health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SCOPE FRAMEWORK FOR THE REVIEW OF THE PHARMACOECONOMICS GUIDELINES

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ACRONYMS:

CBA	Cost-Benefit Analysis
CCA	Cost-Consequence Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CMA	Cost-Minimization Analysis
CUA	Cost-Utility Analysis
EQ-5D	EuroQol 5-Dimensions Questionnaire
HRQoL	Health-Related Quality of Life
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
QALY	Quality-Adjusted Life-Year
SF-6D	Short Form 6-Dimensions health status classification system

1. DEFINITIONS:

Appraisal: the act of examining someone or something in order to judge their or its qualities, success, or needs**.**

Assessment: the act of judging or deciding the amount, value, quality or importance of something, or the judgment or decision that is made

Costs: the expenses incurred in the provision of medical services, treatments, interventions, and pharmaceuticals**.**

Cost-Effectiveness: an assessment of the cost in relation to the effectiveness of an intervention/ technology/transaction.

Comparative Effectiveness research:

evaluates the relative effectiveness of different healthcare interventions, treatments, strategies, or approaches in real-world clinical settings.

Comparative efficacy: the assessment of the relative effectiveness of different interventions or treatments for a specific health condition or disease. It involves comparing the ability of two or more interventions to achieve desired clinical outcomes in controlled settings, typically through randomized controlled trials (RCTs) or other comparative study designs.

Economic evaluation: Economic evaluation is a systematic analysis of the costs and consequences of healthcare interventions, programs, or technologies. It aims to inform decision-making by assessing the relative value of different healthcare interventions in terms of their costs and benefits. Economic evaluation helps decision-makers allocate limited healthcare resources efficiently and maximize the health outcomes achieved within budget constraints.

Efficacy: the extent or degree to which a specific intervention, such as a medication, medical procedure, or therapeutic intervention, achieves its intended outcomes under ideal or controlled conditions. In the context of medicine and healthcare, efficacy is typically evaluated through well-designed clinical trials, where the intervention is tested under controlled settings, often using randomized controlled trials (RCTs) or other rigorous study designs.

Effectiveness Evaluation: the process of judging or calculating the quality, importance, amount, or value of something.

Evidence-based Medicine: Evidence-based medicine (EBM) is an approach to medical practice that emphasizes the conscientious, explicit, and judicious use of the best

available evidence from scientific research in making clinical decisions. It involves integrating individual clinical expertise with the best available external clinical evidence obtained from systematic research, while also considering patient values and preferences. The goal of evidence-based medicine is to optimize clinical decision-making and patient care by applying rigorous scientific evidence to inform diagnostic and treatment decisions, ultimately aiming to improve patient outcomes and quality of care.

Health Technology Assessment:

A multidisciplinary process that systematically evaluates the properties and effects of health technologies and interventions. These technologies can include medical devices, pharmaceuticals, procedures, and systems used in healthcare. The primary aim of HTA is to inform decision-making in healthcare by providing evidence-based information about the clinical effectiveness, cost-effectiveness, safety, and broader social, ethical, and organizational implications of adopting or using specific health technologies.

Pharmacoeconomics: Is a specialized branch of health economics that focuses on the economic evaluation of pharmaceuticals and related healthcare interventions. It involves the application of economic principles and methods to assess the costs and consequences of using medications and other healthcare technologies, with the aim of informing decision-making regarding their allocation, utilization, and reimbursement within healthcare systems.

Quality adjusted life years:

Quality-adjusted life years (QALYs) are a measure used in health economics and outcomes research to quantify the overall health-related quality of life (HRQoL) experienced by individuals or populations. QALYs combine both the quantity and quality of life lived, providing a standardized metric for comparing the impact of different health interventions on patients' well-being.

Safety: In the context of healthcare refers to the absence of harm or adverse effects associated with medical interventions, treatments, procedures, devices, or pharmaceuticals.

Clinical or care pathway: All health-related pathways necessary to model the costs and outcomes relevant to the decision problem.

Consistency: Uniformity of data sources across parameters.

Credibility: A perceived lack of bias, where bias refers to the systematic deviation of the estimated value from the true underlying value.

Decision problem: The decision the economic evaluation is designed to inform.

Deterministic analysis: Data parameters represented by the expected values of individual data elements (i.e., point estimates).

Expert elicitation: The formal elicitation of quantitative input from relevant experts regarding the magnitude of a given parameter and its uncertainty.

Expert input: A potential source of data within the totality of available information, comprising both expert elicitation as well as existing expert elicitation studies.

Expert judgment: The process of eliciting and integrating opinions, insights, and assessments from individuals who possess specialized knowledge, experience, and expertise in a particular field or domain. Expert judgment plays a crucial role in decision-making, problem-solving, risk assessment, and forecasting in various contexts, especially when empirical data or quantitative models are limited, uncertain, or unavailable.

Fitness for purpose: Relevance to the decision problem.

Non-reference case: Alternative methods to those recommended in the reference case to assess methodological uncertainty. Can accompany the reference case and be provided to decision-makers, but the impact of departing from the reference case should be explicitly stated.

Probabilistic analysis: Data parameters are represented by statistical distributions rather than point estimates.

Reference case: A set of recommended methods to be used for all evaluations that promote uniformity and transparency and enable the comparison of results for different technologies and decisions.

Scenario analysis: Alternative scenarios carried out to examine sources of uncertainty (e.g., structural) within the reference or non-reference case analysis. One complete analysis should be provided for each alternative scenario.

Social decision-making viewpoint:

The premise that the health care decision-maker, acting on behalf of a socially legitimate higher authority, seeks to maximize the degree to which an explicit policy objective (e.g., improving the population's overall health) is achieved subject to the available resources.

2. BACKGROUND

The National Drug Policy (NDP) of South Africa, formulated in 1996, is closely associated with the policy goal of Section 22G, aiming to promote the rational use of medicines in sync with the World Health Organization's (WHO) initiative for rational medicine use. Its primary objectives include ensuring quality dispensing and prescribing practices, reducing medicine prices, and encouraging cost-effective prescribing.

Section 22G of the Medicines and Related Substances Act established the Pricing Committee, which recommends to the Minister the implementation of a transparent pricing system for all medicines and scheduled substances sold in South Africa. The Committee is primarily responsible for rationalising medicines' pricing structure in the private sector.

In 2003, the Regulations for a Transparent Pricing System for Medicines and Related Substances were introduced, emanating from Section 22G (2) of the Medicines and Related Substances Act. Subsequently, in 2012, the Pharmaco-Economic Guidelines were published, which stipulated that any applicant of a newly registered medicine or scheduled substance in the same therapeutic class as other medicines or Scheduled Substances must submit comparative data on efficacy, safety, and cost-effectiveness. Unfortunately, these guidelines were not mandatory, and as a result, their rate of adoption was insignificant. Since then, there have not been updates to these guidelines, despite changes in the health sector.

However, with the introduction of health reforms, such as the National Health Insurance (NHI) in South Africa, the current policy guidelines on economic evaluations and assessments of medicines and scheduled substances require a review of legislation in line with the country's policy context.

This Scope Policy Statement aims to broaden the review of the 2012 Pharmaco-economic guideline. It will consider the legislative framework, health policy developments, international best practices, and evidence-based research regarding the implementation of the assessment and appraisal of medicine. The objective is to move closer to a vision of equitable access to affordable medicines in South Africa.

3. THE PURPOSE

The Scope for the Review of the Pharmacoeconomics Guideline will identify the specific topics that will be covered in the review of the Pharmacoeconomic guidelines to ensure that the Guideline is reviewed to strengthen the implementation of the assessment of medicine and scheduled substances in terms of **safety, quality, cost-effectiveness, affordability, and the country context.**

The primary objective is to ensure that the assessment of medicines and scheduled substances is applicable and relevant, considering significant changes in healthcare policies and reforms in South Africa since the publication of the Pharmaco-economic guidelines.

Evidence-based decision-making and guideline development are crucial. Decisions must include the best available evidence, practical knowledge, and real-world data in developing a framework for assessing and evaluating medicines and scheduled substances regarding **safety, efficacy, effectiveness, and cost-effectiveness.**

Aims of this scope document:

- To ensure that the review of the Pharmaco-economic Guideline is in line with the most recent evidence base, a thorough literature review will be conducted of international best practices in the assessment of medicines in terms of safety, efficacy, cost-effectiveness, country context will identify advancements, new methodologies, and emerging trends in economic evaluations and health medicine and scheduled substances assessments of medicines and scheduled substances.

- To ensure a high-quality guideline, we will encourage evidence-based submissions from all stakeholders, including healthcare professionals, economists, policymakers, funders, managed healthcare organizations, pharmaceutical manufacturers, associations, researchers, academia, and the public.

- The intention will ultimately be to propose a Guideline that is focused on the whole health system and: To allow stakeholders to be involved in the guideline development process. By

providing evidence on relevant topics that will be captured in the stakeholder consultation document for consideration in the formal update of the Guideline.

- To identify and pre-moderate the standard and quality of the evidence expected in the evidence dossiers to be submitted in terms of study design, data collection, analysis techniques, and reporting standards.

- The goal is to identify the barriers and challenges to developing, implementing, and applying the guidelines for assessment and economic evaluations of medicines and scheduled substances.

- Identifying potential limitations and biases is important to develop robust recommendations for dissemination and decision-making.

- To gather information to inform the application of equity, affordability, and access in developing guidelines.

- Promote active engagement, disseminate knowledge, and provide recommendations for guideline development.

Initial stakeholder engagement will include the dissemination of the Scope for the Review of the Pharmacoeconomic guideline to create a scope consultation document with recommendations for the PC to deliberate on for recommendation for a review of the Pharmaco-economic Guideline.

Once the document is finalized, it will be published to request comments from all stakeholders interested in Pharmacoeconomics in South Africa.

4. CURRENT LEGISLATIVE FRAMEWORK

The Pharmacoeconomics Guidelines have been published because of the mandate given to the Pricing Committee to develop recommendations for the Minister on implementing a Transparent Pricing System for medicines and scheduled substances. This Transparent Pricing System for medicines and related substances is intended to introduce principles and theories to determine a fair

price to charge for medicines and scheduled substances openly and honestly, without any undisclosed factors.

Section 22G of the Medicines and Related Substances Act 101 of 1965 outlines the provisions for the implementation of the assessment and appraisal of medicines and scheduled substances in South Africa.

Regulation 19 (1) to (7) of the Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances requires applicants for new medicines or scheduled substances in terms of Section of the Medicines and Related Substances Act of 1965 to provide information on

- The name under which the medicine will be sold.
- The composition of the medicine
- The proposed price of the medicine.
- The current price of the medicine in any other country.
- The intended method and cost of distribution of the medicine.
- Information on the disease or condition the medicine is intended for, including its prevalence.
- Details on the efficacy, safety and cost-effectiveness of the medicine compared to others in the same therapeutic class.

Regulation 14 empowers the Director-General to request specific information from individuals or entities such as manufacturers, importers, exporters, wholesalers, distributors, pharmacists, and those licensed per Section 22C(l)(a), who sell medicines.

- The name under which the medicine will be sold.
- The composition of the medicine
- The selling price of the medicine in any specified market or country.
- The volume or quantity and total value of sales of the medicine or Scheduled substance categorised by the type of purchaser.
- The method and cost of distributing the medicine or Scheduled substance within the Republic, including details of the supply chain using which the medicine or Scheduled substance will be accessible to users.

- Details regarding the comparative efficacy, safety, and cost-effectiveness of the medicine or Scheduled substance when compared to other medicines or Scheduled Substances in the same therapeutic class, compiled in a manner consistent with guidelines published by the Director-General in the Gazette from time to time.
- Information about the disease or condition for which the medicine or Scheduled substance will be used in the Republic.
- The prevalence of the disease or condition as established by the applicant.
- According to Regulation 21 of the Medicine Price Regulations, it is mandatory for the Director-General to inform the public about the following:
- The therapeutic value of a medicine or scheduled substance about the manufacturer or applicant's set price.
- The single exit price, strength, dosage form, and pack size of a medicine or scheduled substance.
- The risks associated with a specific medicine or scheduled substance.

Regulation 22 of the Medicine Pricing Regulations empowers the Director-General to declare a medicine or scheduled substance as unreasonably priced and communicate this determination as the Director-General considers appropriate. This regulation outlines the process by which the Director-General may determine that the single exit price of a medicine or scheduled substance is unreasonable and take appropriate action. The process follows:

- **Determination of Unreasonable Price: The** Director-General can determine that the single exit price of a medicine or scheduled substance is unreasonable. This determination is made based on specific criteria or considerations, although the regulation does not explicitly outline what factors contribute to this determination.
- **Communication of Determination:** Once the Director-General determines unreasonable pricing, they must communicate this decision to the relevant manufacturer, importer, wholesaler, or distributor. Communication should include the basis for determination and provide transparency and accountability.
- **Consultation and Representation**: Before finalising the determination, the Director-General must consult with the relevant member of the supply chain. This consultation allows the

affected party to provide input and raise any concerns or arguments regarding the reasonableness of the single exit price.

- **Consideration of Representations**: The Director-General must consider any representations made by the supply chain member during the consultation process. This ensures that all relevant perspectives are considered before making a final decision.
- **Publication of Notice:** If, after consultation and consideration of representations, the Director-General remains unconvinced that the single exit price is reasonable, they have the authority to publish a notice in the Gazette. This notice informs the public of the Director-General's opinion that the price is unreasonable and provides the reasons for this opinion.

Overall, this regulation establishes a process for addressing instances where the single exit price of a medicine or scheduled substance is deemed unreasonable. It ensures that appropriate steps are taken to rectify the situation and protect the interests of consumers and stakeholders in the supply chain.

Regulation 23 clearly outlines the information that must be considered when determining whether a medicine or scheduled substance's Single Exit Price (SEP) is unreasonable. This regulation outlines the factors that the Director-General must consider when deciding whether the price of a medicine or scheduled substance is unreasonable: Consideration should be given to:

- **Single Exit Price in the Relevant Market:** The price at which the medicine or scheduled substance is being sold in the relevant market serves as a baseline for comparison.
- **Prices of Other Medicines in the Same Therapeutic Class:** The prices of other medicines or scheduled substances in the same therapeutic class are considered to assess relative pricing within the market.
- **Prices in Other Countries:** Prices of the medicine or scheduled substance, as well as others in the same class, in countries outside the Republic are taken into account to understand pricing dynamics internationally.
- **Changes in CPI, PPI, and Foreign Exchange Rates:** Changes in the Consumer Price Index (CPI), Producer Price Index (PPI), and foreign exchange rates are considered to evaluate economic factors influencing pricing.

- **Purchasing Power Parity:** Purchasing power parity comparisons between the Republic and other countries where the medicine or scheduled substance is sold are considered.
- **Relative Availability and Safety/Efficacy:** The relative availability of medicines or scheduled substances in the same therapeutic class within the Republic and their safety and efficacy compared to the medicine or scheduled substance under review are assessed.
- **Indications for Registration:** The nature of indications for which the medicine or scheduled substance is registered in the Republic is considered.
- **Market Size:** The market size of the medicine or scheduled substance in the Republic compared to other countries is considered.
- **Information from the Council for Medical Schemes:** Relevant information provided by the Council for Medical Schemes is considered.
- **Obstacles to Access:** The size of the obstacle represented by the single exit price to access the medicine or scheduled substance relative to the public interest in widespread and general access is evaluated.
- **Other Relevant Factors:** The Director-General considers any other factors deemed relevant to the pricing or costs of manufacture or sale of the medicine or scheduled substance.

These factors collectively inform the Director-General's determination of whether the price of a medicine or scheduled substance is unreasonable, ensuring a comprehensive assessment of pricing dynamics and market conditions.

Regulation 17 allows the Director-General to refer information and documentation outlined in Regulation 14 to the Pricing Committee. This entails:

- **Information and Documentation:** Regulation 14 specifies certain types of information and documentation related to pricing of medicines or scheduled substances.
- **Purpose:** This information is being referred to the Pricing Committee to facilitate its performance of its duties as mandated by the relevant legislation (presumably the Act referenced in the regulation). The Pricing Committee is likely responsible for overseeing pricing-related matters, ensuring compliance with pricing regulations, and making recommendations or decisions on pricing issues.

- **Facilitation:** By referring the information and documentation to the Pricing Committee, the Director-General aims to enable the committee to access necessary data and insights to fulfil its responsibilities effectively. This may involve providing the committee with comprehensive information needed to make informed decisions or recommendations regarding pricing matters.
- **Collaborative Process:** This provision suggests a collaborative approach between the Director-General and the Pricing Committee in addressing pricing-related issues within the healthcare sector. It underscores the importance of coordination and cooperation between regulatory bodies or entities involved in pricing oversight.

The regulatory policy of assessing and appraising medicines and related substances in South Africa is outlined above. It identifies specific measures for the Director-General to refer relevant information and documentation to the Pricing Committee. This referral enables the Pricing Committee to perform its duties under the Medicines and Related Substances Act.

Given the above, it is within the Pricing Committee's mandate to recommend a framework and develop policy instruments to recommend a comprehensive framework to facilitate the mandate regarding the Medicines and Related Substances Act, 1965 and the Medicine Pricing Regulations provisions for assessing medicine prices and value to guarantee affordable and equitable access to medication in South Africa.

5. COUNTRY CONTEXT POLICY ISSUES

Evidence-based Healthcare Decision-making takes many forms, including evidence-based medicine (EBM), health technology assessment (HTA), comparative effectiveness research (CER), and economic evaluation. These activities aim to improve healthcare quality and efficiency.

According to the NDP, 1996, the Pricing Committee is responsible for regulating drug pricing, while the development of clinical guidelines falls under the purview of NEMLC. Activities related to EBDM, such as EBM, are generally used when developing clinical guidelines, while HTA is used for pricing and reimbursement.

However, the Director General of the National Department of Health has published two separate guides -The Pharmacoeconomics Guideline in 2012 and the Health Medicine and Scheduled Substances Assessments Methods Guide in 2021.

An assessment of two South African guidelines, namely the Health Medicine and Scheduled Substance Assessments Methods Guide and the Pharmacoeconomic Guidelines, identified strengths and weaknesses[1].

The review of the Pharmacoeconomic Guidelines should consider the limitations of the guidelines to improve the implementation of a single guideline that can be used for decision-making for adopting medicines and scheduled substances throughout South Africa and the health system.

In line with international best practices for developing the remit for assessing technologies, it is essential to indicate that this guideline will only consider medicines and scheduled substances.

In terms of PC remit, we will make recommendations for introducing a system for assessing newly registered medicines in terms of Section 15 as well as previously registered medicines to ensure access to safe, affordable, and cost-effective medicines throughout the lifecycle of drugs and scheduled substances.

[1] Marsh, S. December 2022. HTA94 Two South African Health Technology Assessment Methods Guides: Which One Is More Suitable for the Assessment and Appraisal of Medicines? Value in Health, Vol 25, Iss 12, Supplement S314. Available at https://www.valueinhealthjournal.com/action/showPdf?pii=S1098-3015%2822%2903758-5. Accessed 22 May 2024.

The PC's remit in reviewing this guideline will influence many other aspects of the assessment process, including how the PC will interact with the NDOH, other regulators, other than decision-makers, funders, and the public, what level of transparency is feasible or required, and the involvement of external stakeholders in its processes.

The way the PC recommendations are positioned in the decision-making in the South African healthcare system plays a vital role in promoting a rationalised transparent pricing system for medicine and scheduled substances.

The appraisal and assessment of evidence submissions regarding medicines and scheduled substances are fragmented and inconsistently applied in different organizations, such as medical schemes, the Council for Medical Schemes, and NDOH.

Medicine pricing policy implementation within the remit of the Pricing Committee can only be implemented through a comprehensive system of medicine and scheduled substances assessment.

Implementation of NHI Act for assessment of medicines framework

The National Health Insurance Act contains Section 3(d), which outlines the process for establishing a comprehensive system to assess healthcare technologies within the National Health Insurance (NHI) framework. This provision leads to the creation of the Ministerial Advisory Committee on Health Technology Assessment (HTA), which is crucial in providing expert guidance to the Minister on HTA-related matters.

As specified in Section 22G, the Pricing Committee is the statutory body responsible for implementing an assessment framework for Health Technology Assessment for Medicines. The Pricing Committee takes a proactive approach by reviewing the Pharmacoeconomic Guidelines to ensure its processes align with the broader goal of integrating the Framework for medicines assessment into the National HTA Framework.

By leveraging the existing legislative and policy framework, infrastructure and expertise within the Pricing Committee, the proposed framework from the review of the Pharmacoeconomic Guidelines (2012) can be implemented sequentially, rationally, and pragmatically. This strategic approach ensures that efforts to establish a comprehensive HTA system under the NHI Act are practical and

aligned with existing structures, ultimately facilitating the effective evaluation of and medicines within the national healthcare framework.

6. PROCESS OF THE REVIEW OF THE CURRENT PHARMACOECONOMICS GUIDELINE

The review of the Pharmacoeconomic Evaluation (PEE) Guidelines will be conducted in two stages, each aimed at enhancing the comprehensiveness and effectiveness of the guidelines:

6.1. Comparative Analysis with International Guidelines:

This phase involves comparing the existing PEE Guidelines with guidelines from various international sources. We will examine international guidelines from countries with established health technology assessment frameworks, such as the European Union (EUNetHTA Framework).

The purpose is to identify similarities, differences, strengths, and weaknesses between the existing PEE Guidelines and those of other countries or regions.
This comparative analysis will gain insights into global best practices, approaches, and methodologies in pharmacoeconomic evaluation**.**

A comparative analysis of the 2012 South African Pharmacoeconomic (PEE) guidelines with those of other countries can offer valuable insights into potential shortcomings and areas for improvement. Here are some key steps to conduct this analysis:

- The Review of Guidelines will be performed to review the pharmacoeconomic guidelines from other countries for example Australia, Austria, Canada, China, Croatia, Hungary, Israel, New Zealand, Norway, Portugal, Russia, Taiwan, and the Baltic region, and any identified relevant literature.
- Close attention to the scope, structure, methodology, and key recommendations outlined in each set of guidelines.

The Process will be as follows:

- **Identification of Common Themes:** Identify common themes, principles, and methodologies that are consistently addressed across multiple guidelines. This may include topics such as study design, economic evaluation methods (e.g., cost-effectiveness analysis, budget impact analysis), discounting, modeling techniques, perspective selection, and reporting standards.
- **Comparison with South African Guidelines:** Compare the content and approach of the South African Pharmacoeconomic guidelines with those of other countries. Highlight similarities, differences, strengths, and weaknesses in terms of methodology, guidance provided, and areas covered.

- **Identification of Gaps and Challenges:** Identify any gaps, inconsistencies, or areas where the South African guidelines may be lacking compared to international standards or best practices. This may include missing topics, outdated methodologies, insufficient guidance on certain aspects of pharmacoeconomic analysis, or limited consideration of real-world implementation challenges.
- **Prioritization of Issues for Revision:** Prioritize the identified gaps and challenges based on their significance, potential impact on decision-making, and feasibility of addressing them in the revision of the guidelines. Consider input from stakeholders, experts, and relevant authorities to ensure that key concerns are addressed effectively.
- **Recommendations for Inclusion:** Based on the comparative analysis and prioritization exercise, propose recommendations for updating and revising the South African Pharmacoeconomic guidelines.

These recommendations will be aimed to address identified shortcomings, align with international best practices, and enhance the relevance, rigor, and usability of the guidelines for decision-makers and stakeholders in the South African context.

- **Consultation and Stakeholder Engagement:** Engage with relevant stakeholders, including policymakers, healthcare professionals, researchers, industry representatives, and patient advocates, to solicit feedback and input on the proposed revisions to the guidelines. Ensure that

the revised guidelines reflect the diverse needs and perspectives of stakeholders and are supported by consensus within the healthcare sector in South Africa.

- **Documentation and Reporting:** Document the findings of the comparative analysis, prioritization exercise, and recommendations for inclusion in the revised guidelines. Clearly articulate the rationale behind each recommendation and provide supporting evidence or examples from international best practices to justify proposed changes.

By conducting a comprehensive comparative analysis and prioritization exercise, the South African Pharmacoeconomic guidelines can be updated and revised to better align with international standards, address identified shortcomings, and improve the quality and relevance of pharmacoeconomic analysis in healthcare decision-making.

6.2 . Addressing Shortcomings Highlighted by EUNetHTA Framework Assessment

Domains are to be reviewed to strengthen the previously published guideline.

- Building on the findings from the comparative analysis, this phase focuses on strengthening the existing PEE Guidelines by addressing any shortcomings highlighted by the assessment against the EUNetHTA Framework.
- Specific attention will be given to areas where the PEE Guidelines diverge from or fall short of international standards or best practices.
- Recommendations for enhancements, revisions, or additions to the PEE Guidelines will be developed based on the identified shortcomings.
- The goal is to align the PEE Guidelines more closely with international standards and improve their utility, relevance, and effectiveness in guiding pharmacoeconomic evaluations within the local context.
- Overall, this two-part approach aims to ensure that the PEE Guidelines are robust, comprehensive, and aligned with global standards, thereby facilitating high-quality pharmacoeconomic evaluations that support informed decision-making in healthcare resource allocation.

In the appraisal of the published pharmaco-economic guidelines, some concerns or limitations of the current guidelines have been highlighted:

- Implementation was voluntary and only applied to registered medicines, excluding medical devices, diagnostics, and unregistered drugs.
- the South African Pharmacoeconomic guidelines have gaps in coverage or insufficient detail on some topics.

In In line with international standards for the Review of Health Technology Assessment Guidelines the 2012 PE Guidelines will be reviewed by giving special consideration to specific domains specified in the EUNHTA HTA Core Model

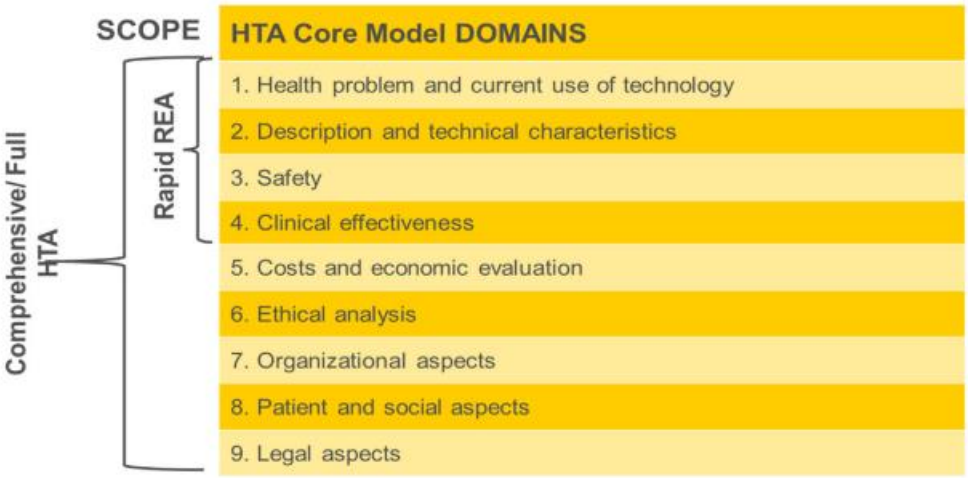

Figure 1: The domains of the HTA Core Model. HTA, health technology; REA, relative effectiveness assessment. (source: The HTA Core Models)

Regulation 19 (1) – (7) provides for the applicant to identify:

a) Health Problems and current use of medicine and scheduled substances

These questions outline the key aspects that must be addressed in assessing health problems and using medicine and scheduled substances. Each question helps provide a comprehensive understanding of the disease or health condition, its management, and the current use of medications and substances in clinical practice.

- **Target Population:** Who is this assessment targeting? Demographics such as age, gender, ethnicity, or specific health characteristics could define this group.
- **Population Size:** How many individuals are in the target population identified in the assessment?
- **Disease or Health Condition:** What specific disease or health condition is evaluated in this assessment?
- **Known Risk Factors:** What factors contribute to developing or exacerbating the disease or health condition?

- **Natural Course of the Disease or Health Condition:** What is the typical progression or development of the disease or health condition over time?
- **Patient Symptoms and Burden of Disease:** What are the common symptoms experienced by patients with this disease or health condition, and how severe is the burden it places on affected individuals?
- **Consequences for Society:** What are the broader societal impacts or consequences of the disease or health condition, such as economic costs, healthcare resource utilization, or societal implications?
- **Alternative Treatments:** What are the typical or common alternatives to the current medicine and scheduled substances being used to manage this disease or health condition?
- **Diagnosis Guidelines and Practices:** How is the disease or health condition currently diagnosed according to established guidelines and in actual clinical practice?
- **Management Guidelines and Practices:** How is the disease or health condition currently managed according to established treatment guidelines and in actual clinical practice?
- **Current Use of Medicine and Scheduled Substances:** For which health conditions, populations, and purposes are the medicine and scheduled substances currently being used? What are the indications or therapeutic uses of these substances according to current medical practice?

b) Description and technical characteristics of the medicine and related substances

These questions cover various aspects of the medicine and scheduled substance, including its characteristics, regulatory status, practical requirements, and the stakeholders' educational needs.

- **Medicine and Scheduled Substance:** What is the specific medicine and/or scheduled substance being assessed, and what are the comparator(s)? This identifies the treatment being evaluated and what it is being compared against.
- **Claimed Benefit:** What is the stated benefit of the medicine and scheduled substance compared to the comparator(s)? This highlights the intended advantage or improvement over existing treatments.

- **Phase of Development and Implementation:** What is the current development and implementation stage for the medicine/scheduled substance and its comparator(s)? This indicates whether the treatment is still in clinical trials, approved for use, or already in widespread clinical practice.
- **Administration and Context of Care:** Who administers the medicine and scheduled substance, and in what context and level of care are they provided? This specifies who is responsible for delivering the treatment and where it is typically administered (e.g., hospital, clinic, home care).
- **Reference Values and Cut-off Points:** Are there established reference values or cut-off points for the medicine and scheduled substance? This clarifies any standardized criteria for assessing the effectiveness or safety of the treatment.
- **Regulatory Status (Marketing Authorization**): For which indications has the medicine and scheduled substance received marketing authorization. This indicates the official approval status for specific uses.
- **Reimbursement Status:** What is the reimbursement status of the medicine and scheduled substance? This refers to whether the treatment is covered by healthcare insurance or reimbursement programs.
- **Investments and Tools Required:** What material investments, special premises, equipment, supplies, data/records, or registries are needed to use the medicine and scheduled substance? This outlines the practical requirements for implementing and using the treatment.
- **Training and Information Needed:** What qualifications, quality assurance processes, skills, training characteristics, and information are needed for healthcare personnel, caregivers, and patients using the medicine and scheduled substance? This addresses the training and education necessary for safe and effective use.
- **Information for Patients and the Public:** What information about the medicine and scheduled substance should be provided to patients, their families, and the general public? This highlights the importance of transparency and education regarding the treatment's benefits, risks, and proper use.

- **Other Manufacturers:** Are there other medicine and scheduled substance manufacturers? This considers the availability of alternative sources for the treatment.

c) Safety

Safety is an umbrella term for any unwanted or harmful effects caused by using medicines or scheduled substances. These questions provide a comprehensive framework for evaluating the safety aspects of the medicine and scheduled substance, considering various factors such as patient characteristics, treatment administration, and potential risks to users and the environment.

- **Safety Compared to Comparator(s):** How does the safety profile of the medicine and scheduled substance compare to the comparator(s)? This evaluates whether the treatment poses more or fewer risks than existing alternatives.
- **Harms Related to Dosage, Frequency, and Medicines:** Are the harms associated with the dosage, frequency of application, or specific technology used in administering the medicine and scheduled substance? This identifies potential risks related to how the treatment is used.
- **Changes in Frequency or Severity of Harms Over Time or Settings:** How does the frequency or severity of harms change over time or in different settings? This assesses variations in safety outcomes under different conditions.
- **Susceptible Patient Groups:** Which patient groups are more likely to be harmed using the medicine and scheduled substance? This highlights vulnerable populations who may be at increased risk of adverse effects.
- **Consequences of False Positive, False Negative, and Incidental Findings**: What are the consequences of false positive, false negative, and incidental findings generated by using the medicine and scheduled substances regarding patient safety? This considers the impact of diagnostic errors or unexpected results on patient well-being.
- **User-Dependent Harms and Occupational Risks**: Are the medicine, schedule, and comparator(s) associated with user-dependent harms? What kind of occupational harm can occur when using the medicine and related substances? This examines risks related to human factors and occupational safety.
- **Risks to Public and Environment:** What risks may occur to the public and the environment when using the medicine and scheduled substance? This evaluates potential hazards beyond direct patient safety concerns.

- **Reducing Safety Risks for Patients, Professionals, and the Environment:** How can safety risks for patients, professionals, and the environment be reduced? This explores strategies for mitigating risks associated with various treatment administration and use aspects.
- **Data and Registry for Monitoring:** What kind of data/records and/or registry is needed to monitor the use of the medicine and the comparator? This addresses the importance of monitoring safety outcomes and collecting relevant data to track adverse events and trends.

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d) Clinical effectiveness:

These questions provide a comprehensive framework for assessing the clinical effectiveness of the medicine or scheduled substance, considering various dimensions of its impact on patient outcomes and quality of life.

While efficacy trials provide valuable insights into a treatment's potential benefits and risks under controlled conditions, effectiveness studies offer a more practical understanding of its real-world performance and utility in diverse patient populations and healthcare settings. Both efficacy and effectiveness are essential in evaluating the impact and value of medicines and scheduled substances.

The effectiveness considers two questions:

1. Can this medicine or scheduled substance work, and
2. does this medicine work in practice?

This assessment commonly uses two definitions: For the purpose of assessing medicine and scheduled substances, both efficacy and effectiveness are considered.

- Efficacy is the extent to which medicine or scheduled substance works (does more good than harm) under ideal circumstances (e.g., within the protocol of a randomized controlled trial [RCT]).

• Effectiveness assesses whether a medicine or scheduled substance does more good than harm when provided under usual circumstances of health care practice (e.g., by a physician in a community hospital treating outpatients)

These research questions focus on assessing the effectiveness of the technology or medicine/scheduled substance in real-world clinical settings and provide a comprehensive framework for assessing its real-world impact and effectiveness across various dimensions of patient outcomes and quality of life.

- **Expected Beneficial Effect on Mortality:** What is the anticipated impact of the technology or medicine/scheduled substance on mortality rates? This evaluates whether the treatment is expected to reduce the likelihood of death related to the disease or health condition.
- **Modification of Effectiveness of Subsequent Interventions:** How does the technology or medicine/scheduled substance modify the effectiveness of subsequent interventions or treatments? This assesses whether the treatment enhances or diminishes the efficacy of other therapies.
- **Effect on Symptoms and Findings:** How does the medicine/scheduled substance affect the severity, frequency, and other characteristics of symptoms and clinical findings associated with the disease or health condition? This evaluates the treatment's ability to alleviate symptoms and improve clinical outcomes.
- **Modification of Morbidity Magnitude and Frequency:** How does the technology or medicine/scheduled substance modify the magnitude and frequency of morbidity related to the disease or health condition? This examines the treatment's impact on reducing illness-related complications and health issues.
- **Effect on Disease Progression or Recurrence:** How does the technology or medicine/scheduled substance affect the progression or recurrence of the disease or health condition? This assesses whether the treatment can slow down disease progression or prevent its recurrence.

- **Effect on Patients' Body Functions:** What is the treatment's effect on patients' physical functions and capabilities? This considers the treatment's impact on improving or restoring bodily functions affected by the disease or health condition.
- **Effect on Work Ability and Return to Previous Living Conditions:** What is the treatment's effect on patients' ability to work and resume their previous living conditions? This evaluates the treatment's role in promoting functional recovery and social integration.
- **Impact on Activities of Daily Living:** How does the treatment affect patients' ability to perform daily activities? This assesses whether the treatment enhances independence and functionality in everyday tasks.
- **Effect on Health-related Quality of Life:** What is the effect of the treatment on patients' overall health-related quality of life? This considers the treatment's impact on physical, emotional, and social well-being.
- **Effect on Disease-specific Quality of Life:** How does the treatment influence disease-specific aspects of patients' quality of life? This examines the treatment's ability to address disease-specific symptoms and challenges.
- **Impact on Non-health-related Quality of Life:** Does knowledge of the treatment result affect patients' non-health-related quality of life? This explores the psychological and social implications of the treatment on patients' overall well-being.
- **Patient Satisfaction:** Were patients satisfied with the treatment? This evaluates patients' subjective experiences and satisfaction levels with the treatment received.

e) Cost and economic evaluation

The focus is on ensuring the efficient allocation of healthcare resources and maximizing the health outcomes achieved with the available budget, considering the specific context and constraints faced by decision-makers in South Africa.

This scope discusses the cost and economic evaluation approach within healthcare resource allocation for medicines and scheduled substances, mainly focusing on South Africa.

Approach to Collective Healthcare Decisions: It is proposed that social decision-making viewpoints regarding healthcare resource allocation be taken. The prominence is on maximizing social welfare or achieving explicit policy objectives, such as improving overall population health with the available resources.

Role of Economic Evaluation: Economic evaluation is highlighted as a crucial tool for informing social decisions in health rather than prescribing social choice. It helps decision-makers assess the efficiency of resource allocation and prioritize interventions that offer the greatest value for money.

South African Context: The proposed approach for economic evaluation within the South African context prioritizes technical efficiency within a limited budget. It aims to improve the maximum possible outcome from a given set of resource inputs.

Supply-side Approach to Cost-effectiveness Threshold: The guidelines will adopt a "supply-side" approach to the cost-effectiveness threshold. Considering budget constraints. This means reimbursing a new medicine or scheduled substance will replace an existing one within the same therapeutic class.

Management throughout the Life Cycle: The recommendations derived from the proposed guidelines will support the management of medicines and scheduled substances throughout their life cycle. This includes decisions on adoption, reimbursement, potential displacement, or disinvestment.

f) Equity and ethical aspects

There is no unique definition of equity, but equity consideration is essential given our social and economic environment. In reviewing the guidelines, consideration must be given to the concept of equity used in the South African healthcare context.

The proposed guidelines will consider equity and ethical aspects associated with the implementation and use of medicine and scheduled substances within the healthcare context. These questions provide a comprehensive framework for evaluating the equity and ethical aspects

associated with the implementation and use of medicine and scheduled substances, ensuring that ethical considerations are integrated into decision-making processes in healthcare.

- **Symptoms and Burden of Disease:** What are the symptoms and burden of the disease or health condition for the patient? This considers the impact of the illness on the individual's health and well-being.
- **Benefits and Harm for Patients:** What are the known and estimated benefits and harms for patients when implementing or not implementing the technology? This assesses the potential positive and negative effects of the intervention on patients' health outcomes.
- **Benefits and Harm for Others:** What are the benefits and harms of the technology for relatives, other patients, organizations, commercial entities, society etc.? This evaluates the broader societal implications of the intervention.
- **Hidden or Unintended Consequences:** Are there any other hidden or unintended consequences of the medicine and scheduled substance and its applications for patients/users, relatives, other patients, organizations, commercial entities, society.? This considers unforeseen impacts beyond the intended outcomes.
- **Ethical Obstacles for Evidence Generation:** Are there any ethical obstacles for evidence generation regarding the benefits and harms of the intervention? This addresses ethical considerations related to research and evidence collection.
- **Vulnerability of Individuals:** Is the medicine used for individuals that are especially vulnerable? This considers the ethical implications of treating vulnerable populations.
- **Autonomy of Patients:** Does the implementation or use of the medicine affect the patient's capability and possibility to exercise autonomy? This evaluates the impact of the intervention on patients' ability to make informed decisions about their care.
- **Respect for Patient Autonomy:** Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used? This explores ways to ensure patient autonomy is respected and supported.
- **Professional Values and Ethics:** Does the implementation or withdrawal of the technology challenge or change professional values, ethics, or traditional roles? This considers the impact of the intervention on healthcare professionals' ethical obligations and roles.

- **Human Dignity:** Does the implementation or use of the technology affect human dignity? This evaluates whether the intervention respects and upholds patients' dignity.
- **Moral, Religious, or Cultural Integrity:** Does the implementation or use of the medicine affect the patient's moral, religious, or cultural integrity? This considers the intervention's alignment with patients' values and beliefs.
- **Privacy Concerns:** Does the medicine invade the sphere of privacy of the patient/user?
- **Distribution of Healthcare Resources:** How does implementation or withdrawal of the medicine affect the distribution of healthcare resources? This examines the equitable allocation of resources.
- **Access to medicine:** Are there factors that could prevent a group or person from gaining access to the technology? This considers barriers to equitable access to the intervention.
- **Realization of Basic Human Rights:** Does the implementation or use of the medicine affect the realization of basic human rights? This evaluates the intervention's impact on fundamental rights such as access to healthcare.
- **Legislative and Regulatory Ethical Challenges:** Can the use of the medicine pose ethical challenges that have not been considered in the existing legislation and regulations? This explores gaps in current ethical frameworks.
- **Choice of Endpoints and Comparators:** What are the ethical consequences of the choice of endpoints, cutoff values, and comparators/controls in the assessment? This considers ethical implications related to study design and outcome measures.
- **Ethical Problems in Economic Evaluation:** Are there any ethical problems related to the data or the assumptions in the economic evaluation? This addresses ethical considerations in economic analyses.
- **Timing of Technology Assessment:** What are the ethical consequences of conducting the technology assessment now? This evaluates the timing of the assessment and its ethical implications.

g) Organizational Aspects

The organizational aspects of implementing a new medicine or technology in healthcare settings involve various considerations and processes to ensure its successful integration into existing workflows and practices.

- **Impact on Work Processes**: The introduction of a new medicine may require changes to existing work processes, such as prescribing, dispensing, administration, monitoring, and documentation. Staff may need to adapt to new protocols, procedures, and workflows to accommodate the use of the new technology.
- **Patient/Participant Flow:** The introduction of a new medicine may impact patient/participant flow within healthcare facilities. This includes considerations such as scheduling appointments, managing waiting times, coordinating follow-up visits, and ensuring continuity of care throughout the treatment process.
- **Involvement of Patients/Participants and Caregivers:** Proper education and involvement of patients, participants, and caregivers are essential for successful implementation. This may involve providing information about the new medicine, instructions for administration, potential side effects, and strategies for adherence to treatment regimens.
- **Staff Education and Training**: Adequate education and training of staff are crucial to ensure competency in using the new technology. Training programs may include hands-on instruction, simulations, role-playing exercises, and ongoing professional development to support staff proficiency and confidence.
- **Cooperation and Communication:** Effective cooperation and communication among multidisciplinary teams are essential for successful implementation. This includes coordination between healthcare providers, support staff, administrators, and external stakeholders to ensure seamless integration and coordination of care.
- **Quality Assurance and Monitoring:** Robust quality assurance and monitoring systems are necessary to assess the safety, effectiveness, and adherence to protocols associated with

the new technology. This may involve establishing quality indicators, conducting audits, collecting feedback, and addressing any issues or concerns that arise.

- **Centralization vs. Decentralization:** The decision to centralize or decentralize the implementation of the new technology depends on various factors, including organizational structure, resource availability, patient population needs, and geographical considerations. Centralization may facilitate standardization and resource efficiency, while decentralization may enhance accessibility and patient-centered care.
- **Access to Technology:** Processes must be in place to ensure equitable access to the new technology for eligible patients/participants. This may involve considerations such as referral pathways, eligibility criteria, financial assistance programs, and addressing barriers to access (e.g., geographic, socioeconomic).
- **Cost Considerations**: Implementing new technology incurs costs related to acquisition, setup, training, maintenance, and ongoing support. Budget impacts should be carefully assessed, and budgetary allocations made to support implementation efforts while ensuring financial sustainability.
- **Resource Utilization and Management:** The introduction of new technology may modify the need for other technologies and the allocation of resources within healthcare facilities. This may necessitate strategic resource planning, reallocation of staff, equipment, and space, and optimization of workflows to maximize efficiency and effectiveness.
- **Management and Decision-Making:** Management teams must address various management problems and opportunities associated with the technology, including resource allocation, risk management, performance monitoring, and stakeholder engagement. Decisions about eligibility criteria for accessing the technology should be evidence-based, transparent, and consistent with organizational priorities and values.
- **Stakeholder Involvement:** Planning and implementation efforts should involve input from a diverse range of stakeholders, including patients, caregivers, healthcare providers, administrators, policymakers, and community representatives. Engaging stakeholders in the decision-making process fosters collaboration, ownership, and support for the technology implementation.
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h) Patient Aspects

Addressing the patient aspect of implementing a new technology in healthcare involves understanding patients' experiences, expectations, perceptions, and needs related to the technology and their condition. Here are some considerations:

- **Experiences of Living with the Condition**: Understanding patients' experiences of living with the condition involves exploring the physical, emotional, social, and practical aspects of their daily lives. This includes symptoms, functional limitations, impact on quality of life, coping mechanisms, and psychosocial support needs.
- **Expectations and Wishes:** Patients may have specific expectations and wishes regarding the new technology, such as improvements in symptom management, quality of life, independence, and convenience. It's essential to understand patients' perspectives and align expectations with realistic outcomes.
- **Perceptions of the Technology:** Patients' perceptions of the technology under assessment can influence their acceptance, adoption, and adherence to treatment. Assessing patients' attitudes, beliefs, and concerns about the technology can provide valuable insights into barriers and facilitators to its use.
- **Burden on Caregivers:** Caregivers play a vital role in supporting patients with chronic conditions and may experience significant burden and stress. Assessing caregivers' needs, challenges, and support preferences can help tailor interventions to address their specific concerns and promote caregiver well-being.
- **Access to Therapies:** Some patient groups may face barriers to accessing available therapies due to factors such as geographical location, socioeconomic status, cultural beliefs, language barriers, or healthcare system constraints. Identifying and addressing these barriers is essential for ensuring equitable access to care.
- **Access Barriers to the Technology:** Factors such as cost, insurance coverage, availability of specialized healthcare providers, transportation, and cultural or linguistic barriers may prevent certain patient groups from gaining access to the new technology.

Efforts to address these barriers may involve advocacy, policy changes, financial assistance programs, and community outreach initiatives.

- Treatment Choices Explanation: Effective communication of treatment choices to patients involves providing clear, understandable information about the benefits, risks, and alternatives to the new technology. This may include discussions about treatment goals, expected outcomes, potential side effects, and implications for daily life.
- Improving Adherence: Communicating specific issues to patients to improve adherence involves addressing practical barriers (e.g., medication schedule, storage requirements), addressing misconceptions or concerns about the technology, providing ongoing support, and monitoring, and involving patients in treatment decisions and care planning. Additionally, providing **education, counseling, reminders, and adherence support tools can help enhance patient engagement and adherence to treatment regimens.**

i) Legal Aspects

Addressing the legal aspect of implementing a new medicine or technology in healthcare involves ensuring compliance with relevant laws, regulations, and ethical standards related to patient rights, informed consent, privacy, and data security.

- **Providing Appropriate Information:** Legal requirements dictate that healthcare providers must provide patients or users with appropriate information about the medicine or technology, including its intended use, potential benefits and risks, alternative treatment options, and any relevant instructions or precautions. This information should be communicated in a clear, understandable manner, tailored to the individual's level of comprehension and language preferences.
- **Consent for Minors and Incompetent** Persons: In cases involving minors or incompetent persons who lack the capacity to provide informed consent, legal requirements specify who is authorized to give consent on their behalf. This may include parents or legal guardians, healthcare proxies, or court-appointed representatives, depending on the jurisdiction and specific circumstances. Healthcare providers must adhere to applicable laws and ethical
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guidelines when obtaining consent for medical treatment or participation in research involving vulnerable populations.

- **Privacy Concerns:** The use of technology may generate additional information about patients that is not directly related to their current care and may implicate their right to privacy. Legal requirements, such as healthcare privacy laws, mandate that patient information be handled confidentially and protected from unauthorized disclosure. Healthcare organizations must implement appropriate measures, such as encryption, access controls, and data breach protocols, to safeguard patient privacy and comply with legal requirements.
- **Informing Relatives about Results:** Laws and regulations vary regarding the disclosure of patient information to relatives or caregivers. In some jurisdictions, healthcare providers may be required to inform relatives about a patient's medical condition or treatment plan with the patient's consent or in cases of emergency. However, providers must balance respecting patient confidentiality with the duty to ensure the patient's best interests and safety.
- **Securing Patient Data:** Legal requirements mandate that healthcare organizations implement appropriate measures to secure patient data and protect it from unauthorized access, disclosure, or misuse. This includes conducting risk assessments, implementing technical safeguards (e.g., encryption, firewalls), establishing administrative policies and procedures (e.g., access controls, data backup), and providing staff training on data security protocols. When implementing new technology, healthcare organizations must ensure that it complies with applicable data protection laws and standards and that appropriate safeguards are in place to protect patient confidentiality and privacy.

7. DECISION PROBLEM

Defining the decision problem is essential for framing the economic evaluation and ensuring that it addresses the specific needs and objectives of decision-makers. Here is how to construct a comprehensive decision problem statement:

- **Interventions to Be Compared:** Clearly specify the interventions that are being compared in the economic evaluation. This includes detailing the treatment options, healthcare technologies, or interventions under consideration, along with any variations or subgroups to be evaluated.

- **Setting(s):** Describe the healthcare settings or contexts in which the interventions will be compared. Consider factors such as healthcare facilities, geographical locations, patient populations, and relevant healthcare delivery systems.
- **Perspective of the Evaluation:** Clearly state the perspective from which the economic evaluation will be conducted. This may include perspectives such as that of the healthcare payer, healthcare provider, patient, society, or a combination of stakeholders. Align the perspective with the interests and objectives of decision-makers.

- **Costs and Outcomes:** Specify which costs and outcomes will be considered in the evaluation. This may include direct medical costs, indirect costs, health outcomes, quality of life measures, and other relevant parameters. Ensure that the chosen costs and outcomes align with the stated perspective and decision problem.

- **Time Horizon:** Define the time horizon over which the costs and outcomes will be evaluated. Consider the duration of the intervention's effects, the natural history of the disease or health condition, and the time frame relevant to decision-making. Ensure that the time horizon is consistent with the perspective and target population.

- **Target Population:** Describe the target population for the evaluation, including relevant demographic characteristics, clinical features, and other factors that define the population of interest. Consider whether the evaluation applies to specific patient subgroups or broader populations.

The target population(s) for the intervention and its expected use should be specified and should be consistent with the decision problem.

Here are some key considerations for defining the target population:

- Demographic Characteristics: Define the demographic characteristics of the target population, including age, gender, ethnicity, socioeconomic status, geographic location, and other relevant factors. Consider whether the intervention is intended for specific demographic groups or for the general population.
- Clinical Characteristics: Specify the clinical characteristics of individuals who are eligible for the intervention based on their health status, medical history, diagnosis, severity of illness, comorbidities, and other clinical factors. Identify any inclusion or exclusion criteria that define the target population based on clinical criteria.
- Decision Problem Consistency: Ensure that the definition of the target population is consistent with the decision problem being addressed in the economic evaluation. The target population should align with the population for whom the intervention is intended to be used or implemented.
- Subgroup Analyses: Identify factors that may lead to different estimates of costs and outcomes across distinct subgroups of the population. These factors could include variations in disease severity, treatment response, baseline risk, patient preferences, or other relevant characteristics. If significant subgroup differences are identified, conduct stratified analyses and present results for each subgroup separately.
- Stratified Analysis: If factors are identified that support the consideration of distinct subgroups within the target population, conduct a stratified analysis to assess the impact of these factors on costs and outcomes.
- Whole Population Analysis: If no significant differences are identified that warrant subgroup analysis, conduct the analysis for the entire target population. In this case, the economic evaluation should provide estimates of costs and outcomes that are applicable to the entire population for whom the intervention is intended.

Factors that may lead to different estimates of costs and outcomes associated with interventions across distinct subgroups of the population should be specified. These could be factors that affect

the natural history of disease, the effectiveness of treatments, or the utilities or costs associated with the disease or treatments.

A stratified analysis with results presented for each subgroup should be provided in the reference case if factors are identified to support the consideration of distinct subgroups. Otherwise, the analysis should be for the entire target population.

- **Comprehensiveness and Clarity:** Ensure that the decision problem statement provides a comprehensive and clear specification of all relevant aspects, including interventions, settings, perspective, costs and outcomes, time horizon, and target population. This clarity facilitates understanding and ensures that the economic evaluation addresses the specific needs and objectives of decision-makers.

By clearly defining the decision problem, economic evaluations can provide decision-makers with actionable insights and evidence to inform resource allocation, policy decisions, and healthcare interventions.

8. TYPES OF EVALUATIONS

The preferred economic evaluation to be recommended should be a cost-utility analysis (CUA) with outcomes expressed as quality-adjusted life-years (QALYs). Any departure from this approach should be clearly justified.

A cost-effectiveness analysis (CEA) with outcomes expressed in natural units is not an appropriate reference case. If convincing evidence is available to show that important patient outcomes are equivalent on virtually all measures, except for survival or quality of life, then a CUA remains the appropriate approach. This allows for the necessary comparison, using the same benefit metric, across all the technologies being considered.

A cost-minimization analysis (CMA) is a costing exercise and not a formal economic evaluation. As such, a CMA is not an appropriate reference case analysis. A CUA remains the appropriate

approach, even where convincing evidence is available to show that important outcomes are similar, as it allows for the analysis of the uncertainty in incremental effect (through probabilistic analysis), facilitating the necessary comparison across all technologies.

A cost-consequence analysis (CCA) should be viewed as a complement to, and not a substitute for, a CUA. A CCA aids in the transparency of the reporting of an economic evaluation, as disaggregated results are presented in terms of costs and outcomes (e.g., events predicted, survival, gains in quality of life).

Where there are important health outcomes from a technology that cannot be captured in a CUA, then these should be reported as additional components within a CCA. If such outcomes can be valued in monetary terms then, additionally, a cost-benefit analysis (CBA) can be undertaken as a non-reference case analysis, with full details provided on the derivation of monetary values for all outcomes included in the evaluation, or justification for why the outcomes were excluded.

9. COMPARATORS

Selecting appropriate comparators is crucial for evaluating the relative effectiveness and cost-effectiveness of a new intervention. Here are key considerations for choosing comparators in economic evaluations within the South African context:

- **Current Standard of Care**: The primary comparator should be the current standard of care or interventions currently used in South Africa for addressing the health condition or problem of interest. This reflects the real-world context and allows for a comparison of the new interventions against existing practices.
- **Multiple Relevant Comparators:** In many cases, there may be more than one relevant comparator reflecting variations in current practice or available treatment options. Consider including multiple comparators to capture the range of treatment strategies used in South Africa and to provide a comprehensive assessment of the new intervention's value proposition.

- **Relevance to Decision Problem:** The choice of comparators should be directly relevant to the decision problem being addressed in the economic evaluation. Consider the specific target population of interest, the healthcare setting, and the jurisdiction for which the decision is being made.
- **Reflect Target Population:** Ensure that the comparators selected reflect the characteristics and needs of the target population. Consider variations in patient demographics, disease severity, comorbidities, and other relevant factors that may influence treatment effectiveness and resource utilization.
- **Reflect Jurisdictional Context:** Take into account the local healthcare context, including resource availability, healthcare infrastructure, clinical guidelines, and regulatory considerations, when selecting comparators. The comparators should be feasible and relevant within the South African healthcare system.
- **Consideration of Non-Pharmacological Interventions:** In addition to pharmacological treatments, consider non-pharmacological interventions or alternative approaches commonly used in South Africa for managing the health condition of interest. These may include lifestyle modifications, behavioral therapies, or other non-drug interventions.
- **Justification and Transparency:** Provide clear justification for the selection of comparators in the economic evaluation. Explain why these comparators are considered relevant and appropriate within the South African context, considering factors such as clinical evidence, guidelines, expert opinion, and stakeholder input.

10. PERSPECTIVE

The perspective of the economic evaluation plays a crucial role in determining which costs and outcomes are included in the analysis and whose interests are being considered. Defining the perspective of the economic evaluation and considering potential alternative perspectives, analysts can provide decision-makers with a comprehensive understanding of the costs, outcomes, and implications of healthcare interventions within the context of publicly funded healthcare in South Africa

- **Perspective of the Publicly Funded Healthcare Payer:** The perspective should align with that of the publicly funded healthcare payer in South Africa. This typically includes costs borne by the healthcare system, such as direct medical costs associated with interventions, healthcare provider fees, hospitalizations, medications, and other healthcare services covered by public funding.
- **Relevance to the Decision Problem:** The perspective chosen should be directly relevant to the decision problem being addressed in the economic evaluation. It should reflect the interests and objectives of the decision-maker responsible for allocating healthcare resources within the publicly funded system.
- **Consistency of Costs and Outcomes:** Both costs and outcomes included in the analysis should be consistent with the chosen perspective. This means that only costs directly incurred by the healthcare payer and outcomes that directly impact the healthcare system should be considered.
- **Non-Reference Case Analyses:** If perspectives other than the reference case perspective are of interest to the decision-maker and could substantially impact the results, these should be included as additional non-reference case analyses. For example, perspectives such as those of patients, caregivers, employers, or society at large may provide valuable insights into the broader economic and social implications of healthcare interventions.
- **Reporting Results:** Results from non-reference case analyses should be reported separately from the reference case. Clearly identify the costs and outcomes included in each additional perspective and quantify and describe the impact of these components on the results compared to the reference case.

11. TIME HORIZON

Defining the appropriate time horizon for an economic evaluation is essential for capturing all relevant costs and outcomes associated with the interventions being compared. Here is how to approach determining the time horizon within the context of the decision problem:

- **Relevance to Decision Problem:** The time horizon should be directly related to the decision problem being addressed in the economic evaluation. Consider the nature of the health condition, the expected duration of the intervention's effects, and the time frame over which relevant costs and outcomes occur.
- **Capture of Relevant Differences:** Ensure that the time horizon is long enough to capture all relevant differences in future costs and outcomes between the interventions being compared. This may involve considering the natural history of the disease, the duration of treatment effects, potential long-term consequences, and the time frame over which benefits accrue.
- **Condition-Specific Considerations:** Tailor the time horizon to the specific characteristics of the health condition under evaluation. For chronic conditions or diseases with long-term implications, a longer time horizon may be necessary to capture the full impact of interventions on health outcomes and costs over time.
- Likely Impact of the Intervention: Consider the expected impact of the intervention on the natural history of the disease and the trajectory of patient outcomes. If the intervention is expected to have long-term benefits or delayed effects, a longer time horizon may be warranted to adequately assess its cost-effectiveness.
- **Decision-Maker Preferences:** Consider the preferences of the decision-maker responsible for allocating healthcare resources. Some decision-makers may prioritize short-term costs and outcomes, while others may be more interested in long-term implications and sustainability.
- **Sensitivity Analysis:** Conduct sensitivity analyses to explore the impact of varying the time horizon on the results of the economic evaluation. This can help assess the robustness of the findings and provide insights into the uncertainty surrounding the optimal time frame for decision-making.

12. DISCOUNTING

The choice of discount rate can significantly affect the present value of future costs and benefits, thus influencing decision-making and project evaluation. Discounting is a crucial aspect of

economic evaluation that involves adjusting future costs and benefits to their present value. Here is how to approach discounting within the context of project evaluation and decision-making:

- **Significance of Discount Rate:** The choice of discount rate is pivotal as it affects the present value of future costs and benefits. Higher discount rates prioritize immediate returns, while lower discount rates give more weight to future benefits. It's essential to consider the appropriate discount rate that reflects the time value of money and the opportunity cost of capital. For South Africa consensus should be reached on how the discount rate will be calculated.
- **Reference Case Discount Rate:** In the reference case, costs and outcomes occurring beyond one year should be discounted to present values at a rate determined by the South African National Treasury for public projects. This rate should reflect the prevailing economic conditions, inflation expectations, and risk factors specific to South Africa.
- **Sensitivity Analysis:** Given the uncertainty surrounding discounting assumptions, it's crucial to assess the impact of varying discount rates on the economic evaluation results. Conduct sensitivity analyses by comparing the reference case results to those from non-reference case analyses using different discount rates, such as around 5%.
- **Interpretation of Results:** Comparing results across different discount rates helps understand the sensitivity of the analysis to changes in discounting assumptions and uncertainties. Decision-makers can use this information to assess the robustness of the findings and make informed choices about project evaluation and resource allocation.
- **Consideration of Time Horizon:** Ensure consistency between the chosen discount rate and the time horizon of the evaluation. Longer time horizons may warrant lower discount rates to reflect the importance of future benefits and costs appropriately.
- **Transparency and Reporting:** Document the chosen discount rate and rationale in the economic evaluation report. Provide detailed explanations of how discounting was applied and how variations in discount rates impact the results. Transparency in discounting assumptions enhances the credibility and usefulness of the economic evaluation.
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13. PROCESS OF ECONOMIC EVALUATION

Economic evaluations can be conducted alongside clinical trials or through modeling studies, each approach offering distinct advantages and considerations:

13.1. Economic Evaluation Alongside Clinical Trials:

Real-world Data: Utilises real-world data collected during the clinical trial, providing direct evidence on the effectiveness and costs of interventions.

Internal Validity: Allows internal validity by controlling confounding factors through randomization and blinding.

- Prospective Design: Data collection occurs prospectively, reducing the potential for recall bias and ensuring timely and relevant information.
- Limited Time Horizon: This horizon is typically limited to the duration of the clinical trial, which may not capture long-term costs and outcomes.
- Generalizability: Findings may have limited generalizability beyond the trial setting, as patient populations and protocols may differ from routine clinical practice.
- Resource-Intensive: Collecting economic data alongside clinical data can be resource-intensive, potentially increasing the burden on study participants and research teams.

13.2. Modeling Studies:

Long-Term Perspective: Allows for the assessment of long-term costs and outcomes beyond the duration of clinical trials, providing insights into the lifetime impact of interventions.

- **Generalizability:** Can be more generalizable to broader patient populations and settings by incorporating data from multiple sources and extrapolating beyond trial data.
- **Flexibility:** Offers flexibility to explore various scenarios, parameters, and assumptions through sensitivity analyses.
- **Cons:**

- Data Requirements: Relies on data from multiple sources, including clinical trials, observational studies, registries, and literature reviews, which may introduce uncertainty.
- **Assumptions:** Highly dependent on model assumptions, which may vary in their accuracy and reliability.
- **Complexity:** Models can be complex and require specialized expertise in health economics, epidemiology, and modeling techniques for development and interpretation.

Choosing between these approaches depends on factors such as the research question, available data, time and resource constraints, and the preferences of stakeholders and decision-makers. In some cases, a hybrid approach combining elements of both clinical trials and modeling studies may provide the most comprehensive and informative economic evaluation.

13.3. Modelling

Model conceptualization and development should address the decision problem.

The model should be consistent with the current understanding of the clinical or care pathway for the health condition and the interventions being compared. The scope, structure, and assumptions should be clearly described and justified.

Researchers should consider any existing well-constructed and validated models that appropriately capture the clinical or care pathway for the condition of interest when conceptualizing their model.

The choice of modelling technique should be justified. The approach should be no more complex than is necessary to address the decision problem.

Baseline natural history should be representative of the target population considered in the decision problem.

The model should be validated, including an assessment of the face validity of the model structure, assumptions, data, and results.

Models should be subjected to rigorous internal validation.

This process should involve quality assurance for all mathematical calculations and parameter estimates, and these processes and their results should be reported. Models should also be evaluated for external validity.

Effectiveness

A comprehensive search of the available data sources should be conducted to inform the estimates of effectiveness and harms associated with the interventions. Report the included studies and methods used to select or combine the data.

The data sources should be assessed based on their fitness for purpose, credibility, and consistency. Describe the trade-offs among these criteria and provide justification for the selected source(s). Incorporate the potential impact of the trade-offs in the reference case probabilistic analysis or using scenario analysis.

Researchers should evaluate and justify the validity of any surrogate end points used for parameter estimation. Uncertainty in the association of the surrogate to the final clinical outcome should be reflected in the reference case probabilistic analysis. This uncertainty can also be explored through appropriate scenario analyses. The existence of multiple potential surrogates should be reflected in the analysis of uncertainty. When considering the use of biomarkers as surrogate end points, the researcher should evaluate and justify the validity of the biomarker and the degree to which the biomarker satisfies the criteria of a surrogate end point.

Appropriate methods for extrapolating estimated effectiveness parameters to longer-term effects should be adopted. Uncertainty in the extrapolated estimates can be considered in the reference case through a probabilistic analysis that incorporates the correlation around the parameters within the survival function. Scenario analysis exploring structural uncertainty should also be conducted.

13.4. Measurement and Valuation of Health

The QALY should be used as the method for capturing the value of the effect of an intervention.

Health preferences (i.e., utilities) should reflect the health states in the model and be conceptualized to address the decision problem.

Health preferences should reflect the general South African population.

In the reference case, researchers should use health preferences obtained from an indirect method of measurement that is based on a generic classification system (e.g., EuroQol 5-Dimensions questionnaire [EQ-5D], Health Utilities Index [HUI], Short Form 6-Dimensions [SF-6D]). Researchers must justify where an indirect method is not used.

The selection of data sources for health state utility values should be based on their fitness for purpose, credibility, and consistency. Describe the trade-offs among these criteria and provide justification for the selected sources.

13.5. Resource Use and Costs

In the reference case, researchers should systematically identify, measure, value, and report all relevant resources based on the perspective of the publicly funded health care payer.

When a range of perspectives is relevant to the decision problem, researchers should classify resources and their associated costs in categories according to each perspective, reporting results separately for the reference case perspective and any additional non-reference case perspectives.

Resource use and costs should be based on South African sources and reflect the jurisdiction(s) of interest (as specified in the decision problem).

Where substantial variation exists in practice patterns or costs among or within the jurisdiction(s) of interest specified in the decision problem, the researcher should consider these sources of variation when conducting the evaluation.

When valuing resources, researchers should select data sources that most closely reflect the opportunity cost, given the perspective of the analysis. Fees and prices listed in schedules and formularies of South African Ministries of health are recommended as unit-cost measures when considering the perspective of the public payer, as long as they reflect actual payments. In other instances, total average costs (including capital and allocated overhead costs) may be relevant. Where costs are directly calculated or imputed, they should reflect the full economic cost borne by the decision-maker.

When a broader societal perspective is of interest to the decision-maker, the impact of the intervention on time lost from paid and unpaid work by both patients and informal caregivers as a result of illness, treatment, disability, or premature death should be included in an additional non-reference case analysis.

13.6. Analysis

The expected values of costs and outcomes (as defined by the publicly funded health care payer perspective) for each intervention should be estimated.

The economic evaluation should be assessed based on the incremental cost-effectiveness ratio (ICER). Estimates of net monetary benefit may also be provided.

For analyses with more than two interventions, a sequential cost-effectiveness analysis should be conducted following standard rules for estimating ICERs, including the exclusion of dominated interventions.

In the reference case, expected values of costs and outcomes should be derived through probabilistic analysis, whereby all uncertain parameters are defined probabilistically:

In most cases, the probabilistic analysis will be a Monte Carlo simulation. An appropriate form of probability distribution should be employed based on standard rules that reflect the nature of each variable. Correlation among parameters should be incorporated, as it can affect both expected values and their degree of uncertainty.

13.7. Uncertainty

Probabilistic analysis should examine uncertainty regarding the value of each parameter. Methodological uncertainty should be explored by comparing the reference case results to those from a non-reference case analysis that deviates from the recommended methods to examine the impact of methodological differences.

The impact of uncertainty on each intervention's estimated costs and outcomes should be presented using cost-effectiveness acceptability curves (CEACs) and cost-effectiveness acceptability frontiers (CEAFs).

When the decision problem includes the option of commissioning or conducting future research, value-of-information analysis may be helpful to characterize the value of these options and design future research and should be included in the reference case analysis.

Structural uncertainty should be addressed using scenario analysis. Probabilistic analyses should be presented for each scenario.

14. SOURCES OF DATA

Economic evaluations in clinical trials and model studies rely on various data sources to assess the costs and outcomes associated with different interventions. These sources include clinical trials, administrative databases, patient records, and electronic health records (EHRs), surveys, cost databases, literature reviews and meta-analyses, expert opinion, and modelling studies.

Clinical trial data is crucial to providing information on the effectiveness, safety, and resource use associated with different healthcare interventions. In economic evaluations, researchers use this information to estimate costs, health outcomes, and quality of life.

Large administrative databases, such as those maintained by healthcare systems, insurers, or government agencies, contain detailed information on healthcare utilization, costs, and outcomes, making them valuable real-world data sources for economic evaluations.

Patient records and EHRs also provide detailed information on patient characteristics, diagnoses, treatments, and healthcare utilization, which researchers can use to estimate costs, outcomes, and resource use associated with different interventions. Such a database is lacking in South Africa, the challenge will be establishing a centralized database.

Surveys of patients, healthcare providers, or other stakeholders can provide valuable data on preferences, quality of life, healthcare utilization, and costs. Surveys may be used to collect primary data or to validate and supplement data from other sources. Cost databases containing cost data for healthcare services, treatments, and resources are essential for economic evaluations, and may include published cost studies, reimbursement data, or cost estimates from healthcare providers and institutions.

Systematic literature reviews and meta-analyses synthesize existing evidence from published studies. Researchers can use these reviews to identify relevant costs, outcomes, and effectiveness data for their economic evaluations. In cases where data are limited or unavailable, expert opinion may be used to estimate costs, outcomes, or other parameters for economic

evaluations. Expert opinion should be based on the best available evidence and may be supplemented by formal expert elicitation techniques.

Economic modelling studies use mathematical models to simulate different interventions' long-term costs and outcomes. These models use data from multiple sources, including clinical trials, administrative databases, surveys, and expert opinion, to inform model parameters and assumptions. Researchers can conduct comprehensive economic evaluations by combining data from these various sources to inform healthcare policy and practice decision-making.

The dissemination of decisions regarding the assessment and implementation of medicines is a crucial aspect of healthcare policy and practice. Here is how this process typically unfolds:

- **Decision-Making Body:** A decision-making body, such as a regulatory agency, health technology assessment (HTA) organization, or formulary committee, evaluates the available evidence on medicines to determine their safety, efficacy, and cost-effectiveness. This body may consist of healthcare professionals, researchers, policymakers, and other stakeholders.
- **Assessment Process:** The assessment process involves reviewing available data from clinical trials, real-world studies, economic evaluations, and other sources to inform decision-making. This may include evaluating the clinical benefits of the medicine, its potential risks and side effects, its cost-effectiveness compared to alternative treatments, and its impact on public health.

15. DISSEMINATION OF RECOMMENDATIONS

Decision Outcome: Based on the assessment findings, the Pricing Committee make recommendations to the Minister of Health for implementation by the Director-General which may include one of several outcomes:

- ❖ Approval for marketing and use in clinical practice at the proposed price.
- ❖ Conditional approval, with requirements for additional data or post-marketing surveillance to review price.

- ❖ Rejection or denial of approval due to safety concerns, lack of efficacy, or other reasons.
- ❖ Recommendation for specific conditions of use, such as restrictions on patient populations or monitoring requirements.

Dissemination of Decision: Once a final decision is made, it is crucial to disseminate it to relevant stakeholders, including healthcare providers, patients, policymakers, payers, and the pharmaceutical industry. This may involve:

- ❖ Publishing the recommendation on the various regulatory agency's website, HTA organization, or other relevant authority.
- ❖ Issuing press releases or public statements to communicate the decision to the media and the public.
- ❖ Providing guidance documents or educational materials to healthcare providers and patients on the implications of the decision for clinical practice.
- ❖ Engaging in stakeholder consultations or public hearings to gather feedback and address concerns.

Implementation: Implementation of the decision involves translating it into action within the healthcare system. This may include:

- ❖ Updating clinical guidelines, formularies, or reimbursement policies to reflect the decision by medical schemes and NDOH.
- ❖ Providing training to healthcare providers on the appropriate use of the medicine.
- ❖ Monitoring and evaluating the decision's impact on patient outcomes, healthcare utilization, and costs.
- ❖ Adjusting the decision based on new evidence or changing circumstances.

Challenges for Implementation

- ❖ Synchronizing implementation of recommendation guidelines Medicine Price Legislation with the Medical Schemes Act.

16. CONCLUSION

The legislative framework within the Regulations Relating to a Transparent Pricing System for Medicines and Related substances, is broad and allows for a number of medicine and health system characteristics to be included in the assessment of medicines, including effectiveness, safety and cost-effectiveness.

In order for any guidelines developed and implemented in relation to the regulations, the pricing Committee needs to ensure that guidance addresses all of these aspects of assessment, and that the guidelines inform relevant decisions for benefits available under current and future health systems offerings.

We trust that this scope will be sufficient to elicit stakeholder comments and proposals for reasonable considerations, criteria and a way forward to ensure that we can implement a robust and consistent approach for medicines assessment for the Republic and the citizens and patients which the various structures serve.