or scenario.

An additional aspect of uncertainty related to economic evaluation in health is Methodological uncertainty, which is the uncertainty associated with methodological choice such as the way in which effects are represented, and comparators chosen, or the perspective of analysis and discount rate used. The specification of the reference case as part of this Guide should minimize methodological uncertainty, and ongoing research to refine and improve economic evaluation methods will assist in reducing Methodological Uncertainty within the EDP HTA program further.

Management of uncertainty within reference case analysis involves systematically identifying areas of Parameter, Evidence Source and Structural Uncertainty and transparently representing the range of uncertainty with explanation of the implications of uncertainty where appropriate. Scenario analysis should be used in Comprehensive CEA where it is expected that there is significant Structural Uncertainty. Management of Parameter Uncertainty involves the use of deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA); a Basic CEA would usually be limited to one-way deterministic sensitivity analysis, which a Comprehensive CEA should represent deterministic and PSA.

One-way deterministic sensitivity analysis involves varying one parameter within it expected range and reflecting how the change influences the results. It is a useful approach when seeking to represent simple parameter variation and is generally well understood by non-experts. Within a reference case analysis, one-way deterministic sensitivity analysis should be represented in the form of a tornado diagram.

One-way sensitivity analysis is limited in that it is highly uncommon for only one parameter to vary at one time. Probabilistic sensitivity analysis facilitates a more complete understanding of the uncertainty associated with an analysis by assigning all relevant parameters within a model a sampling distribution and drawing randomly from the distribution with multiple iterations to represent the joint parameter distribution. Further application of these methods within the EDP HTA program will facilitate more extensive methods and examples of analysis to assess parameter uncertainty. For further details on approach to one-way and PSA, readers are referred to Drummond et al (28).

3.2.5.3 Presenting the results of a Cost-Effectiveness Analysis

The summary results of a CEA should be presented clearly and transparently in table form and on a cost-effectiveness plane, and utilising the Cost-Effectiveness Analysis Template. A cost-effectiveness plane is a graphical representation of results with costs on the vertical axis and effects on the horizontal axis. The costs and effects of one or more interventions are plotted on the plane which allows simple visual representation of relative cost and effect. The tabular representation of costs and effects should align to Table 28 below.

Table 28. Table for presenting the results of a cost-effectiveness analysis

	Cost	Health Outcome	Incremental cost	Incremental outcome	Incremental cost-effectiveness ratio
Comparator intervention					
New intervention					

3.2.5.4 Interpretation of results

A cost-effectiveness ratio is a summative representation of incremental costs relative to incremental effects. It therefore represents the rate at which, on the margin, the health intervention can be expected to convert money (health spending) into health compared to current treatment. The correct intuitive interpretation of the ICER is that an intervention with a higher ICER (i.e. an intervention that costs more money to generate one unit of health) is not as good value for money as an intervention with a lower ICER (i.e. an intervention that costs less money to generate a unit of health). Importantly, the use of the ICER also facilitates representation of the opportunity costs, which is the estimation of the lost health to the general population as a result of investing money in a health intervention rather than investing elsewhere in the health system.

Recent analysis estimated the marginal productivity of health spending in the South African public sector (34). It is estimated that approximately R38,500 of marginal spending will avert one DALY, meaning that the impact of investing R38,500 at the margin of the health system is expected to generate one year of full health (free from disability) for one person. Extrapolating this to the EDP HTA process, this estimate can be used as a cost-effectiveness threshold to interpret the results of a Comprehensive CEA under a simplifying assumption that one DALY averted is approximately equivalent to one QALY gained.

This means that an intervention that is below R38,500 per QALY gained can be interpreted as likely to be cost-effective in the South African public system, and an intervention that is above R38,500 can be interpreted as likely to be not cost-effective in the South African public health system.

It is important to note that the cost-effectiveness of a health intervention is only a representation of the likely health benefit that it represents to the health system taking the opportunity cost of spending into account. As “health maximization” is not the only objective of a health system, it is highly likely that some health interventions found to be cost-effective will not represent appropriate investments for the public health system, while other interventions not found to be cost-effective will be considered appropriate investments. The CEA results should be interpreted within an accountable decision framework to facilitate coherent, transparent and consistent decisions.

3.2.5.5 Decision modelling

Assessing the net costs and effects of a technology selection decision requires projection of the expected impacts in terms of health and expenditure within the clinical pathway in the South African context. The analysis that incorporates the relevant evidence to make these projections is termed decision analytic modelling (or simply decision modelling). Decision modelling is a powerful tool to produce evidence to assist decision-makers as it allows multiple types of evidence to be considered and future impacts to be predicted. However, models are only generalised simulations representing the mathematical relationships between parameters. A common adage that “all models are wrong, some are useful”[7] indicating that a model does not aim to perfectly reflect the impact of the introduction of a new technology, but can provide useful evidence within the decision process.

[7] George Box (1919-2013)

Both the Basic CEA and Comprehensive CEA approaches will require some form of decision modeling. There are multiple decision modelling techniques used within HTA processes internationally, from decision trees, cohort-level state-transition models (such as Markov models), patient-level state-transition models (i.e. microsimulations) and more complex techniques including discrete event simulation models, agent-based models and system dynamic models (35). This guide does not provide comprehensive step-by step instructions on how to develop a decision model, and readers are referred to the main texts (36) and good practice guidance for decision model development and reporting (37).

The main decision modelling approaches recommended within the Basic and Comprehensive CEA approaches are Decision Trees and Markov models. The distinction between the Basic and Comprehensive forms of the models will be related to the extent and approaches to eliciting, generating and synthesizing evidence and the complexity of the model structures.

A Decision Tree can be the simplest form of decision modelling and consists of decision nodes, chance nodes and distinct branches that enable calculation of payoffs associated with each branch in terms of health effects and costs. An example of a decision model is shown below adapted from a recent HTA developed to inform a selection decision on the EML (Wilkinson et al, 2018). The decision model calculated the expected costs and health effects associated with providing either of the low-molecular weight heparins (LMWH) fondaparinux or enoxaparin to patients that were indicated for post-surgical prophylaxis of venous thromboembolism (VTE). The "event" of VTE was incorporated in the decision model, in addition to the unwanted effect of "major bleed", which is also a consideration when deciding which of the LMWHs and is associated with additional costs and health effects. The probabilities of moving to each branch were informed from the literature and the health impacts and costs associated with each branch were calculated. This enabled a calculation of the net expected health effects and costs associated with using either fondaparinux or enoxaparin in the South African public health sector.

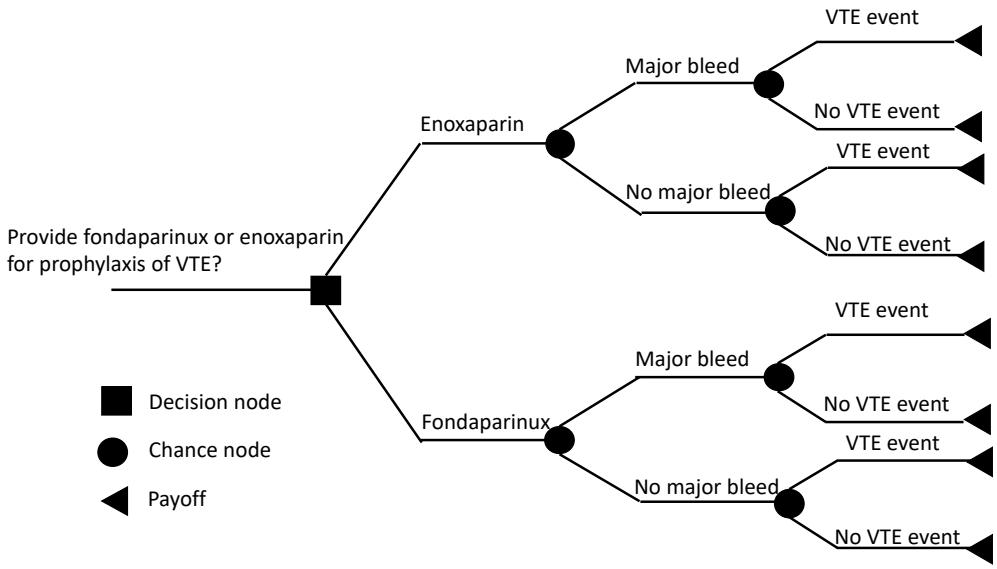

Figure 5. Example of a simple decision tree structure

VTE – Venous thromboembolism

Wilkinson et al 2018 (unpublished)

A major limitation of the decision tree decision model is that it cannot incorporate the impact of time, with all events and associated payoffs occurring at a single point in time. This makes a decision tree useful for modelling single event or time limited occurrences such as post-surgical prophylaxis of VTE. Many decisions however, particularly related to non-communicable diseases, require modelling that

can accommodate cost and effects over a longer time period and probabilities of moving between states. The Markov model is a commonly used in this situation and a simplified example is shown below, where patients exist in mutually exclusive states of either “sick”, “well” or “dead”. A Markov model can have many more states depending on the nature of the intervention and clinical pathway of the disease. A Markov model is constructed for each intervention arm and will have unique costs and health effects associated with each state and transition probabilities of moving from one state to another over a specified time period.

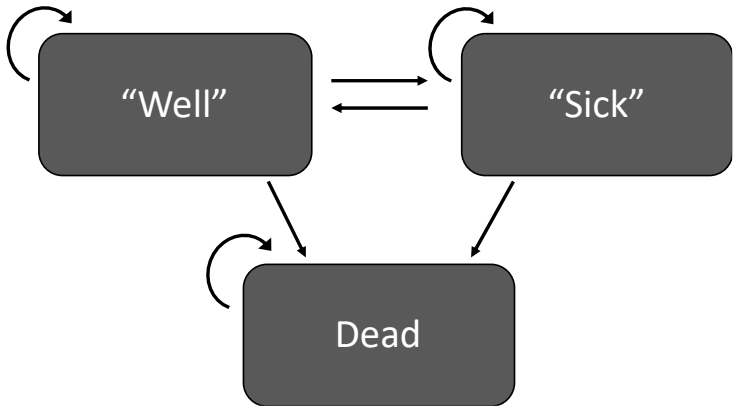

Figure 6. Representation of Markov model states

Model transparency

A fundamental aspect of decision modelling is that the analysis should not introduce unnecessary complexity or uncertainty into the decision-making process. A decision model aims to assist decision-making and if committee makers cannot engage with the decision modelling approach, structure and results then the decision model has failed to assist the process. In addition to clear reporting of results and parameters used, reporting of decision trees must report all branch probabilities and health and cost payoffs for all branches. Markov models must report all state transition probabilities and the costs and health effect values for each state.

Decision modelling in support of the HTA process may be conducted in any relevant software package (such as Excel, TreeAge, Stata or R) but an Excel-based executable version of the model must be provided to NEMLC and the relevant ERC. This means that if analysis is conducted in a software package which is not Excel, an export function must be used to translate not only analytical findings, but all parameters and model structures.

3.2.6 PRICING ANALYSIS

Pricing comparison methodology is invaluable for obtaining good estimates and ranges of technology acquisition costs for the economic analyses when a technology is not currently funded, and a set price point has not been provided. Furthermore, these estimates can in turn help inform price negotiations[8]. Analysis can be conducted on international prices (International Price Analysis) and/or on local prices (Local Price Analysis). Sustainable supply of a technology is an important consideration, thus another analysis to include is an assessment of the market supply (Active Pharmaceutical Ingredient Global Supply Analysis). The Pricing Analysis Template should be used when reporting the results of the Pricing Analysis.

3.2.6.1 Key Principles

The following key principles should be applied when conducting pricing analyses:

- The price that should be represented is the ex-manufacturer, exclusive of VAT, and any other fees or mark ups including distribution or pharmacy fees
- Where ex-manufacturer, ex-VAT, ex-mark up prices cannot be obtained, a price can be included in the analysis but with clear description of what is represented within the price and the source.
- Prices must be adjusted to real USD and ZAR, using average exchange rate from the previous 90 days at the date of the analysis, with the date that the exchange rate was obtained clearly stated.
- Ensure that prices compared are matched in terms of strength and formulation for each technology and/or daily dose per person appropriate for the HTA topic.
- Pricing should also be sourced for comparators as it provides a better understanding of the relative price of the technology in local context.

It is important to note that prices may not reflect confidential discounts or rebates given to the manufacturer.

3.2.6.2 International Pricing Analysis

Comparing prices across countries can help provide a good reference point for cost estimates on new medicine or revision of prices on existing technologies.

The *Medicine Prices, Availability, Affordability and Price Components* website (published by Health Action International [HAI] in collaboration with WHO)(38) and *Medicine price information sources* webpage (published by WHO)(39) can be used to search for medicine prices across sectors and regions in a countries.

At a minimum, the price of the medicines in publicly available country markets listed below should be provided. Pricing from other national markets can be provided where the analyst can obtain a credible source and can identify ex-manufacturer prices that do not incorporate VAT or any other mark ups or logistics fees.

[8] Important to note that there are numerous factors involved with price negotiation which are the beyond the scope of this document i.e. volume, market share, bundles.

Publicly available international markets:

- Australia: https://www.pbs.gov.au
- New Zealand: https://pharmac.govt.nz
- England and Wales: http://www.drugtariff.nhsbsa.nhs.uk

An appropriate source for obtaining the 90-day average exchange rate is www.xe.com. Prices can be compared across countries in the same price type (i.e. reimbursement value) for the new medicine and comparators. Averages costs per price type can be determined with either the median or mean values depending on number of values available. For instance, less than four values a median value may be for appropriate.

3.2.6.3 Local Pricing Analysis

In South Africa, after a medicine has received market approval from the South African Health Product Regulatory Authority (SAHPRA), the price at which the particular brand and formulation of medicine is sold is notified to the Department of Health. This price constitutes the Single Exit Price (SEP), and is the price at which the medicine must be sold to all buyers with the exception of public sector facilities. This provides a consistent price for each brand and formulation of a medicine in the private sector. The Department of Health is required to publish and up to date list of the SEP. Third-party applications detailing the SEP are available and may be used if an up to date Department of Health list is unavailable. The Medicine Price Registry details the SEPs and can be found on the following website: https://medicineprices.org.za

Local Pricing Analysis requires that the SEP and the price at which the public sector is obtaining a medicine and its comparators is detailed clearly. Prices for comparators already funded can be sourced from the Master Health Product List found on the National Department of Health's website: http://www.health.gov.za/tenders/

For the comparators, the SEP and Master Health Product List prices can be compared to each other as well as the average prices determined from the International Pricing Analysis. The difference between the SEP and Master Health Product List price of the comparators can be utilised to achieve an estimated price for the new medicine. This estimated price result, the SEP and the average international price can then be compared for the new medicine.

3.2.6.4 Active pharmaceutical ingredient global supply analysis

Continued access to new and existing medicine is a vital consideration. Thus, a search of active manufacturers producing the medicine should be conducted. The following website can be utlised for medicines by searching for the active pharmaceutical ingredient:

https://www.apisourcing.net/database/

The analysis should conduct a search of any issues related to supply of technologies globally and in South Africa.

4. EVIDENCE APPRAISAL

This section provides brief information on how evidence gathered and produced under Stage 1 and Stage 2 of the TA process can be appraised to ensure it is fit to use for informing decision-making related to selection of medicines to the EML. Further specification of appraisal methods and the interaction with the decision-making process will be developed in further iterations of this Guide in consultation with stakeholders and existing committee structures.

Appraisal is a critical step in a HTA process, applying a quality and consistency check on the analysis and ensuring that the analysis aligns to the needs of the decision. Failure to adequately appraise the evidence can lead to inconsistent and sub-optimal decisions, and it is important that appraisal is conducted consistently and independently of the assessment functions.

The Evidence Appraisal methods should be read in conjunction with a HTA Process Guide which will determine the role in terms of Appraisal of the different actors within the HTA process, including the EDP secretariat, NEMLC, ERCs and contracted external experts.

The methods for Appraisal should adapt to the status and approaches used for conducting analysis and generating evidence. Under the current process, the EDP secretariat, ERC and contracted external experts undertake the majority of analysis. If the EDP HTA process is expanded to incorporate wider stakeholder input for the analysis (such as eliciting HTA Technical Reports from manufacturers or consultancies), a more rigorous Appraisal methodology and process will be required to reflect the explicit interests of those conducting the analysis.

It is expected that the Assessment and Appraisal process will be iterative under current analytical resource capacity, meaning that as aspects of analysis are appraised, the analyst or Reviewer will be asked to adjust and correct for any elements found to be insufficient at the Appraisal step.

A key tool in the Appraisal of evidence produced in the Assessment phase is this Guide. The approach to appraising the each type of analysis performed in the EDP HTA Process should apply the methodological specifications of this Guide. Major questions that should be considered when appraising the evidence include:

- Is the analysis relevant to all groups of patients who could potentially use the technology as described in the TA Scope?
- Is the indication being assessed consistent with the conditions of registration as determined by SAHPRA?
- Is the comparator justified?
- Has a thorough search for relevant clinical evidence been conducted?
- Have the clinical evidence presented been appraised appropriately?
- Does the key clinical evidence in the Technical Review Report support the indication being assessed?
- Are the clinical outcomes of the studies clearly defined, relevant and justified from a South African perspective?
- How relevant (generalisable) is the analysis to clinical practice in South Africa?
- What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?
- What further analyses should be carried out to enhance the robustness or completeness of the results to enable decision-making?
- Have non-health factors been taken into account?
- What are the relevant research recommendations as a result from the analysis?

The main output of the Appraisal step is a validation of the Evidence to Decision Framework (EtDF) that is included in the Technical Review Report. The EtDF serves to indicate key evidence taken into account by the Committee and its views on the evidence and highlight any areas of contention and uncertainty that have arisen during the Committee discussion.

A validated EtDF is used to form the recommendations under the EDP HTA process and communicate and consult on recommendations. The process for communication and consultation will be developed further in a HTA process guide.

ABBREVIATIONS

AGREE II	Appraisal of guidelines and research and evaluation II
AH ERC	Adult Hospital Level Expert Review Committee
AMSTAR	A MeaSurement Tool to Assess Systematic Reviews
BIA	Budget Impact Analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-Effectiveness Analysis
CPG	Clinical Practice Guideline
DALY	Disability Adjusted Life Year
EDP	Essential Drugs Programme
EML	Essential Medicines List
ERC	Expert Review Committee
EtDF	Evidence to Decision Framework
EUnetHTA	European Network for Health Technology Assessment
GIN	Guidelines International Network
GPS-Health	Guidance for Priority Setting in Health Care Framework
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HITAP	Health Intervention and Technology Assessment Program
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
MPR	Medicine Price Registry
NDoH	National Department of Health
NEMLC	National Essential Medicines List Committee
NICE	National Institute for Health and Care Excellence
PICOS	Population, Intervention, Comparator, Outcomes, Study Design
PHC ERC	Primary Health Care Level Expert Review Committee
PH ERC	Paediatric Hospital Level Expert Review Committee
PI	Prescribing Information
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PTC	Pharmaceutical and Therapeutics Committee
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trials
RR	Rapid Review
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority

SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SORT	Strength of Recommendation Taxonomy
SR	Systematic Review
STG	Standard Treatment Guideline
TA	Technology Assessment
T&Q EMR	Tertiary and Quaternary Level Essential Medicines Recommendations
T&Q ERC	Tertiary and Quaternary Level Expert Review Committee
UHC	Universal Health Coverage
WHO	World Health Organisation

GLOSSARY

ABC Analysis	The ABC analysis is an inventory categorization method, used to monitor costs and the rational use of medicines. Items are divided into 3 categories (A, B and C) based on value of usage over a period of time. The ABC analysis uses the following value classification (using percentage of cumulative value): • Group A items - 80% of expenditure and an estimated 20% of total items. • Group B items - 15% of expenditure and an estimated 30% of total items. • Group C items - 5% of expenditure and an estimated 50% of total items.
Basic cost-effectiveness analysis	A cost-effectiveness analysis conducted under Stage 2 of the EDP HTA process requiring fewer resources than a Comprehensive cost-effectiveness analysis
Brief Technical Review Report	An urgent, abbreviated Technical Review Report to inform a decision regarding the inclusion or exclusion of the medicine to the EML or T&Q EMR. Completed by one reviewer in 1-2 weeks.
Budget impact analysis	An analysis conducted under Stage 2 of the EDP HTA process to estimate the potential financial consequences due the introduction of a technology from a defined budget perspective.
Comprehensive cost-effectiveness analysis	A cost-effectiveness analysis conducted under Stage 2 of the EDP HTA process which requires more resources than a Basic cost-effectiveness analysis
Cost-comparison analysis	An analysis conducted under Stage 2 of the EDP HTA process comparing only direct costs related to the technology being assessed, and its comparators
Cost-effectiveness analysis	Used to compare costs and effects of treatment alternatives using a common outcome measure e.g. cost per hospitalisations averted or exacerbations treated. Generates a summary measurement of efficiency (a cost-effectiveness ratio)
Equity considerations	A contextual assessment of the impact on equity in the South African context as a result of listing the medicine on the EML. Included in the Technical Review Report
Essential Drugs Programme	The EDP is a unit within the Affordable Medicines Directorate and is the secretariat for NEMLC and the ERCs
EDP HTA Reference Case	The set of methodological specifications that should be applied consistently to determine the approach to a Basic CEA or Comprehensive CEA.
Essential Medicine	A medicine that satisfies the priority health care needs of the population and is selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness. The EML status of a medicine is independent of its pack size but is dependent on its dosage form and indication.
Essential Medicines List	The list of medicines determined by the National Essential Medicines List Committee (NEMLC) appointed by the Minister of Health and maintained by the Essential Drugs Programme (EDP). The national EML is deemed to satisfy the priority health care needs of the population.

Expert Review Committee	Technical advisory committees that make recommendations to NEMLC regarding a specific technology after an assessment of the available clinical and cost-effectiveness evidence
Feasibility considerations	A contextual assessment of the likely health system readiness for implementing the use of the technology being assessed
Health Technology Assessment	HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system (INAHTA definition)
Lead Reviewer	ERC member or contracted external reviewer responsible for drafting the TA Scope and conducting the analysis under the EDP HTA process
Multiple Technology Topic	A technology topic that comprises multiple technologies in the same class for the same indication
National Essential Medicines List Committee	The non-statutory, advisory committee appointed by the Minister of Health, responsible for the development and management of the national EML and STGs. The STGs and EML guide clinical practice at all public sector health establishments and inform procurement of medicines in the public sector.
Pricing Analysis	An analysis conducted under Stage 2 of the EDP HTA process. Comparison of prices for a specific technology and formulation in selected countries (International Pricing Analysis) and in South Africa (Local Pricing Analysis)
Rapid Systematic Review	An additional clinical analysis conducted under Stage 2 of the EDP HTA process requiring lower resources than a standard systematic review
Rapid Review of Economic Evaluations (RREE)	An analysis conducted under Stage 2 of the EDP HTA process. A review of economic evaluations conducted by HTA agencies or published in peer reviewed journals
Single Technology Topic	A technology topic that comprises a single technology for a single indication
Standard Systematic Review	An additional clinical analysis conducted under Stage 2 of the EDP HTA process requiring more resources than a rapid systematic review
Standard Technical Review Report	A Technical Review Report compiled for to inform a decision regarding the inclusion or exclusion of the medicine to the EML or T&Q EMR. Completed by 2 or more reviewers over 3-4 weeks.
Standard Treatment Guidelines	The implementation mechanism of the EML which provides guidance to health care professionals on the use of medicines which appear on the EML and consists of a collection of chapters containing disorder groups, background information on the disorder, treatment regimens, as well as other relevant information.
Technical Review Report	Report compiled for every TA under Stage 1 of the assessment
Technology Assessment	Formal assessment of a technology that has undergone topic prioritisation and been selected for assessment by NEMLC
Technology Assessment Code	Code assigned to each topic identified by EDP for assessment
Technology Assessment Motivation form	Form template utilised for stakeholders to formally nominate a medicine topic for assessment and potential inclusion on the EML

Technology Assessment (TA) Scope	Document utilised to gather fundamental information such as PICOS for Stage 1 of a TA
Technology Topic	An item involving a technology or multiple technologies proposed for assessment for selection onto the EML
Therapeutic Review	A topic that comprises either multiple technologies from different classes for a single indication, or a single technology with multiple indications within the same therapeutic area
Topic detailing	Second step of the topic prioritisation process whereby technology topics classified as single or multiple technology topics are inputted into the Topic Identification Database and general information on the topic is collected
Topic Identification and Classification	First step of the topic prioritisation process whereby technology topics nominated and identified by NDoH are collected and categorised according to technology type and type of assessment required
Topic Identification Database	Excel tool utilised to conduct the first steps of the topic prioritisation process 'Topic Identification and Classification' and 'Topic Detailing'
Topic Ranking	A step in the topic prioritisation process whereby technology topics that fulfilled screening criteria are assessed on several weighted prioritisation criteria resulting in a ranking of topics for selection in order of priority.
Topic Prioritisation	The process of choosing which technologies should be considered within the EDP HTA process
Topic Prioritisation Framework	Framework developed to guide the technology topic prioritisation process
Topic Prioritisation Tool	Tool utilised to rank technology topics during step 4 of the topic prioritisation process ('Topic Prioritisation') that have passed Topic Screening
Topic Referral	A step in the Topic Prioritisation process whereby the ranked list of medicine topics is presented to NEMLC for review and final selection.
Topic Screening	A step in the Topic Prioritisation process whereby technology topics are screened for eligibility to be assessed through the EDP HTA process.

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APPENDIX 1. ECONOMIC EVALUATION CRITICAL APPRAISAL CHECKLIST

Questions:	Yes/No*	Score**
1. Was a well-defined question posed in answerable form?		
1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?		
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?		
2.1. Were there any important alternatives omitted? 2.2. Was (should) a do-nothing alternative be considered?		
3. Was the effectiveness of the programme or services established?		
3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Was effectiveness established through an overview of clinical studies? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?		
4. Were all the important and relevant costs and consequences for each alternative identified?		
4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?		
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?		
5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? 5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?		
6. Were the cost and consequences valued credibly?		
6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as donated clinic space), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?		
7. Were costs and consequences adjusted for differential timing?		
7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was there any justification given for the discount rate used?		
8. Was an incremental analysis of costs and consequences of alternatives performed?		
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?		
9. Was allowance made for uncertainty in the estimates of costs and consequences?		
9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed? 9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)? 9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?		
10. Did the presentation and discussion of study results include all issues of concern to users?		
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. ICER)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups? 10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)? 10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?		
Total		**/10**

Adapted from Drummond M et al.(28)