HEALTH TECHNOLOGY ASSESSMENT METHODS GUIDE 2022–2027

To inform inclusion or exclusion of medicines for the South African national Essential Medicines List

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HEALTH TECHNOLOGY

ASSESSMENT METHODS GUIDE

2022–2027

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RECORD OF UPDATES

Date	Version	Summary of changes
14 June 2021	1.2	Draft HTA Methods Guide issued for comment [public consultation initiated on 15 July 2021]
11 July 2022	2.0	Major revision of HTA Methods Guide based on consultation responses received

Table of Contents

Templates ii
Foreword iii
Acknowledgements iv
Abbreviations vi

CHAPTER ONE: Background 1
CHAPTER TWO: Introduction 4
CHAPTER THREE: Medicine/s assessment scope development 9
CHAPTER FOUR: Assessment 12
4.1 Stage 1: Technical review report 12
4.2 Stage 2: Additional analysis 27
CHAPTER FIVE: Evidence checklist 59

Glossary 60
References 62

APPENDICES 66
APPENDIX ONE: Expert opinion 66
APPENDIX TWO: Estimation of healthcare resource utilisation and costs 67
APPENDIX THREE: Evidence-to-decision framework 75
APPENDIX FOUR: Areas for further research and/or consultation 77

Templates

A major benefit of using a Methods Guide within a Health Technology Assessment (HTA) process is consistency and comparability in gathering and reporting information. The application of this HTA Methods 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. Medicine/s Assessment Motivation Template
2. Medicine/s Assessment Scope Template
3. Technical Review Report Template
4. Rapid Review of Economic Evaluations Template
5. Cost-Effectiveness Analysis Template
6. Cost-Minimisation Analysis Template
7. Budget Impact Analysis Template

Foreword

The purpose of the Health Technology Assessment Methods Guide is to provide detailed guidance on the processes and methods to follow when prioritising topics for assessment, developing a scope for a technology assessment, assessing a medicine or group of medicines, and reporting the assessment findings. These findings will be submitted for use in guiding decision making related to the inclusion or exclusion of medicines on South Africa's Essential Medicines List (EML). The Guide is designed to be used within the existing decision-making context of the Essential Drugs Programme (EDP) and does not include guidance on the accompanying process, resource requirements, or relevant legislative frameworks.

This first version of the Guide serves as an introduction to the EDP health technology assessment (HTA) methods and will be used as a baseline on which to build further methods specification, in consultation with stakeholders. The approach to medicine/s assessment described in this Guide will be piloted using the current analytical and technical capacity of the EDP and its contributors, and the learning will influence future updates. It is expected that the Guide will be updated regularly as the methods become established and accepted, while the frequency of later updates will be dependent on changes in the HTA landscape in South Africa and international good practice. Specific areas for further research, and methodological and procedural development, is included in Appendix 4.

Although this Guide deals predominantly with the medicine/s assessment, as the scope grows, the HTA process will be expanded to include medical devices in the future. The Guide can be used by anyone who prepares technical documentation for medicine assessments but is specifically designed to be used as part of the EDP EML review process, as coordinated by EDP staff.

The Guide was developed to promote comparability across medicine assessments by providing clear guidance on the methods for gathering, producing and reporting evidence on clinical efficacy, safety, cost-effectiveness and affordability, as well as factors like equity, feasibility and acceptability. The Guide presents the preferred methods for the assessment of medicines, so adaptation of the methods and templates will be required in some instances to address the many different types of review questions that fall within the remit of the EDP work plan.

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DIRECTOR-GENERAL: HEALTH
DATE: 01 September 2023

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i The EDP coordinates the assessment of all medicines that fall within the scope of the EML, the Standard Treatment Guidelines, and the Tertiary and Quaternary Hospital Level Essential Medicines Recommendations. The scope of this Guide applies to medicines only in the form of an individual medicine or a class of medicines to be added or removed from the EML. Medicines are defined in line with the definition of the South African Health Products Regulatory Authority (SAHPRA) definition of an "orthodox medicine" (55).

Acknowledgements

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 methods that have been put into place in the review of the EML and Standard Treatment Guidelines.

In particular, this guide builds on the following documentation produced by the South African Department of Health and its associated committees:

- Essential Drugs Programme Reviewer's manual (1)
- Methods guide for rapid reviews for COVID-9 medicine reviews (2)
- Previous medicine reviews and economic analyses (3)
- Guidelines for Pharmacoeconomic Submissions in South Africa (4)

In addition, the development of the Guide included a review of the methods 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
- The Pharmaceutical Benefits Scheme (PBS), Australia https://www.pbs.gov.au/
- Republic of the Philippines Health Technology Assessment, Philippines https://hta.doh.gov. ph
- Health Intervention and Technology Assessment Program (HITAP), Thailand https://www. hitap.net
- Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, International https://www.gradeworkinggroup.org/
- Cochrane Training, International https://training.cochrane.org
- Canadian Agency for Drugs and Technologies in Health (CADTH), Canada https://www. cadth.ca
- Pharmaceutical Management Agency (PHARMAC), New Zealand https://pharmac.govt.nz
- The Professional Society for Health Economics and Outcomes Research (ISPOR) https:// www.ispor.org/
- Haute Autorité de Santé (HAS), France https://www.has-sante.fr/
- 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
- Scottish Medicines Consortium (SMC), Scotland https://www.scottishmedicines.org.uk
- All Wales Medicines Strategy Group (AWMSG), Wales https://awmsg.nhs.wales
- National Centre for Pharmacoeconomics (NCPE Ireland), Ireland http://www.ncpe.ie
- The International Decision Support Initiative Reference Case for Economic Evaluation, https://idsihealth.org/resource-items/idsi-reference-case-for-economic-evaluation/

This Guide was drafted under the Better Health Programme South Africa by Tommy Wilkinson and Maryke Wilkinson in consultation with the staff of the Essential Drugs Programme (EDP), National Department of Health and the supporting ministerially appointed Expert Review Committees and National Essential Medicines List Committee. Background contextual information for the Guide was developed with assistance from Kim MacQuilkan.

The United Kingdom's (UK) Better Health Programme (BHP) is a global health system strengthening programme led by the UK Foreign, Commonwealth and Development Office (FCDO) and delivered in South Africa by Mott MacDonald.

The NDOH team thanks all the stakeholders who responded to the public consultation on the first iteration of the HTA Methods Guide. Feedback and input not only improved the contents of the HTA Methods Guide but also confirmed the need to further develop and strengthen HTA systems and processes in South Africa.

For their extensive and highly technical review of all aspects of the Guide, we would like to thank:

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- The International Decision Support Initiative (iDSI)

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We note that providing a response to consultation on the HTA Methods Guide does not necessarily indicate endorsement of content.

Abbreviations

AGREE II	Appraisal of guidelines and research and evaluation II
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
CMA	Cost-Minimisation Analysis
CPI	Consumer Price Index
DALY	Disability Adjusted Life Year
EDP	Essential Drugs Programme
EML	Essential Medicines List
EUnetHTA	European Network for Health Technology Assessment
GIN	Guidelines International Network
GPS-Health	Guidance for Priority Setting in Healthcare Framework
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HITAP	Health Intervention and Technology Assessment Programme
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
NICE	National Institute for Health and Care Excellence
PICOST	Population, Intervention, Comparator/s, Outcome/s, Study Design/s, Time Horizon
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SAHPRA	South African Health Products Regulatory Authority
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
WHO	World Health Organization

CHAPTER ONE

Background

ASSESSMENT OF MEDICINES IN SOUTH AFRICA'S PUBLIC HEALTH SYSTEM

The Essential Drugs Programme (EDP) established under the National Drug Policy (1996) (5) aims to ensure that affordable, good quality essential medicines are always available, in adequate amounts, in appropriate dosage forms, and to all South African citizens. Healthcare demands are continually growing in the resource-limited environment in which the South African public health sector operates. New medicines entering the South African market hold the potential for improved health outcomes but often at an additional cost to the health system, while medicines already in use do not always represent the most cost-effective approaches to managing the health of the population. 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.

To make these complex healthcare decisions, the EDP aims to utilise the best available evidence using an approach that is systematic, unbiased, and transparent. Like many other developing health technology assessment (HTA) systems, the EDP faces many challenges in its medicine review process, including limited technical expertise in South Africa to effectively produce and interpret evidence, lack of resources and weak health data infrastructure. The HTA Methods Guide will help reduce some of these challenges and is designed to be used as part of the EDP process using existing skills and capacity.

The process of determining which medicines are included in the Essential Medicines List (EML) is briefly described below for context but falls outside the scope of the HTA Methods Guide.

OVERVIEW OF ESSENTIAL MEDICINES LIST ASSESSMENT PROCESS

The EML is a list of medicines that should be available to all South African citizens when they access the public health system at a particular level of care. Addition or removal of essential medicines on the EML takes place after an assessment of the available evidence (considering efficacy, safety, cost-effectiveness, affordability and other relevant issues), and forms part of the broader Standard Treatment Guideline review process. The Standard Treatment Guidelines are the implementation mechanisms for the EML and provide guidance to healthcare professionals on the rational use of the essential medicines at a particular level of care.

The Tertiary and Quaternary Level Essential Medicines recommendations 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. The EDP unit coordinates the assessment of all medicines that fall within the scope of the EML, Standard Treatment Guidelines, and Tertiary and Quaternary Level Essential Medicines recommendations.

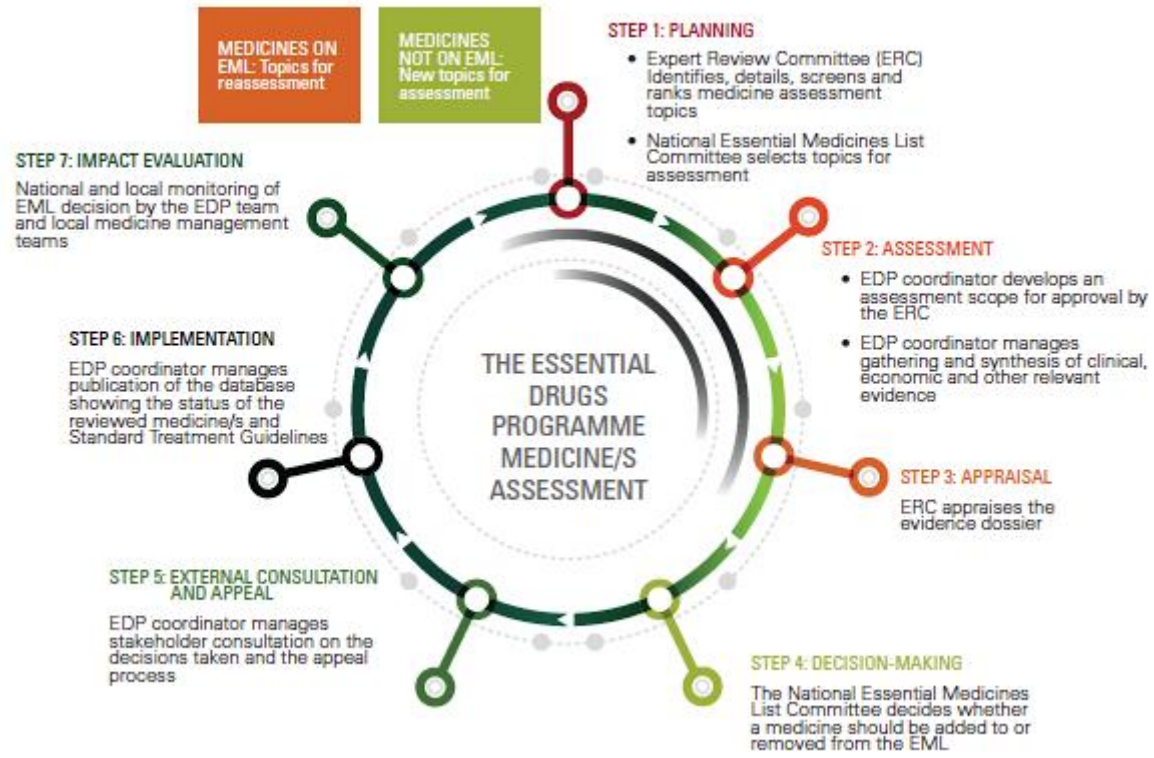

Figure 1. The Essential Drugs Programme medicine/s assessment process

EDP – Essential Drugs Programme, EML – Essential Medicines List

Expert Review Committees are technical advisory committees convened through the EDP to support creation and maintenance of South Africa's EML, Standard Treatment Guidelines, and Tertiary and Quaternary Level Essential Medicines recommendations. There are currently three Expert Review Committees, each aligned with specific levels of care: (1) Primary Healthcare and Adult Hospital Level, (2) Paediatric Hospital Level, and (3) Tertiary and Quaternary Level. The recommendations made by the Expert Review Committees feed into the National Essential Medicines List Committee, which is the designated decision-making authority responsible for selecting (or deselecting) the medicines that should be available for use in the public sector at a particular level of care.

Medicine topics are identified through established routes, including medicine motivation forms submitted by stakeholders. Topics can be "new" medicines to be considered for addition to the EML, medicines that are currently on the EML but its position should be re-assessed (i.e., to consider removal from EML), or new indications for medicines already listed on the EML. Only medicines approved for use by the South African Health Products Regulatory Agency

(SAHPRA) can be considered for listing on the EML. Medicine topics are screened and ranked in order of priority by the Expert Review Committees (process coordinated by EDP staff), with the final selection of topics for assessment determined by the National Essential Medicines List Committee.

Prior to initiating the assessment of the medicine/s, the assessment scope is developed by an EDP review coordinator, in collaboration with the lead reviewer assigned to that review (typically a member of the relevant Expert Review Committee) and other stakeholders, and this scope must be approved by the Expert Review Committee. The scope of a review may include the assessment of one or more new medicines (used for a single indication), and the medicine/s may be compared to multiple comparators, if relevant.

The preparation of the technical documentation for medicine assessments (termed "medicine/s assessment" in this Guide) is commissioned and/or managed by an EDP staff member. Medicine/s assessment teams for a particular topic usually consist of the lead reviewer and independent reviewers with experience in conducting evidence syntheses co-opted to support the assessment process.

The Expert Review Committees appraise the evidence produced and make recommendations to the National Essential Medicines List Committee. The National Essential Medicines List Committee reviews the recommendations and evidence appraised by the Expert Review Committees and makes the decision to approve an update to the EML, Standard Treatment Guidelines, or Tertiary and Quaternary Hospital Level recommendations, or not.

The decision made by the National Essential Medicines List Committee is made available to stakeholders for comment, with the relevant medicine/s assessment documents published on the National Department of Health website. Any comments received are reviewed and addressed by the relevant Expert Review Committee, after which the final recommendation is sent to the National Essential Medicines List Committee for ratification. Decisions made in the development of the National EML can be appealed (6).

The medicine/s review process convened by the EDP is summarised in Figure 1. This simple representation is focussed on the direct technical inputs and outputs of the EDP HTA process for medicines only, with the unit or committee responsible for the activity indicated in brackets.

CHAPTER TWO

Introduction

In coordinating medicine/s assessments the EDP considers the urgency of the decision, the level of uncertainty and available resources. A two-tiered approach to medicine/s assessments is thus proposed in the HTA Methods Guide.

Stage 1 assessment involves development of the Technical Review Report using a consistent approach to identifying, selecting, assessing and presenting basic evidence relating to the medicine/s under review compared to its comparator/s. It is expected that in most cases the Technical Review Report would yield enough evidence to inform a decision regarding inclusion or removal of medicine/s on the EML or the Tertiary and Quaternary Level Essential Medicines recommendations. However, the Technical Review Report may need to be augmented by one or more of the Stage 2 analyses if there is significant uncertainty that cannot be addressed using the methods proposed for a Stage 1 assessment.

The need for one or more Stage 2 analyses can be identified:

- *Prior to* development of the Technical Review Report – in which case the Stage 2 analyses and the Technical Review Report will be produced at the same time (preferred option)
- *During* development of the Technical Review Report when gaps in the evidence base become apparent – in which case the Stage 2 analyses will be produced around the same time as the Technical Review Report
- *After* appraisal of evidence by the Expert Review Committee and/or the National Essential Medicines List Committee – in which case the Stage 2 analyses will be produced after the Technical Review Report

The types and level of evidence that should be produced (Stage 1 assessment and/or different types of Stage 2 analyses) to inform a decision regarding the inclusion or removal of medicine/s on the EML or the Tertiary and Quaternary Level Essential Medicines Recommendations will be documented in the Medicine Assessment Scope (and updated as needed), with the initial scope and any subsequent changes to the scope approved by the relevant Expert Review Committee.

Given the constraints on analytical resources and available evidence, the use of limited analytical resources to produce Stage 2 analyses must be prioritised to make decisions in situations with the highest level of uncertainty. In addition, the process for quality assuring any Stage 2 analyses and a clear indication of how the findings will inform the EML decision need to be determined before undertaking the analyses.[ii]

[ii] See Appendix 4: Areas for further research and consultation. A framework for quality assessment of Stage 2 analyses and the methods for appraisal and decision-making are not included in this Guide as it requires further consideration and engagement. These work areas should be prioritised to enable more explicit guidance in future iterations of the Guide.

The production and use of Stage 2 analyses must be consistent in order to enable coherent and procedurally sound decision-making. As the use of Stage 2 analyses to inform decision-making in South Africa evolves, these methods should be updated and refined to improve specificity and fitness for purpose for particular decision problems.

Stage 1: Technical Review Report

A Technical Review Report will be compiled for all medicine/s assessments. The Technical Review Report will contain the medicine/s details, a description of the scope of the assessment, an evaluation of the comparative clinical evidence, a calculation of the acquisition costs of the medicine/s and comparator/s, identification of relevant healthcare costs, a summary of decisions made by other HTA agencies (if available), as well as a description of the equity, patient values and preferences, acceptability, and feasibility considerations.

Stage 2: Additional analysis

For medicine topics that require different or more complex analytical assessment of the clinical and economic data than that which is provided in the Technical Review Report, trade-offs will need to be made between certainty of evidence, urgency and available resources. Additional analysis may not necessarily reduce the uncertainty associated with the decision and careful consideration should thus be given to the value of any additional analysis conducted. For example, if there is insufficient clinical evidence to support the use of a medicine, there is no value in conducting an economic evaluation on that topic.

Expert clinical input is required when producing Stage 2 analyses to ensure that assumptions are plausible and reflect clinical practice scenarios. Quality assurance of the analyses (from both a clinical and technical perspective) should be conducted prior to appraisal by Expert Review Committees.

More than one type of Stage 2 analyses can be commissioned, and the analyses can be completed sequentially or in parallel to each other and/or to the Technical Review Report.

Figure 2 presents typical considerations when determining the appropriate Stage 2 analysis for the medicine/s assessment.

A Stage 2 assessment of the clinical evidence by means of a systematic review may be required if, compared to existing treatments, there is significant uncertainty regarding the clinical effect of a medicine (see Section 4.2.1: Systematic Review).

If there is significant uncertainty about the cost-effectiveness of a medicine used in the South African public health sector, it is advisable to first conduct a detailed review of published economic analyses and economic evidence to determine whether a new economic evaluation is warranted based on quality and applicability criteria (see Section 4.2.2.1: Rapid Review of Economic Evaluations). This includes a review of analyses published by other HTA agencies and analyses produced to inform medicine access decisions in the South African private sector. If a *de novo* economic evaluation is to be conducted, this Guide details the specifications for three sub-types: a cost-effectiveness analysis using natural units (CEA), a cost-utility analysis.

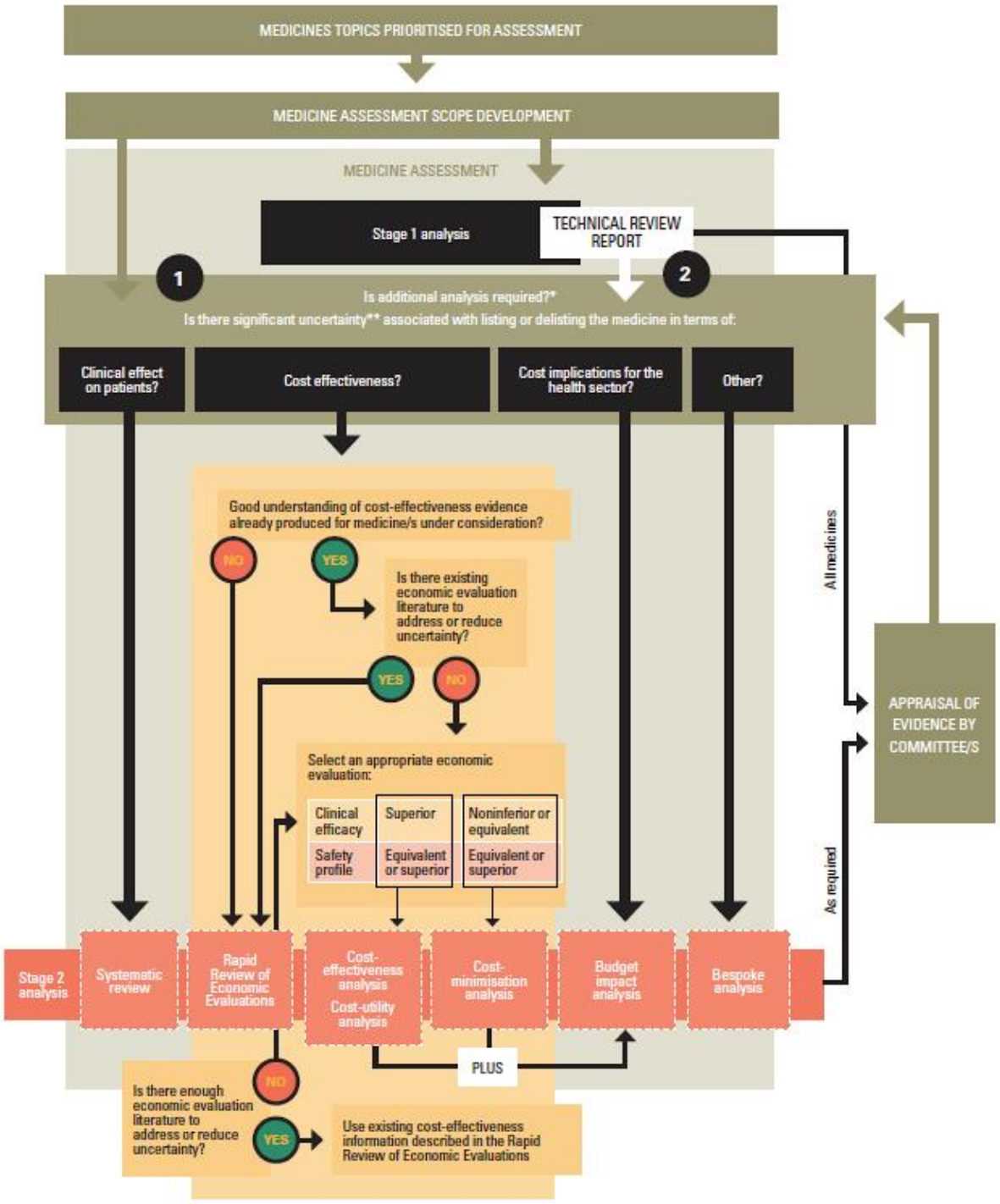

Figure 2. Determining type of analysis required for medicine/s assessment

* Need for additional analysis may be determined (1) prior to the development of the Technical Review Report as part of the medicine/s assessment scope development, and conducted in parallel with the Technical Review Report development, or (2) during the development of the Technical Review Report based on gaps in the evidence base identified, or (3) after appraisal of evidence by the Expert Review Committee and/or the National Essential Medicines List Committee

** Significant uncertainty that will not be addressed by evidence presented in the Technical Review Report

(CUA) (see Section 4.2.2.2: Cost-effectiveness analysis and Cost-utility analysis) and a cost- minimisation analysis (CMA) (see Section 4.2.2.3: Cost-minimisation analysis).

Due to limited analytical resources available at this time, it is expected that economic evaluations will be conducted for a limited number of medicines per year (prioritised based on level of uncertainty regarding cost-effectiveness and the potential budget impact), with the expectation that the number of economic evaluations conducted will increase as capacity and resources for HTA functions grow.

A CEA/CUA should only be initiated to inform decisions about medicines where there is confidence that there is superior clinical efficacy compared to the comparator/s, but for which the cost-effectiveness in the South African context is uncertain.

Undertaking a resource-intensive CEA/CUA when it is not entirely necessary limits the analytical capacity to undertake other analyses. If the clinical efficacy o f a medicine is non-inferior or equivalent to the comparator/s and the safety profile superior or equivalent, a CMA should be sufficient to answer an economic review question.

A budget impact analysis (see Section 4.2.3: Budget impact analysis (BIA)) can be requested as an additional Stage 2 analysis by itself, but should be conducted alongside a CEA/CUA/CMA to ensure that both "value for money" and "affordability" (in terms of expected impact on local budgets) are considered.

If another type of analysis (not described in this Guide) should be conducted to address a particular review question, the remit of the analysis must be clearly described in the medicine/s assessment scope. For example, use of qualitative evidence (primary studies or reviews) may be required to inform understanding of some review questions.

An outline of each type of Stage 2 analysis is given in Table 1. A detailed description of the methods is provided later in the document.

TABLE 1. STAGE 2 ADDITIONAL ANALYSIS

Type		Description	Resource requirements	Estimated lead time*
Clinical	Systematic Review	Aims to identify, appraise and synthesise all the empirical evidence that fits pre- specified eligibility criteria to answer a specific research question. Researchers use explicit, systematic methods selected to minimise bias. This will produce more reliable findings to inform decision-making (7).	High	Analyses: 6 months + Quality check: 1 month
Cost-effectiveness	Rapid review of economic evaluations (RREE)	Reviews economic evaluations conducted by health technology assessment agencies or published in peer-reviewed journals.	Medium	Analyses: 2-3 months Quality check: 1 month
	Cost-Effectiveness Analysis (natural units)	Compares costs and effects of treatment alternatives using a common outcome measure e.g., cost per hospitalisations averted or exacerbations treated.	Medium to high	Analyses: 3-6 months Quality check: 1 month
	Cost-Utility Analysis	Compares costs and effects of treatment alternatives using a generalised outcome measure that incorporates positive and negative effects on mortality and morbidity e.g., Quality Adjusted Life Year (QALY) or Disability Adjusted Life Year (DALY) averted.	High	Analyses: 3-6 months Quality check: 1 month
	Cost-Minimisation Analysis	Compares cost of two regimens or formulations. Analysts consider aspects like costs of treatments and human resources, and clearly state the assumptions made when conducting the analysis.	Medium	Analyses: 2-3 months Quality check: 1 month
Cost implications	Budget Impact Analysis	Assesses the potential financial consequences of introducing the medicine/s in a particular level of care.	Medium	Analyses: 2-3 months Quality check: 1 month
Bespoke	Variable	Specifies what is needed and how the additional analysis will assist the decision problem e.g., pricing analysis; analyses for multi-disease programmes; qualitative data analysis to evaluate equity, preferences, values and/or acceptability; WHO Essential Medicines List information; regulatory status of medicine/s in other countries.	Dependent on analysis required	Dependent on analysis required

* Estimated lead times will be revised based on feedback from pilot projects to reflect feasible timelines that balance efficiency with quality, and adequately take into account the varied availability of South Africa-specific data. Although revisions to analyses are often required in the course of a medicine assessment, the time and resources required for this have not been taken into account in the estimated lead times.

CHAPTER THREE

Medicine/s assessment scope development

A clear, well-defined scope developed for each medicine/s assessment will provide a framework for gathering and analysing the evidence required for decision-making by defining what the medicine/s assessment will and will not examine. This will ensure that the findings presented to the relevant committees for appraisal and decision-making will be fit for purpose.

The medicine/s assessment scope will be developed by an EDP coordinator, in collaboration with the lead reviewer and other stakeholders. It is important that the medicine/s assessment scope is drafted with input from clinical and methodological experts, and other relevant stakeholders, to ensure all review questions are identified and clearly defined. Areas where there is significant uncertainty must be identified in the scoping stage, and careful consideration given as to:

1. how best to assess that uncertainty (if possible) – potentially through the generation of evidence using one or more of the analytical approaches described in this Guide
2. the options that are available if the uncertainty cannot be addressed through standard analytical methods and decision makers need to be provided with other types of information or means to aid judgement

The medicine/s assessment scope, and any changes made to it through the course of a medicine/s assessment, must be approved by the Expert Review Committee that will be appraising the evidence.

The scope will include a clear statement about why the assessment is required, accompanied by the review question/s[iii] which can be adapted from the following statement:

> *To assess the [efficacy/ safety/ cost/ cost-effectiveness/affordability/ specify other] of the use of [medicine x1, medicine x2] compared to [comparator y1, comparator y2] for [patient population and disease/condition] in [healthcare setting]*

The medicine/s assessment scope will also provide detailed information about the target Population (including the disease or condition treated or prevented), Intervention/s (medicine/s being assessed), Comparator/s, Outcome/s, preferred Study design/s used to generate evidence included, and the Time horizon (PICOST) that will be considered in the assessment. See Table 2 for a description of the PICOST strategy.

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iii Presenting review questions separately may be more practical in some instances (e.g., clinical and cost-effectiveness review questions). Additional review questions might relate to matters beyond clinical efficacy, costs and cost-effectiveness, e.g., specific implementation considerations.

Recommendations and decisions regarding medicines always involve a balance between health benefits and harms, which requires the inclusion of a comprehensive range of outcomes in the medicine assessment scope. Consideration of all outcomes that are important or critical to patients is required as a minimum; consideration of outcomes important to others (e.g., carers and wider public) are to be included when possible. Availability of outcome data should not determine the choice of outcomes. If there is a lack of or limited evidence available for an important outcome this should be acknowledged (8).

In addition to noting the desirable and undesirable consequences of a medicine to be assessed, any potential issues relating to equity, implementation/feasibility or the acceptability of the medicine/s should also be identified and listed in the scope.

Analyses involving costs and resource use must be conducted from the public-sector payer perspective.

If a medicine (intervention) has more than one indication for which it should be assessed, a separate medicine-assessment scope must be developed for each indication. However, it is possible for more than one medicine to be assessed in a medicine assessment for a single indication.

TABLE 2. PICOST APPROACH TO MEDICINE/S ASSESSMENT SCOPE DEVELOPMENT

Criteria	Details
Population	• Population eligible to receive the medicine/s being assessed. • Include specifics on condition/disease (including severity of disease), age, sex, comorbidities, clinical history and subgroups.
Intervention	• Description of medicine/s being assessed and its proposed place in the current care pathway. • Will it replace a current treatment, be a substitute, be an add-on therapy, or, is it a new treatment if none currently exists? • Include specifics of dose and dosing schedule, duration, delivery mode (including who will administer the intervention/s, if relevant), co-intervention/s, setting (e.g., inpatient/ outpatient) and prescriber level.
Comparator	• All potential comparators should be noted, with an explanation of which comparator/s are selected for the assessment and why. Possible comparators include medicines currently used in clinical practice, medicines recommended in relevant clinical guidelines, best supportive care, or no intervention. • For most assessments, the most relevant comparator/s will be the treatment/s most likely to be replaced with the medicine/s being assessed, or the treatment most often prescribed currently for the management of the disease/condition. • Only medicines approved for use by the South African Health Products Regulatory Agency can be included as comparator/s. • If multiple comparators are included in the assessment scope, it must be made clear whether the recommendations formulated will provide guidance on (1) the inclusion/removal of the intervention medicine on the EML, and (2) whether the recommendations will also indicate a preference for one medicine over the others. • Selection of the comparator/s should not be based on data availability. • When the review question relates to removing a treatment from the EML, the treatment already on the EML will be the comparator. • Include specifics of dose and dosing schedule, duration, delivery mode (including who will administer the intervention/s, if relevant), co-intervention/s, setting (e.g., inpatient/ outpatient) and prescriber level for all comparators that will be assessed in the review.
Outcomes	• Critical and important clinical outcomes directly related to the quality and/or length of a patient's life should be identified and ranked by relative importance. See GRADE handbook for steps for considering the importance of outcomes (8). Clinical outcomes should be specific to the population of interest, may include measures relevant to a particular stage of disease, and should include adverse as well as beneficial outcomes, where relevant. • Critical and important outcomes to be assessed in the Technical Review Report and any additional (Stage 2) analyses should be presented separately. • Use of composite endpoints and surrogate outcomes* should only be considered when evidence about population-important outcomes is lacking (8)
Study designs or data sources to be included	• For clinical efficacy review questions, the following stepwise approach to study design inclusion is proposed (in order of preference): • Systematic reviews and meta-analyses, controlled trials, observational studies. • Data from relevant clinical practice guidelines and health technology assessments should also be considered for inclusion. • Assessment of considerations beyond clinical efficacy will require use of economic and socio-ethical evidence often generated using other study designs or approaches, eg., economic evaluations, costing studies, model-based studies, qualitative studies and cross-sectional studies.
Time horizon/s	• Lifetime or sufficient to capture all relevant differences in costs and effects between the intervention medicine/s and comparator/s. • May vary for clinical and economic outcomes. • The time horizon may be based on a specific line of therapy or treatment sequencing (e.g., for cancer interventions).

CHAPTER FOUR

Assessment

It is essential that the evidence utilised to inform medicine/s use recommendations is trans- parent, relevant and of the highest standard. This section sets out the methods of evidence syntheses to assess the clinical and economic impact of the medicine/s, as well as the relevant equity, feasibility, and acceptability considerations. These methods aim to standardise[iv] the approach to medicine/s assessments and ensure a rigorous product is used to inform EML decisions in the best interest of people in South Africa.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) (9) is the preferred approach for presenting and rating the quality and strength of the evidence included in the medicine/s assessment. GRADE offers a transparent and structured process not only for developing and presenting evidence profiles and summary of findings tables for evidence (especially clinical evidence), but also for carrying out the steps in the HTA process that are not described in this Guide e.g., recommendations developed by bringing together the clinical efficacy evidence with considerations of values and preferences of patients and society.

4.1 STAGE 1: TECHNICAL REVIEW REPORT

The medicine/s assessment scope will specify the population, intervention/s, comparator/s, outcome/s, study design/s and time horizon that will be used to guide the medicine/s assessment and production of the technical documents, including the Technical Review Report.

The Technical Review Report will contain the intervention medicine/s details, a description of the review question/s, an assessment of the comparative clinical evidence (including appraisal of the evidence quality), the costs associated with acquisition of the medicine/s and comparator/s (and associated technologies) plus identification of other relevant costs, a summary of decisions made by other HTA agencies (if relevant), equity considerations, patient preference, values and acceptability considerations, and feasibility considerations. The analyst/s should seek evidence relating to all these domains. Reporting should be aligned to the Technical Review Report template. Any potential conflicts of interest and/or funding received to conduct the review must be declared by the analyst/s and stated in the Technical Review Report.

The official form (Medicine Assessment Scope Template) should be completed and sent to EDP before the review is undertaken. Section 4.1.1 is focussed on the identification, selection, quality appraisal and presentation of clinical evidence, while the approach to evidence generation and reporting for other domains (costs, HTA decisions, considerations of equity, acceptability and feasibility) is presented in sections 4.1.2 to 4.1.6).

iv There may be circumstances under which medicine/s assessments need to be produced urgently, for example in the case of a pandemic. The methods used to prepare those reports may differ from the approach described in here, e.g., see Methods guide for rapid reviews for COVID-19 medicine reviews (3).

4.1.1 Assessment of the clinical evidence

The objective of the clinical evidence assessment is to find, select, critically appraise and describe the clinical evidence relevant to the PICOST review question.

The clinical evidence presented in the Technical Review Report on the efficacy of the medicine/s as compared to its comparator/s will build on existing evidence syntheses where possible; data from primary studies are to be selected for assessment and reporting only if high quality, recent systematic reviews of randomised controlled trials (RCTs) are not available. The approach is similar to the methods followed when conducting an "umbrella review", which is in essence a review of systematic reviews (10).

The proposed methods involve identifying, comparing and critically appraising published systematic reviews and meta-analyses that address the clinical review question, and reporting the best available evidence to decision makers. If no appropriate or recent systematic reviews are available, evidence from RCTs should be presented (in addition to systematic reviews, if relevant). In the absence of appropriate systematic reviews and RCTs, observational studies may be reported. This approach has been adapted from guidance issued by the Cochrane Rapid Review Methods Group (11). Inclusion of other types of evidence beyond systematic reviews, meta-analyses and RCTs (e.g., findings from qualitative studies or cohort studies, registry data, or input from clinical experts) may be needed to improve understanding of the clinical evidence and provide the context for a decision to list or remove one or more medicines from the EML. Relevant recommendations and information sourced from good quality clinical practice guidelines and health technology assessments should also be presented in the Technical Review Report if they are aligned to the medicine/s assessment review question/s.

Assessment of considerations beyond clinical efficacy is likely to require review of economic and socio-ethical evidence generated using study designs or approaches other than systematic reviews and RCTs, and/or necessitate the production or sourcing of new information (e.g., costing analysis, expert opinion). See Sections 4.1.2 to 4.1.6 for more detail.

4.1.1.1 Search strategy and data sources

A systematic search of scientific databases should be conducted to identify all relevant literature for consideration in the assessment of the clinical evidence. In addition, grey literature searches should be conducted to identify relevant clinical practice guidelines, HTA reports and policies.

Systematic literature search

The medicine/s assessment scope is used to inform an explicit search strategy. The search strategy must be reported separately for each relevant review question. An information specialist or experienced reviewer should be involved in determining the search strategy to ensure it meets acceptable methodological standards. 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 (12).

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

- Search terms derived from the population and intervention components of the review question/s. Search terms must be reported separately for each database searched.
- Databases searched
    - The databases searched will be adapted to the topic area as identified by an information specialist or experienced reviewer.
    - Two or more databases should be searched. Examples of databases to search for medicine efficacy/effectiveness studies: Medline (via PubMed), Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Embase, Epistemonikos, and SciELO.
- Limits applied to the search
    - Time period: If a time period is specified for the search, a clinical or methodological justification for restrictions must be provided.
    - Study design: Research evidence of the best quality should be sourced. As part of the PICOST development the most appropriate types of evidence required to address a particular review question will be agreed on.
    - Language: English language publications only.

Grey literature search

A grey literature search should be conducted to identify relevant clinical practice guidelines and other guidance documents (e.g. HTA or regulatory reports). Sources to search include websites of organisations that produce and/or publish clinical practice guidelines or health technology assessments, and medicine regulatory bodies. Although Table 3 lists potential sources, analysts may also check other relevant repositories.

As there is currently no central repository for South African clinical practice guidelines, local guidelines and policies need to be identified using search engines like Google, and by searching governmental and professional society websites and/or South Africa-based journals like the South African Medical Journal (SAMJ). Stakeholders engaged as part of the scoping process should also be asked to identify and provide any guidance documents they are aware of that may be relevant to the review.

TABLE 3. POTENTIAL SOURCES OF INFORMATION 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 Department of Health Guidelines	South Africa	https://www.idealhealthfacility.org.za/
South African Medical Journal (SAMJ)	South Africa	http://www.samj.org.za/
National Institute for Health and Care Excellence (NICE)	England and Wales	www.nice.org.uk/guidance
The National Authority for Assessment and Accreditation in Healthcare (INEAS)	Tunisia	https://www.ineas.tn/publication-0
Scottish Intercollegiate Guidelines Network (SIGN)	Scotland	www.sign.ac.uk
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
HEALTHTECHNOLOGY ASSESSMENT REPORTS		
National Institute for Health and Care Excellence (NICE)	England and Wales	https://www.nice.org.uk/guidance/published?type=ta
Australian Government Department of Health	Australia	https://www.pbs.gov.au/pbs/industry/listing/elements/pbacmeetings/psd/public-summary-documents-by-product
Health Intervention and Technology Assessment Program (HITAP)	Thailand	https://www.hitap.net/en/news-document/document
Haute Autorite De Sante (HAS)	France	https://www.has-sante.fr/jcms/fc_2876008/en/medicament
National Authority for Evaluation and Accreditation in Health	Tunisia	http://www.ineas.tn
International HTA Database	Multinational	https://database.inahta.org/
Institute for Clinical and Economic Review (ICER)	USA	www.icer.org
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/
HEALTH PRODUCT MEDICINE 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)	USA	https://www.fda.gov
GENERAL SOURCES		
Canadian Agency for Drugs and Technologies in Health (CADTH)	Canada	https://www.cadth.ca/index.php/grey-matters-practical-tool-searching-health-related-grey-literature-0

* HAS mainly assesses the relative clinical value of the drug

Expert opinion

Anecdotal evidence or reports from clinical experts regarding the clinical benefit of a medicine should be provided as supporting evidence to contextualise clinical findings and issues relevant to the local context even though it is unlikely that this will be sufficient to support the use of a particular medicine. An approach to eliciting expert opinion is presented in Appendix 1: Expert Opinion.

4.1.1.2 Selection of evidence

Research evidence of the best possible quality should be selected to address review questions, agreed as part of the PICOST development. The use of evidence from studies conducted in South Africa might be required in some instances, especially if prevalence and incidence are important.

Each systematic review, study or guidance document must be assessed against prespecified eligibility criteria. The population, intervention and comparison components of the PICOST strategy form the basis for the eligibility criteria.

The results of database and grey literature searches should be presented graphically in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (13).

Systematic literature search

Title and abstract as well as full-text screening of records retrieved through database searches should be done in duplicate (i.e., the same search is performed by two independent reviewers). Selection of relevant data sources to address a clinical efficacy question will follow a stepwise approach to inclusion based on study design, according to the order shown in Figure 3 below.

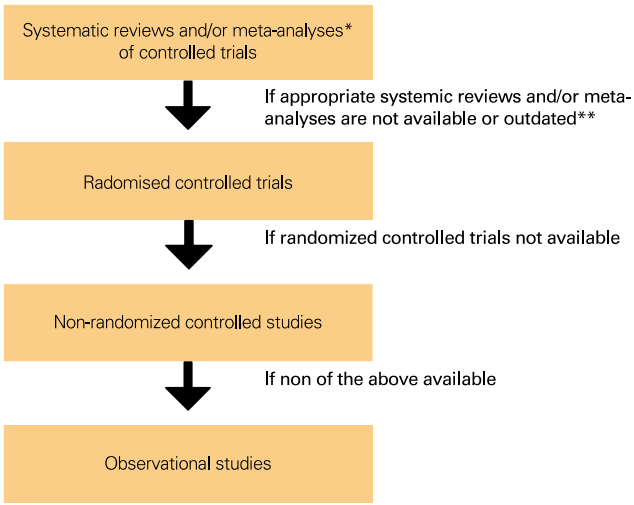

Figure 3. Stepwise approach to inclusion of clinical efficacy studies based on study design

* Including network-meta-analysis if no direct RCTs available

** If high quality, relevant systematic reviews and/or meta-analyses are identified but potentially outdated, a search for primary studies (starting after the search end date specified in the systematic review) should be conducted to ensure all the most up-to-date evidence is identified and presented.

This stepwise approach to inclusion of studies based on study design aims to minimise the risk of bias arising from certain types of study designs. Observational studies, such as controlled cohort and case-control studies, are subject to a range of biases that may lead to over-estimation of the true benefit of the treatment given to the intervention group. Data from other types of quasi-experimental non-randomised designs, for instance, "before-and- after" studies, case series with historical controls, and comparisons of results of two or more single-arm studies, are subject to major and (often) non-quantifiable biases (4). However, use of evidence originating from non-randomised controlled studies may be required to estimate the secondary clinical performance of therapy (such as quality of life, adverse drug reactions, hospitalisation, etc.) where randomised trials are not available or to provide supplementary or contextual information to evidence sourced from systematic reviews and/or RCTs.

Grey literature searches

Identification and selection of clinical practice guidelines and other guidance documents may be completed by a single reviewer.

Relevant clinical practice guidelines and other guidance documents can be identified by assessing medicine review questions and recommendations/decisions made in guidance development (e.g., development of clinical practice guideline or HTA) and by comparing its eligibility to the EDP medicine/s assessment review question/s. If a systematic review of good quality was conducted to inform a relevant recommendation or decision, and detailed methods and findings from the systematic review are available, the systematic review may be presented alongside any other systematic reviews identified.[v]

4.1.1.3 Data extraction

In this step, one reviewer extracts relevant data from selected publications, clinical practice guidelines, and guidance documents, after which the accuracy and completeness of the extracted data must be checked by a second reviewer.

Data fields to extract from the selected publications[vi] include the following:

- study design (including number of studies if relevant, methods, location, sites, groups)
- participant characteristics (specify any relevant subgroups)
- intervention characteristics (specify details including healthcare setting / level of care, conditions of administration)
- comparator/s characteristics (specify details including healthcare setting / level of care, conditions of administration)
- outcomes assessed (specify if critical or important outcomes)

Numerical data for outcomes of interest. Should include at a minimum if it is non-inferior or superior to the comparator, as well as the assumed risk [control group risk of outcome], the corresponding risk [risk of outcome after the intervention is applied], the relative effect [for dichotomous outcomes, this will usually be presented as a risk ratio, odds ratio, or hazard ratio], and the absolute effect [for dichotomous outcomes, the number of fewer or more events in treated/exposed group as compared to the control group](8).

v Include these systematic reviews in the PRISMA diagram under "additional records identified through other sources" if not identified through database searching.

vi Most of these data fields will be needed to produce GRADE evidence profiles

Minimum data fields to extract from clinical practice guidelines and other guidance documents:

- name of the organisation that produced the guidance, and the date of publication
- description of how well the decision space aligns with the medicine assessment review question
- recommendation/decision
- other contextual information required to understand the recommendation/decision

4.1.1.4 Appraisal of evidence sources

Every publication and clinical practice guideline selected for inclusion in the Technical Review Report should be appraised using an appropriate checklist. A single reviewer can rate the risk of bias for the included evidence, with full confirmation of all judgements (and supporting statements) by a second reviewer.

- For systematic reviews and meta-analyses: Use A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) checklist (14), which can be found at https://amstar.ca/ Amstar Checklist.php
- For clinical practice guidelines: Use the Appraisal of Guidelines and Research and Evaluation (AGREE) II tool (15), 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 .
- For randomised controlled trials: Assess risk of bias using the standard Cochrane Risk of Bias Assessment Tool 2.0 (16), 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.
- For non-randomised and/or observational studies: Use relevant tools, e.g.:
  - Centre for Evidence-Based Medicine (CEBM) Oxford appraisal tools (17) https:// www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools,
  - National Institutes of Health (NIH) checklists (18) https://www.nhlbi.nih.gov/health- topics/study-quality-assessment-tools,
  - Critical Appraisal Skills Programme (CASP) checklist (19) https://casp-uk.net/casp- tools-checklists/
- For qualitative studies: Use relevant tools, for example:
  - Critical Appraisal Skills Programme (CASP) checklist (19) (https://casp-uk.net/casp- tools-checklists/)
  - GRADE-CERQual for assessing confidence of evidence from reviews of qualitative research (20) https://www.cerqual.org/
- For network meta-analysis: Assessing the risk of bias and quality of a network meta-analysis is more challenging than for a regular meta-analysis. Therefore, if data from a network meta-analysis is included in the Technical Review Report, the quality must be assessed by an expert in the field of network meta-analysis. The approach to undertaking network meta-analyses presented in the Cochrane Handbook (21) can be used to appraise risk of bias and quality.

4.1.1.5 Evidence synthesis

Systematic reviews, meta-analysis and network meta-analysis: The results of systematic reviews and meta-analyses may be presented as a narrative synthesis. Outcomes measured and the measures of effect with reported ranges should be compared across studies and presented in summary tables along with a description of the methodological quality of the study (see GRADE handbook for approach to producing GRADE evidence profile and summary of findings table) (8). Efficacy data and safety data should be presented separately whenever possible to facilitate interpretation of the results.

If data from a published network meta-analysis is included in the Technical Review Report, presentation of the findings may require input from an expert in the field. If a new network meta-analysis is conducted, the use of accessible and user-friendly tools like NetMetaXL should be considered (22).

Primary studies: If no acceptable systematic reviews are available, or if new RCTs have been published since the search end-date of relevant systematic reviews identified, primary studies should be summarised narratively along with a description of the methodological quality of the studies. If included RCTs are sufficiently homogeneous in terms of design, population, interventions and comparators, and report the same outcome measures, the reviewer may choose to undertake a meta-analysis, using standard Cochrane methodology (23).

Clinical practice guidelines and other guidance documents: Relevant recommendations/ decisions will be summarised narratively with all the relevant recommendations presented in a table.

Information on adverse drug reactions listed in the medicine's Prescribing Information approved by South African Health Products Regulatory Agency (SAHPRA) (24) should be reviewed and included if not assessed adequately in the clinical evidence included.

4.1.1.6 Interpretation of clinical efficacy and safety evidence

The conclusions from the clinical data as supporting clinical superiority, similarity, non-inferiority or equivalence compared to the comparator/s assessed for each patient-relevant clinical efficacy and safety outcome may be presented as follows:

> "In [target population and disease or condition to be treated], [proposed medicine/s] is no worse than/as effective as/more effective than [comparator/s] at improving/reducing [outcome/s]"

The strengths and limitations of the data must also be reported. Ultimately, the information provided must enable the relevant Expert Review Committee and National Essential Medicines List Committee to determine:

1. the balance between benefits and harms for the medicine/s under assessment
2. the degree of confidence they have in the estimates of clinical effect

4.1.2 Assessment of costs

A comparison of the acquisition costs of the intervention medicine/s (and associated technologies) and comparator/s is presented in the Technical Review Report. In addition, any significant costs or savings that might be incurred if the intervention medicine is approved for use in the public health sector should be identified and listed in the Technical Review Report. Only costs that differ based on the intervention implemented should be reported (e.g., nurse's time if method of administration differs between intervention/s and comparator/s).

The costs in the Technical Review Report are presented in nominal terms, undiscounted over time, and calculated from the public payer perspective.

Judgements regarding the certainty/limitations of the costing analysis must be stated in a manner that allows decision-makers to clearly understand the implications thereof.

4.1.2.1 Cost of medicines and associated technologies

See Appendix 2: Estimation of healthcare resource utilisation and costs for the approach to calculating pharmaceutical costs. Table B in Appendix 2 may be adapted to report the estimated drug acquisition costs.

Note that if the medicine/s being assessed is co-administered with another medicine (and this is different from the medicine co-administered with the comparator/s) or if acquisition of a medicine delivery system/device for administration not included in the medicine acquisition price is required, the utilisation rates and costs for these components must be calculated and reported.

If relevant, costs incurred in preparing and dispensing medicines should also be identified and reported.

4.1.2.2 Other costs to the health system

Any significant costs incurred or savings made if a medicine is approved for use should be identified and listed. However, a detailed cost analysis (beyond calculation of pharmaceutical costs) is not required in the production of the Technical Review Report.

Potential costs include:

- cost of healthcare services related to the prescribing, administration and monitoring of the medicines (e.g., healthcare professional staff time, laboratory tests)
- cost of managing adverse events
- cost or cost savings to the public health sector budget not captured elsewhere. This includes irretrievable costs e.g., when the adoption of the medicine requires infrastructure to be commissioned/adapted

Information on the potential health system costs might provide an indication of the potential usefulness of a Stage 2 analysis.

4.1.3 Summary of Health Technology Assessment (HTA) agency decisions

Inclusion of a summary of HTA agency decisions in the Technical Review Report will provide insight into how other HTA agencies have structured analyses and managed unique attributes of the medicine to come to a particular decision. It is not intended that this summary infers or that it be used to adopt specific determinations made by other HTA agencies considering the country-specific differences between South Africa and other contexts.[vii]

It is not necessary to provide a full description of the analytical approach taken by different HTA agencies in the Technical Review Report. A simple tabulation and/or narrative summary of decisions made should provide sufficient information to help identify if further analysis is likely to be of value and/or inform general statements regarding a medicine's cost-effectiveness (as assessed for other settings).

Table 3 (Potential Sources of Information to include in Grey Literature Search, page 15) lists the HTA agencies that publish their HTA decisions.

4.1.4 Feasibility considerations

A description of "feasibility of implementation" considerations should be presented in the Technical Review Report. Economic, operational, legal and other factors will affect the degree to which medicine/s can be successfully implemented and monitored. An overview of some of the potential considerations is presented in Table 4.[viii]

Feasibility statements may be supported by expert opinion, gathered from working groups or individuals with expertise in health systems and/or ethics/legal issues, when published research evidence is missing or inadequate. Experts include healthcare professionals, patients, patient group representatives, healthcare administrators, economists, health system researchers, lawyers and those who can provide contextual information or have unique insight into the health condition and health system operations. See Appendix 1: Expert opinion for a proposed approach to obtaining expert opinion. Clinical practice guidelines and other guidance documents (e.g. HTA reports) may also provide useful insight into feasibility issues that might be relevant to the South African context.

Feasibility considerations may be presented as a narrative summary that clearly states whether the feasibility considerations are significant (i.e., that the intervention probably cannot be implemented or only with significant disruption to the health system).

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vii Country-specific differences include differences in resource use and costs, opportunity costs, quality of life estimates, analytical perspective, population characteristics (e.g., prevalence), population background mortality, etc.

viii This section will evolve in future iterations of the Guide as the domains and criteria most relevant to the South African context are determined.

A brief description of the type and quality of the evidence used to produce the statement/s should also be provided. For example:

- If published research is used: Is the evidence applicable to South Africa, to the intervention under review and to the way in which the intervention will be implemented in South Africa? Does evidence from different settings agree or is there discordance between different settings?
- If expert opinion is used: Was there a representative sample of knowledgeable experts with a good degree of concordance between responses?

TABLE 4. FEASIBILITY CONSIDERATIONS

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

Source: Adapted from EUnetHTA HTA Core Model 3.0 (25)

4.1.5 Patient preferences and values, and acceptability considerations

A description of the relevant stakeholder preference and value considerations, and the acceptability of the medicine/s under review should be presented in the Technical Review Report. Social, cultural, religious and other factors will affect the values and preferences of patients and other stakeholders, and may influence whether they will find a medicine acceptable and/or suitable to address their needs.

The reviewer should consider the relative importance of the medicine/s to all or most stakeholders identified and assess how much variability there is likely to be in the views of different stakeholders.

The type of stakeholder views that should be considered[ix] includes: "patient and carer knowledge, attitudes, expectations, moral and ethical values, and beliefs; patient goals for life and health; prior experience with the intervention and the condition; symptom experience (for example breathlessness, pain, dyspnoea, weight loss); preferences for and importance of desirable and undesirable health outcomes; perceived impact of the condition or interventions on quality of life, well-being or satisfaction and interactions between the work of implementing the intervention, the intervention itself, and other contexts the patient may be experiencing; preferences for alternative courses of action; and preferences relating to communication content and styles, information and involvement in decision-making and care"(8).

Relevant stakeholders to consider include but are not limited to: patients, family and important others, relevant community groups or religious organisations that may influence uptake of health services, healthcare professionals, healthcare institutions, heads of pharmaceutical services, pharmaceutical and therapeutics committees, national programmes, and the general public.

In addition to published research evidence (if available), stakeholder acceptability and preference statements can also be supported by expert opinion. Experts include patients, patient group representatives, family and important others, clinicians, healthcare administrators, social scientists, public health researchers or others who may have contextual information or unique insight. See Appendix 1: Expert opinion for a proposed approach to obtaining expert opinion.

Clinical practice guidelines and other guidance documents (e.g., HTA reports) may also provide useful insight into patient preferences, values and acceptability issues that might be relatable to the South African context.

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ix This section will evolve in future iterations of the Guide as the domains and criteria most relevant to South Africa are determined.

If stakeholder acceptability and preference considerations are presented as a narrative summary, a brief description of the type, relevance and quality of the evidence used to produce the statement/s should also be provided. For example:

- If published research is used: Is it applicable to South Africa, the intervention under review and the way the intervention will be implemented in South Africa? Does evidence from different settings agree or is there discordance between different settings?
- If expert opinion is used: Was there a representative sample of knowledgeable experts with a good degree of concordance between responses?

Stakeholder acceptability and preference considerations may also be analysed using a matrix to assess the potential impact of implementing or not implementing the medicine/s across all relevant stakeholders (see Table 5 which can be adapted based on the PICOST or disease area). This approach will help identify the areas where values might differ between stakeholders.

TABLE 5. PATIENT PREFERENCES AND VALUES, AND ACCEPTABILITY 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				
Community groups or religious organisations				
Healthcare professionals				
Healthcare institutions				
Heads of Pharmaceutical Services (HOPS)				
Pharmaceutical and Therapeutics Committees				
National Programmes				
General public				
Others (provide details)				

4.1.6 Equity considerations

An equity impact statement must be included in the Technical Review Report. The statement should indicate the potential impact that listing or delisting the medicine/s on the EML will have on the distribution of health benefits and harms for the general population, as well as its impact on equity in health for marginalised groups. Marginalised groups include (but are not limited to) populations or people who have diseases that have been historically disadvantaged or underserved due to discrimination, neglect, or geographic location. It is important to allow for the possibility that a medicine assessment decision might exacerbate disparities rather than mitigate them, and that equity in health need to be considered from multiple perspectives.

The Guidance for Priority Setting in Health Care (GPS-Health) framework (26), initiated by the World Health Organization (WHO), provides a map of equity criteria[x] 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, and other social and financial effects. See Table 6 for an overview of the criteria and relevant equity questions.

TABLE 6. EQUITY CRITERIA TO CONSIDER WHEN MAKING HEALTHCARE ALLOCATION DECISIONS (ADAPTED FROM GPS-HEALTH FRAMEWORK)

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 has the best possible outcomes 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)?
	Populations with limited options*	Have you considered whether the intervention has special value because it offers a treatment option for a disease/ condition for which no treatment option existed previously?
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 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 disproportionately affect some groups because of their race, ethnicity, religion or 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 the welfare of individuals and society by protecting the productivity of the target population?
	Care for others	Have you considered whether the intervention has special value because it enhances welfare by protecting the ability of the target population to take care of others?
	Catastrophic health expenditure	Have you considered whether the intervention has special value because it reduces catastrophic health expenditure on the target population?

*Added based on stakeholder feedback (not in GPS-Health framework) (26)

The equity impact statements can be supported by expert opinion in addition to published research evidence (if available). Experts include clinicians, patients, patient group representatives, economists, ethicists, social scientists, historians, public health researchers or others who may have contextual information or unique insight into the health condition or medicine/s of interest. See Appendix 1: Expert opinion for a proposed approach to obtaining expert opinion. Clinical practice guidelines and other guidance documents (e.g. HTA reports) may also provide useful insight into equity issues that might be relevant to the South African context.

x This section will evolve in future iterations of the Guide as the domains and criteria most relevant to the South African context are determined.

The equity considerations can be presented as a narrative summary. A brief description of the type, relevance and quality of the evidence used to produce the statement/s should also be provided. For example:

- If published research is used: Is it applicable to South Africa, the specific intervention and the way the intervention will be implemented in South Africa? Does evidence from different settings agree or is there discordance between different settings?
- If expert opinion is used: Was there a representative sample of knowledgeable experts with a good degree of concordance between responses?

4.1.7 Summary of findings

The summary of the findings must be presented in a format that compliments the Evidence to Decision Framework (see Appendix 3: Evidence to decision framework) that will be used by the Expert Review Committee to make recommendation/s regarding the medicine/s to the National Essential Medicines List Committee. The strength of a recommendation and decision will be determined by the following domains:

- the degree of confidence the committee has in the estimates of its clinical effect (quality of the evidence) considering both benefits and harms
- the balance between benefits and harms
- resource implications
- the feasibility of implementation of the decision
- the values and preferences of individuals affected by the recommendation (i.e., the importance people assign to the outcomes associated with the medicine) the impact the decision will have on health equity

The evidence to support a judgement on each of these domains must be presented in a manner that will allow the committees to determine the magnitude of the impact that the medicine/s will have on that domain (e.g., minor, major, none, uncertain). This evidence will be used to inform a recommendation regarding a medicine, for which the strength of the recommendation need to be:

- strong for/against the medicine
- conditional for/against the medicine
- recommendation in context of research
- no recommendation

4.2 STAGE 2: ADDITIONAL ANALYSIS

4.2.1 Systematic review

Some clinical research questions are best addressed through an up-to-date, systematic review of published, peer-reviewed literature. Although a well-conducted systematic review can be a time-consuming and resource-intensive process, because of the rigorous methods applied to ensure bias is minimised, 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 more extensive[xi] systematic review of the clinical evidence for the medicine/s under review is required, it should be commissioned from a research unit with researchers experienced in conducting systematic reviews. Standards for conducting and reporting systematic reviews have been published by multiple research organisations, including the Cochrane Collaboration (27) and the Center for Reviews and Dissemination (CRD) (28), and should be used as guidance documents when conducting a systematic review. Methods must be transparent, with reporting adhering to PRISMA guidelines and limitations clearly noted.

Scheduling systematic reviews and the commissioning thereof need to be part of a considered work plan with due consideration of the potential time and resource challenges.

4.2.2 Economic evaluation

4.2.2.1 The role and use of economic evaluation in informing decision-making within the Essential Drugs Programme (EDP)

Economic evaluation can provide important information to assist in good-quality decision-making that aligns with principles of universal healthcare, including equity and efficiency. Economic evaluation provides a basis on which to manage trade-offs when incorporating considerations beyond efficiency in the decision-making process, such as prioritising investment for previously disadvantaged populations.

Economic evaluation is the term broadly used for the comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes and effects) (29).

Many types of economic evaluation can be applied to decision-making in health; the major types are listed in Table 7. Although there are 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 each type has 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 comparator/s are chosen or timeframe for the analysis) will also reflect the context, decision problem and the needs of the decision maker.

xi ~~More extensive~~ than the approach proposed to produce a Technical Review Report.

TABLE 7. 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 (an incremental cost-effectiveness ratio [ICER]).
Cost-Utility Analysis*	An analysis used to compare costs and effects of treatment alternatives using a generalised outcome measure representing utility (QALY or DALY averted). The ICER in a cost utility analysis enables representation of the opportunity cost of an investment decision relative to other marginal health system investments.
Cost-Minimisation Analysis	An analysis in which the costs of different interventions that provide the same benefits are compared.
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, ICER – Incremental Cost-Effectiveness Ratio, QALY – Quality-Adjusted Life Year

* Cost-utility analysis is a specific form of cost-effectiveness analysis. For the purposes of this guide, an economic evaluation representing health outcomes in natural units will be referred to as a CEA and an economic evaluation using a utility measure for health effect will be referred to as a CUA.

Given the constraints on analytical resources and data available in South Africa, it is expected that economic evaluations will only be conducted for a limited number of medicines per year, prioritised according to level of uncertainty regarding cost-effectiveness and the potential budget impact of the EML decision. There is an expectation that the number of economic evaluations conducted will increase as capacity and resources for HTA functions grow.

If addressing uncertainty regarding the cost-effectiveness of the intervention medicine/s will have a significant impact on a EML review decision, Figure 2 can be used to determine what type of Stage 2 analysis should be conducted in order to make the most efficient use of available resources. Each Stage 2 analysis will generate a stand-alone report that will be added to the technical documents that inform decision-making.

A Rapid Review of Economic Evaluations (RREE) should be conducted in the first instance if understanding of the economic evidence regarding the medicine/s under review is limited, and it is not clear if existing analyses could potentially address or reduce the uncertainty regarding a medicine's cost-effectiveness.

If it is decided that a new economic evaluation should be conducted, a choice between conducting a cost-effectiveness analysis using natural units (CEA), a cost-utility analysis (CUA) or a cost-minimisation analysis (CMA) is needed. If a RREE has already been conducted, the potential to adopt or build on existing economic evaluations can be explored. A CEA/CUA is appropriate where clinical evaluation indicates that the proposed medicine is therapeutically superior to the main comparator, but likely to result in additional costs to the health system OR therapeutically inferior to the main comparator, but likely to result in lower costs to the health system (30). A CMA is appropriate where there is a therapeutic claim of non-inferiority, the safety profile is equivalent or superior (in both nature and magnitude), and use of the proposed medicine is anticipated to result in equivalent or lesser costs to the health system (30).

Application of a CEA, CUA or CMA requires prioritisation of analytical resources to

make decisions in cases with the greatest uncertainty regarding cost-effectiveness and a matching of available evidence to the requirements of the decision problem. However, regardless of resources and time available, it is important that the methods and approach for conducting economic evaluation 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.

4.2.2.2 Rapid Review of Economic Evaluations

The global market dynamics that influence the timing of introduction of new medicines, typically result in the South African public health sector receiving motivations for medicines after implementation in many high-income countries and regions including North America, Japan, the United Kingdom (UK), many countries in Europe, Australia and New Zealand. Many middle-income countries with developing and established HTA systems, such as Thailand, India, China, Tunisia, Mexico and Brazil, may also be considering the introduction of medicines to their public health systems before or at a similar time to South Africa. In addition, global institutions and development partners frequently conduct economic evaluations on medicines that have specific relevance for low and middle-income country context, such as the WHO-CHOICE program (31) at the World Health Organization (WHO). In South Africa, a growing number of research units are conducting and publishing economic evaluations that may be of relevance to a decision within the EDP medicine/s assessment process, and economic evaluations are being produced to inform medicine access decisions in South Africa's private sector.

In many cases, there is thus an extensive body of economic evaluations relating to medicine/s being assessed through the EDP medicine assessment process in published peer-reviewed literature and in grey literature published on institutional websites. A rapid review of published economic evaluations and HTA agency reports can provide important information to inform the medicine/s assessment 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 (32).

Objectives of the Rapid Review of Economic Evaluations (RREE)

A summary of HTA agency decisions is provided in the Technical Review Report. The RREE takes that work a step further by presenting the approach and content of the analysis that informed those recommendations, in addition to the results and final determination. The objectives of the RREE are to:

- improve/provide understanding of the existing economic evidence for the medicines under consideration, and/or identify gaps in the economic evaluation literature, which may motivate for de novo analysis to be conducted for the South African setting avoid duplication of analysis and evidence synthesis if evidence exists that may be applicable to the South African context and relevant to the decision-making process
- identify decision analytic model structures used to assess cost-effectiveness in other contexts
- identify model parameters and determine potential sources of information to inform additional analysis (should it be required)

- identify ethical, legal and other social issues that were relevant to the assessment of the medicines in other contexts

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
4. summarise and present the findings (figure 4)

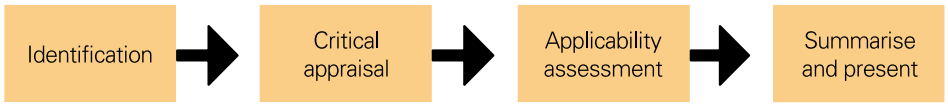

Figure 4. Steps in the rapid review of economic evaluations process

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.

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 include a search of databases for published economic evaluations and HTA agency reports (some examples listed in Table 8) in addition to searching websites of individual HTA agencies that publish detailed health technology assessments (see Table 3).

TABLE 8. EXAMPLES OF 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
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 Organization CHOosing Interventions that are Cost-Effective

Analysts should identify economic evaluations and HTA reports that assess the medicine/s for the indication defined in the medicine/s assessment scope. In order to be eligible for further consideration (and proceed to Step 2: Critical Appraisal), sufficient information needs to be

available in the identified publications of economic evaluations (i.e., full text articles available for review) and the reports from HTA agencies (i.e., detailed descriptions of methods and findings). A list of included studies should be presented. Analysts should not predetermine exclusion criteria of economic evaluations based on measurement of the health outcomes, and should consider inclusion of CMA, CEA and CUA as appropriate (including analysis reporting of cost/ DALY averted and cost/QALY). As the objective of the RREE is to provide generalised information about approaches to the assessment of the medicines 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 into the economic evaluation of the medicines in the South African context. A PRISMA diagram should be developed, with studies excluded at Steps 1, 2 and 3 reported. Clear reasons for studies excluded at each stage should be provided.

Step 2: Conduct critical appraisal of included economic evaluations

In the critical appraisal step, the quality of an economic evaluation is assessed. This information 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 therefore its usefulness in the EDP medicine/s selection process. The economic evaluations identified in Step 1 must be appraised using critical appraisal checklists for economic evaluations, e.g., the Quality of Health Economic Studies (QHES) instrument (33), or the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (34). The use of other checklists developed to appraise modelling studies (e.g., Philips et al 2004 (35)) may be more appropriate to assess the quality of cost-effectiveness studies that rely on decision models. Analyst judgement should be used to determine the most applicable critical appraisal tool to be used. Application of the critical appraisal checklists will enable further iterations of this guide to specify a single critical appraisal checklist. Note that the CHEERS checklist is developed for use by researchers reporting economic evaluations, and editors and peer reviewers evaluating publication potential. When using the CHEERS checklist for critical appraisal in the EDP HTA process, each item in the CHEERS checklist can be assigned a "yes", a "no" or "partially", based on the reporting in the economic evaluation with full scoring reported.

Based on the findings of the critical appraisal and judgement of the analyst (in consultation with the medicine/s assessment review team), only economic evaluations that have a sufficient level of quality should progress to Step 3, the applicability assessment.

Step 3: Applicability assessment

The applicability of an economic evaluation or HTA report to the South African context is an important consideration when interpreting its findings and recommendations. An economic evaluation conducted in the context of a high-income country health system might have substantial differences in cost structures (in terms of medicines, 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 the reference case analysis recommend for CEA/CUA in the EDP medicine assessment process (Table 13) may also have limited applicability. For example, an economic evaluation

with costs incorporated from a different perspective than that of public-sector payer will produce findings that are substantially different to an analysis conducted for the EDP medicine assessment process.

Assessing context and methodological applicability of economic evaluations and HTA reports enables determination of the extent to which its findings can inform the medicine/s assessment process. This RREE does not provide a comprehensive assessment of transferability (36) but offers a limited number of applicability questions to aid in interpretation.

The applicability checklists (Tables 9 and 10) 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 the relevant Expert Review Committee and National Essential Medicines List Committee 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 medicine assessment process. However, as the purpose of the RREE is not only to identify analytical results but also to gain understanding of 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 medicine assessment process. Therefore, the applicability scores alone are not reason enough to exclude an economic evaluation. The context and methods applicability checklists are presented in Table 9 and Table 10 respectively.

TABLE 9. CONTEXT APPLICABILITY CHECKLIST

	Yes/ No/ Unsure	Score ("yes" = 1 point)	Justification for score
Population similar to South African patients?			
Medicine/s administered in a similar way as it would be in the South African public sector?			
Comparator/s similar to the comparator/s defined in the Technical Review?			
Clinical management of patients indicated for the medicine/s being assessed similar to the South African public sector?			
Health system context similar to the South African public sector?			
Significant differences in costs and cost structures compared to the South African public sector?			
	Total score	/6	

Source: Adapted from Drummond et al (36)

The methodological applicability checklist[xii] (see Table 10) seeks to determine applicability/ alignment to the proposed methods for CEA/CUA in the EDP medicine assessment process (see Table 13). Where "no" or "unsure" is entered in the applicability checklist, the analyst should describe the relevant aspect of the economic evaluation or HTA report and the extent to which it influences interpretation of the analysis.

TABLE 10. METHODOLOGICAL APPLICABILITY CHECKLIST

	Yes / No / Unsure	Score (yes=1point)	Justification for score
Is the type of economic evaluation a cost-minimisation analysis, a cost-effectiveness analysis or 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 natural units (e.g., mortality), Quality Adjusted Life Years or Disability Adjusted Life Years avoided? (not relevant if cost-minimisation analysis)			
Is the analysis over a time horizon that captures all relevant differences in costs and effects between the intervention medicine/s and comparator/s?			
Are costs reported from the perspective of a third-party payer (e.g., public sector payer)?			
Are costs and effects discounted at an annual rate of 5%?			
	Total score	/6	

Source: Adapted from NICE Guidelines Manual (37)

Once the applicability assessments of the relevant economic evaluations of sufficient quality have been completed, the economic evaluations should be ranked according to their applicability to the South African context.

Step 4: Summarise and present

The final step of the RREE is to present summaries of the most relevant economic evaluations and HTA reports from other HTA agencies in a transparent and consistent manner (see Table 11 and Table 12) and provide guidance on if/how those economic evaluations can be used to inform decision-making. Examples are: whether the findings from the economic evaluations provide sufficient indication of a medicine's cost-effectiveness in the South African context, whether the analysis can be adapted, or whether a de novo cost-effectiveness analysis for the South African setting is likely to be useful.

The limitations of the review should be clearly described, e.g., utility scores used, cost-effectiveness thresholds applied. When summarising the cost-effectiveness results, findings should be adjusted to South African Rand (ZAR) and a consistent year of analysis – preferably the year of the medicine/s assessment for inclusion/removal from the EML. See Appendix 2 for guidance on adjustment of costs.

Explanatory notes should be provided with the summaries of the economic evaluations and HTA reports as needed.

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

TABLE 11. SUMMARY TABLE: HTA REPORTS

	HTA report 1	HTA report 2	Add more columns, as needed
Country + HTA agency			
Year			
Indication			
Intervention			
Comparator/s			
Time horizon			
Economic evaluation type			
Modelling approach			
Key (structural) assumptions			
Results			
Cost-effectiveness drivers			
Major areas of uncertainty			
Ethical, social, legal issues			
Recommendation			
Context applicability score /6			
Methods applicability score /6			

TABLE 12. SUMMARY TABLE: PUBLISHED ECONOMIC EVALUATIONS

	Economic evaluation 1	Economic evaluation 2	Add more columns, as needed
Author			
Year			
Context (country and health system)			
Indication			
Intervention			
Comparator/s			
Time horizon			
Economic evaluation type			
Modelling approach			
Key (structural) assumptions			
Results			
Cost-effectiveness drivers			
Major areas of uncertainty			
Critical appraisal findings			
Context applicability score /6			
Methods applicability score /6			

Cost-effectiveness analysis and cost-utility analysis

The methods for economic evaluation described in this section aim to provide a minimum level of quality and consistency to inform decision-making within the EDP HTA process. As the use of economic evidence to inform decision-making in South Africa evolves, these methods should be updated and refined to improve specificity and fitness for purpose for decision problems.

The concept of "cost-effectiveness" in its simplest form refers to the amount of investment required (the cost) to achieve a unit of health (the effect), and how this compares to other competing investments that could be made in the South African public health sector. Cost- effectiveness is not an absolute characteristic of a health intervention (i.e., an intervention could be cost-effective in one context and cost-ineffective in another) and is dependent on multiple factors, including local clinical practice and patient population, the relative prices and costs, and the marginal productivity of the health system for which a decision is made. Since there is always uncertainty about the cost-effectiveness of an intervention's use in a health system, an economic evaluation can be helpful in reducing that uncertainty. However, the outputs of an economic evaluation can never automatically determine a decision outcome about listing or removing a medicine on the EML and the economic evaluation should be viewed as only one part of the evidence base that informs that decision.

An assessment of cost-effectiveness only cannot address uncertainty about whether the potential intervention is "affordable" (able to be financed sustainably from applicable budget). Where there is significant uncertainty about affordability, a budget impact should be conducted. Given the dynamic interaction between cost-effectiveness and affordability (38), it is preferable to conduct a budget impact analysis and cost-effectiveness analysis together. However, this must be balanced with available analytical time and resources.

The South African Essential Drugs Programme Reference Case

A CEA/CUA should only be initiated to inform decisions about medicines when there is confidence that there is superior clinical efficacy compared to the comparator/s, but for which the cost-effectiveness in the South African context is uncertain. Undertaking a resource- intensive CEA/CUA when it is not entirely necessary limits the capacity to undertake other analyses. If the clinical efficacy of a medicine is non-inferior or equivalent to the comparator/s and the safety profile is superior or equivalent, a CMA should be sufficient to answer an economic review question.

The methodological specifications for a CEA/CUA are detailed in Table 13 in the form of a reference case – 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 developing locally relevant economic evaluation methods in low and middle-income countries (39). The EDP HTA reference case also incorporates some elements of the existing South African Pharmacoeconomic Guidelines (4) issued by the NDOH in 2012 to inform appropriate regulation of pharmaceutical pricing in SAs private sector.

TABLE 13. RECOMMENDED GUIDANCE FOR EDP REFERENCE CASE ANALYSIS

Component	Description	
Analytical question	Clear and unambiguous description of: • The intervention medicine/s; • The intervention/s against which it is being compared; • The indication for which it is used; • The population that would receive it; and, • The platform in which it would be applied.	
Comparator/s	• 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	Cost-effectiveness analysis (natural units)	Cost-utility analysis
Time horizon	Lifetime or sufficient to capture all relevant differences in costs and effects between the intervention medicine/s and comparator/s	
Health effects source	Technical Review Report, existing literature (e.g., published systematic reviews 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 (including life-years saved)	QALYs gained or DALYs averted
Valuing health effects	• No additional valuation of health effects with natural units represented. • Health effects as represented in literature or with simple extrapolation. • Life years saved (if used) calculated by difference in Years Life Lost (YLL) between intervention medicine/s and comparator/s. YLL calculated as sum of difference between age of death compared to full life expectancy as defined by WHO global health observatory for South Africa.	If QALYs used: • HRQoL measurement from South African patients and/or carers using a validated HRQoL instrument (such as EQ5D). • Valuation of HRQoL from established value set, or HRQoL transferred from other setting with applicability checklist applied. If DALYs averted used: • Applicable disability weight from Global Burden of Disease Study (2019) to calculate years lived in disability (YLD). • YLL calculated as per cost-effectiveness analysis.
Weighting of effects	None. It is proposed that health effects are reported without any weighting to reflect social value judgements such as equity.	
Representing costs and resource use	South African data sets and basic cost synthesis and primary data collection are necessary.	
Parameterisation (general)	Parameters sourced from published, peer-reviewed sources preferred. Use of expert opinion and opportunistic data are necessary, with clear documentation and rationale.	
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. • Use of probabilistic sensitivity analysis where feasible.	

DALY – Disability Adjusted Life Year, HRQoL – Health Related Quality of Life, QALY – Quality Adjusted Life Year, WHO – World Health Organization, YLD - Years Lived in Disability, YLL – Years Life Lost

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 medicine/s assessment 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 health system platform (i.e., facility type) in which it would be applied

As the substantive detail of the intervention medicine/s and comparator/s characteristics and use will be defined in the Technical Review Report, it is sufficient for the CEA/CUA Report to simply list the items in the list above and refer to the existing Technical Review Report. It is imperative that there is coherence and coordination between the Technical Review and Economic Evaluation.

Comparator/s
As an economic evaluation is a comparative analysis, the comparator/s against which the intervention medicine is assessed will be a major determinant of the analytical results. A reference case analysis should choose comparator/s that represent current practice within the South African public sector, as these are the interventions most likely to be displaced by the introduction of the intervention medicine/s.

Depending on the indication, "current practice" may represent another medicine or a non- pharmaceutical intervention such as lifestyle advice or a surgical intervention. Best supportive (or minimal) care may also be considered an appropriate comparator when no active treatment options are available. In cases where the intervention medicine/s is/are to be used as an adjuvant treatment to existing therapies, the comparator/s would be existing therapies, where the intervention being assessed would not displace existing therapies but be added to existing therapy.

The approach to selecting the comparator/s should be done transparently and in consultation with the relevant Expert Review Committee, aligning to the comparator/s identified in the medicine/s assessment scope and Technical Review. In the first instance, the analyst should identify the normative comparator/s, as recommended in the existing Standard Treatment Guidelines or other National Department of Health programme guidance. Where there is significant uncertainty as to whether the recommendations in the Standard Treatment Guidelines represent current practice, the analyst should seek expert input from the relevant Expert Review Committee to identify the predominant or most common comparator/s for the intervention medicine/s. Where the current practice in the South African public sector is not considered to represent ideal, effective, or efficient care, additional analysis that compares the intervention to best supportive (or minimal) care should be conducted. 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 analyses to reflect treatments offered at different levels of care.

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 sector payer, 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 most patients, care is offered free at the point of use under the larger policy aim of Universal Health Coverage. In this context, the public sector is the purchaser of healthcare, which means that healthcare spending in one area will have a direct implication on the ability of the public sector to purchase healthcare in another area. It is therefore imperative for an analysis to represent a scenario that reflects the impact of public sector spending in isolation from other costs that may be associated with accessing care. Therefore, the EDP reference case analysis requires that the perspective on costs is that of the public health sector payer. 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 medicine, a non-reference case analysis should be conducted (in addition to the base case analysis).

Within a reference case economic evaluation, costs that fall on donor or non-government organisation (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 assumption has limitations because in practice there may be very limited scope in the short term for donor/NGO budgets to be reallocated to general public-health spending. However, this reflects a longer-term assumption of eventual transition from donor/ NGO funding, particularly for health commodities. Where medicine/s investment decisions are expected to have significant impact on donor and NGO budgets, these costs can be reflected separately in scenario analyses.

Health outcomes included in a reference case analysis should reflect direct health effects experienced by patients and health effects on informal caregivers where relevant (with health effects on careers presented as a scenario analysis). 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 carers. It is important that a similar standard of evidence generation and synthesis is used to identify and represent informal carer health impact. In addition to direct health effects, analysis of interventions in treatment and prevention of infectious disease should include the dynamic effects associated with changes in onward transmission of disease where relevant.

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 14 below and are informed by the methods used by the Canadian Agency for Drugs and Technologies in Health (CADTH). While analysis from perspectives other than the public sector can be conducted and considered within the HTA process, these are conducted as non-reference case analyses.

Further detail on the approach to measurement and representation of costs is detailed in Appendix 2: Estimation of healthcare utilisation and costs.

TABLE 14. 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
Type of cost				
Costs to the public sector	√		√	√
Examples: medicines, medical devices, procedures; equipment, facilities, overheads; healthcare providers; hospital services ; diagnostic, investigational, and screening services; informal caregivers' healthcare costs; rehabilitation in a facility; community-health worker costs; long-term care in nursing homes				
Costs to other government departments			√	√
Examples: Criminal justice system; Affordable housing; Education				
Costs to donors and NGOs	√		√	√
Examples: Medicines, medical devices, procedures; Staffing and facilities; Public health messaging				
Costs to medical aid schemes		√		√
Examples: 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				√
Examples: 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				√
Examples: 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				
Type of outcome				
Health effects relevant to patients and informal caregivers	√	√	√	√
Examples: health-related quality of life; life-years gained; clinical morbidity				
Non-health effects relevant to patients and informal caregivers			√	√
Examples: Information available to patients; Reduction in criminal behaviour; Better educational achievements				

Source: Adapted from Canadian Agency for Drugs and Technologies in Health (CADTH) methods Manual, 4th Edition (40)

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 medicine/s and comparator/s. Where there are significant mortality differences between the intervention and comparator/s 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 medicine. Therefore, a reference case analysis for a CEAs/CUA should be long enough to incorporate all significant differences in terms of costs and effects; commonly this will mean a life-time time horizon. If a shorter time horizon is agreed upon by the Expert Review Committee, the report should explicitly detail the expected impact of the shorter time horizon on both the intervention and comparator in terms of costs and/or effects.

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 in high-income country contexts but aligns to the recommendations of the SA Pharmacoeconomic Guidelines (2012) and is expected to be more closely aligned to the SA context (41). 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 CEA or CUA is conducted.

Sourcing, representing and valuing health effects

The economic evaluation should be conducted in coordination with the assessment of clinical effect within the HTA process. The approach to sourcing and generating clinical evidence is detailed in the Assessment of the clinical evidence section. The sourcing of clinical effects represents a significant proportion of the analytical time in conducting an economic evaluation and the approach should be aligned to the needs of the analytical problem and confirmed by the Expert Review Committee. For some economic evaluations, sufficient evidence on clinical effects may have been sourced as part of the Technical Review. Where additional clinical information is required beyond that, analysts should identify evidence from published systematic reviews, primary studies and the RREE, adhering to the clinical sourcing approach in the EDP HTA process. Where more extensive parameterisation is required, the analyst should conduct de novo searches of the literature for additional systematic reviews and primary studies, with a de novo systematic review conducted if needed.

Representing health effects

The way health effects are represented within an economic evaluation has a major influence on how results can be used and interpreted and the required assumptions and supporting data. Depending on the information required to inform the decision problem, the economic evaluation within the HTA process should represent health effects in either natural units (CEA) or as a generalised utility measure (CUA).

When conducting a CEA using natural units, health effects are represented in basic forms, such as "alive or dead", "sick or well", "infected or not infected" or as directly reported from a clinical trial. Natural units have advantages as an intuitive measure of health impact and can easily be interpreted in economic evaluation with ratios such as "cost per life year 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. A CEA using natural units should be applied in the HTA process when the information required to inform the decision is primarily related to the technical efficiency in achieving a specific health outcome, and when the additional analytical resources required to conduct a CUA, and potential uncertainty introduced through a generalised measure of health, would not aid the decision-making process.

There are significant limitations to using only natural units of health in an economic evaluation. Many medicines and other health interventions have positive and negative direct and indirect health impacts, particularly related to unwanted effects of treatment. Using a health impact measure that incorporates only positive health impacts can result in bias towards interventions with less favourable unwanted-effect profiles. In addition, a major consideration in measuring health is not only whether a person is alive or dead but also the quality of life in which that life is lived. A generalised outcome measure that combines morbidity and mortality can reduce bias against interventions or disease states where there is substantial morbidity or impact on quality of life.

An added benefit of using a generalised outcome measure is that it enables decision-makers to compare health across disease states, meaning that regardless of which populations are gaining or losing health, the "opportunity cost" of a decision to list a medicine on the EML in terms of lost population health can be represented. A CUA using a generalised health outcome measure should be applied in the HTA process when there are significant positive and negative health effects on mortality and morbidity between the intervention and comparator, and it is considered that quantitatively representing the opportunity cost of the medicine is required to inform the decision of whether to list it on the EML.

Specification on the approach to transforming outcomes observed in literature to a representation of effects appropriate for an economic evaluation (such as converting probability of survival over short term to life years saved) or mapping health outcomes to health state utility values is beyond the scope of this Guide and may require significant technical expertise. Analysts should apply the relevant best methodological practice tailored for economic evaluation within a HTA process (e.g., NICE Decision Support Unit) and ensure transparent reporting of approach.

The generalised measures of health that should be used within the HTA process are the Quality Adjusted Life Year (QALY) or the Disability Adjusted Life Year (DALY) averted:

- 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. 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 for 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 expected to be produced from an intervention relative to its comparator/s enables calculation of incremental QALYs, and when this is expressed as a ratio of the increment costs between the intervention and comparator/s, enables calculation of the incremental cost-effectiveness ratio (ICER), a summary metric of a cost-effectiveness analysis.

- The DALY can be conceptualised as the inverse of the Quality Adjusted Life Year (QALY) and measures the number of years in a particular health state multiplied by the burden (or morbidity) associated with that health state. In this way, the positive health impact of a medicine is the extent to which it can reduce or "avert" DALYs.

There are important differences between the theoretical underpinnings, valuation and calculation of the QALY and the DALY,[xiii] and the analyst should clearly provide a justification for the choice of the outcome measure based on local context, expert input and available data.

Considering the benefits and limitations of conducting either a CEA using natural units or a CUA, careful consideration of the context of the decision should be taken when determining the approach to representing health effects. The limitations that the use of a particular measure introduce for the interpretation of results should be clearly described.

Valuing health effects

Applying the QALY within a CUA requires a consistent and transparent approach to valuing and calculating the health-related quality of life (HRQoL). A CUA 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 CUAs for the EDP HTA process, it is acknowledged that this approach is unlikely to be possible for most 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.[xiv] 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 value 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 is acceptable in the EDP HTA process as it allows for approximation of the QALY and consideration of the wider opportunity cost of decisions. However, analysts should apply the applicability checklist (see Table 15) when any use of a secondary HRQoL is applied, and provide a justification of the country tariff and HRQoL value applied.

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xiii It is beyond the scope of this method guide to provide comprehensive methodological detail on each of the outcome measures, and readers should refer to Drummond (2015) for further details.

xiv 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 conducted in the HIV/AIDS and vaccination therapeutic areas. A range of valuation approaches forHRQoL were applied, but an important finding was that only 15% of HRQoL estimates were measured in the local South African population. A recent systematic review also found that whilst there is a body of South African specific HRQoL data that could be used for CEAs (123 publications, representing 104 studies), most of the studies may not be suitable due to their observational nature (56)

TABLE 15. 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

Applying the DALY-averted in a CUA also requires consistency and transparency in calculating and representing the differences in years lived in disability (YLD) and years of life lost (YLL) between the intervention medicine/s and comparator/s.

Years lived in disability should be valued by assigning the most relevant and applicable disability weight as reported by the most recent Global Burden of Disease Study estimates (42). Where alternative disability weights are used, the report should explain the justification for alternative weights.

Years of life lost should be calculated as the sum of the difference between expected age of death for people receiving intervention medicine/s and comparator/s compared to full life expectancy at birth in South Africa, as defined by WHO Global Health Observatory.The value for life expectancy at birth for both sexes should be used unless the patient cohort is a specific gender (e.g., assessing interventions in cervical cancer where the life expectancy at birth for females should be used to calculate years of life lost).

There is limited synthesis or complex analysis involved in valuing health effects in CEA using natural units, as the main consideration is that there is transparent and coherent representation of the required natural health units. If the CEA represents cost per life year saved, the incremental life years saved should be calculated in the same manner as the years of life lost components of DALYs averted for a CUA calculation above, where incremental years of lives lost-averted is equivalent to "life years saved".

Weighting of effects
A reference case analysis should not weight any health outcomes based on additional preference or value considerations such as disease severity, deservedness of the population group, or age of the expected patient cohort (i.e., age weighting should not be applied). This ensures that the results of the economic evaluation to be presented reflect costs and health effects only and enables the opportunity cost of the decision to be reflected consistently. Value judgements and considerations other than efficiency should be incorporated into the EDP HTA process. They should, however, be considered at the point of decision-making rather than as a component of the analysis above.

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/s. Parameters relating to progression of disease and underlying clinical effects, utilisation 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 is an important consideration for the efficiency and productivity of the EDP HTA process. An overarching principle in parameterisation is that all sources are transparently reported, with assumptions and approximations clearly explained.

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. If cost-effectiveness is very different between sub-groups, the medicine use recommendation may differ for the groups assessed. 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 that the ethical implications of differentiating a decision based on sub- group characteristics are considered before the analysis is undertaken. Any sub-group analysis should be incorporated within the medicine/s assessment scope and confirmed with the relevant Expert Review Committee before analysis is undertaken.

Uncertainty

A fundamental characteristic 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 that 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 misrepresent uncertainty; 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 on 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 using 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 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 associated with methodological choice such as the way in which effects are represented, and comparator/s chosen, or the perspective of analysis and discount rate used. The specification of the reference case as part of this Guide should minimise methodological uncertainty, and ongoing research to refine and improve economic evaluation methods, will assist in further reducing methodological uncertainty within the EDP HTA programme.

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 where it is expected that there is significant structural uncertainty or where it is expected that there may be significant changes in the management of disease and key parameters over time.

Management of parameter uncertainty involves the use of deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). One-way deterministic sensitivity analysis involves varying one parameter within its 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 of key parameters should be represented as a minimum and in the form of a tornado diagram (with parameter ranges represented using a 95% confidence interval from source literature or ranges considered realistic in the SA context in the view of the Expert Review Committee).

One-way sensitivity analysis is limited - 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.

Probabilistic sensitivity analysis is strongly encouraged in conducting of economic evaluations for the EDP HTA process but is not considered an absolute requirement at this time given existing analytical capacity constraints. Application of these methods within the EDP HTA process will facilitate capacity strengthening and the use of more extensive ways to represent uncertainty, including probabilistic sensitivity analysis. For further details on approach to one- way and probabilistic sensitivity analysis, readers are referred to Drummond et al (29).

Decision modelling

Assessing the net costs and effects of medicine/s EML listing/delisting decisions 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 that represent the mathematical relationships

between parameters. A common adage – "all models are wrong, some are useful" – indicates that a model does not aim to perfectly reflect the impact of the introduction of a medicine but can provide useful evidence within the decision-making process.

There are multiple decision-modelling techniques used within HTA processes internationally, from decision trees, cohort-level state-transition models (such as Markov models), and patient- level state-transition models (i.e., microsimulations) to more complex techniques including discrete event-simulation models, agent-based models and system dynamic models (43). 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 (44) and good-practice guidance for decision- model development and reporting (45).

A RREE should be conducted to identify and review decision model structures used to determine cost-effectiveness of the medicine/s under assessment in other contexts, identify model parameters, and potential sources of information that could inform the economic evaluation.

The main decision-modelling approaches recommended for economic evaluations in the EDP HTA process are Decision Trees and Markov models. 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.

Below is an example of a decision model (see Figure 5) adapted from an HTA developed to inform a medicine-inclusion 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 (fondaparinux or enoxaparin) to patients who were indicated for post- surgical prophylaxis of venous thromboembolism. The "event" of venous thromboembolism 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 low-molecular-weight heparins 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. 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. A decision tree is thus useful for modelling single-event or time-limited occurrences such as post-surgical prophylaxis of venous thromboembolism.

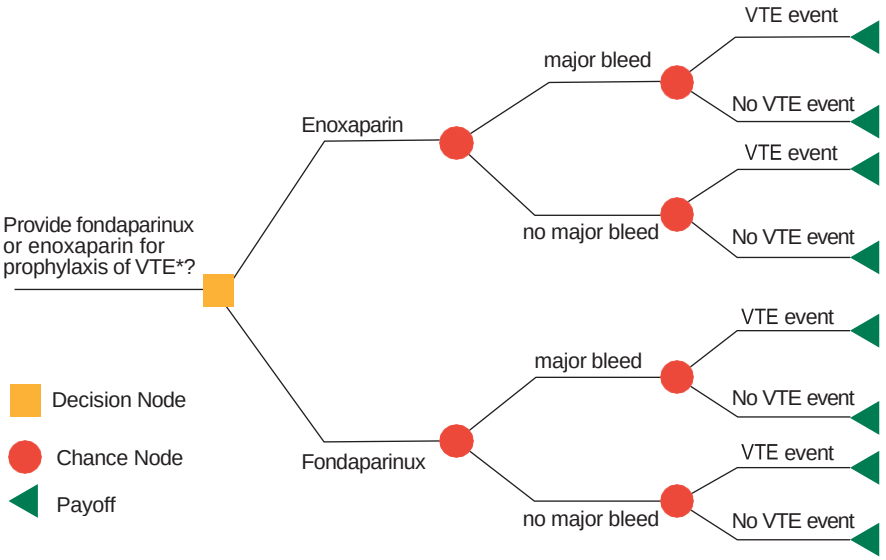

Figure 5. Example of a simple decision-tree structure (Wilkinson et al 2018 [unpublished])

*VTE – Venous thromboembolism

However, many decisions, particularly those related to non-communicable diseases, require modelling that can accommodate cost and effects over a longer period and probabilities of moving between states. The Markov model is commonly used in these cases; a simplified example is shown below (see Figure 6), where patients exist in mutually exclusive states of "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.

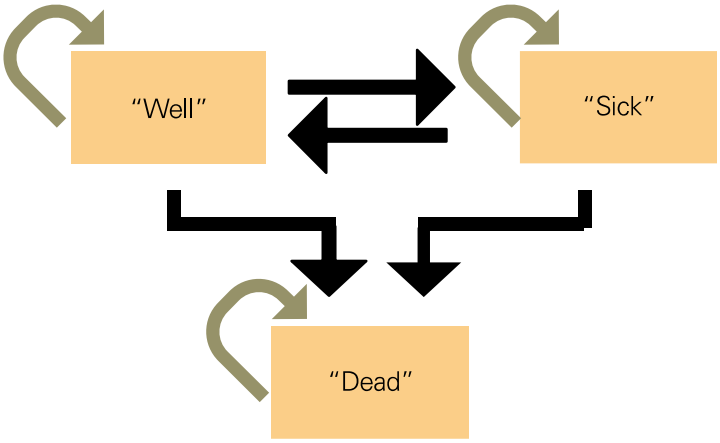

Figure 6. Representation of Markov model states

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 members 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 EDP 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 the relevant Expert Review Committee and the National Essential Medicines List Committee. This means that if analysis is conducted in a software package other than Excel, an export function must be used to translate not only analytical findings, but also all parameters and model structures.

Model validation
The complexities and expertise involved in developing a decision analytic model mean that even with transparent reporting, it may be difficult for non-experts to effectively assure validity. Within the EDP HTA process, it is recommended that any decision analytic modelling is reviewed by expert/s independent of the analytical team conducting the economic evaluation. The independent expert/s should not necessarily be Expert Review Committee members and may be based in South Africa or internationally.

Presenting the results of the Economic Evaluation

CEA and CUA results are 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/s.

$$\frac{\text{Cost (intervention)} - \text{Cost (comparator)}}{\text{Effect (intervention)} - \text{Effect (comparator)}}$$

Reporting CEA and CUA 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.

The ICERs should be presented clearly and transparently in table form and on a cost-effectiveness plane, utilising the Cost-Effectiveness Analysis Template (Attachment 5). A single "base case" should be determined based on judgement of the most feasible parameterisation and structure for the analysis, with scenario analysis enabling representation of alternative ICERs.

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 medicines 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 16 below.

TABLE 16. TABLE FOR PRESENTING THE RESULTS OF A COST-EFFECTIVENESS ANALYSIS

	Cost	Health outcome	Incremental cost	Incremental outcome	Incremental cost-effectiveness ratio
Comparator					
Add more rows, as needed					
Medicine being assessed					
Add more rows, as needed					

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 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 less value for money than 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, an estimation of the lost health to the general population as a result of investing money in a health intervention rather than elsewhere in the health system.

Recent analysis estimated the marginal productivity of health spending in the South African public sector (46). 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 an indicative cost-effectiveness threshold to interpret the results of a CUA; with a simplifying assumption that one DALY averted is approximately equivalent to one QALY gained where the CUA uses the QALY as an outcome measure.

This means that an intervention below R38,500 per QALY gained can be interpreted as likely to be cost-effective in the South African public system, and an intervention above R38,500 can be interpreted as not likely to be 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 maximisation" 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 CUA results should be interpreted within an accountable decision framework to facilitate coherent, transparent and consistent decisions (43–45).

4.2.2.1 Cost-minimisation analysis

This section describes the approach to conducting a cost-minimisation analysis (CMA) as a Stage 2 analysis within the EDP HTA process.[xv]

A CMA is an analytical technique in which the costs of different interventions that provide the same benefits are compared. The use of CMA may be attractive as it can be conducted with reasonably limited analytical resources. However, determining (and agreeing) which clinical endpoints should be used to decide whether the intervention/s and comparator/s provide the same health benefit (considering both efficacy and safety outcomes) is not always straightforward. In practice, it is relatively rare for two interventions to provide exactly the same benefits.

A CMA should only be conducted in the EDP HTA process when the relevant Expert Review Committee confirms that there is reasonable certainty that there is similar or non-inferior health benefit between the intervention medicine and its comparator/s in the management of the therapeutic indication for which it is being considered, and the anticipated cost of the new medicine/s is similar or lower than existing treatments. If there are differences in clinical outcomes between the intervention/s and comparator/s, the implications of these differences on the cost-effectiveness of intervention/s should be explored by conducting a CEA or CUA as Stage 2 analysis.

Whenever possible, a CMA should be augmented by a budget impact analysis (Stage 2 analysis) to ensure that both cost-effectiveness and affordability of intervention medicine/s are considered.

xv The approach to cost-minimisation analysis presented here builds on analytical approaches by the National Institute for Health and Care Excellence (NICE), UK and the Pharmaceutical Benefits Advisory Committee (PBAC), Australia.

Considerations for conducting cost-minimisation analysis

Table 17 provides an overview of factors that needs to be considered when conducting a CMA to allow appropriate quantification of resource use for the medicine/s and comparator/s.

TABLE 17. CONSIDERATIONS FOR CONDUCTING COST-MINIMISATION ANALYSIS

Component	Methods requirement
Comparator/s	• Existing practice within the South African public health sector (can be multiple where variation in practice exists). • Ensure comparator/s aligns with comparator/s used in Technical Review
Costs represented (list not exhaustive)	• Medicines and associated technologies: costs related to acquisition, preparation and dispensing of medicines • Healthcare services: costs related to prescribing, administration, and monitoring of medicines (e.g., staff time, laboratory tests) • Adverse events that incur a cost due to monitoring/management required (e.g., medicines used, hospitalisation) • Costs or cost savings not captured elsewhere (e.g., cost averted due to disease prevented)
Time horizon	Must be sufficient to capture significant cost differences between the intervention and comparator/s (e.g., cost of treatment, laboratory tests, medical devices).
Discounting	Discount rate of 5% on costs required for a time horizon longer than a year
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 • Use of probabilistic sensitivity analysis where feasible
Perspective	National public sector payer perspective. Medicines listed on the EML is provided at no cost to patients.
Health outcomes	Not required

Identifying and estimating costs

The approach to identifying and estimating healthcare costs is presented in Appendix 2. All direct healthcare costs incurred by the public health sector that are likely to change[xvi] due to the implementation of the medicine/s under review should be identified and presented in the CMA.

Costs due to adverse events should be minimal (if reported at all) as health outcomes are expected to be similar for the intervention medicine/s and its comparator/s.

Summary of costs

Estimated costs should be reported using Tables B to D in Appendix 2, and a summary provided in Table 18 (to be adapted as needed).

The cost and healthcare resource use assumptions and values must be reviewed by expert/s who is/are independent of the analytical team conducting the CMA prior to appraisal by the Expert Review Committee.

xvi Only direct health costs with an expected difference between the proposed medicine/s and comparator/s should be presented. Costs assumed to be the same for the interventions compared do not need to be presented as they will not affect the decision (to include/exclude the medicine/s from the EML).

TABLE 18. COST-MINIMISATION ANALYSIS: SUMMARY OF RESULTS: Total costs associated with the intervention medicine/s and comparator/s [insert time period over which costs are represented]

	Intervention	Comparator	Add more columns, as needed
Medicine costs			
Healthcare service costs			
Other costs			
Total costs			
State the time horizon			

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.

Sensitivity analysis in a CMA should align to the methodological approach described for CEA / CUA and should represent relevant Parameter, Evidence Source, and Structural Uncertainty. At a minimum, one-way deterministic sensitivity analysis in the form of a tornado diagram should be used to represent uncertainty in key parameters. Probabilistic Sensitivity Analysis is encouraged where feasible when conducting CMA to represent the percentage likelihood that an intervention is cost saving.

Subgroup analysis

It might be necessary to conduct a subgroup analysis due to large, suspected differences in treatment costs between sub-groups as it could result in different medicine use recommendations for the groups assessed. A subgroup could be a clinically defined 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 the ethical implications of differentiating a decision based on sub-group characteristics are considered before the analysis is undertaken. Any sub-group analysis should be incorporated within the medicine/s assessment scope and confirmed with the relevant Expert Review Committee before analysis is undertaken.

Interpretation of the cost-minimisation analysis

The general interpretation is that if the net costs for the intervention medicine/s are greater than the costs associated with the comparator/s, the intervention is unlikely to be the most cost-effective option in the public health sector, as no additional clinical benefit would have been established prior to initiating the analysis (i.e., the medicine cost more without providing additional benefit). If the net costs of the intervention medicine/s are less than the costs associated with the comparator/s, it is likely that the new medicine represent a good investment (i.e., medicine cost less with similar benefits). However, the results should be interpreted with due consideration of any significant uncertainty in the sensitivity analysis.

4.2.3 Budget impact analysis

A Budget Impact Analysis (BIA) provides information about the estimated financial consequences of introducing one of more medicines 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 principal concerns of a BIA are the financial implications of funding a medicine for the total eligible population over time a specific period while a CEA/CUA represents costs relative to effects on health and is principally concerned with the expected efficiency o f funding a medicine. A BIA does not represent the full economic consequences (such as loss of productivity or health impacts) or the non-health-related costs (such as other public department costs, for instance, social development in the case of substance abuse) of funding a medicine.

Therefore, the information provided by a BIA is complementary to CEA/CUA results as the affordability (impact of funding decision on a specific budget constraint) of the proposed medicine/s is a vital consideration for decision-makers in addition to cost-effectiveness. BIA results are likely to be a useful aid to implementation and post-decision budget planning and preparation purposes.

4.2.3.1 Analytical framework

When using a BIA in decision-making it is critical 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 (47–50) and provides directions on how a BIA should be conducted and reported when estimating the financial impact of selection or removal of medicines on South Africa's EML. This framework underpins the approach and calculations in the EDP HTA process which is flexible a nd expandable according to particular analytical needs. A BIA should be conducted in accordance with the BIA Template.

Perspective

The BIA should be conducted from the perspective of the national public sector payer and should represent two different budget constraints: the pharmaceutical budget and the larger public health system budget. Most of the public healthcare budget in South Africa is currently distributed to provinces. However, EML medicine/s inclusion decisions require a national perspective to determine relevance for the country. Therefore, the assumptions and data used in the BIA to estimate the size and characteristics of the eligible patient population as well as the relevant resource use costs should reflect the current and proposed healthcare practices in the public health sector.

In specific instances that have known additional funders (e.g., with HIV) and impact on different budgets is relevant to the decision problem, one budget line per funder should be presented, including the cost of all items borne by this funder (and excluding all costs not borne by any of the relevant funders).

Intervention

The analyst must consider the following information (described in the Technical Review Report) regarding the medicine/s under assessment:

- Licenced treatment indication
- Route of administration and dosage
- Population of interest including sub-populations
- The setting in which the medicine is to be administered (e.g., PHC clinic or tertiary hospital)
- Related diagnostic tools
- Associated technologies (e.g., co-administered medicines or medicine delivery systems/devices)
- Additional information, education and communication costs

Comparator/s

The comparator/s listed in the medicine/s assessment scope (and economic evaluation, if conducted) must be used as comparator in the budget impact calculations. The same information categories outlined above for the medicine/s must be described, and relevant data collected by the analyst.

Eligible population

Determining the eligible population over the specified period of analysis (annual and five-year suggested) is a vital component of the BIA. Eligible patient population estimates should be projected over the specified period of analysis.

For many assessments, mid-year population estimates for South Africa (for specific age groups and/or gender, if applicable) as well as prevalence and/or incidence data will be required to determine the eligible patient population (see Table 19 for potential data sources). However, in some instances the size of the incident/prevalent patient population might be available (e.g., data documented in official disease registries) and can be used if the data source is deemed credible.

In addition, any relevant sub-groups should be identified and separated (if appropriate). The proportion of the eligible population that will be accessing public sector healthcare services (i.e., not private healthcare services) should also be identified.[xvii] The analyst can assume that 80% of South Africa's population will access public sector healthcare services (51), unless different utilisation rates can be justified. The analyst should also consider the likelihood that patients will be offered and/or be initiated on treatment (e.g., due to access restrictions, initial loss to follow up after diagnosis), as well as discontinuation rates, when determining the estimated number of eligible patients to be treated each year. Any assumptions regarding patients who discontinue treatment (and the impact of this on costs) must be stated. An analyst should also consider whether adoption of the new technology is likely to increase demand (and therefore increase the eligible population) over time.

xvii Estimate based on CMS Industry Report 2020 which stated that less than fifteen percent of South Africa's population are enrolled in private voluntary health insurance, and the assumption that a proportion of uninsured patients will also access private sector healthcare paying out of pocket.

TABLE 19. POPULATION ESTIMATES DATA SOURCES

Source	Description	Weblink
Statistics South Africa	Presents causes of death, work and labour, education, crime and gender statistics for South Africa.	http://www.statssa.gov.za
GBD results tool	Presents Global Burden of Disease Study 2019 (GBD 2019) data	http://ghdx.healthdata.org/gbd-results-tool
Institute for Health Metrics and Evaluation (IHME)	Provides standardised information on population health for individual countries which allows international comparison.	http://www.healthdata.org/south-africa
District Health Barometer	Provides national health systems information	https://www.hst.org.za/publications/Pages/HSTDistrictHealthBarometer.aspx
Other Health Systems Trust publications	Repository of public health resources	https://www.hst.org.za/publications
Burden of disease resource materials produced by SAMRC	Provide information on the trends in the country's health status as well as causes of disease.	https://www.samrc.ac.za/intramural-research-units/BOD-resource-materials

Status quo and implementation scenarios

A BIA consists of two or more scenario analyses: the status quo scenario and the implementation scenario/s.

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

The **status quo scenario** presents the current estimated cost of treating the indication for which the medicine/s is/are being considered in 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 the proportion of patients currently accessing treatment relative to prevalence estimates, in addition to representing known and unknown national variation in care, as data might be difficult to obtain from official sources. Assumptions must be clearly described and referenced.

The implementation scenarios that should be presented are:

- Rapid adoption of the medicine/s (one- and five-year estimates)
- Slow adoption of the medicine/s (one- and five-year estimates)

The **rapid-adoption scenario** should represent a phased approach under an assumption that there are few or no delays in supply and that eligible patients will access the medicine/s where indicated. This may change based on the type of access; for example, medicines used in primary-care clinics may be more rapidly adopted than medicines that require access to specialists at a tertiary hospital.

In the **slow-adoption scenario** the prescribing and uptake of the medicine/s or indication is constrained. This may be due to, for example, required training of healthcare professionals, complex supply-chain arrangements, additional equipment required for implementation, or known limitations with access to healthcare providers.

The rapid-/ slow-adoption scenarios should be developed in consultation with clinical experts and consider major health-system elements that may impact implementation of the medicine/s should it be approved. It is important that all assumptions made in developing the different scenarios are clearly detailed and referenced.

Market share
In the BIA, the market share of a medicine is the proportion of the eligible patient population that will receive that medicine. The estimated market share of the intervention medicine/s and the comparator/s must be outlined for each year of analysis (one to five years), totaling 100% each year across all treatment options.

In the status quo scenario the existing market share of the comparator/s is not affected by introduction of a medicine. 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 medicines (intervention medicine/s and comparator/s). Justification for market- share percentages chosen for each technology must be provided and references provided. Potential sources to inform the adoption scenarios and market share estimations include drug- utilisation data (if available) and input from clinical experts (see Appendix 1: Expert Opinion for a proposed approach to obtaining expert opinion).

Resources and costs
The approach to identifying and estimating healthcare costs is presented in Appendix 2. All direct healthcare costs incurred by the public-health sector that are likely to change,[xviii] due to implementation of the medicine/s under review, as well as any medical cost offsets associated with the treatment (e.g., reduced use of hospital or emergency services), should be identified and presented in the analysis.

Wherever possible, published RCT estimates should be used as primary data sources for efficacy and safety estimates. Other data sources include other types of peer-reviewed published data, reliable local data and if required, expert opinion.

Unless otherwise indicated, costs are presented on a per annum basis. Full-year costs should be calculated, even if the medicine/s are to be implemented only part-way through the year.

Time horizon

A budget impact analysis should be conducted over a one- and five-year-time horizon, with the five-year time horizon presented in annual increments and costs not discounted over time. Costs should not be annualised; rather, they must be allocated to the year in which it is expected they will be incurred. For example, if the implications of funding a medicine require specific equipment to be acquired, the costs should be presented in the year in which equipment is acquired.

xviii Only direct health costs with an expected difference between the proposed medicine/s and comparator/s should be presented. Costs assumed to be the same for the interventions compared do not need to be presented as they will not affect the decision (to include/exclude the medicine/s from the EML).

Uncertainty methods and scenario choices

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

- Variation in the price of the medicine/s under evaluation.
- Variation in the uptake of the medicine/s in both the rapid and slow scenarios.
- Variation in the assumptions underpinning eligible population.

4.2.3.2 Budget impact model

The BIA should be performed using the simplest possible design to generate credible and transparent estimates. In some assessments use of dynamic health-condition models will be required to represent changes in the eligible population and treatment patterns/options that cannot be captured by a simple cost calculator approach. A health-condition model should account for those entering and leaving the eligible population over time and reflect health outcomes and their related costs in the total affected population for each year after the new intervention is introduced into clinical practice. The model should be consistent with that used for the CEA/CUA regarding clinical and financial assumptions (52).

At the very least, validation of the model must include face validity with decision-makers on the analysis framework and parameters, as well as verification of the model and formulas for calculation.

4.2.3.3 Interpreting results of the budget impact analysis

The findings of the BIA should be reported using the Budget Impact Analysis template, and the analyst must provide information about the input parameter values and calculations at a level of detail that would allow another modeler to replicate the analysis (52).

The findings should reflect two di fferent bu dget co nstraints: the ph armaceutical bu dget and the larger public health-system budget. Medicine purchases usually have a direct and clearly quantifiable impact on the pharmaceutical budget, while the cost implications of other healthcare costs might be less certain and attributed to different healthcare budgets. The health system budget impact will, however, give an indication of affordability across the health system, and results of the analysis can thus be used to aid budgeting and planning following the decision. It is expected that decision-makers will require more certainty about the clinical benefit of the medicine/s if a large impact on the budget is likely.

When interpreting the findings from the BIA, it is important that decision-makers can differentiate between expected estimated expenditure (something that needs to be purchased, e.g., tablets) and expected estimated resource costs (e.g., clinic visit) in order to assess the feasibility of implementing an intervention. Negative expenditure will save money, while negative costs

will save resources but not money. Analysts must present the findings in a manner that will illustrate this distinction.

There is currently no formal budget impact threshold to guide decision-making in the EDP HTA process. Accurate cost accounting of current and projected spending on pharmaceuticals relative to an established and known pharmaceutical budget will provide a quantitative indication of whether the expected budget impact of a decision to fund a medicine is deemed affordable.

CHAPTER FIVE

Evidence checklist

This section provides a summary of how evidence gathered and produced under Stage 1 and Stage 2 of the medicine/s assessment process can be checked to ensure it can be used to inform decision-making related to inclusion or removal of medicines on the EML.

It is expected that assessment and appraisal will be iterative under current analytical resource capacity, which means that as aspects of analysis are appraised, the analyst will be asked to adjust and correct for any elements found to be insufficient at the appraisal step. Further specification of evidence appraisal methods and the interaction with the decision-making process falls outside of the scope of this HTA Methods Guide.

Major questions that should be considered when checking the evidence include:

- Is the analysis relevant to all groups of patients who could potentially use the medicine/s as described in the medicine/s assessment scope?
- Is the indication being assessed consistent with the conditions of registration as determined by SAHPRA?
- Are the comparator/s justified?
- Has a thorough search for relevant clinical evidence been conducted?
- Has 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?

Glossary

Budget impact analysis	An analysis conducted under Stage 2 of the EDP HTA process to estimate the potential financial consequences resulting from the introduction of the medicine/s from a defined budget perspective
Cost-minimisation analysis	An analysis conducted under Stage 2 of the EDP HTA process comparing only direct costs related to the medicine/s being assessed, and its comparator/s.
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).
Cost-utility analysis	Used to compare costs and effects of treatment alternatives using a generalised outcome measure that incorporates positive and negative effects on mortality and morbidity e.g., Quality Adjusted Life Year (QALY) or Disability Adjusted Life Year (DALY) averted. Generates a summary measurement of efficiency
Equity considerations	A contextual assessment of the impact on equity in the South African context as a result of listing or removing medicine/s on the EML. Assessment included in the Technical Review Report
Essential Drugs Programme (EDP)	The EDP is a unit within the Affordable Medicines Directorate and is the secretariat for the National Essential Medicines List Committee and the Expert Review Committees
EDP HTA Reference Case	The set of methodological specifications that should be applied consistently to determine the approach to a cost-effectiveness analysis or a cost-utility analysis
Essential medicine	A medicine that satisfies the priority healthcare 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 (EML)	The list of medicines determined by the National Essential Medicines List Committee appointed by the Minister of Health and maintained by the Essential Drugs Programme (EDP). The national EML is deemed to satisfy the priority healthcare needs of the population
Expert Review Committee	A technical advisory committee that makes recommendations to the National Essential Medicines List Committee regarding medicines after an assessment of the available clinical and cost-effectiveness evidence
Feasibility considerations	A contextual assessment of the likely health-system readiness for implementing medicine selection/deselection decisions

Health Technology Assessment (HTA)	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 to promote an equitable, efficient, and high-quality health system (INAHTA definition)
Lead Reviewer	An Expert Review Committee member or contracted external reviewer responsible for drafting the medicine/s assessment scope and conducting the analysis under the EDP HTA process.
National Essential Medicines List Committee (NEMLC)	The non-statutory, advisory committee appointed by the Minister of Health, responsible for the development and management of the national EML and Standard Treatment Guidelines, which guide clinical practice at all public-sector health establishments and inform procurement of medicines in the public sector
Rapid Review of Economic Evaluations (RREE)	An analysis conducted under Stage 2 of the EDP HTA process that consists of a review of economic evaluations conducted by HTA agencies or published in peer- reviewed journals
Systematic Review	An additional clinical analysis conducted under Stage 2 of the EDP HTA process. The systematic review requires more resources than the rapid systematic review conducted to produce the Technical Review Report
Standard Treatment Guidelines (STGs)	The implementation mechanism of the EML that provides guidance to healthcare professionals on the use of medicines on the EML. It consists of a collection of chapters containing disorder groups, background information on the disorder, treatment regimens and other relevant information
Technical Review Report	The initial comprehensive assessment undertaken for all medicine topics selected for review under the EDP HTA process to inform a decision regarding inclusion or removal of the medicine/s on the EML or Tertiary and Quaternary Level Essential Medicines Recommendations
Medicine/s Assessment	Formal assessment of one or a group of medicines that has undergone topic prioritisation and been selected for assessment by the National Essential Medicines List Committee
Medicine Assessment Motivation Form	A form template used by stakeholders to formally nominate medicine topics for assessment under the EDP HTA process
Medicine/s Assessment Scope	A document used to gather fundamental information, such as PICOST, for a medicine assessment
Medicine Topic	An item involving a medicine or multiple medicines proposed for assessment for inclusion or removal on the EML

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Appendix 1

Expert opinion

Expert opinion is an essential element of all HTA processes. It can help to set the context of the medicine/s assessment by defining the place of the medicine/s in the clinical care pathway, identifying and describing patterns of resource use, highlighting potential feasibility and acceptability issues, and predicting which resources will be used and how often each will be used to manage outcomes reported.

A deliberately transparent and thorough approach to obtaining expert opinion is required to reduce subjectivity, minimise bias and improve trust in the evidence gathered.

If expert opinion is used in a medicine/s assessment, details should be presented as an attachment to the main technical document with clear cross-references with the main text. Expert opinion presented as part of the medicine assessment should include the following:

- justification of the need for expert opinion
- description of the methods used to obtain and collate the opinions, including details of the persons from whom opinions were sought
- a summary of the opinions obtained, together with the extent of any variability in the opinions
- an indication of how the opinions have been used in the main body of the submission
- justification of the approach used in the sensitivity analysis to reflect any variability in the opinions obtained

A description of the methods used to obtain and collate the expert opinion must be provided, and must include:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated and their educational qualifications
- the number of experts who declined to participate
- whether a declaration of potential conflict(s) of interest was sought from all experts or medical specialty groups whose opinions were sought
- a copy of the informed consent form provided to the experts at the time of collecting their opinion
- the method used to collect the opinions
- the medium used to collect the opinions
- the questions asked or the tool used to gain the opinion from the expert
- whether iteration was used in the collation of opinions and, if so, how it was used
- the number of responses received for each question
- whether all experts agreed with each response, and, if not, what approach was used to finalise the estimates
- the approach used to present the variability in the opinions

Appendix 2:

Estimation of healthcare resource utilisation and costs

Direct healthcare costs incurred by the public health sector that are likely to change[xix] due to the implementation of the medicine/s under review need to be identified and quantified in order to be reported in the Technical Review Report and used in Stage 2 analyses. Although the type of costs presented and analyses conducted will vary based on the scope and objectives of the different types of reports, the approach to determining the quantity and unit cost of resources and calculating costs are similar. This appendix provides general guidance on identifying and estimating healthcare costs associated with intervention medicine/s and comparator/s.

General statements

- Prices relevant to the public health sector should be used to estimate healthcare costs.
- Different types of costs (e.g. clinic visits, laboratory tests, medicines) must be presented in disaggregated form, with all steps to calculate the costs clearly described. This includes estimating the quantity of the inputs, criteria for allocating shared costs, and any costs excluded.
- The cost of each resource should be calculated by multiplying the quantity of the resource provided/used by its unit cost for each treatment group/disease state.
- The approach to identifying resource-use data and unit costs must be reported and justified, with sources for all inputs provided. When multiple estimates are identified, a justification for the input chosen for the base-case analysis should be provided, and the impact of alternative options explored in sensitivity analyses where appropriate.
- If costs are unlikely to make a difference to the overall analysis and a decision is taken to exclude those costs from the analysis (e.g., low-cost laboratory test), the cost should still be identified and justification for its exclusion provided.

The natural unit and quantity of units of healthcare resources provided to patients in each treatment group, or to patients remaining in a health state for a relevant time period, should be calculated based on the medicine's approved SAHPRA indication, and with consideration of the setting in which it will be implemented.

The methods used to identify and select the quantity of resources provided/used must be reported. Whenever possible, the Standard Treatment Guidelines or other National Department of Health clinical guidelines (if available) should be used to determine normative utilisation estimates for parameters such as frequency of administration, duration of treatment, and utilisation of medical services at the most likely level of care.

In some cases, the quantity of resources required/provided will need to be determined or adjusted based on published literature (directly relevant to the South African setting), expert opinion (see Appendix 1 for a proposed approach to obtaining and reporting expert opinion), South African registry data, or other sources of information. See Table A for potential data sources.

xix Only direct health costs with an expected difference between the proposed medicine/s and comparator/s should be presented. Costs assumed to be the same for the interventions compared do not need to be presented as they will not affect the decision to include/exclude the medicine/s from the EML.

TABLE A. DATA SOURCES FOR ESTIMATING DIRECT HEALTHCARE COSTS

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	http://www.mpr.gov.za/
Laboratory tests and investigations	National Health Laboratory Service (NHLS)	NHLS price list for most recent year should be requested from the EDP secretariat.
Staff salaries	Department of Public Service and Administration (DPSA) circulars	https://www.dpsa.gov.za/
Tariffs for inpatient care	Uniform Patient Fee Schedule	https://www.health.gov.za/uniform-patient-fee-schedule/
Healthcare 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

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

Unit costs should be obtained from recent, validated South African data sources wherever possible (see Table A for potential data sources) and presented in South African Rand (ZAR) in a consistent year of analysis – preferably the year of the medicine/s assessment for inclusion/removal from the EML.

- If costs need to be sourced from published literature or other historical data sources (e.g. previous EML analyses), the methods used to identify and select those publications/data sources must be described. Every effort should be made to find costs directly applicable to the South African setting (e.g., costing studies conducted for the South African setting).
- Costs must be adjusted to reflect costs in the year of analysis and the South African public healthcare setting, and may thus require adjustment for inflation and currency in some instances. Figure 7 outlines the proposed approach to adjusting costs based on the setting and timing of the published study or analysis. Currency exchange rates and consumer price index (CPI) and inflation rates are available on the World Bank Open Data site: https://data. worldbank.org/.

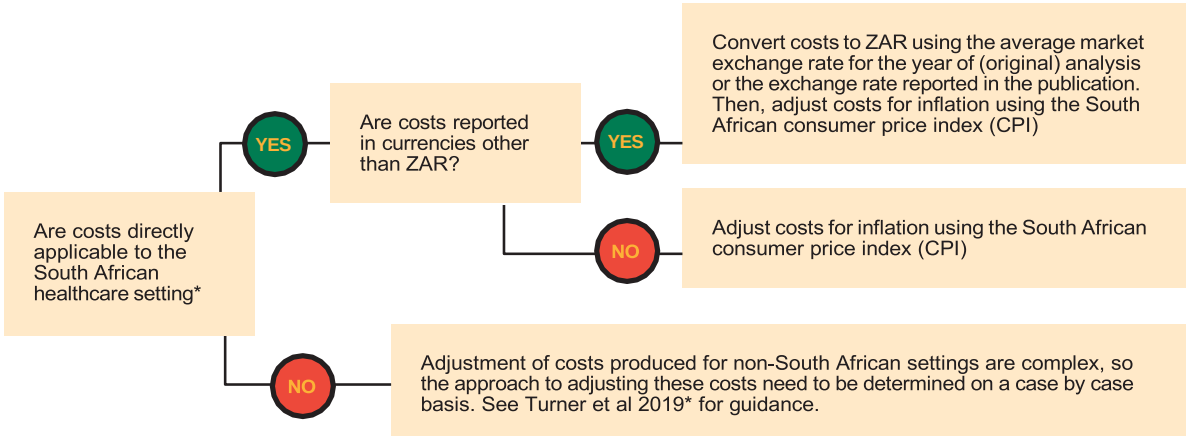

Figure A. Approach to adjustment of costs sourced from secondary sources ~

Study was conducted in South Africa or analysis produced for South African setting.

**Turner et al 2019 (53)*

The manner in which the quantity and cost of resources is presented will vary for the different types of reports, but is likely to reflect: one day of treatment, a course/cycle of treatment, and/ or treatment for the full time horizon (if different from course/cycle of treatment). A course length of a year should be used for medicines used to manage chronic conditions (e.g., diabetes), and the average length of a course/cycle of treatment should be used for acute treatments (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 resource use and costs for the relevant time periods should be presented.

Types of costs that may be relevant to EML decision-making include:

- cost of medicines and associated technologies (e.g., co-administered medicines, medicine delivery systems/devices required for administration) which includes costs relating to the acquisition, preparation and dispensing of medicines cost of healthcare services relating to the prescribing, administration and monitoring of the medicines (e.g., healthcare professional staff time, laboratory tests)
- cost of managing adverse drug reactions (e.g., hospitalisation, medicines used to treat adverse drug reactions)
- cost or cost savings incurred to the public health sector not captured elsewhere

Cost of medicines and associated technologies

Estimation of equi-effective doses and dosing schedules

Identify whether the medicine/s and comparator/s are intended to be used for a fixed course of treatment (e.g., short-course antibiotic, short-term adjustments to treatment due to a temporary change in circumstances like pregnancy) or whether it will be used on an ongoing basis (e.g., chronic medicine), and calculate medicine quantity accordingly:

- **Fixed course of treatment**: quantity estimated for the entire duration of therapy (e.g., five days).
- Ongoing use: quantity estimated for one year.

The doses and dosing schedule at which the proposed medicine/s and comparator/s will have the same effect (equi-effective doses) must be described/calculated, with supporting evidence provided. Proposed doses and dosing schedules must be compared to current practice in South Africa through input from local clinical expert/s.

When dosing is not uniform (e.g. it is based on weight, severity of disease), appropriate averages and/or ranges must be calculated or obtained from a literature search. If treatment regimens vary over time (e.g. tuberculosis or antiretroviral treatment), the disaggregated doses and costs for the relevant time periods should be presented. For medicines intended to be used indefinitely, the "steady state"xx dose comparison might be most relevant.

Drug wastage assumptions (e.g. due to vials that cannot be stored once it has been opened) should be stated and incorporated in the calculations if relevant.

xx Average dose after dose titrations are complete and after excluding participants who discontinue the medicine.

Associated technologies

If the medicine/s being assessed is co-administered with another medicine (and this differs from the comparator) or require acquisition of a medicine delivery system/device for administration that is not included in the medicine acquisition price, the utilisation rates and costs for these components must be calculated and reported. The lifespan of the associated devices should be taken into account when calculating the quantity required.

Prices of medicines and associated technologies

The approved wholesaler price (ex-manufacturer price) should be used to calculate the cost of equi-effective doses for intervention/s, comparator/s, and associated technologies. A consistent year of analysis should be used.

If available, public sector tender prices for medicines must be sourced from the latest Master Health Product List (https://www.health.gov.za/tenders/) with the contract and item number referenced for each medicine. If a medicine is not currently available for use in the public sector, a request should be made to the medicine manufacturers/distributers to provide an estimated price for public health sector procurement.[xxi] If no potential price is provided by the manufacturers/distributers, but a Single Exit Price (SEP) is available for the medicine (private sector price), the SEP should be used to present medicine acquisition costs, even though a reduction in price may be likely 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. See the South African Medicine Price Registry for the latest published SEP (http://www.mpr.gov.za/). Plausible alternative price scenarios should be explored in a sensitivity analysis (e.g., assumption that public sector price will to be 60% of SEP).

Table B can be adapted to report the estimated cost for the medicine/s, comparator/s and associated technologies. The costs of associated medicines or technologies must be reported separately and as part of the overall treatment regimen.

If relevant, costs incurred in preparing and dispensing medicines should also be identified and reported.

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xxi Based on experience in Thailand and other countries, HTAs should not use market price as technology cost as it represents willingness to pay of a company when economies of scale are lacking (especially if products are not reimbursable at that time). Therefore, a price survey among companies requesting their pricing when the product is reimbursable and/or reaches scale is proposed.

TABLE B. ACQUISITION COSTS OF THE INTERVENTION/S AND COMPARATOR/S [INSERT TIME PERIOD OVER WHICH COSTS ARE REPRESENTED]

	Intervention	Source	Comparator	Source	Add more columns for additional interventions and comparators, as needed
Pharmaceutical formulation					
Method of administration					
Average dose/s and dosing schedule/s					
Average daily dose					
Dose adjustments					
Acquisition cost for smallest available pack size					
Cost of one dosing unit					
Cost of treatment for one day					
Average length of a course of treatment					
Wastage assumptions					
Cost of a course of treatment~					
(Anticipated) average interval between courses of treatment					
(Anticipated) number of repeat courses of treatment					
Add more rows for associated medicines/ devices, as needed					

Table adapted from the NICE cost-comparison submission template (54)

~ Cost of a course of treatment after wastage assumptions taken into account.

Healthcare services costs related to prescribing, administration, and monitoring of medicines

The healthcare services required to prescribe, administer and/or monitor medicine/s should be reported separately (e.g., clinic visits, monitoring tests) and compared for intervention medicine/s and comparator/s. Healthcare services costs associated with the routine management of the condition/disease should not be reported unless it is expected to change based on the medicines administered. Relevant healthcare resources to report may include (but are not limited to):

- Health facility/ health professional resource (type and duration) required to prescribe, administer and/or monitor the medicine/s being assessed
  - Consider the level of care
  - Depending on the intervention medicine/s and comparator/s, this may be captured as healthcare professional time, healthcare visits, inpatient days etc.
  - E.g., infusions require physicians and/or non-physicians time in inpatient/outpatient setting, more regular clinic check-ups required to monitor response to certain medicines
- Laboratory tests or investigations required to monitor the medicine/s being assessed, e.g., INR when warfarin is used
- Screening, diagnostic and/or other investigational practices required if specific to one of the treatment options

Resource use assumptions and inputs must be reviewed and agreed by healthcare professionals familiar with the clinical scenario and setting under review.

Table C can be adapted to report the estimated cost of healthcare services associated with the prescribing, administration, and monitoring of intervention medicine/s and its comparator/s.

TABLE C. HEALTHCARE SERVICES COSTS OF THE MEDICINE/S AND COMPARATOR/S [INSERT TIME PERIOD OVER WHICH COSTS ARE REPRESENTED]

	Intervention	Source and justification	Comparator	Source and justification	Add more columns for additional interventions and comparators, as needed
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 (54)

Costs of management of adverse events

Adverse events that incur a cost impact through treatment/management costs should be identified and reported. As there are normally many adverse events associated with medicines, only costs incurred due to the following types of adverse events need to be calculated:

- Adverse events likely to have a significant impact on the patient and/or the healthcare system (such as severe adverse events grade 3 or more, as reported in the clinical studies)
- Adverse events that occur at a high frequency (5% or more of patients)
- Adverse events found to be significantly different between the treatments

For each adverse event included in analysis, the costs associated with its management (e.g., medicines used, clinic/hospital appointments, inpatient care) should be reported separately, with the inputs clearly referenced.

Assumptions about adverse events and inputs used must be reviewed and agreed by healthcare professionals familiar with the clinical scenario and setting under review.

Table D can be adapted to present the healthcare resources associated managing adverse events due to the intervention medicine/s and comparator/s.

Cost or cost savings incurred by the public health sector budget not captured elsewhere

Any other costs or savings to the health system not captured elsewhere should be tabulated in a similar format suggested above. Examples include:

- significant changes in infrastructure required to implement a medicine,
- cost savings resulting from changes to the clinical care pathway
- cost offsets due to differences in patient outcomes with the different treatment options (e.g. disease progression averted)

TABLE D. ADVERSE EVENT/S RESOURCE COSTS OF THE INTERVENTION MEDICINE/S AND COMPARATOR/S [INSERT TIME PERIOD OVER WHICH COSTS ARE REPRESENTED]

	Intervention	Source and justification	Comparator	Source and justification	Add more columns for additional interventions and comparators, as needed
ADVERSE EVENT 1					
Resource 1					
Unit cost					
Number of units per course of treatment					
Cost of [Resource 1] per person experiencing [ADVERSE EVENT 1] per course of treatment					
Probability of person experiencing the adverse event over the course of treatment					
Average cost per person of [Resource 1] to manage [ADVERSE EVENT 1]:					
Per course of treatment					
Per day					
Over full time horizon					
Resource 2					
Unit cost					
Number of units per course of treatment					
Cost of [Resource 2] per person experiencing [ADVERSE EVENT 1] per course of treatment					
Probability of person experiencing the adverse event over the course of treatment					
Average cost per person of [Resource 2] to manage [ADVERSE EVENT 1]:					
Per course of treatment					
Per day					
Over full time horizon					
Average cost per person for management of [ADVERSE EVENT 1]					
Per course of treatment					
Per day					
Over full time horizon					
Add more rows, as needed					

Source: Adapted from the NICE cost-comparison submission template (54)

Appendix 3:

Evidence-to-decision framework

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE OF BENEFIT</td><td>What is the certainty/quality of evidence?
<table><tr><td>High</td><td>Moderate</td><td>Low</td><td>Very Low</td></tr><tr><td></td><td></td><td></td><td></td></tr></table>
High quality: Confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>Provide findings for each comparison</td></tr>
<tr><td>EVIDENCE OF BENEFIT</td><td>What is the size of the effect for beneficial outcomes?
<table><tr><td>High</td><td>Moderate</td><td>Low</td><td>Very Low</td></tr><tr><td></td><td></td><td></td><td></td></tr></table></td><td>Provide findings for each comparison</td></tr>
<tr><td>QUALITYT OF EVIDENCE OF HARM</td><td>What is the certainty/quality of evidence?
<table><tr><td>High</td><td>Moderate</td><td>Low</td><td>Very Low</td></tr><tr><td></td><td></td><td></td><td></td></tr></table>
High quality: Confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>Provide findings for each comparison</td></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
<table><tr><td>High</td><td>Moderate</td><td>Low</td><td>Very Low</td></tr><tr><td></td><td></td><td></td><td></td></tr></table></td><td>Provide findings for each comparison</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
<table><tr><td>Favours intervention</td><td>Favours control</td><td>Intervention = Control or Uncertain</td></tr><tr><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:</td><td></td></tr>
</table>

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
FEASIBILITY	Is the implementation of this recommendation feasible? Yes / No / Uncertain	
RESOURCE USE	How large are the resource requirements? More intensive / Less intensive / Uncertain	
VALUES, PREFERENCES, ACCEPTIBILITY	Is there more important uncertainty or variability about how much people value the options? Minor / Major / Uncertain Is the option acceptable to key stakeholders? Yes / No / Uncertain	
EQUITY	Would there be an impact on health equity? Yes / No / Uncertain	

Appendix 4:

Areas for further research and/or consultation

The Guide represents the current recommended approach for the conduct of analysis in support of the EDP HTA process. The development of this Guide and associated consultation identified a series of methodological and procedural areas that require further research and stakeholder engagement in the context of South Africa's developing HTA landscape. The areas are listed below.

Areas for further consideration that fall within the scope of the current HTA Methods Guide

1. **Quality assurance process.** An explicit process for quality assurance of evidence in line with the requirements of the Guide would formalise an approach to both internal peer review (e.g. by experts directly engaged in the EDP HTA process, or an internal sub-committee) and external peer review (e.g. independent reviewers).
2. **Approach to eliciting expert opinion**
   - Expert opinion and advice are essential elements of all HTA processes. However, a deliberately transparent and thorough approach to obtaining expert opinion is required to reduce subjectivity, minimise bias and improve trust in the evidence gathered.
   - An initial approach to obtaining expert opinion is presented in Appendix 1 of the Guide, but the development of more detailed methods, describing how and when experts will be engaged and the way their input will be incorporated into the HTA process, should be prioritised.
3. **Stakeholder engagement and involvement**
   - The approach to engaging and involving patients, clinicians and other important stakeholders in the HTA process is not addressed in the HTA Methods Guide. It is expected that more explicit procedural guidance on stakeholder engagement would be useful to the EDP HTA process.
   - Important considerations related to stakeholder engagement include:
     - In which steps are stakeholders engaged?
     - How are stakeholders identified?
     - How is stakeholder feedback solicited?
     - Do stakeholders participate individually or as a representative of a group?
     - How is conflicts of interest managed?
     - What is the most efficient mechanism or structure to manage stakeholder engagement and involvement?

4. **Further definition and methodological guidance relating to domains "Equity in health", "Patient preferences and values, and acceptability" and "Feasibility"**
    - The proposed approach to representing and assessing "Equity in health", "Patient preferences and values, and acceptability" and "Feasibility" is included in the Guide. Further engagement with a broad set of stakeholders at local and national levels and incorporating experience gained from applied use of the proposed approach will strengthen the existing process.
    - Consideration should be given to the domains and criteria assessed, whether a greater weight should be assigned to any of the criteria, and/or whether specific methods should be used to assess any of the criteria.
5. **Use of economic evaluations produced for other settings**
    - While capacity and resources to produce economic evaluations in South Africa is still evolving, the potential to use economic evidence generated elsewhere should be explored, with due consideration of the important differences that will limit its applicability.
6. **Interpretation and use of Stage 2 analyses**
    - Further consideration is required to determine how and when the results from cost- effectiveness analysis, cost-utility analysis and budget impact analysis will be used to inform EML decisions.
    - Areas where clarity is required include:
        - How medicine topics will be prioritised for economic evaluation and/or budget impact analysis.
        - Who will be responsible for conducting and quality assuring the analysis.
        - How the results will be translated/conveyed to committee members to ensure they understand the evidence and its limitations (this includes determining the cost-effectiveness and budget impact thresholds used).

Areas for further consideration that will expand the scope of the HTA Methods Guide

1. **HTA Methods Guide for non-medicine technologies**
    - Multiple respondents to the public stakeholder consultation outlined important differences in the approach to HTA for medicine and non-medicine technologies. Further consideration and consultation are required to determine how and if the HTA Methods Guide for medicines can be expanded or adapted to be applicable to non-medicine technologies.
2. **More explicit guidance for appraisal and decision-making**
    - Further guidance in the following areas would assist the HTA process:
        - How evidence is appraised and utilised by Expert Review Committees when making recommendations.
        - How recommendations from the Expert Review Committee and associated evidence is used to inform EML decision-making by the National Essential Medicines List Committee.

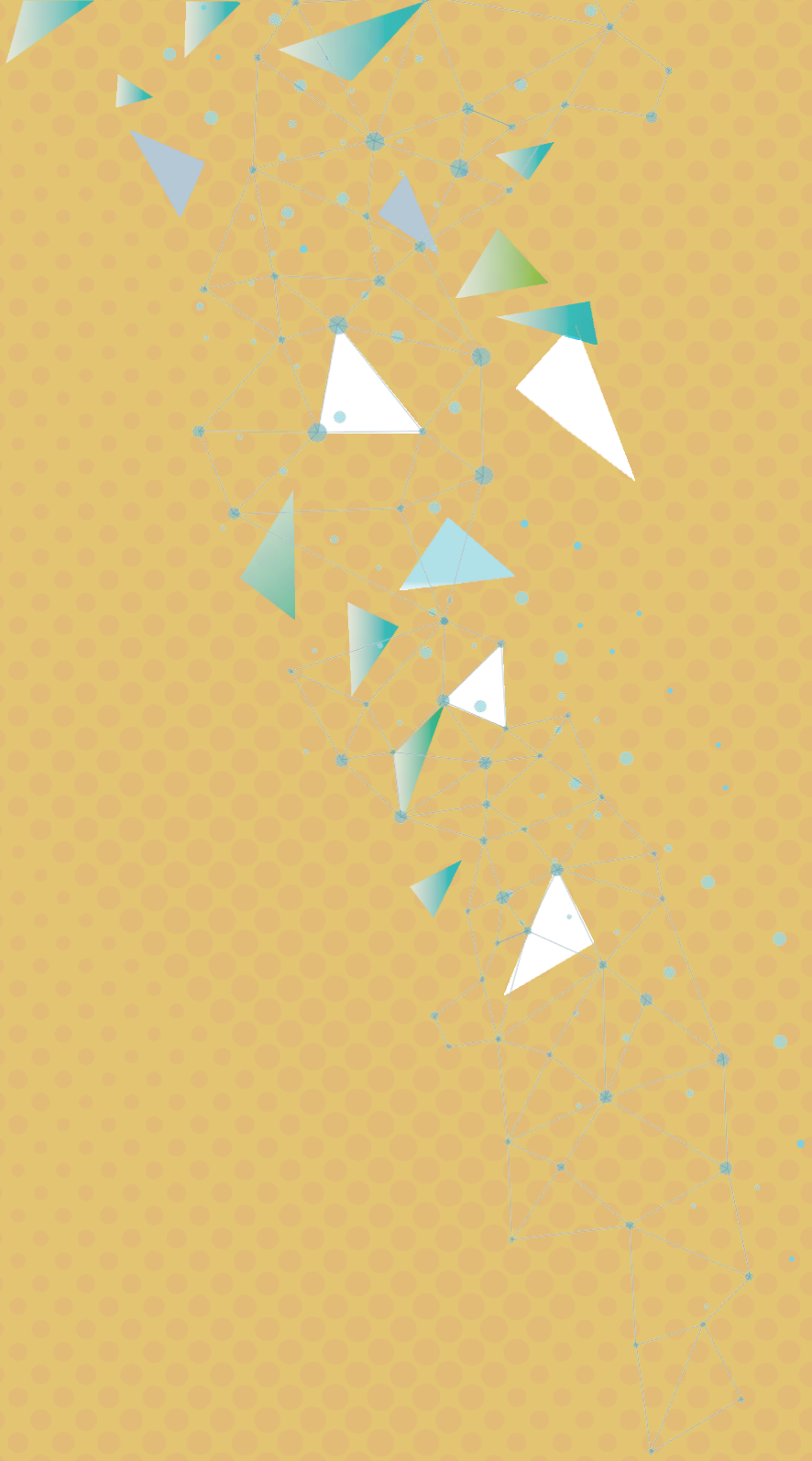
3. Develop methods for additional Stage 2 analyses routinely conducted for the EML process (e.g., assessment of multi-disease programmes)

Areas for further consideration that are directly linked to the implementation or use of the HTA Methods Guide

1. **HTA process guide**
    - Developing an HTA Process Guide will describe the HTA journey through the different stages of an assessment and outline where different stakeholders can expect to feed into (or receive updates on) the process.
    - An HTA Process Guide will provide clarity on the roles and responsibilities of organisations and stakeholders involved in the HTA process and expected timelines for the different stages of the HTA process.
2. **Standardisation of costing parameters through development of a costing database**
    - Development of a basic costing database with costs routinely used in EML analyses will help to further standardise the analyses presented for EML decision- making and streamline the approach to analysis.
3. **Commissioning framework for analysis**
    - A framework for commissioning EML-related analyses, as well as the quality assurance thereof, is vital to ensuring that consistent and high-quality analysis is available to inform EML decision-making.

Areas for further consideration that relate to the use and implementation of HTA in South Africa

1. **Link between HTA and pricing**
    - This iteration of the Guide does not propose methods for assessing and collating international pricing of medicines to be used as evidence within the EDP HTA process. Further research and consultation should establish explicit pricing analysis methodology and the role of pricing information in determining inclusion or exclusion of a medicine on the EML in the context of current and future legislation and policy initiatives.
2. **HTA capacity strengthening**
    - The feasibility of implementation of the HTA Methods Guide was questioned by multiple respondents who cited a lack of capacity and resources in the National Department of Health and the South African HTA community. In particular, the importance of having skilled and experienced analysts conducting the analyses, upskilling stakeholders to enable their meaningful contribution to the HTA process, and the ability of the committees to interpret and use the information were noted.
    - An HTA capacity assessment should be conducted to inform a plan to utilise and develop HTA capacity in South Africa. Linkages with international institutions should be considered.
    - A budget to fund the capacity assessment and capacity building initiatives, as well as the production of analyses to inform the EDP HTA process, should be considered.



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