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| Health Technology Assessment |
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# Learning Objectives

Health Technology Assessment aims to improve the performance of health systems, contribute to informed policy decision-making in healthcare related to the use of cost-effective healthcare technologies and the efficient use of healthcare resources, and to create healthcare equity. The assessment and appraisal functions of an HTA are two significant instruments that can be performed by different institutional agencies. Some health interventions initially thought to be beneficial have, after careful evaluation, turned out to be harmful or of no benefit. This has led to the development of the concept of Evidence Based Medicine (EBM), which refers to the use of best evidence in decision-making about individual patients. The EBM Pyramid is a model that helps people comprehend the way different levels of evidence are weighed for healthcare related decision-making. Each study design is reviewed and analyzed based on its relative strengths and shortfalls.

The primary function of health technology assessment is to assess clinical efficiency and cost effectiveness of health technologies. Based on the assessment, the role of HTA is to provide advice to relevant authorities and to review and make appropriate recommendations to federal and institutional agencies. Specific recommendations can result in outcomes such as financing, approval for application, or the support or rejection of implementation. Modern innovation in healthcare and the development of advanced therapies have led to improved health treatments and patient recovery rates, while exerting a burden on healthcare expenditures. Developing oversight strategies for price monitoring of pharmaceutical products is the responsibility of governments, irrespective of a country’s level of economic development or GDP index. HTA is becoming a major gamechanger in priority setting and price negotiations for national and institutional agencies in healthcare. Clinical practice guidelines (CPG) are formulated based on the data acquired by systematic reviews of evidence and the evaluation of therapeutic treatment options. Horizon scanning is referred to as a systematic examination of information to identify potential threats, risks, emerging issues, and opportunities. Healthcare decision-making is based on value-based and science-based needs and framework. Strategies like Multicriteria Decision Analysis (MCDA) allow evaluations based on multiple factors that can influence decisions.

One of the key objectives of HTA is policy research that focuses on priority setting and efficient resource allotment. Thus, low- and middle-income countries (LMICs) identify HTA as an efficient policy apparatus. There is considerable demand for evidence to recommend and shape Universal Health Coverage policies (UHC), such as benefit insurance, strategies for upgrading standards, and overall quality to advance healthcare access and services. Politics, ethics, and rights are core to designing health benefits package for UHC.

# Unit 1 – Defining Health Technology Assessment

**Study Goals**

On completion of this unit, you will be able to …

… define health technology assessment.

… understand the context, extent, and interventions of HTA.

… identify the purpose and tools of HTA.

# 1. Defining Health Technology Assessment

## Introduction

Health Technology Assessment (HTA) is defined as a bridge between “evidence” and “policy” in healthcare (Velasco-Garrido & Busse, 2005). It is a multidisciplinary process that uses specific methods to determine the value of health technologies at different stages of their developmental cycle (O ‘Rourke et al., 2020). Its purpose is to guide governance and policymaking to promote an effective, unbiased, well-structured, and optimal health system (O ‘Rourke et al., 2020). HTA involves structured assessment of the characteristics, effects, or impacts of healthcare technology. There are different forms of policy research and analysis on health and resource use, such as foresight, economic analysis, systems analysis, and strategic analysis. HTA investigates the short- and long-term medical, societal, organizational, and economic impacts of health and resource use, as well as the application of health technology (Velasco-Garrido & Busse, 2005).

## HTA Context

The context in which HTA research is conducted influences the assessment strategies applied and the degree, scope, and magnitude of the evaluation. The sphere and scale of the assessment differs based upon the entity commissioning the study and the purpose of the assessment. It is important to evaluate various aspects of technological or therapeutic intervention, such as the type of interventions within health systems and the interventions on health policy economics, health infrastructure financing, and running healthcare facilities (O‘Rourke et al., 2020).

### Historical Context of HTA

Distinctions in country-specific health systems globally reflect the diverse social and political complexities of each country. In 1965, the Committee on Science and Astronautics of the U.S. House of Representatives reiterated the necessity for policy makers to have the knowledge required to enable an assessment of the overall impact of health technology (Goodman, 2014). This led to the formation of the Office of Technology Assessment (OTA), an organization for unbiased evaluation of various technologies including medicine and healthcare (O’Donnell et al., 2009). The OTA framework was adapted by several European countries including Austria, Denmark, France, Germany, the United Kingdom, the Netherlands, Sweden, and the European Community.

The earliest version resembling the HTA model, known as the Swedish Council for Health Technology Assessment and Assessment for Social Services (SBU), was established in Sweden in 1987, focusing exclusively on healthcare interventions for healthcare policy makers and patients (Hailey, 2009). The purpose of SBU was to guide healthcare policy decisions focused on the effective use of available resources. In Australia, the Australian Pharmaceutical Benefits Advisory Committee (PBAC) was assigned a similar role. In Canada, the Conseil d’évaluation des technologies de la santé (CETS) was formed at the provincial level in Quebec, which was later renamed the Agence d’évaluation des technologies et des modes d’intervention en santé (AETMIS). At the national level, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) was established in 1989. CCOHTA was reorganized as the Canadian Agency for Drugs and Technologies in Health (CADTH) and was responsible for reviewing drugs and recommendations (O’Donnell et al., 2009).Later, the UK established the National Institute for Clinical Excellence (NICE) in 1999, to steer and guide technological progress and advance therapeutic treatment (Charlton, 2020).

#### After the OTA was eliminated, the U.S. has adapted different versions of HTA since the 1990s (Mulligan et al., 2020). Several HTA-like associations and third-party organizations such as the Blue Cross Blue Shield Association Technology Evaluation Center (BCBS TEC) and the Emergency Care Research Institute (ECRI) have guided decision-making by providing healthcare assessments. The Drug Effectiveness Review Project (DERP) focused on randomized clinical trials and health policy-based decision-making. In addition to DERP, BCBS TEC and ECRI, dossiers recommended by the Academy of Managed Care Pharmacy have been adapted by many public and private healthcare bodies. This provides access to standardized clinical and economic information necessary for decision-making. In 2006, the Institute for Clinical and Economic Review (ICER) was established. The U.S. is still awaiting the creation of an official HTA institution. Such an organization should first focus on clinical impact and gradually include economic assessment and evaluation of healthcare technologies. If a national organization for HTA is established, collective efforts will be needed to engage public and private healthcare institutions and stakeholders to work together. Similarly, in countries such as Brunei, Darussalam, Malaysia, Singapore, and Thailand, UHC is provided to citizens, together with a developed HTA model (Van Minh et al., 2014). The ASEAN nations of Indonesia, the Philippines, and Vietnam have initiated UHC, but the HTA model remains to be implemented (ASEAN Reports, Chongsuvivatwong et al., 2011). Cambodia, Lao People’s Democratic Republic (PDR), and Myanmar conduct periodic HTA assessments. Each of these nations is diverse, however, health infrastructure, healthcare-related economic and financial decisions, public health investment, and stakeholder needs should be addressed by UHC.

### Contextual Aspects of Policy Questions

HTA practices have been initiated by health policy makers, healthcare managers, and administrators, and were commissioned by third-party payers, patient advocates, and HTA institutions. HTA is significant as it assesses the medical, ethical, and socioeconomic impact of adapting modern technologies or changes to existing technologies and implementing structural or organizational changes. It is necessary to address safety, economic, and ethical concerns for any urgent healthcare technology, practice, or policy-related issue.

HTA is policy-oriented and supports evidence-based decision-making related to resource allocation, market investment, drug licensing, health-benefit coverage, insurance, reimbursement, and future research funding. Various contextual factors influence HTA reports, further impacting health systems, including health policy-decision makers, regulatory authorities, third party agencies, pharmaceutical companies, healthcare facility managers, and civil servants (Velasco-Garrido & Busse, 2005).

As described, the context in which HTA is performed defines the strategy to be employed, as well as the degree and scale of the assessment. For instance, a recommendation regarding the purchase of advanced medical equipment necessary for a hospital to enter a new clinical research arena must be made by a healthcare facility. To make this decision, the institutional and economic impact is of utmost significance; however, the impact on patient health will be of least concern as that is the subject of research investigation.

### Self-Check Questions

1. Please list three key reasons for HTA development.

*It aids in evidence-based decision-making.*

*HTA is evaluation of impact of healthcare technology.*

*HTA addresses financial decision-making, economic impact and resource allocation.*

1. Please mark the correct statements.

* *HTA deals with a range of interventions within the health system.*
* *HTA acts as a bridge between evidence and policy in healthcare.*
* *HTA evaluates characteristics and impact of health care technology.*

1. Please complete the following sentence:

HTA is a multidisciplinary process that uses definite methods to determine the *value* of health technology at various stages in its *developmental cycle*.

## HTA Objectives

The primary aim of HTA is to improve the performance of health systems for health gains, enhance informed policy decision-making in healthcare for improving uptake, promote the use of new cost-effective healthcare technologies, achieve the efficient use of healthcare resources, and create healthcare equity. HTA reports can impact regulatory guidelines with respect to market access, third party coverage for reimbursements, health coverage, the speed with which modern technology is employed, healthcare guidelines, patient and clinical awareness, technology implementation by users, research priorities, data collection, technology marketing, and resource allocation (Goodman, 2014).

The six-stage model illustrating HTA impact from study to health and economic outcomes includes the following (Millar et al., 2021, Goodman, 2014):

1. “awareness” from relevant stakeholders
2. “acceptance” of a justified basis for action
3. “policy processes” that use HTA reports
4. “policy decisions” thatrefer to HTA reports
5. “practice”defined asprecise action in accordance with policy decisions
6. “outcomes” defined as health and economic results based on policy reform

The Six-Stage Model for HTA Impact (based on Millar et al., 2021)

### HTA Goals

HTA intends to guide and propose safe, efficient, and patient-friendly healthcare policies and ensure best outcomes and decisions for stakeholders (Health Equality Europe et al., 2008). For example, the role of HTA is significant for determining and impacting the following healthcare aspects:

1. **Patient treatment and reimbursement policy**

Decisions by HTA will determine whether patients should receive reimbursement for specific treatments like operative surgery or chemotherapy; which subgroup of patients should receive treatment and when; the patient shortlisting criteria that will be followed for reimbursement; and the treatment duration covered by reimbursement.

1. **Impact of the pharmaceutical industry**

HTA guidelines play a significant role in aiding recommendations for the use of pharmaceuticals. Both HTA agencies and pharmaceutical companies need to work together to overcome the existing challenges. The economic impact and cost effectiveness for market approval are assessed. Clinical trials are planned to evaluate the economic and patient benefits as well as relevant clinical endpoints. The pharmaceutical industry pursues harmonization of international guidelines for economic evaluation.

1. **Impact of technology on healthcare**

One of the key goals of HTA is to assess the impact of technology on healthcare services. Technology has a key role in reviewing proof or evidence from existing users. Clinical trial reviews, financial assessment, and impact on healthcare services can be efficiently assessed by HTA. Law and ethics in public health reflect societal values in the context of social, economic, demographic, epidemiologic, and political changes specific to each country. As technology and societies continue to evolve, new health challenges arise (Tulchinsky, 2014). The impact of technology from a legal perspective is highly relevant, e.g., the use of the abortion pill or certain "lifestyle" drugs. These are not mere ethical debates but involve country-specific legislation and expertise.

1. **Priority setting**

Setting the right priorities is significant for appropriate resource allocation of public funds; for example, in the case of whether public money should be spent on establishing a palliative care facility, a cancer research department, or a psychiatric clinic. Selecting patient-specific treatment regimes, some patients may be responsive to certain therapies while others may not respond. Healthcare organizations must prioritize decisions on implementing modern technologies.

Impact of HTA (based on Bowen et al., 2009)

Key elements in a health technology assessment:

* unmet medical requirements
* clinical treatment or healthcare technology that address needs
* evidence or technology review from current users
* economic viability and value of technology

The review of existing evidence will reveal if the technology is effective, relevant, and applicable in the current country-specific healthcare setting or whether it has become obsolete and needs to be replaced. If the technology is still functional, how does it support the stakeholders and who is directly affected? What are the costs to healthcare service providers and patients? Are the priorities right, and have alternate opportunities been explored?

### Impact Mapping of Cost Effective and Equitable Healthcare System

Impact mapping is performed to model and analyze the impact of HTA institutions. General outcomes and consequences are profiled using a reverse mapping strategy to determine how individual steps influence the impact of HTA (Millar et al., 2021). HTA’s impact can be assessed using the following criteria:

1. efficient management of HTA studies
2. optimum application of HTA for schedule and goal setting as well as policy conceptualization and formation
3. successful engagement and exterior conversation
4. excellent organizational influence and involvement of HTA institutions in healthcare structures and systems
5. efficient application of HTA as a strategy for the health technology price deal
6. effective administration and application of policy reforms

### Self-Check Questions

1. Please complete the following sentence:

*Practice* means precise action in accordance with *policy* decisions.

1. The six-stage HTA impact model includes the following stages...

* *awareness*
* *policy decisions*
* *policy process*
* *management*

1. Please complete the following sentence:

The goal of HTA is to guide and propose *safe, efficient, patient-friendly* health-carepolicies and ensure the best outcomes and decisions for stakeholders.

## 1.3 HTA Instruments

The assessment and appraisal functions of an HTA are two significant instruments, which can be performed by distinct institutional agencies. The assessment function may be conducted by one entity, whose role is to critically review the evidence, while a separate entity may carry out the appraisal function, the objective of which is to review the existing evidence, considering broader aspects. Accordingly, advice or suggestions are provided based on the assessment and appraisal (Health Equality Europe et al., 2008).

**Assessment**

This is the procedure by which the health technology institution assesses the existing evidence to reach a valid outcome regarding the technology being assessed.

### Assessment

The **assessment** process varies for each country, depending on country-specific needs and requirements (Velasco-Garrido & Busse, 2005). It also varies with the assessment purpose. HTA assessments related to medicines are initiated by the company with dossier submission to the relevant healthcare agency. In the case of nondrug related interventions, a systematic review of existing publications is performed. The dossier contains comprehensive evidence regarding the efficiency of modern technology and a comparison of existing technologies. The economic impact of recent technology on a health system’s finances or its **cost-effectiveness** is also assessed by the HTA.

Furthermore, a comparative cost-effectiveness evaluation—an additional clinical benefit—is measured. The assessment tends to include more quantitative elements, while the appraisal incorporates more qualitative elements, such as legal and ethical aspects. Elements include:

**Patient pool:** The subpopulation to be included in the HTA study.

**Cost effectiveness**: The ratio that commonly measures the costs associated with a unit of benefit, or the benefit produced with a unit of costs.

**Disease impact:** The qualitative analysis of untreated patients, including additional costs to the public exchequer.

**Intervention:** How an administered drug acts on patients when delivered, for example, by intravenous injection or oral tablet.

**Efficacy and effectiveness of therapeutic intervention:** Efficacy trials, referred to as explanatory trials, indicate whether an intervention leads to the expected outcome. Effectiveness trials, referred to as pragmatic trials, assess the scale of the advantageous effect in clinical situations. Study designs detailing the effectiveness trials are created depending on situations of everyday clinical practice and the results necessary for clinical research and everyday decision-making (Gartlehner et al., 2006).

**Cost effectiveness:** Cost effectiveness is calculated by analyzing the same outcome from distinct treatments and interventions, such as the number of cardiac arrests prevented and number of mortalities prevented. Cost efficacy is one of the decisive criteria deciding whether additional interventions should be prioritized.

**Monetary impact:** It is important to analyze the economic impact of HTA with regards to implementation costs. Some of the HTA-sponsored studies do not cover the total cost of applying new treatments into practice, such as training requirements. These can prevent new treatments being taken up and should be considered in the economic analysis (Guthrie et al., 2015).

**Innovation:** Innovations in healthcare, such as precision-medicine interventions, are expected to boom in the coming years. Innovation will transform the way the healthcare industry functions, encompassing various aspects from patientcare to healthcare management and assessment. For instance, complexity and unpredictability regarding delivery of therapies employing biomarker data and applying advanced AI-based technologies will be challenging. However, global healthcare systems will have to reassess their strategies and assessment systems to implement changes and upgrade redundant systems, continually evaluating the monetary value of new treatments and services (Love-Koh et al., 2018).

**Availability of therapeutic alternatives:** Alternate therapeutic interventions to replace traditional therapies and treatment strategies need to be discussed.

**Health equity:** The evaluation of how novel therapeutic treatments may influence uniform access to healthcare resources, for example, if people with a low socioeconomic level should be prioritized for treatment.

**Public health impact:** The assessment of how change in treatment may generally affect public health, for example, advanced therapy to treat cancer may reduce the mortality rate of cancer patients.

HTA institutions in each country have adapted guidelines to make decision-making more uniform and justified for HTA agencies in various countries.

### Appraisal

HTA aids in decision-making at the policy, clinical, and management levels. Reimbursement discussions among healthcare providers concerning novel health technology can be

complex; thus, HTA influences these negotiations and decisions. The analysis of evidence should be separate from appraisal and decision-making (Hettle et al., 2017). Entities such as regulatory agencies, public sector HTA agencies, government-sponsored institutions, and organizations performing appraisals will make suggestions depending on the results of evidence assessment, in addition to cues from regional healthcare policies and impact and stakeholder declarations. Based on HTA procedures, the outcome is either to include or exclude the new therapy or technology for or from reimbursement, respectively, in health insurance agencies. Available evidence regarding an intervention may not always constitute full proof. Thus, multiple strategies, including published scientific literature or clinical trial-based evidence, should be used for making valid conclusions. A group is assigned the task of appraisal procedures to make recommendations. Economic impact is one important consideration by HTA agencies if a new therapy is recommended for market launch. In the case of national emergencies, how can economic impact be managed by HTA agencies and a wider group of stakeholders?

For example, the UK’s National Institute for Health and Care Excellence (NICE) is responsible for conducting HTA on behalf of the National Health Service (NHS). NICE has a group for citizens who employ a citizens’ jury model to inform and aid NICE appraisal committees with their functions (Charlton, 2020). To justify its recommendations to the NHS about which technologies to fund, NICE has adopted two complementary ethical frameworks: a procedural framework—accountability for reasonableness (AfR); and a substantive framework—an ethics of opportunity costs (EOC) that is based on the concept of allocative efficiency. Findings from a study that empirically investigates the normative changes to NICE’s approach analyze whether these enhance or diminish the fairness of its decision-making, as judged against these frameworks. Accelerating the characterization and rationale of NICE’s strategy and undermining the strain of evidence that emphasizes technologies downplay its association to EOC. This indicates a reduction in allocative efficiency and a switch in the manner that NHA delivers to various users, accommodating those who benefit directly from NICE’s guidance. These modifications diminish NICE’s commitment to AfR by reducing the transparency of its decision-making and by supporting the implementation of concepts that cannot be demonstrated to meet the associated circumstances. This indicated a requirement for the meaningful upgrading of NICE’s approach, or the adequate communication of the ethical reasoning on which it relies. These reports highlight the necessity for empirical work to assess the impact of these policy reforms on NICE’s implementation of HTA.

The citizen’s council has suggested the following changes (NICE, Citizens council meeting report, 2008). The Examples for Assessment and Appraisal process are provided by NICE and elaborated here (Goobermann-Hill et al., 2008).

**Assessment process examples**

* Phase 1: Members of the public and patients can suggest topics of interest through an online form, which the NICE appraisal committee can take up for consideration.
* Phase 2: Technology that is used by the patients is compared with alternate medication or therapy.

**Appraisal process examples**

* The appraisal starts with consultation of the appraisal committee with groups of stakeholders such as patients or caregivers, hospitals, public, technology producers, and clinicians, who are applying this technology in healthcare settings.
* After data collection, an assessment report on clinical efficiency and economic efficiency of the technology is generated.
* The appraisal committee critically reviews the report.
* Evidence and suggestions from clinicians and other stakeholders are invited.
* The appraisal committee provides provisional or arbitrary reports regarding technology. Suggestions and comments from stakeholders are invited.
* All comments and suggestions are considered in discussion, after which recommendations are made to NICE.
* The final report is published by NICE for use by government agencies such as the NHS and stakeholders who directly intend to use the technology.

### Self-Check Questions

1. Please complete the following sentence:

*Assessment* and *Appraisal* are important instruments of HTA.

2. Which of the following statements are correct.

* *Assessment and Appraisal may be done by the same agency.*
* *Assessment and Appraisal may be performed by different healthcare agencies.*
* *Assessment and Appraisal may be performed either by the same or different agencies.*

3. Who can perform assessment?

*Assessment can be performed by any healthcare agency; their role is to critically review the evidence.*

Summary

HTA is a diverse and multi-disciplinary process. HTA aims to regulate governance in healthcare. HTA involves structured assessment of characteristics and impacts of healthcare technology. There are various types of policy research and analysis on health and resource use, such as foresight, economic analysis, systems analysis, and strategic analysis. Historically, country specific HTA guidelines consider distinct socio-political complexities prevalent in each country. The HTA review influences health-policy based decision-making. The overall purpose of HTA is to impact patient treatment and insurance reimbursement policies and market drug approval policy and assess the impact of technology, priority setting, and impact mapping. Two key instruments of HTA are assessment and appraisal, which can be conducted by one or more institutional agencies. Assessment focuses on the critical review of the evidence and appraisal focuses on the review of existing evidence. Based on assessment and appraisal, new suggestions and policy changes are recommended by institutional agencies.

# Unit 2 – Basic Principles of Evidence Based Medicine (EBM)

**Study Goals**

On completion of this unit, you will be able to …

* Learn basic principles of evidence-based medicine.
* Understand the three theories of causation.
* Learn to search for medical literature and design a research study.

# 2. Basic Principles of Evidence-Based Medicine (EBM)

## HTA serves as a bridge that links research and decision-making. It provides the knowledge developed in scientific research for making decisions. HTA collects and analyses data from research and uses it for making recommendations. HTA shares fundamental principles with evidence-based medicine (EBM) and clinical practice guidelines and develops best practice initiatives (Perleth et al., 2001). HTA is policy-oriented, while EBM focuses on supporting decision-making at the clinical and patient level.

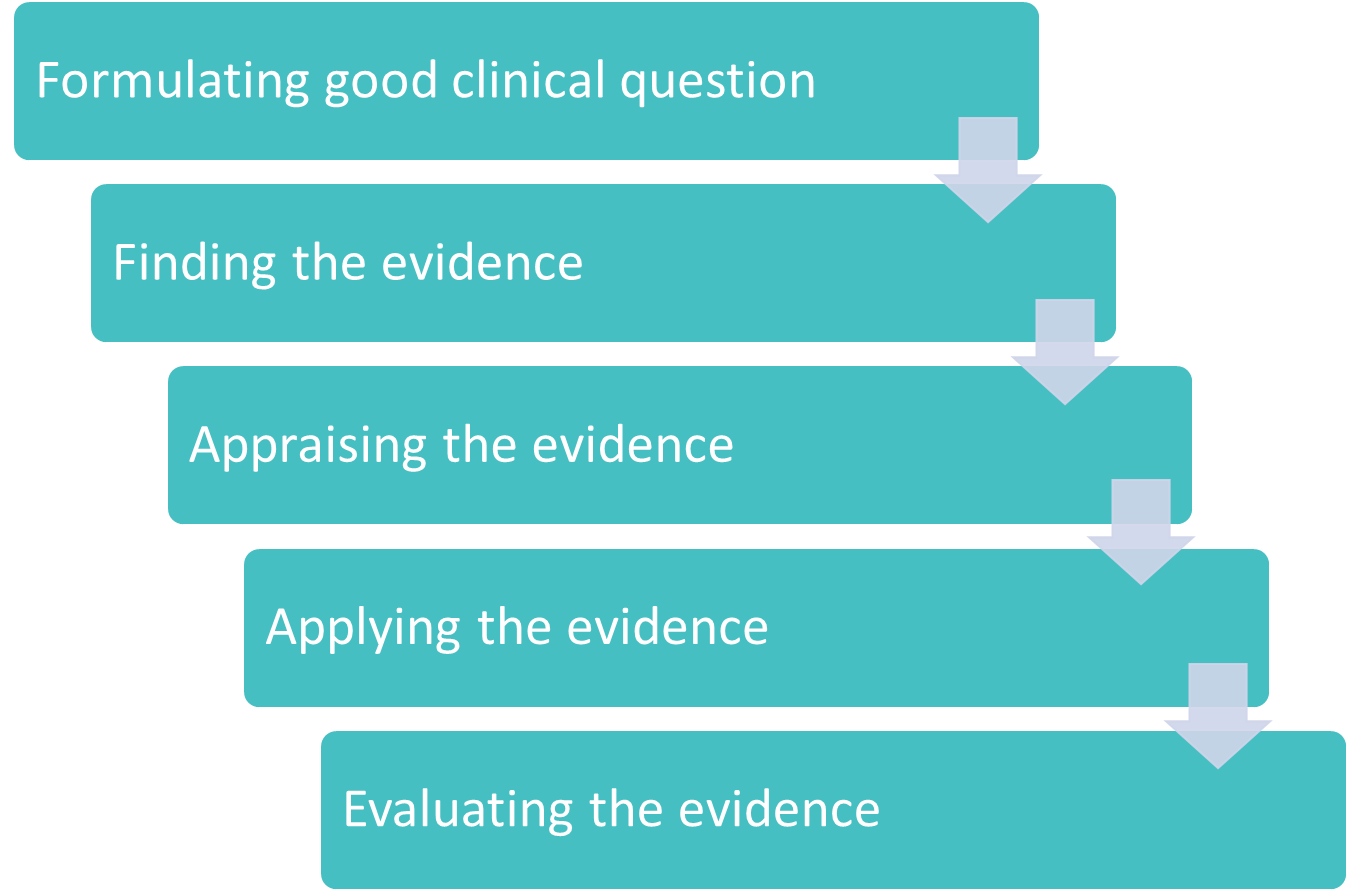
## What is Evidence-Based Medicine?

The concept of EBM, introduced in the 1980s, has great clinical relevance (Pannucci et al., 2010). It is defined as a combination of clinical proficiency, patient principles, and best available information in the decision-making process related to patient healthcare (Masic et al., 2008). EBM promotes scientific data-driven and research literature-based decision-making by clinicians. Randomized control clinical trials provide valid scientific proof of the benefits and harmful effects of new and existing drugs. It is significant for predicting accurate diagnoses, make precise prognoses, and devising effective therapeutic treatment plans (Akobeng, 2005). EBM refers to the use of best evidence in decision-making about individual patients. Decision makers need information about available options and potential consequences. Some interventions thought to be beneficial, after careful evaluation, turn out to be harmful or of no benefit. This has led to the emergence of EBM (Akobeng, 2005).

#### The Five-step EBM model

The practice of EBM involves five key steps: transforming information needs into answerable questions; identifying best evidence to respond to questions; critical review of the evidence for its validity and usefulness; applying the results of the appraisal into clinical practice; and evaluating performance (Sackett et al., 2000).

Five-step Model of Evidence-based Medicine



#### Formulating a good clinical question

The first step is to formulate a good clinical question. “Background questions,” referred to as “general questions,” and “Foreground questions,” referred to as “patient-oriented questions,” are important for the clinicians to know to formulate good research questions (Aslam & Emmanuel, 2010). For instance, in the case of a child suffering from a hereditary disorder, which was inherited from the mother, and the mother is expecting another baby, how could the probability of transmitting the hereditary disease be eliminated?

Good clinical questions should be framed in PICO (P: Patient or Problem, I: Intervention, C: Comparison, O: Outcome) format (Akobeng, 2005). *Population or problem* refers to a particular subpopulation, features, and sociodemographic profile regarding the specific age range, sex, and case history. *Intervention or treatment of interest* refers to therapeutic treatments, procedures, diagnostic tests, risk of predictive factors, or corrective treatment or surgical procedure. *Comparator or control* is significant to compare an advanced treatment or therapy to an existing therapy. *Outcome* refers to the result of the intervention, which should be measured quantitatively and accurately, and be reproducible (Aslam & Emmanuel, 2010). For example, “Is adherence to daily exercise associated with reduced risk of obesity?” In this case, the population refers to the adult population with a history of obesity, the intervention is the daily exercise, the control is no exercise, and the outcome is a reduction in obesity.

In addition to PICO, FINER (feasible, interesting, novel, ethical, and relevant) criteria should also be followed in framing research questions (Hulley et al., 2007). Feasible refers to sufficient time, staff, and funding resources by following a well-designed study design of a research question with a defined scope, sufficient sample size, and trained research staff. Research questions should be made interesting to scientists, healthcare professionals, researchers, and principal investigators. The novel criterion suggests that the research should result in new publications and literature search findings, with expert supervision from senior investigators and research experts. Ethical guidelines are expected to be followed by complying with the regulatory requirements that entail approval from the Institutional Review Board. The research must have relevant impact on clinical practice guiding research and health policy. According to the FINER criteria, feasibility is assessed by conducting a proof-of-concept study. Cost effectiveness is maintained by hiring a statistician and bio-informatician, selecting a cheaper design and outcomes, and assessing the cost of each component of the study, staff members, and other infrastructural resources. In case a sufficient number of patients is not reached from the target population, inclusion and exclusion criteria can be modified accordingly.

#### Finding the evidence

After a good clinical question has been formulated, the second step is to search for relevant evidence that will provide the answer to the clinical question. Evidence can be sourced from medical journals and electronic databases, which treat specific problems and diseases. These sources are expected to be valid, clinically relevant, accessible, comprehensive, and user friendly (Masic et al., 2008).

#### Appraising the evidence

It is important to assess the validity and significance of published information and evidence. The articles must be critically assessed by careful evaluation and analysis of methodology, contents, and conclusions. The appraisal of evidence should be conducted with an objective for evaluating and judging the validity of the methodology and whether an identical strategy should be adapted? Thus, skills to critically evaluate the evidence should be acquired, similar to other clinical skills.

#### Applying the evidence

The fourth crucial step deals with the application of evidence in the process of EBM. Decisions are required about how to apply acquired information and knowledge to situations concerning each patient. It is important to answer several questions before applying the decisions to the results of the study. Are the patients in the study identical to the patient cohort in the study in question? Is the healthcare system ready to treat the patients and are facilities up to standards? What alternative options are available? Do the side effects of the drug or procedure exceed the benefits of the treatment? Are the results adequate for the patients, and do they align with patient values? It is important to take necessary steps in consultation with the patients if there are any chances of harm to the patient.

#### Evaluating the evidence

The final step is the evaluation of the evidence-based approach and the efficiency of its application in a clinical setting to patients. It is important to evaluate whether specific evidence applied to patients will be beneficial and to what extent the results can be replicated by research. If there are any discrepancies, it will be imperative to answer why some patients do not respond in the expected way to the modifications introduced and how that can be modified.

### Self-Check Questions

1. Name the five steps from the five-step EBM model.

*Formulating good clinical question*

*Finding the evidence*

*Appraising the evidence*

*Applying the evidence*

*Evaluating performance*

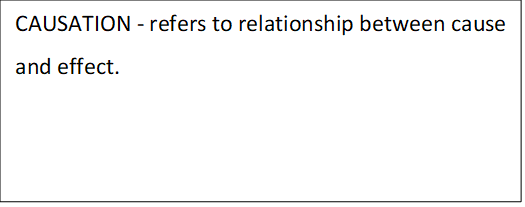
2. What is the PICO model?

* *Population*
* *Intervention*
* *Comparator*
* *Outcome*

3. FINER stands for *Feasibility*, Interesting, *Novel,* Ethical, and *Relevant.*

## 2.2 Causation

**Causation** can have different meanings when elucidated and understood from different perspectives (Kerry et al., 2012). The three general distinct theories of causation are as follows: Interventionism, Counterfactual dependency, and Regularity.



### Interventionism or Interventionist Theory of Causation

The interventionist theory of causation suggests that causal relations can be analyzed by systematic interventions (De Grefte & Gebharter, 2020). Over the years, different definitions of interventionism have been introduced. It was originally more about the causal connections between random variables (e.g., alcohol drinking habit is causally relevant for whether liver cancer occurs) than about the causal relations in peculiar events (Satish drank each day from 1995 to 2010, resulting in liver cancer in 2013). Interventionism refers to the addition of an intervention to the existing scenario (Kerry et al., 2012), for instance, the impact of introducing modern technology or a drug medication to a particular population. Why do we conduct Randomized Control Trials (RCTs) and observational studies? How do strategies employed at one end might connect with those such as case studies and research reports? Causation can be deduced from interventionism exclusively. Thus, it is important to include dominant research methods, which are fundamental to evidential frameworks.

### Counterfactual Dependency

Counterfactual refers to the “control” or “reference group.” Kerry et al. consider a counterfactual as the truth maker of causation (Kerry et al., 2012). Events occur consecutively, one after the other, but causation is observed if similar regularity is missing in the second situation. Thus, in healthcare, causation is counterfactually dependent. The accounting issue still exists for causal claims depending on observational studies. For instance, drinking alcohol leads to cancer. It could comply with the **GRADE** statement, that entails the Grading of Recommendation, Assessment, Development, and Evaluation. According to Hume, this is considered a counterfactual condition, and causation can be completely depicted by complying with the three criteria including temporal priority, contiguity, and constant conjunction (Hume, 1739; Kerry et al., 2012).

**GRADE**: refers to grading of recommendations, assessment, development, and evaluation.

### Regularity

Regularity refers to the perspective of causation that provides theoretical and logical views for aiding making causal claims from observational studies. Continuous regularity of one event after the other is observable. According to Hume, medical science has no difficulty in interpreting any causes beside regularity. Thus, causation is said to be one event followed by another event (Hume, 1739).

### Dispositional Account of Causation

Dispositional account of causation refers to an account that offers an appropriate solution to the identified problem. Based on evidential frameworks, it is demonstrated that causation can be better investigated and understood using established methods and causal accounts. A dispositional account highlights the significance of background situations in understanding causes. The association of causes to specific case-by-case situations in an evidence-based–practice framework is elaborated (Kerry et al., 2012). Dispositionalism considers causation to be primitive, such that causation cannot be reduced to noncausal effects (like regularity or counterfactual dependence). Research strategies such as RCTs make causal claims; however, they rely on a Humean view, which considers causation as an observed series of events with and without counterfactual support. It leads to interventionism defined as anything in a new situation that may causally influence the situation.

Dispositionalism is associated with counterfactuals, in the sense that counterfactual truths have dispositions as their truth makers. Counterfactually deduced results are considered clinically valuable, like outcomes from RCTs. Counterfactual dependency suggests that previous records of results or outcome will be a cause of this; in contrast, a dispositional account only counts those factors as causes, which favor the outcome. For instance, consider the case of two alcoholics; the probability of them receiving a cancer diagnosis will be distinct. A person who drinks alcohol and is genetically prone to suffer from cancer is more likely to have cancer compared with someone with no family history of cancer. Causation is associated with the habit of drinking alcohol, and it is linked with different physiological responses, rather than statistical outcomes.

Dispositionalism connects to regularities, as there is a force that inclines toward the effect (Copley, 2018). This suggests that there is a regularity from cause to effect, like drinking alcohol or smoking leading to cancer. But all those who smoke or drink may not have cancer. Thus, the presence of a tendency is not sufficient to generate an effect. If an effect does not occur due to a cause, this may be a counter example of dispositionalist causation. Identical causes in distinct scenarios may lead to generating distinct results and conclusions. For instance, if two medications are administered separately, they may lead to different outcomes; alternatively, when two medicines are taken together, the outcome might be completely different.

### Factors Supporting Causal Relationships

A causal factor can be defined as an unplanned, unexpected cause of an event. Therefore, the elimination of the factor will prevent the event from occurring or will de-accelerate the intensity of the event. According to the Federal Drug Agency, in an individual case report it is almost impossible to know accurately whether a specific event was caused by a particular product. There are no international standards or criteria for evaluating causality in specific or individual cases. For instance, in cases like brain stroke or cardiac arrests, it is difficult to establish causality. Thus, rigorous case control and long-term cohort studies will be required, which can be monitored for a longer period. It may be difficult to identify causality in cases of polypharmacy, that is, where patients are taking multiple drugs, of heterogeneity in clinical response, or in cases of disease history. The following factors support causal relationships, including strength of the association between factors, consistency of the association, biological plausibility (in clinical studies), and the dose-response relationship in cases of drug approvals (Kerry et al., 2012).

For instance, risk factors occur more often in people with specific outcomes. The risk factors studied precede the effect, and changes in the risk factors precede the effect.

### Self-Check Questions

1. Complete the following sentence:

Three theories of causation are *Interventionism, Counterfactual dependency,* and *Regularities*.

1. Mark the correct statements below:

* *Counterfactual refers to a control or reference.*
* *Interventionism refers to the addition of an intervention to the existing scenario.*
* The ongoing occurrence of one event after the other is not observable.
* *Dispositional account of causation is described as a causal ontology for EBM.*

1. Complete the following sentence:

In healthcare, *causation* is meant to be counterfactually dependent.

## 2.3 Searching the Medical Literature

Literature searches are conducted for compiling and writing the introductory section of all quantitative and qualitative journal articles (including review articles) (Siddaway et al., 2019). Before searching the literature, the research question is assessed in the context of the study design, required sources are determined, it is verified that it is interesting and significant, the literature review is conducted, the data are analyzed, and the research outcome is summarized (Cooper et al., 2018).

Research Question Identification

Identifying a research question based on the PICO model is the first step. This helps researchers generate keywords which can be used for a database search at a later stage. With the PICO model, the question is divided into subquestions and concepts, which can lead to an either wider or more in-depth search (Thompson et al., 2019). A preliminary exploratory search is performed with databases like PubMed Clinical queries, Google, Books, DynaMed, and UpToDate. It should be confirmed whether the question or part of the question has not been previously investigated by any researcher. The research question should be confirmed based on a preliminary investigation.

Planning the Literature Search

Generally, the available literature on any topic is enormous; therefore, careful planning is necessary to search for the most relevant and useful publications and references during a literature search. Past literature not only provides information on a particular topic, but it also provides insights into the types of areas and approaches to the topic taken by previous researchers. What are the overstudied and understudied research questions? What was the rationale for the study? Which methodology proved to be useful? What were the drawbacks of the previous methodologies? What were the findings applied and were those strategies beneficial or not? All these questions can be efficiently answered by planning an effective literature search, which saves plenty of time and resources. It helps to interpret ideas and identify drawbacks and opportunities. A systematic and well-structured review of previous research studies may aid in designing a good research question (Grewal et al., 2016).

* A literature search can be planned by employing the following available research methods, which can be used efficiently by the database selection**.** Databases such as Medline, Embase, Scopus, and Web of Science are used to conduct literature searches. The search strategy is defined with keywords and index terms. High impact references are identified by finding those references that are most cited on the topic. Articles may be either research or review articles. Initiating the search with a high impact reference will be useful in identifying and shortlisting the most cited and relevant publications on the topic. It is important to select keywords together with subject headings as this may lead us to novel concepts on the topic. Symbols like asterisks (\*) are used with search terms to provide additional combinations of the root term. Instead of abbreviated words, full forms should be used to achieve the best search outcome. Subheadings are used to describe vocabulary terms within the database. Headings and subheadings indicate the most significant information from an article. Medical Subject Headings (MeSH) used in PubMed provide database of such terminology, known as MeSH terms. Boolean language termslike AND, OR, and NOT can be used to include, exclude, or add a few terms. Clear inclusion and exclusion criteria are specified. Any peculiar features of the articles that we expect to be included in the literature search should be specified. Criteria such as date of publication, article type, language, and study type can also be included.

### Conducting the Literature Search

### The literature search should be conducted by customizing the search based on the particular database. Databases retain a record or history of search strategies employed during literature searches and a record is maintained on the search portals. Citation mining should be applied to search for additional literature, which may have been overlooked during the primary search. This involves further searching for the key citations to mine relevant references. The Web of Science, Google Scholar, or Scopus were used to search these references.

Saving and Sharing

Most of the databases like PubMed offer the opportunity to save, store, and share the searched literature. It is possible to save several search iterations of the selected strategy. Similarly, references can be saved for organizing, storing, and sharing using the **reference managers**. Reference managers can store references in searchable databases, attach PDFs, auto-generate citations, and create references in a selected formatting style in manuscripts; there is also a possibility of sharing references with other users, in addition to synchronizing them with other electronic devices. Most of the newer reference managers focus on the aspects of collecting and storing references and writing manuscripts. A number of these newer tools are web-based in order to facilitate and accelerate the process. Many reference managers now have integrated PDF viewers for research articles. Reference managers are also being upgraded to handle other types of literature and scholarly content, ranging from presentation slides to blog posts and web links. Open-source software and open standards play a key part in reference management.

**Reference managers**

Common reference managers are EndNote, Mendeley, Zotero, Refworks, Papers, Jabref, and CiteULike.

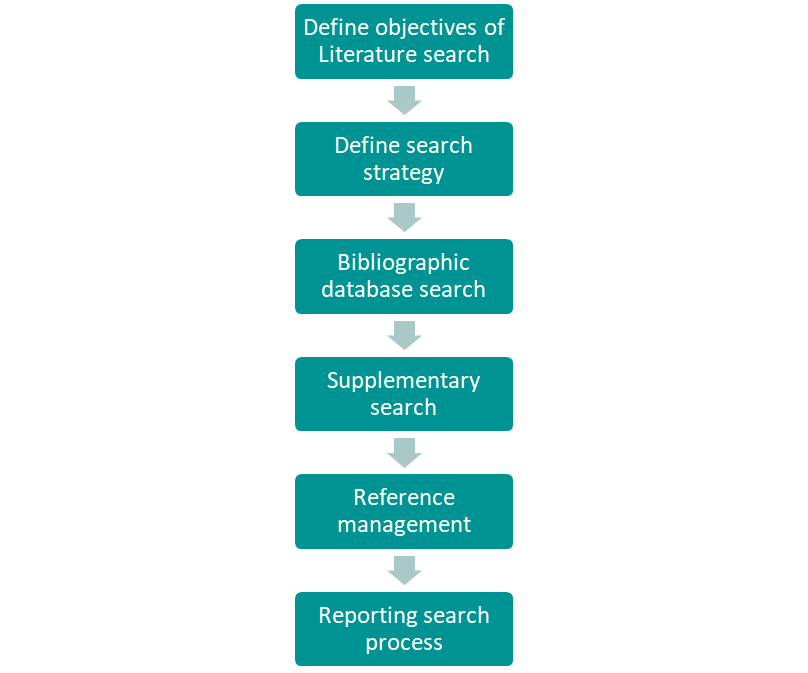
Tools like Mendeley, EndNote, Citavi, and Zotero are commonly used by researchers to manage databases of academic references. Software like Zotero are a free open-source product that can be used by any researcher.

Staying Updated

Databases are constantly being updated with the most current information and the most recently published literature. Email-alerts of new publications can be set up from a specific database. Based on mesh terminology, information regarding any new publication on the topic of interest is communicated. Similarly, social media and journal subscriptions are other means of staying updated regarding any recent publications in the field.

Various stages involved in literature searches are included in the flowchart below.

**Flowchart Depicting Various Stages Involved in a Literature Search (Cooper et al., 2018)**



### Tools and Resources

### Medical literature can be categorized as primary, secondary and tertiary literature (Maggio et al., 2013). **Primary literature** includes original research data and peer reviewed research articles published in journals, conference proceedings, dissertations, and correspondence.

### Secondary literature includes evaluations from primary source articles such as abstracting and indexing services, review articles, meta-analyses, and practice guidelines.

#### Tertiary literature includes summarized collections of primary and secondary literature sources such as reference textbooks, encyclopedias, and handbooks.

### Self-Check Questions

1. List the various stages involved in a literature search.

*Define objectives of literature search.*

*Define search strategy.*

*Bibliographic database search.*

*Supplementary search.*

*Reference Management.*

*Reporting search process.*

1. Complete the following sentence.

Primary literature includes *original research* data and *peer-reviewed* articles.

1. Complete the following sentence.

The first step in identifying a good research question is based on the *PICO model* and *FINER criteria.*

## 2.4 Study Design and Strength of Evidence

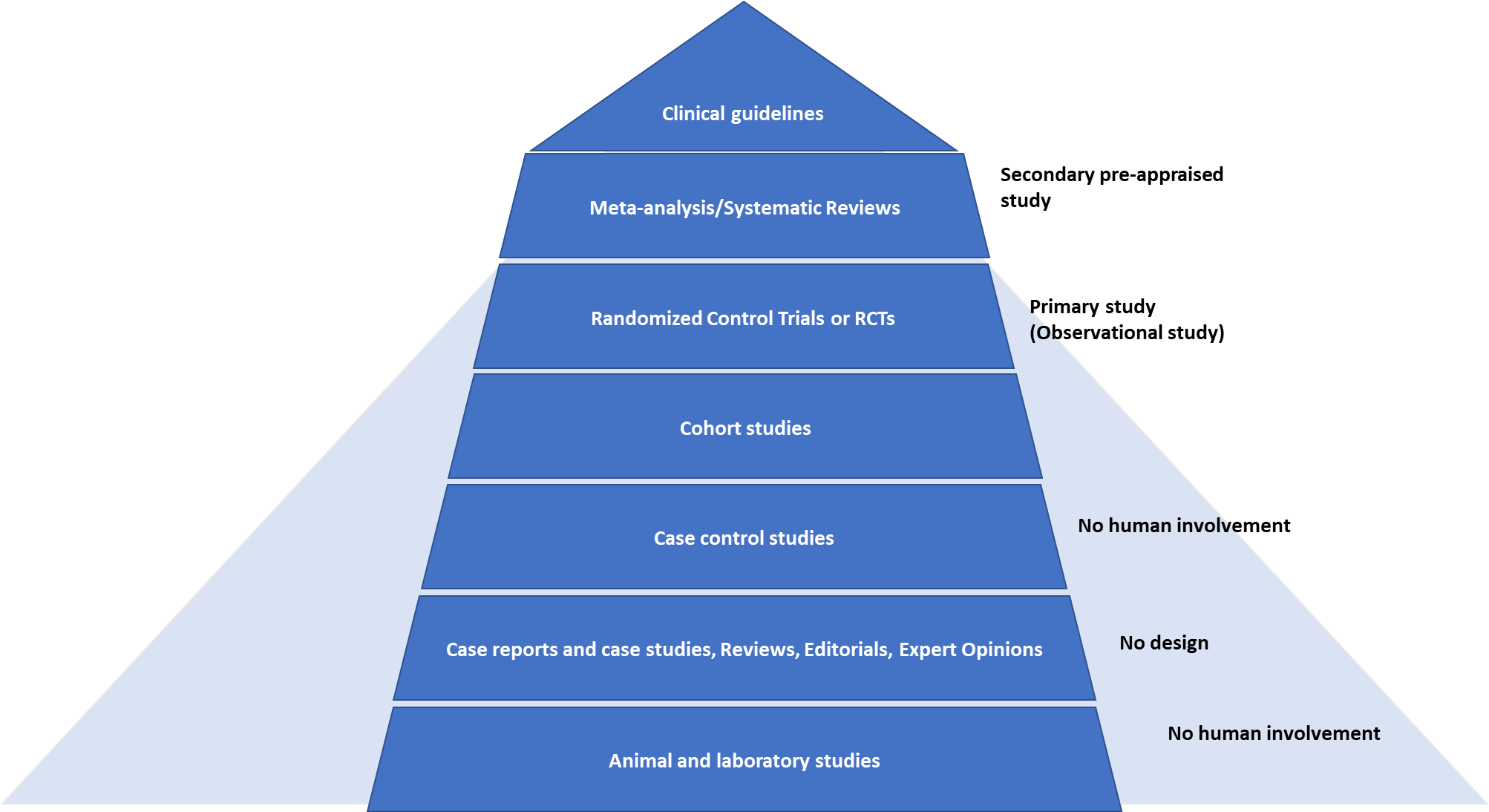
The evidence is drawn from research; thus, it is important to consider the hierarchy of research design and the quality of research execution. However, there is no universal hierarchy and study designs can be ranked in any order (Velasco-Garrido & Busse, 2005). The hierarchy of studies for obtaining evidence RCTs, controlled observational studies, and uncontrolled studies such as case reports. The hierarchy is dependent on the issue being investigated. The Centre for Evidence-Based Medicine (CEBM) has outlined different levels of evidence for clinical research questions dealing with diagnosis, prognosis, therapy, and treatment benefits.

For instance, cohort studies involving a group of people are rated higher than individual case studies as they are followed over many years to ascertain how specific variables such as smoking habits, exercise, occupation, and geography may affect outcome. In contrast, individual case control studies (for rare diseases, for example) may not have a large enough study group to collect sufficient evidence and data.

### Levels of Evidence

The EBM Pyramid is an illustration to facilitate comprehension of how the various levels of evidence are weighed for healthcare-related decision-making.

Evidence-Based Medicine Pyramid (EBM)



Each study design is reviewed and analyzed based on the relative strengths and shortfalls of each design. Each level of the pyramid represents a distinct type of study design. As we move through the different study designs, we become more confident that results are correct, that statistical error has been minimized, and that there is a reduced bias from confounding variables that could have influenced the results.

Distinct levels of evidence include systematic review or meta-analysis, evidence from RCTs, evidence from well-designed control trials without randomization, case control or cohort studies, systematic reviews, single descriptive or qualitative studies, and expert committees(Burns et al., 2011; Murad et al., 2016)

The GRADE approach is a system for grading the quality of evidence and strength of recommendations that is clear, comprehensive, valid, and pragmatic; it is increasingly being adopted by organizations around the world.

|  |  |  |
| --- | --- | --- |
| Table. GRADE Recommendations and Evidence Levels Grade of Recommendation | Evidence Level | Type of Study |
| A | 1a | Systematic review of (homogeneous) RCTs |
| A | 1b | Individual RCTs (with narrow confidence intervals) |
| B | 2a | Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects |
| B | 2b | Individual cohort study / low-quality RCTs |
| B | 3a | Systematic review of (homogeneous) case-control studies |
| B | 3b | Individual case-control studies |
| C | 4 | Case series, low-quality cohort, or case-control studies |
| D | 5 | Expert opinions based on nonsystematic reviews of results or mechanistic studies |

### Meta-Analysis and Systematic Reviews

Asystematic review is a comprehensive, structured, systematic, and transparent means of collecting, appraising, and processing evidence to answer a well-defined question. In contrast, a meta-analysis is a statistical procedure for combining numerical data from multiple studies. A meta-analysis aims to reduce bias at all stages of the review process.

Systematic review involves the systematic searching of literature (Cooper et al., 2018). It is a multistage process initiated by the person who is assigned or eligible to conduct a literature search. A literature search comprises various stages, including establishing the objectives of the literature search, defining a search strategy, searching bibliographic databases, arranging references, and reporting the search process. A systematic review focuses on reviewing the literature and medical evidence available to answer clinical questions (Charrois, 2015).

Meta-analysis entails reviewing literature using statistical tools to analyze and interpret numerical data from research studies. All systematic reviews cannot represent the analyzed/reviewed numerical data, thus a meta-analysis is needed (Charrois, 2015). During 1991 to 2014, a sharp increase of 2,700 percent was recorded in the total number of published systematic reviews and meta-analyses (Niforatos et al., 2019).

When a systematic literature review or meta-analysis is conducted, in case the quality of studies is not properly assessed or if a strategy or methodology is not correctly implemented, the outcome may be biased and inaccurate. Moreover, when systematic reviews and meta-analyses are properly implemented, the results may be on par with large-scale RCTs, which are unexpected in individual or case-control studies.

### Randomized Control Trials

RCTs are well planned and have a specific purpose to prevent selection bias by the random scatter of patient characteristics (e.g., age, sex, diagnosis history) which may affect results (Akobeng, 2005). Inclusion and exclusion criteria are established for the patients (Charrois, 2015). RCTs provide substantial proof of the efficiency of interventions because the procedures employed minimize the risk of confounding variables which may distort the results (Akobeng, 2005). The scientific evidence of RCTs is considered the most reliable for reaching a conclusion about the effectiveness of a new intervention or treatment. Not all clinical studies will require RCTs; thus, alternate observational study designs might be required. Randomization refers to assigning study participants to experimental or control groups at random. Appraising an RCT is a process that determines how robust and effective the trial procedure is, the scale and efficacy of the treatment outcome, and the practical usefulness of the result to patients or the population.

### Cohort Studies

### Cohort studies follow a group of people over an extended period to monitor the impact of drug exposure on their health outcomes. Such studies can be used to detect the long term impact of a daily dietary habit, for instance, that long-term alcohol drinking habits lead to cancer diagnosis. An additional intervention group is included as a reference control for comparison. It may be challenging to have cohort studies as blinded studies.

### Case-control Studies, Case Reports, and Case Series

As the name suggests, this is the first stage of testing an observation. Case series reports include very few participants who are administered similar treatment and receive follow-up treatment. Case-control studies analyze retrospective data and compare it to a control group that has received no treatment. A small number of participants is a challenge for analysis (Cooper et al., 2018).

### Self-Check Questions

1. Please complete the sentence:

*Different* levels of pyramid represent *different* kinds of study design.

1. Please complete the sentence.

Case-control studies analyze *retrospective* data and compare it to a *control group* with no treatment.

1. List levels of evidence.

*Meta-analysis and systematic reviews*

*Randomized Control Trials*

*Case-control studies*

*Case reports*

## 2.5 Sources of Bias

Bias is the tendency to diverge or differ from accuracy in data collection, data analysis, interpretation and publication, which can cause flawed data interpretation and outcomes. Bias can take place either deliberately or unintentionally (Šimundić, 2013). It is considered the structured likelihood of elements involved with a plan and actions.

The following precautions should be taken to avoid research bias (Pannucci et al., 2010):

* Bias during trials can occur at either pre- or post-trial stages due to failures at multiple levels. These may include a lack of clinical significance of the study question, missing data, poorly identified criteria and outcomes (for instance sub-standard diagnostic measures and parameters), selectively reported results, flawed interpretation, and duplicity of results.
* **Pre-trial bias -** This may involve a flawed study design, selection bias, or channeling bias.Bias in the study designcan be prevented by outlining the risks and expected results, keeping in view the purpose of the study, and following an established, standardized methodology. To avoid bias, data collection should be blinded. Bias during selectioncan be avoided by following strict inclusion and exclusion criteria for patients and preventing skewed outcomes. Channeling bias can beavoided by structuring cohorts using rigorous selection criteria.
* **Bias during study trial -** Interviewerbias can be minimized byfollowingstandardized interview procedures and when interviewees are blinded to exposure status. Chronology bias in research or clinical trial studies can be controlled by excluding traditionally used reference controls. Recall bias is avoided by using objective and subjective data sources in specific circumstances. Objective data sources can be used anytime; in contrast, subjective data references should be cross-checked and tallied with research and clinical data. Transfer bias can occur when patients relocate; a study plan is designed to ensure the number of patients in the cohort. Exposuredescription requires that drug treatments be predescribed together with the dose-regimen.Valid results are considered the valid outcomes and findings from the study. Finally, to avoid performance bias during operative procedures, the study population needs to be stratified.

* **Bias after trial -** Citation bias can be prevented by registering for a trial in a clinical trial registry. Confounding bias can be avoided with a study design or during analysis (Lane et al., 2007).
* **Bias in data collection –** Research studies focus on investigating an event or occurrence of an event of interest. Thus, a limited number of samples are studied to investigate specific treatment groups or a population of interest. Data collection is performed without selection bias. Selection bias is avoided by adhering to rigorous exclusion and inclusion criteria during this data collection (Šimundić, 2013). While collecting data for research, there are numerous ways by which researchers can introduce bias in the study. If, for example, during patient recruitment, some patients are more or less likely to enter the study than others, such a sample would not be representative of the population in which this research is conducted.
* **Bias in data analysis -** Data can be analyzed with a bias toward a preferred conclusion to support a particular research hypothesis. Bias can occur through the misappropriation of results, fabricating false data, or by removing or excluding results, all of which produce negative results that contradict the hypothesis. Bias can be created by opting for weak statistical tests for the sake of showing statistical significance. For instance, if the study aims to demonstrate that one biomarker is associated with another in a cohort of patients, but this connection is not significant in a complete cohort. In this case, researchers may try to divide the patients into various subgroups until they achieve statistically significant differences. If this patient subgroup is not included or mentioned in the original research hypothesis, this type of data analysis would be considered unethical and not generalizable to the whole population.
* **Bias in data interpretation -** To avoid bias in interpreting data, appropriatestatistical tests are employed for data analysis. Results are reported as the statistical significance of observed relationships (Šimundić, 2013), for example, a discussion of observed differences and associations despite being nonsignificant, a debate on the basis of statistical significance overlooking clinical significance, deriving interpretations on causality, or extrapolation of results to the general population.
* **Publication bias -** There is a tendency among journals to publish research studies with positive findings and outcomes compared with negative results. However, publishing negative results are useful for the scientific community, as scientists will avoid repeating similar experiments and save research time and resources (Šimundić, 2013, Tenny & Varacallo, 2018). The medical literature, especially the results of cohort studies, provides evidence of publication bias. A systematic review of 20 cohort studies using RCTs indicate that studies with statistically significant results have a higher chance of being published than those with nonsignificant outcomes. Similarly, another systematic review by Schumacker et al. in 2014 examined the results from 23 cohort studies and reported that studies with statistically significant outcomes have higher chances of being published than others (DeVito and Goldacre, 2018).

### Self-Check Questions

1. Complete the following sentence:

*Bias* is any tendency to diverge or differ from accuracy in *data collection, data analysis, interpretation*, and publication, which can cause flawed analysis and outcomes.

1. Which of the following statements are correct?

* *Publication bias is the tendency among journals to publish research studies with positive findings.*
* *Pretrial bias may involve publication bias and flawed study designs.*
* *Channeling bias**can be**avoided by structuring cohorts using rigorous selection criteria.*

1. Complete the sentence.

Bias after trial includes *citation* and *confounding* bias.

## 2.6 Meta-Analysis and Systematic Reviews

A literature review is different from reviewing literature. It provides a detailed, in-depth understanding of the existing evidence to enable the authors and readers to make valid inferences (Siddaway, et al. 2019). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement is designed to guide reviewers to report their objectives, methodology, and findings in an unbiased manner. The updated PRISMA 2020 guidelines propose new reporting guidance that indicates advances in methodology to identify, select, appraise, and synthesize studies. The PRISMA checklist provides a transparent reporting system for compiling systematic reviews and meta-analyses (Page et al., 2021). Salient features of the 27-point PRISMA checklist are outlined below.

#### Title

The title should identify the report as a systematic review.

#### Abstract

Title – Identify the article as a systematic review.

Background (Objectives) - Provide an explicit statement of the main objective(s) of the review or the question(s) the review addresses.

Methods – Specify the the inclusion and exclusion eligibility criteria for the review. Information sources specify the databases and registers used to identify studies and the date when each was last searched. Risk of bias specifies the methods used to assess risk of bias in the included studies. Synthesis of results specifies the methods used to present and synthesize results.

Results - Provide the total number of included studies and participants and summarize the relevant characteristics of the studies. Present the results for the main outcomes, preferably indicating the number of included studies and participants for each. If a meta-analysis was performed, provide a report of the summary estimate and confidence/credible intervals. If comparing groups, indicate the direction of the effect (i.e., which group is favored).

Discussion - Provide a brief summary of the limitations of the evidence included in the review (e.g., study risk of bias, inconsistency, and imprecision), a general interpretation of the results, and the important implications.

Additional information – Mention the funding sources and registration details including name and number.

#### Introduction

Rationale - Describe the rationale for the review in the context of existing knowledge.

Objectives - Provide an explicit statement of the objective(s) of the review or the question(s) the review addresses.

#### Methods

Eligibility criteria - Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.

Information sources - Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify the selected studies. Specify the date when each source was last searched or consulted.

Search strategy – Present the full search strategy for all databases, registers, and websites, including any filters and limits used.

Selection process - Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of the automation tools used in the process.

Data collection process - Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of the automation tools used in the process.

Data items - List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.

Study risk of bias assessment - Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process.

Effect measures - Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.

Synthesis methods - Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis). Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions. Describe any methods used to tabulate or visually display results of individual studies and syntheses. Describe any methods used to synthesize results and provide a rationale for the choice(s). If a meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.

Reporting bias assessment - Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).

Certainty assessment - Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.

#### Results

Study selection - Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review. Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.

Study characteristics - Cite each included study and present its characteristics.

Risk of bias in studies - Present assessments of risk of bias for each included study

Results of individual studies - For all outcomes, present, for each study the summary statistics for each group (where appropriate) and an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.

Results of syntheses - For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. Present results of all statistical syntheses conducted. If a meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. Present the results of all investigations of possible causes of heterogeneity among study results. Present the results of all sensitivity analyses conducted to assess the robustness of the synthesized results.

Reporting biases - Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.

Certainty of evidence - Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

#### Discussion

Provide a general interpretation of the results in the context of other evidence. Discuss any limitations of the evidence included in the review. Discuss any limitations of the review processes used. Discuss implications of the results for practice, policy, and future research.

#### Additional information

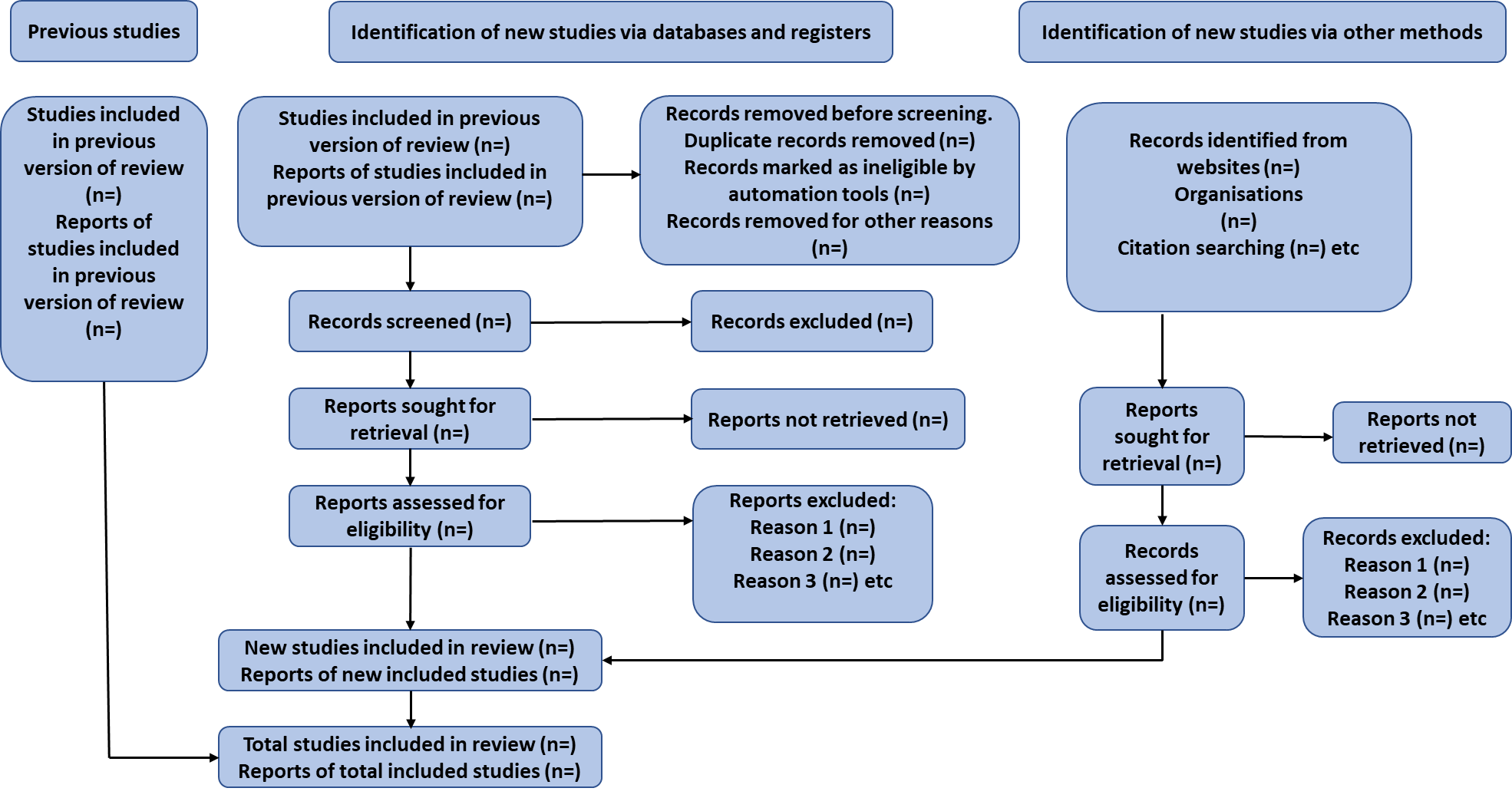
Registration and protocol - Provide registration information of the review, including the registration name and number, or state that the review was not registered. Indicate where the review protocol can be accessed, or state that a protocol was not prepared. Describe and explain any amendments to information provided at registration or in the protocol.

Support - Describe sources of financial or nonfinancial support for the review and the role of the funders or sponsors.

Competing interests - Declare any competing interests of the review authors.

Availability of data, code and other materials - Report which of the following are publicly available and where they can be found: template data collection forms, data extracted from included studies, data used for all analyses, analytic code, and any other materials used in the review.

PRISMA 2020 Flow diagram format for systematic reviews (adapted from Page et al., 2021)



It is believed that implementing PRISMA 2020 will enable readers of the review to accurately evaluate the applicability and validity of the findings. The implications of the review report will aid policy makers, healthcare providers, and decision makers to develop efficient recommendations for policy preparation and application.

The differences between systematic reviews and meta-analyses are outlined below: A systematic review involves the systematic searching of the literature (Cooper et al., 2018). It is a multi-stage process initiated by the person assigned or eligible to conduct the literature search. Various stages of literature search involve establishing the objectives of literature search, defining a search strategy, searching bibliographic databases and supplementary literature, arranging or sorting references, and reporting the search process. A systematic review focuses on reviewing the literature and medical evidence available to answer clinical questions (Charrois, 2015). In contrast, a meta-analysis deals with reviewing the literature using statistical tools to analyze and interpret numerical data from published research studies. All systematic reviews cannot represent the analyzed/reviewed numerical data; thus, meta-analysis is needed (Charrois, 2015). Systematic reviews should be able to meet the following objectives (Baumeister et al., 2013):

* Make unbiased and valid inferences from a specific research study or data.
* Review literature critically and in an unbiased manner.
* Develop hypotheses and analyze theories to accurately interpret data and identify how separate or independent studies could be interlinked.
* Critically discuss the effect and impact of existing policies and how future studies can provide new research directions.

### Reasons for Systematic Literature Review

Systematic reviews are more detailed and of high quality. They are more critical and less biased, making them eligible for publication in higher impact journals. They are considered to have a novel and significant perspective. The inclusion and exclusion criteria in the review are very clearly stated. Inferences and conclusions can be linked to the available evidence. It is easy to conduct and compile a systematic review in a structured manner compared with other kinds of review articles. A series of sections and subsections are included to give a coherent flow to the whole review. (Baumeister et al., 2013). Systematic review articles may also highlight if a replication crisis exists in science, and if it can be resolved (Nelson et al. 2018).

### Steps in a Systematic Review

Scoping is done to determine scope of the review article. A research question or topic is defined for reviewing. The research question is described and the subtopics to be covered within the scope of the research question are listed and shortlisted. The novelty of the research topic is discussed, and whether similar questions have been answered earlier is established. After the research question has been finalized, the existing literature on the topic is reviewed. It is determined if the systematic review will be an upgrade of an existing review article or if a new review article should be conducted on a novel research theme and topic. The next steps for compiling the systematic review are planned. Keywords for the literature search are identified, and the terminology is searched with alternate terms. The selection criteria are established, the inclusion and exclusion criteria are further refined, and the validity of the criteria are verified. Criteria may include research questions, concepts, variables, research designs for quantitative or qualitative studies, participants, time frame, and data. Data is organized and arranged systematically. The literature search is performed in two distinct electronic databases, such as Medline, EMBASE, or ISI. The outcome of the literature search result is investigated and analyzed; if rnecessary, additional literature is searched for any relevant publications. After the literature search and screening, references are exported to a citation manager. Identified publications are read and inclusion criteria are rechecked for eligibility to be included in the study. All the significant and relevant information is used in the review. To evaluate the quality of the study, different tools are used.

### Reasons for Conducting Meta-Analysis

A meta-analysis is used to conduct a quantitative review, to analyze data from different publications that examined and investigated similar hypotheses. A meta-analysis analyses quantitative data from a group of studies, instead of performing qualitative analysis (Siddaway et al., 2019). These identical research studies investigate similar data extracted from comparable research designs. A meta-analysis analyses effect sizes and quantifies uncertainty using confidence intervals. Traditionally, some amount of uniformity or heterogeneity is achieved in study outcomes, as effect sizes can be impacted by varying characteristics. Diverse sources may result in heterogeneity of the studies enrolled in the meta-analysis. Heterogeneity caused by sampling inaccuracy also exists as each study employs an independent sample. Other variables such as the number of participants, exposure or treatment regime, and study design can lead to population effect size.

Forest plots are used to represent the study effect size and associated confidence intervals; thus, the distribution can be estimated. Meta-analysis data from all the studies can be analyzed to assess the effect on the population.

### Self-Check Questions

1. Please mark the correct statement:

* *Literature is reviewed critically in an unbiased manner.*
* *Systematic reviews make unbiased and valid inferences from research studies.*
* Systematic reviews deal with reviewing literature using statistical tools to analyze and interpret numerical data from research studies.

1. Please complete the following sentence:

Meta-analysis is used for a *quantitative* review and to analyze data from different publications that examined and investigated *similar hypotheses*.

1. List of reasons for conducting a systematic review

*Systematic reviews are more detailed and of high quality. They are more critical and less biased, making them eligible for publication in higher impact journals.*

Summary

EBM emerged as a concept in healthcare three decades ago. It involves the use of the best available evidence for making informed decisions about individual patients. EBM underscores the significance of scientific data-driven and research literature-based decision-making by clinicians. EBM includes formulating good clinical questions based on PICO and FINER models. Literature searches are performed with respect to the study design, required sources are determined, data are analyzed, and research outcomes are summarized. The theories of causation include the interventionist theory of causation, counterfactual dependency, and regularity. The factors that support causal relationships include strength of the association between factors, consistency of the association, biological plausibility (in clinical studies), and the dose-response relationship (in drug approvals). Precautions should be taken to prevent research bias at the various stages, including pre-trial bias, bias during trials, bias after trial, bias during data collection, bias in data interpretation, and publication bias. The literature review provides a detailed, in-depth understanding of existing evidence to enable authors and readers to make valid inferences.

# Unit 3 – Functions of Health Technology Assessment

**Study Goals**

On completion of this unit, you will be able to …

… understand the functions of HTA.

… understand market access, HTA assessment, and approval.

… price policies and clinical guidelines.

# 3. Functions of Health Technology Assessment

The function of HTA includes ‘Assessment’ of clinical evidence and economic analysis necessary for decision-making, and ‘Appraisal’ process involving aspects like strategy, ability and potential (Bertram et al., 2021). Based on the assessment, the role of HTA is to provide advice to relevant authorities and to review and make appropriate recommendations to federal and institutional agencies (Scaletti, 2014). HTA mechanism encompasses various significant functions including legal arrangements and institutional systems as outlined below in the figure.

Overall Functions of HTA (Bertram et al., 2021)

Timeline

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## 3.1 Market Access

Market access to healthcare technologies requires diligent evaluation, keeping in mind the stakeholders’ interests and standpoints (Ducournau et al., 2019). Different stakeholders including patients, pharmaceutical companies, manufacturers, hospitals, health insurance companies, government health agencies and public funding institutions, have diverse perspectives with regards to market access of novel healthcare technologies and products. A process is established to ensure all appropriate stakeholders, especially patients who would benefit from these advanced healthcare technologies, get rapid and equal access at an appropriate price. At the same time, patients ought to benefit from timely access to therapeutic interventions that offer clinical and economic value.

### Market Authorization Process

Market access is initiated by national registration and approval for market authorization. Regulatory agencies need clinical proof from **sponsors** for safe use and optimum quality and standards. Due to absence of any binding compliance and requirements for proof of clinical effectiveness, information regarding market registration is not enough for any decisions regarding market access. Therefore, more clinical proof is required from the sponsor. Steps are being initiated to acquire more substantial clinical evidence to support decisions regarding market access. Market authorization is initiated by an independent organization with no influence of HTA agencies in the decision-making process. Market authorization occurs prior to HTA assessment; thus, the two institutions need to establish a healthy working arrangement (Bertram et al., 2021).

**Sponsor**

It refers to an agency, company or individual that initiates, manages and finances clinical trial operations.

### Significance of Regulatory Evidence and Access Evidence in Market Access

Market authorization is provided based on the following factors: primarily quality, safety and efficacy of the technology referred to as ‘regulatory evidence‘. Further, recommendations regarding medical coverage and reimbursement procedures are made by determining the value of relevant health technology, which is referred to as ‘access evidence‘ (Lakdawalla et al., 2018). Access evidence indicates the value of technology to patients, healthcare providers, and healthcare payers by analyzing the advantages of novel technology compared with routine clinical interventions, for instance, better clinical outcomes and improved quality of life (Akehurst et al., 2017). Clinical effects and benefits of health technology to patients are assessed by pharmaceutical companies or technology manufacturers and reviewed in HTA. This allows HTA agencies to recommend guidelines relevant for medical coverage and reimbursement decisions (Ducournau et al., 2019). Different national jurisdictions and disparities create a bottleneck, though efforts are being made to harmonize the process.

### Self-Check Questions

1. Please complete the following sentence.

*The function of HTA includes ‘Assessment’ of clinical evidence and economic analysis necessary for decision making, and ‘Appraisal’ process involving aspects like strategy, ability and potential.*

1. Please mark the correct statements.

* *Marketing authorisation (for a particular indication) is granted based on pharmaceutical quality, efficacy, safety and the benefit-risk-ratio.*
* *Secondly, medical coverage and reimbursement procedures at par with the value of relevant health-technology are taken into account, referred to as ‘access evidence‘.*
* An element of an HTA core model, ‘Ontology’ refers to how the problem should be addressed or reported.

1. Please complete the following sentence:

Market access is initiated by *national registration* and *approval* for market authorization.

## 3.2 HTA Assessment and Appraisal

Within HTA, assessment refers to assessing clinical evidence and economic analysis or cost-effectiveness of a health technology. Appraisal refers to a kind of suggestion or advice regarding application of technology (Sandman and Heintz, 2014). As outlined in the figure below, Assessment, Appraisal, and Recommendations are interrelated to each other.

Association between Assessment, Appraisal, and Recommendations (adapted from Bertram et al., 2021)

Graphical user interface, application

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Different HTA institutional agencies have specific roles of assessment and, thereafter, appraisal of health technology (Sandman and Heintz, 2014). This distinction in functional roles is clearly demarcated in countries like the United Kingdom, i.e., The National Institute for Health and Care Excellence (NICE) conducts the appraisal and recommends new technologies to the National Health Service (NHS).

Similarly in Sweden, the Swedish Council for Health Technology Assessment (SBU) can only perform technology assessments, in contrast, the county council undertakes the appraisal role. This prevents political intervention and vested interests from influencing a fair evaluation and assessment of health technology (Banta et al., 2009).

### Value Assessment and Appraisal Model

Several studies have employed the Multi-Criteria Decision Analytic (MCDA) model in assessment and appraisal of pharmaceutical drugs used as therapeutic agents also known as **orphan drugs.**

**Orphan drug**

Pharmaceutical products expected to be used for detection, prognosis, treatment, or safeguarding from life-threatening ailments and rare disorders.

This could be one of the best proven strategies for pricing and reimbursement-based decisions with regards to health technologies and products. In a multi-criteria decision analysis study, stakeholders assess and appraise orphan drugs implementing the value measurement concept. Ratings are pre-discussed, and scores lead to realistic assessment and appraisal scenario (Baran-Kooiker et al., 2018). Cohorts of public health stakeholders comprising of clinicians and healthcare professionals, chairs or representatives of specific patient groups, officials from health agencies and executives representing pharmaceutical industry, were included in the 307-participant study in Bulgaria. Participants served a role in decision-making on drug reimbursement. A heterogeneous mix of members regarding age, sex, geography, pathology etc. were selected to avoid any bias. Stringent threshold criteria confirms that only therapies used to treat medical conditions with value and money incentive were allowed reimbursement via public funds (Iskrov et al., 2016).

HTA Components Assessment and Appraisal (adapted from Teutsch et al., 2005)

Assessment

Evidence review/analysis

Appraisal

Evidence-based decision making

Evidence review

Key questions

Financial budgeting

Clinical studies

Financial limits

Feasibility

Equity

Values

**Decision**

Choices

### Ethical View on Appraisal

Diverse types of ethical appraisal can lead to various possibilities and outcomes. Appraisal can have different implications based on regulatory or organizational context (Sandman and Heintz, 2014). An appraisal with a positive outcome leads to implementation of technology or financial allocation for enabling technology access for patient use. Neutral appraisal would lead to a non-decisive outcome on the technology. A negative appraisal leads to barring application of the technology (Blank, 2010). In addition, incentives like funding allocations are often based on appraisal decisions. Ethical decisions can lead to different possibilities and implications. If a clinical **intervention** is ethically necessary to use, possible outcome will be an influence on financial incentives, compulsory implementation, supporting application in the healthcare system. If an intervention is ethically not apt to be implemented, it should be prohibited for use. Various ethical reasons prevent application and use of an intervention, in that scenario a convincing argument barring the use of an intervention should be presented. In contrast, if there are strong ethical reasons supporting implementation of an intervention, in that case a strong reason should support funding or use of an application. The ethical assessment of HTA is distinctive from the assessment of other features like effectiveness, cost-effectiveness, social consequences etc. Ethical analysis directs actions and results in a conclusion, which can be referred to as an appraisal.

**Intervention**

This is an action performed to evaluate, improve, upgrade, or maintain a person’s health.

### Self-Check Questions

1. Please list three kinds of appraisal outcomes.

*An appraisal with positive outcome leads to implementation of the technology or financial allocation for enabling technology access for patient use.*

*Neutral appraisal would lead to a non-decisive outcome on the technology.*

*A negative appraisal leads to barring application of the technology.*

1. Please mark the correct statements.

* *Assessment is referred to as the process to assess a criterion for decision-making.*
* HTA Assessment refers to a kind of suggestion or advice regarding applications of technology.
* *Several HTA institutional agencies either focus exclusively on assessment or appraisal of the health technology.*

1. Please complete the following sentence:

The Swedish Council for Health Technology Assessment (SBU) can only perform technology *assessments*, in contrast the government or county council undertakes the *appraisal* role.

## 3.3 Price Policies and Procurement

Innovation in healthcare and the development of advanced therapies has led to improved health treatment and patient recovery rates, though exerting a burden on healthcare expenditure (Callea et al., 2017). Developing strategies to have an oversight on price monitoring of pharmaceutical products is the responsibility of the governments, irrespective of the economic stature or GDP index of the country (Vogler et al., 2019). HTA is turning into a major gamechanger in setting priorities and price negotiations for national and institutional agencies in healthcare. Relevant policy changes and amendments are introduced by national governments to attain UHC by providing safe, efficient, and affordable medicines and vaccines, which is one of the Sustainable Development Goals (SDG) recommended by the United Nations (Glassman et al., 2017). UHC refers to providing all kinds of health facilities including prevention, treatment, and post-treatment care across geographical boundaries to the global population irrespective of their region, religion, and financial status. Nevertheless, a quest to have affordable and homogenous access to healthcare should not weaken or puncture the financial dynamics of the healthcare industry and system.

Different financing and policypricing criteria are used to set prices for pharmaceutical and healthcare products (Vogler 2019). ‘External price referencing‘ allows price setting in other countries, ‘Internal price setting‘ is done to set prices within the same country, ‘Value based pricing‘ sets additional therapeutic value to the products, ‘Conditional pricing‘ offers pricing based on specific conditions like health outcome or procurement orders, ‘Tendering‘ refers to best offer based on pricing and in reference to other bids, and ‘Cost-plus pricing‘ deals with production and Research and Development (R&D) costs.

Buyer-side traders refers to the investing institutions in financial markets, have trading strategies which are important with respect to access to pharmaceuticals in low and middle-income (LMIC) countries (Borges dos Santos, 2019). According to the world-bank criteria, fifty-five countries fall into the LMIC group, and twenty amongst them fall into low-income group with an income of less than USD 1,000 gross national income (GNI) per capita and, are considered, for example, currently eligible to seek vaccination support through a Global Alliance for Vaccines and Immunisation (GAVI) partnership (WHO guidelines 2020).

There are several aspects which are impacted by pricing policy. These aspects include homogenization of prices, establishing fair procurement policies and cost-plus pricing across countries. It is imperative to establish criteria for setting prices of each new product, ensure a fair margin with equitable profit sharing, acquisition of Intellectual Property Rights (IPR), and healthcare technology rights by governmental agencies in broader public interest.

Table. Description of Pricing Policy Impact and Limitations

|  |  |  |
| --- | --- | --- |
| **Pricing Policy** | **Impact** | **Limitations** |
| **External pricing policy** | Have low pricing, Can lead to major public wealth saving, | Not easily accessible, non-transparent, expertise needed, volatile |
| **Internal reference pricing** | Reimbursement policy with identical medication clustered, Public funding, promotes use of generic medicine, Patient pays difference in price, | May vary across countries |
| **Value based pricing** | Authorities set pricing, Payment of pharmaceutical drugs connected to evidence-based value assessments, Assess through HTA | No incentives for manufacturers, Enhanced capacity required, Nation-specific value assessment |
| **Procurement** | Strategic purchasing by stakeholders and effective procurement process | Not done centrally, widely performed in low-income countries |
| **Pricing negotiations** | Mutual strategic agreement on medicine prices, price kept confidential | - |

Overview of Pricing Policies (adapted from WHO Collaborating Center from Pharmaceutical Pricing and Reimbursement Policies)

Graphical user interface, text, application, chat or text message

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WHO guidelines are based on the following key principles for establishing country-specific pricing policies, which need to be implemented (WHO guidelines, 2020).

* The combination of diverse drug pricing policies that fulfills supply and demand.
* Transparency allows clarity in forming transparent policies and decisions.
* Legal guidelines allow adequate legislative framework. If regulation is introduced, efficient implementation will be required to ensure compliance (e.g., incentives, enforcement, price monitoring system, fines).
* Encouraging use of optimum quality generic medicine by implementing schemes to promote the application and usage of such medication to enable health equity amongst all.
* Association with other countries to encourage knowledge exchange regarding pricing policy and their effect.

### Self-Check Questions

1. Please mention the key elements of External Reference Pricing.

*Have low pricing, and can lead to lower public health expenditure,*

1. Please complete the statement.

Relevant policy changes and amendments are introduced by national governments to attain *UHC* by providing safe, efficient, and affordable medicines and vaccines.

1. Please list two principles of WHO guidelines for policy pricing:

*Transparency allows clarity in forming transparent policies and decisions.*

*Legal guidelines allow adequate legislative framework.*

## 3.4 Clinical Guidelines

Clinical practice guidelines (CPG) are developed recommendations to assist clinical practitioners and patient decisions to optimize patient care for clinical pathologies and treatment (Graham et al., 2011). These guidelines ought to be formulated based on the data acquired by a systematic review of evidence and an evaluation of pros and cons of alternative therapeutic treatment options. These guidelines draw inferences from the research quality of associated scientific publications and an evaluation of the strengths and weaknesses of a specific therapy and intervention. CPG guidelines should be formulated by a group of experts, panel should represent affected cohorts, patient groups, subgroups and prioritize accordingly. These guidelines should depend on standard procedures to avoid any bias, distortions and conflicts of interest. Obsolete and outdated guidelines should be updated as soon as new evidence is available.

According to the CPG manual of the U.S. Institute of Medicine (IOM), practice guidelines are formulated using stringent proof-based strategy with the strength of evidence for each one clearly expressed (Graham et al., 2011).

* These guidelines should be realistic, practical, and quantifiable.
* Clinical actions and measures evolve from clinical practice guidelines and are applied in improving standards.
* These actionable measures are implemented into public description, liability, the strength of evidence and degree of interest should be appropriate to explain the charge of execution and accomplishment.
* Application of CPG remains a prime preference to those with the most compelling evidence.
* Those with the most compelling proof and the greatest influence and effect on population morbidity and mortality.
* Research should be performed on investigating the strategies to efficiently apply clinical practice guidelines and the effect of their use as standard counts.
* Different agencies recommend specific guidelines based on national and institutional interests.

### Generating Evidence-Based Clinical Practice Guidelines (CPGs)

CPGs include suggestions to harmonize patient care that are guided by evidence and data from systematic reviews. These reviews provide a comprehensive view on the pros and cons of alternative therapy and treatment care options. This includes an assessment of research literature and a fair review of strengths and weaknesses of a specific therapy. Reviewing literature allows healthcare workers to choose the most suitable and preferred treatment option. Depending on country-specific local jurisdictions, CPG guideline formulation may vary. In some countries, a commission on public health and/or science together with the board of directors may oversee formulation and agreement on CPG guidelines (Graham et al., 2011).

### Eight-Point Criteria for CPG Development

Principal standard features for establishing effective CPG guidelines include: establishing clarity, ensuring no conflict of interest, category of people focusing on guideline development, CPG guideline-systematic review, ensuring strength of evidence, suggesting recommendations, external review and upgrading (Reames et al., 2013).

### Standard Guidelines

Standard guidelines for CPG development are as mentioned below (Kredo et al., 2016):

Patient-focused CPG development occurs in collaboration with external organizations like medical organizations and societies. A clinical subject for CPG is recommended, keeping in view the following criteria: Lack of evidence-based guidelines on the specific clinical topic. Topic should comply with the strategic objectives and strategies. Clinical Guidelines recommended by British HTA agency, NICE makes evidence-based recommendations on prevention and management of specific diseases to strategically plan a wide range of healthcare services and interventions to upgrade public healthcare services and overall citizen health.

A systematic evidence report on the topic is provided with the availability of a funding source.

### Conflict of Interest

To avoid conflict of interest and bias in CPG development, certain criteria should be kept in consideration (Norris et al., 2012). Members, chairs, co-chairs, collaborators, and sponsors should not have any conflict of interest in guideline development.

**Intellectual COI** – Actions creating scope of an attachment with a specific perspective that may influence a subject regarding particular recommendations.

Any **financial or intellectual conflict of interests,** involvement, or activities falling under the ambit or scope of CPG should be declared by members through a written declaration prior to their involvement in CPG development. Professional involvement in clinical guideline development, which could amount to conflict of interest, or official involvement by oneself or a close family member (spouse, siblings, children) in similar activities within the past 3 years should be declared prior to official engagement in the guideline development activities. Disclosures and conflict of interest declarations are then reviewed by staff prior to the recruitment on CPG development panel.

**Financial COI** - Material interest that could influence, or be perceived as influencing, an individual’s point of view.

If required, members can divest themselves from related financial, marketing, or advisory responsibilities from board of specific organizations whose interests are being influenced by the CPG recommendations. In necessary scenarios, relevant clinical specialists drawing salaries or remuneration may have to withdraw from the services, if a conflict of interest exists.

### Constitution of CPG Panel

A mutually agreed timeline is proposed with a goal to fulfill the CPG development task in the specific time period. A document with specific activities and list of actions is maintained and updated during the process. Members may be requested to volunteer and participate in specific tasks like compiling assignments to develop suggestions and provide supporting evidence. An outline is developed with an overview of the significant questions for recommendations and evidence-sharing. Members will communicate via different modes, like conference calls, electronic communication, publication and active dissemination via press articles, editorials and conducting literature reviews (Kredo et al., 2016).

### Framing Guidelines

Identification of scope of guidelines, which covers rationale, is the first step. Methodology needs to be mentioned like summary of literature search, use of evidence reports, including search terms, dates, outcomes assessed, and important questions are addressed. Recommendations are based on the evidence from the linked articles. Grading of the strength of evidence and recommendation is performed. Panel writing assignments are allocated to involved members of the panel. Draft is compiled with the appropriate recommendations.

### Self-Check Questions

1. Please list the key reason for constituting a panel for formulating Clinical Practice Guidelines.

*The purpose of CPG panel is to complete the CPG development task within a specific timeframe.*

1. Please list the eight-point criteria for CPG development.

establishing clarity,

*ensuring no conflict of interest,*

*category of people focusing on guideline development,*

*CPG guideline-systematic review,*

*ensuring strength of evidence,*

*suggesting recommendations,*

*external review and*

*upgrading.*

1. Please complete the following sentence:

Members of CPG panel communicate via *conference calls, electronic communication, publication* and active dissemination via press articles, editorials and conducting literature reviews.

## 3.5 Horizon Scanning

Horizon scanning refers to a structured assessment of available data and knowledge to recognize viable challenges, dangers, upcoming problems, and chances. Horizon scanning is like a ductile tool with various robust and reliable strategies (Hines et al., 2019). It can impact decision-making by recognizing pros and cons, possibilities, and drawbacks ranging from institutional to global level. Additional research is required to earmark the most efficient strategies that will include substance to this scenario and predict innovations and progress. The European Medicines Agency (EMA) is proposing to look at the accessibility of innovative medicines by employing horizon scanning. Based on horizon scanning, the outcome will be further shared with the Regulatory Science Strategy and the European medicines regulatory network strategy of the EMA (Bujar and Liberti, 2017, O’Dwyer et al., 2017,). Horizon scanning was earlier employed as a foresight strategy by Japan in the 1970’s, and since has been applied in diverse sectors for policy and strategy planning (Plüddemann et al., 2010).

### Methodology for Horizon Scanning

A systematic review is conducted to map horizon scanning activity. Data are acquired by Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA guidelines) (Moher et al., 2009). As illustrated in the flowchart below Literature is screened and filtered using inclusion and exclusion criteria, data are extracted, analyzed and scanning strategy is mapped.Search strategy is applied by screening databases like Medline and Embase bibliographic databases (Hines et al., 2019). Inclusion and Exclusion criteria is applied by screening a match of key words in abstract or title with the methodology in the specific field or across different fields. Full texts of the articles are screened in the next round, with a detailed foresight methodology or horizon scan. Priority areas included science and technology, a collaborative or integrated strategy is applied, to perform horizon scanning across a period of 10 to 15 years.

Steps involved in Horizon Scanning (adapted from Grossman et al., 2019)

Scanning or Identification

Filtration

Prioritisation

Assessment

Dissemination

Upgrading information

Information is sourced through diverse sources for signal identification including scientific and biomedical literature review, patents, inputs from industry and industry associations, media, institutional agencies, expert committees, federal government bodies, international conferences, and meetings.

Table. Criteria for Filtration, Prioritization, Signal assessment, Dissemination, and evaluation for horizon scanning. (adapted from Hines et al., 2019)

|  |  |
| --- | --- |
| Criteria for horizon scanning | |
| Filtration | Viable effect, magnitude of impacted people, originality, degree of change or transformation, proof, departmental influence, validity, stakeholder interest, strategy preference, evolution step, moral compliance, predetermined time |
| Prioritization | Potential impact on outcomes, population size, variable impact, time-period, evidence of effectiveness, relevance to strategic priorities, Novelty, Expertise availability |
| Signal assessment | Impact, Level of innovation, Risk assessment, Legal and ethical issues, market barrier, Stakeholder perception, Required actions and impact time |
| Dissemination | Format, methods, audience, frequency, upgrading |
| Evaluation | Short, medium, long term, Process and output audit, Validation, Focus groups, Metrics, Database access |

Table. Methodology employed for Filtration, Prioritization, Signal assessment, Dissemination, and evaluation for horizon scanning. (adapted from Hines et al., 2019)

|  |  |
| --- | --- |
| Methods employed in Horizon Scanning | |
| Filtration | Classification criteria, automated text-mining strategies, individual and group filtration, peer review, expert involvement |
| Prioritization | Qualitative, quantitative, semi-quantitative approach, grading, risk analysis, signal homogenization, expert, and public consultation |
| Assessment | ExpertLens, Driver analysis, Scenario planning, Peer review, Expert, user, and policymaker participation |

Horizon-scanning as a strategy is being used globally and is now being combined with artificial intelligence to self-evaluate its signal regulation. Further research needs to be conducted to evaluate and implement more effective methods beneficial for diverse group stakeholders.

### Self-Check Questions

1. Please list methods for Filtration step in horizon scanning.

*Classification criteria,*

*automated text-mining strategies,*

*individual and group filtration,*

*peer review,*

*expert involvement*

1. Please mark the correct statements.

* Expert Lens is a prioritization method in horizon scanning.
* *Qualitative and quantitative approaches are used for prioritization in horizon scanning.*
* *Automated text-mining strategies are filtration methods in horizon scanning.*

1. Please list criteria for Signal assessment in horizon scanning:

*Impact,*

*Level of innovation,*

*Risk assessment,*

*Legal and ethical issues,*

*Market barriers,*

*Stakeholder perception,*

*Required actions and*

*Impact time*

**Summary**

Assessment of clinical efficacy and cost effectiveness of health technologies is considered as the primary function of HTA. Based on the assessment, HTA provides guidance and recommendations to federal and health agencies, like National Health Service (NHS) in the United Kingdom. Healthcare technologies need rigorous assessment based on the interest and need of various stakeholders including patients. A systematic mechanism is incorporated to ensure health equity amongst all stakeholders. HTA assessment and appraisal can lead to recommendations and establishment of criteria for relevant decision-making. HTA is playing a key role in setting priorities and price negotiations for national and institutional agencies in healthcare. Necessary amendments and modifications in policy are introduced by national governments to attain UHC by providing safe, efficient, and affordable medicines and vaccines, as one of the Sustainable Development Goals (SDG). A structured assessment to investigate challenges, risks, issues, and opportunities referred to as horizon scanning is being implemented in various sectors. It can influence decision-making by identifying opportunities and challenges across regional, national, and international levels.

# Unit 4 – Reimbursement of Medicines and HTA

**Study Goals**

On completion of this unit, you will be able to …

… understand HTA decision-analytics

…. recognize health-related quality of life

…. interpret real-world data

## 4.1 Decision-Analytic Models

Healthcare decision-making is based on value-based and science-based needs and frameworks. Distinct factors and complex steps involved in healthcare systems at various stages from diagnosis to treatment require systematic strategies and methods to analyze based on the existing evidence (Baltussen et al., 2006). Inferences drawn from diverse sources like scientific research-based evidence, medical need, financial burden, societal, ethical, and legal perspective lead to crucial decision-analytic models (Goetghebeur et al., 2012). To improve decision-making models in healthcare, several governments and institutional HTA agencies are taking steps to have clarity within their health systems to fix accountability and responsibility in this direction.

## Decision-Making Tools and Frameworks

During the process of decision-making, each therapeutic intervention is scored based on a set of criteria, keeping the associated benefits and drawbacks in consideration (Goetghebeur et al., 2012).

#### EVIDEM Framework

An exemplary framework linking HTA and Multicriteria Decision Analysis (MCDA) is the Evidence and Value: Impact on DEcisionMaking (EVIDEM) framework. The purpose of developing EVIDEM was to generate a core MCDA model that can be applied by decision makers as an associated tool and that supports the deliberative process (Goetghebeur et al., 2008, 2012). The EVIDEM framework is accessible worldwide via THE EVIDEM Collaboration. It consists of an MCDA and an HTA module (Goetghebeur et al., 2012). A comprehensive analysis of more than 20 jurisdictions globally resulted in decision criteria on which the EVIDEM framework was based. The MCDA approach integrates those fifteen decision and scoring criteria. The framework can serve as a rough base to build upon a finer model for advising on healthcare interventions, policy foresight and strategies.

#### Decision Criteria

Multicriteria Decision analysis (MCDA) allows evaluation based on the criteria listed in the table below that can influence decisions (Baltussen et al., 2007, 2010). By employing MCDA criteria, the decision problem statement is identified to pin down all the necessary elements that can influence the decision and set a relevant criterion for decision-making.

Table. Elements of the MCDA model Decision Criteria

|  |  |
| --- | --- |
| Decision and Scoring Criteria | |
| Disease impact | Severity and Population size  (Not severe-moderate-severe) |
| Intervention context | Clinical guidelines and Comparator interventions limitations  (no-minor-major limitations) |
| Intervention outcomes | Effectiveness, improvement of safety and tolerability, improvement of patient-repoRted outcomes (PRO)  (Low-minor-major improvement) |
| Type of benefit | Public health interests and type of medical service  (no-minor-major risk) |
| Economics | Budget impact, cost effectiveness, impact on other spending  (Substantial-no expenses-cost effective) |
| Quality of evidence | Adherence to decision-making institutions, accuracy in evidence reporting, relevance and validity of evidence  (Low-High Adherence-Inconsistent-Consistent-Low-High relevance) |

#### Decision framework

The decision framework comprises of comprehensive protocols for the collection, analysis, assessment, interpretation, and presentation of evidence for each decision criterion (HTA module) to produce HTA reports that are connected into the Multi-Criteria Decision Analytics (MCDA) model (Goetghebeur et al., 2012). This model allows to test feasibility and utility of interventions, enabling knowledge exchange, and appraisal of healthcare interventions (Goetghebeur et al., 2012).

#### Example depicting Multi-step Decision Analytic modelling criteria

A two-criteria HTA report is developed by investigators based on extensive analysis from 15-point decision criteria. Appraisal group provides appraisal on the significance of each of the criteria and later appraise the drug by grading the criteria. A discussion is conducted to collect feedback from all participants. Flowchart below depicts the complete process involved in drug appraisal.

Flowchart Depicting Multistep Decision Analytic Modelling Criteria (adapted from Goetghebeur et al., 2011)

Review Literature for each drug

HTA report for each drug

Panel outlook

Drug Appraisal

Discussion

Investigator/

Researcher

Panel (Experts, Clinicians, Medical staff, Pharmacists, Health Economists, Epidemiologists)

### Structure of Breast Cancer Screening Model Using Decision Analytic Modeling Approach

Here, we describe an example depicting decision analytics for breast cancer screening options from a national mammography screening program for Vietnamese women reported by a recent study (Nguyen et al., 2018). Total expenditure and implications of implementing breast cancer screening initiative for specific age groups of women were assessed in contrast to lack of screening in existing scenario. Breast cancer occurrence rates are constantly increasing in Vietnam, in contrast poor prognosis has resulted in higher mortality rates. With a regular screening policy, the probability of detecting cancer early will be much higher and can lead to better survival. If breast cancer screening is performed every 2 years or not performed, cancer may or may not be diagnosed. If a cancer diagnosis is made, patients may be diagnosed as positive or negative in both scenarios. According to the screening strategy being assessed, females beyond 45 years of age screened by mammography. Broadly women were categorized into 4 groups based on their age range: 45 to 49 years, 50 to 54 years, 55 to 59 years, and 60 to 64 years. The entire population (100%) was expected to participate in the screening program. Based on the data from the national breast cancer screening initiative, the effect of the involvement on the cost-effectiveness of mammography screening was assessed in the range of 23.6%–100%. The expenditure and results of breast cancer screening were analyzed and correlated with no screening, combining 5 percent mammography screening at private hospital with no screening for the remaining population, and 10 percent mammography screening with no screening for the rest of the population. A decision analytic modeling strategy was employed to diagnose breast cancer patients as illustrated in the figure below. Patients with breast cancer detection were further examined to confirm the diagnosis and disease stage (Stage 1, 2, 3, 4 or metastatic cancer). Markov chain analysis was applied to evaluate the expenditure and increased survival time based on timely detection. Different stages considered in the Markov model are relapse post-therapy, localized relapse, relapse in other body organs, mortality due to relapse and mortality due to other comorbidities. Patients with local relapse may stay stable or may suffer relapse in other body organs or die due to breast cancer or other diseases. Patients with Stage 4 diagnosis may stay stable or die due to other sickness. This model covers assumptions encompassing the entire lifespan of the patient.

Decision tree for breast cancer screening options (adapted from Nguyen et al., 2018)

Diagram

Description automatically generated

### Self-Check Questions

1. Please list the steps involved in decision framework for drug approval.

*Review literature for each drug*

*Compile HTA report for each drug*

*Panel outlook*

*Appraisal*

*Discussion*

1. Please mark the correct statements.

* An economist conducts literature search on each drug.
* *Panel of experts provide a panel outlook on the specific drug report.*
* *Investigator conducts literature search and compiles reports for each drug.*

1. Please complete the following sentence:

*The EVIDEM* framework is based on decision criteria from the comprehensive analysis of more than 20 jurisdictions from around the world.

## 4.2 Effectiveness Versus Efficacy

Approval of a pharmaceutical drug for use is provided based on evidence of a positive efficacy-safety index, which refers to the degree up to which the drug exerts more harm than benefit (Nordon et al., 2016). Efficacy-safety index is measured by employing RCTs. “Efficacy-effectiveness gap” (EEG) refers to the existing pitfalls and supportive supplementary scientific evidence on‘efficacy‘ and effectiveness. It is important to understand how this concept influences clinical and policy decisions.

|  |
| --- |
| **Efficacy**  It refers to as the outcome of a therapeutic treatment under preferred and regulated conditions. |

|  |
| --- |
| **Effectiveness** – It evaluates whether an intervention exerts more benefits than impairment when administered under usual circumstances of healthcare practice. |

### Tenets of Efficacy-Effectiveness Gap

Different ways to understand EEG have been suggested. EEG has been classified into three different categories like the effect of healthcare settings, strategies to measure the effect of drugs, and the interplay between drug and dependent aspects.

According to the first principle of EEG, discrepancies in the healthcare system in real life may specify why effectiveness results cause dismay compared with efficacy results. Therefore, all features of healthcare in real life should meet the benchmark of experimental conditions with different grades of intervention like medical regulations, knowledge transfer, approaches for increasing patient-adherence, etc. Real impact of these laudable interventions is difficult to evaluate. This principle does not consider effectiveness to be superior to efficacy. The patient-doctor network is key to patient compliance and leads to a better result. Doctors should select the best treatment strategies for each patient to enhance the probability of having a favorable outcome. The second principle of EEG states that the strategy employed to assess the impact of a drug influences the outcome of drug use, thus there is an EEG. Both efficacy and effectiveness investigations provide answers to complementary questions. According to the third principle, advocating the therapeutic impact of a drug is the outcome of interplay between biological and dependent aspects like patient or healthcare related aspects. Irrespective of the study design, the impact of a drug in various conditions like routine clinical trials or in real may differ, leading to inconsistent results (Nordon et al., 2016).

### Example of Efficacy and Effectiveness

Terms ‘Efficacy’ and ‘Effectiveness’ can be further explained with examples from the literature. The efficacy and effectiveness of the impact of COVID-19 vaccines is evaluated by reviewing the literature. To compare the efficacy and effectiveness of seven COVID-19 vaccines, a comprehensive systematic literature review was conducted by including different databases to identify studies reporting vaccine effectiveness or efficacy. Based on the inclusion criteria, we reviewed 42 reports which indicated that COVID-19 vaccines have resulted in decreased infection rates, milder symptoms, reduced hospital stay and lower death rates. Specific vaccines are more effective against different variants, like Pfizer is more effective against B1.1.7 and B1.1.8 variants. Irrespective of high effectiveness of a vaccine it is necessary to check their effectiveness against any new covid strain (Mohammed et al., 2022).

A wider contrasting view on efficacy and effectiveness influences research, policy, and polity-based decisions for policy approval, for added patient value, for regulating the pricing and maintaining cost effectiveness, and the public financing and sponsoring of healthcare expenditure (Romero et al., 2013).

### Self-Check Questions

1. Please mark the correct statement.

* *Efficacy refers to ideal-world scenario.*
* Efficacy refers to real-world scenario.

1. Please mark the correct statements.

* Effectiveness trials are referred to as explanatory trials.
* *Effectiveness trials are referred to as pragmatic trials.*

1. Please complete the following sentence:

*Efficacy-safety index* refers to the degree up to which the drug exerts more harm than benefit.

## 4.3 Health-Related Quality of Life

Terms ‘Health’ and ‘Quality of Life’ (QoL) existed much before the term ‘Health-Related Quality of Life’ (HRQoL) became relevant (Karimi, 2016). World Health Organization (WHO) described ‘health’ as a form of holistic physical, social and psychological welfare (WHO, 2014). This shaped the formation of Medical Outcomes Study Short Form Family of Measures, SF-36 and the EQ-5D, also known as measures of health-related quality of life. The concept of HRQoL has existed since 1940’s, however it was proposed in its current form in 1990’s (Testa et al., 1996). Conceptually HRQoL encompasses physical, social, and psychological spheres. Each sphere can be quantified subjectively (using patient reports and perception) or objectively (using clinical diagnostic data). Measuring and assessing the quality of life was significant to evaluate health-related consequences beside mortality and natural activity (Karimi, 2016).

### Measures of Health Status

HRQoL is measured to assess the effectiveness of an intervention (Fryback, 2010). It is imperative to measure HRQoL because of clinical and policy issues. From a clinical perspective, it is imperative to assess the effect of care on the patient and status of patient health. HRQoL measures are used to oversee the change in health of the patients, prior to-, during and after the treatment, or intervention like surgery. We know that health status can be measured on a generic basis or a disease-specific basis. The three spheres, physical, psychological, and social domain are measured on a general basis. How healthy do we feel? That is a general health condition. If we perform a comparison within diseased conditions, in that scenario HRQoL scales and measures will be different. We must be inquisitive about the severity or mildness of the disease, symptoms, or behavior of the patient. HRQoL questionnaires report health by measures of functioning (capacity to perform activities) and well-being (physical, mental and social). Model and measurement scales of HRQoL frameworks are presented below. It spans across X, Y and Z planes, spanning beyond the subjective, objective; and social, physical, and psychological spheres across health domains. This model represents a broadly applied tool to capture HRQoL like SF-6D and EQ-5D.

HRQoL Conceptual Framework

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### HRQoL Data Pyramid

As illustrated in the HRQoL Data Pyramid, generic, disease-specific, and health-related indicators are represented. ‘HRQoL indexes‘ referred to as preference-weighted aggregate scores summarizing overall health. ‘Generic Health status profiles‘ refers to vectors of health status domain scales. ‘Disease-specific domains‘ do not cover all health domains (Romero et al., 2013). Multi-attribute classification systems like SF-36 and EQ-5D are termed as the measures of ‘health status’, health-related quality of life (HRQoL), or ‘quality of life’ (QoL), and can develop both health profiles and index values. SF-36 includes physical functioning, role limitations, social functioning, pain, psychological health and vitality. EQ-5D comprises mobility, daily actions, self-care, pain, discomfort and anxiety (Karimi, 2016). Both SF-36 and EQ-5D encompass queries covering WHO classification strategy of deterioration, activity and association check,

HRQOL Data Pyramid for Population health (adapted from Fryback, 2010)

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### Contextual model of HRQoL

Several research studies are investigating HRQOL index and contextual factors impacting HRQOL in different cohorts of healthy and diseased population. For instance, a recent study investigates HRQOL predictors and factors impacting Covid-19 patients (Chen et al., 2020). As illustrated in the figure below, the contextual model of HRQOL includes social, cultural, demographic, healthcare related aspects. This model amalgamates the conventional HRQoL model, social setup, qualitative and quantitative research studies, and cultural literature (Ashing-Giwa, 2005). The socio-ecological aspect is frequently excluded in HRQoL studies. The contextual model of HRQoL is apprised by the conventional HRQoL model, the Biopsychosocial model, quantitative and qualitative studies with survivors, oncology literature, the multicultural and psychological literature. Various dimensions can differ amongst various ethnic groups. The socio-ecological aspect will include dimensions like socio-economic state, life burden and social support. Socio-economic state encompasses income, education, employment status, ethnicity. For instance, lower socio-economic state indicates poor degree of survival leading to poor HRQoL. Cultural aspect includes dimensions like ethnicity, spirituality, global view, interconnectedness, acculturation and beliefs. For example, different ethnic minorities suffer challenges and disparities in healthcare access leading to varying HRQoL outcomes. Survivors draw strength from spirituality, faith and cultural belief system. Demographic factors like age and sex affect HRQoL outcomes and survivorship. Healthcare systemic factors influence HRQoL like specific treatment and follow-up checkup. Other variables like general health and comorbidities may influence HRQoL (Ashing-Giwa, 2005).

Contextual model of HRQOL (adapted from Ashing-Giwa, 2005)

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### Self-Check Questions

1. Please list contextual factors impacting HRQOL.

*Health efficiency*

*Demography*

*Culture*

*Society*

1. Please mark the correct statements.

* ‘*Generic Health status profiles‘ refers to vectors of health status domain scales.*
* *‘Disease-specific domains‘ do not cover all health domains.*

1. Please complete the following sentence:

*Health-related quality of life (HRQOL) is an individual’s or a group’s perceived physical and mental health over time.*

## 4.4 Real-World Data

Real-World Data (RWD) refers to the data derived from non-conventional sources like electronic health databases, patient registries, repositories, clinical records, and patient-reported data. Different pharmaceutical and health agencies define RWD as data collected by any non-interventional methodology and non-traditional strategy. Various stakeholders like regulatory agencies, HTA institutions, and pharmaceutical industries are exploring the possibility to use RWD data for various reasons. Regulatory agencies encounter challenges in decision-making based on the available conventional data from RCTs. As regulatory agencies consider RCT data unpredictable to rely on- in terms of real-world effectiveness. Thus, RWD complements the evidence from RCTs and aids in making valid decisions and provides opportunities to make HTA better (Makady et al., 2017).

### Significance of RWD

### With the global digital revolution, an enormous amount of healthcare and patient data are accessible to various stakeholders. RWD provide opportunities to use this data as clinical evidence concerning the therapeutic effect, treatment benefits and potential side effects of pharmaceutical drugs and therapies. Pharmaceutical and medical industry are complementing and combining this data into their regulatory and experimental systems. RWD can transform future clinical research by coordinating with healthcare providers, pharmaceutical companies and claim payers or sponsors. Healthcare providers should take evidence-based decisions, remove gaps in healthcare, and allow easier patient enrollment in clinical studies. Pharmaceutical companies can plan better trial design, patient recruitment strategies, proof of treatment efficacy, and more efficient clinical engagement (Grimberg et al., 2021).

With RCTs, data extrapolation to real-world clinical scenario is difficult. Therefore, HTA authorities are investigating the possibilities to use real-world data to increase efficacy of relative effectiveness assessments (REAs). REAs can be explained as the degree up to which a treatment or therapy benefits the patient, in contrast to the situation when multiple therapies are administered to the patient under clinical supervision. With increasing healthcare costs, emergence of modern healthcare technologies, and advanced healthcare and pharmaceutical products, country specific HTA authorities are looking for efficient procedures for relative effectiveness assessments (REAs) of commonly used drugs (Makady et al., 2017).

### Challenges associated with RWD

RWD may bring along some challenges and risks for different stakeholders and institutions with respect to its application. Various challenges have been identified at People, Technological and Organizational level as illustrated in the Figure below (Grimberg et al., 2021).

RWD Challenges (Adapted from Grimberg et al., 2021)

#### Diagram Description automatically generated

#### ‘People’ aspect

From people’s perspective, poor perception and knowledge of applications of RWD prevents its use. It is important to create public awareness regarding the advantages of RWD, importance of data privacy and protection. At the same time, it is imperative to educate healthcare regulators and professionals regarding the clinical significance of RWD. It is necessary to determine the pros and cons of RWD during application, as it can be either advantageous or disadvantageous (Grimberg et al., 2021). Regulatory institutions like FDA (Food and Drug Administration) have suggested recommendations on the use of RWD data in clinical studies and a risky strategy to ensure that RWD is trustworthy and reliable (FDA Framework, 2018). It is important to have knowledge to get an in-depth understanding of RWD, able expertise to analyze it and make valuable interpretations useful for decision-making.

#### ‘Technological’ Aspect

Technology plays a key role in RWD generation with digital revolution and easy access to technology by one and all (Grimberg et al., 2021). However, diverse country specific data formats and cybersecurity risk are some obstacles preventing RWD applications globally. Unified RWD formats and data models like Observational Medical Outcomes Partnership are being developed as an independent database for rigorous analysis (OHDSI, 2019). Necessary steps should be taken to avoid cybersecurity risks like illegal access to and use of RWD, and prevention of cyber-attacks, like ‘’WannaCry’’ attack reported in 2017 (Armis, 2019).

#### ‘Organizational’ Aspect

Transformation of RWD into RWE for regulatory applications should be arranged in an organizational system. Certain risks should be prevented to have a robust organizational structure. Assurance of optimum data quality is important to have good RWE. Partial or substandard data from poor-quality patient registries and observational studies affects the quality of RWD. Data standardization is another important parameter, as gap in data collection, processing and reporting may influence data quality. Thus, regulatory institutions are making attempts to recommend implementation of uniform data standards (FDA Framework, 2018). Absence of co-ordination amongst distinct institutions at regional and global level is a major hindrance in deriving substantial RWE from RWD. Robust governance structures are important to enable various stakeholders and organizations to have timely access to RWD. Legal compliance and stricter ethical regulations might pose any threat; thus, it must be ensured that legal frameworks do not hinder the use of RWD. Cost benefit analysis is recommended to assess the costs and expected benefits from the RWD (Grimberg et al., 2021).

RWD opens new opportunities for various stakeholders, especially pharmaceutical industry for access to clinical data. Evidence from RWD will be crucial for development and approval of new drugs, therapies and products, if different challenges discussed above can be addressed in appropriate manner (Grimberg et al., 2021).

### Self-Check Questions

1. Please list any three areas to draw real-world evidence (RWE).

*Hospital Registries*

*Healthcare databases*

*Patient data*

1. Please mark the correct statements.

* *Federal Drug Agency (FDA) has defined RWD as “Data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources”.*
* *European Medicines Agency (EMA) has defined RWD as “Healthcare related data that is collected outside of randomized clinical trials”.*
* Federal Drug Agency (FDA) has defined RWD as “Data that are electronically generated and stored by medical institutions”.

1. Please complete the following sentence:

Research Initiatives like the Innovative Medicines Initiative GetReal Consortium (IMI-GetReal) focus on exploring *policies* and *methodologies* for applying real-world data in drug development.

**Summary**

Decision-analytics in healthcare depend on value-based and science-based requirements and fundamentals. Strategies like Multicriteria Decision analysis (MCDA) enable assessment depending upon various factors and criteria that can impact decisions. By implementing MCDA criteria, decision-based problem statements are structured to identify required elements that can impact the decision and fix useful guidelines for making decisions. Approval for use of a pharmaceutical drug is granted based on proof of efficacy-safety index. Efficacy-safety index can be derived from the data generated in clinical studies that often employ RCTs. RCTs provide an insight on the ‘effectiveness’of the drugs prior to market launch. The notion of “efficacy-effectiveness gap” (EEG) refers to the existing pitfalls and supportive supplementary scientific evidence on efficacy and effectiveness. It is important to understand how this concept influences clinical and policy decisions. Conceptually HRQOL encompasses physical, social, and psychological spheres. Each sphere can be quantified subjectively using patient reports and perception or objectively using clinical diagnostic data. HRQOL is measured to assess the effectiveness of an intervention. It is necessary to measure HRQOL because of clinical and policy issues. From a clinical perspective, it is important to evaluate the impact of care on the patient and status of patient health. HRQOL measures are used to oversee the change in health of the patients, prior to-, during and after the treatment, or intervention like surgery.

# Unit 5 – HTA in Benefit Package Design

**Study Goals**

On completion of this unit, you will be able to …

… understand the role of HTA in Health Benefit Package Design

… define evidence-based priority setting.

… comprehend ethics, rights, and political economy.

# 5. HTA in Benefit Package Design

## Introduction

One of the key objectives of HTA is policy research that focuses on priority setting and efficient resource allocation. Thus, Low- and Middle-Income Countries (LMIC) identify HTA as an efficient policy apparatus. There is considerable demand for evidence to recommend and shape UHC policies like benefit coverage, strategies for upgrading standards, and overall quality level to advance healthcare access and services (Tantivess et al., 2017).

Monitoring and evaluation of health benefit package design can be performed by following the cyclic steps illustrated below.

Monitoring and Evaluation of Health Benefit Package Design (adapted from Glassman et al., 2017)

Diagram

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## 5.1 Evidence-Based Priority Setting

HTA institutional mechanisms are efficiently functioning in high-income countries like Australia, European countries, and Canada. Most low- and middle-income countries (LMIC) do not have such institutional HTA systems in place, thus there exists a gap in interconnecting evidence and policy. In nations where **UHC (UHC)** exists, there are challenges to cover financial costs. Regional research infrastructure and facilities are insufficient to provide evidence for HTA-related decision-making. Different factors like poor know-how, expertise, and skill gap amongst responsible authorities, policy legislators, and HTA-related staff influences evidence-dependent verdict. Different international agencies have started special local and global HTA initiatives like conferences, workshops, and trainings for skill development. The Asian regional initiative HTAsiaLink and South American associations like RedETSA, PAHO, and IADB work in close cooperation with each other (Tantivess et al., 2017).

**UHC (UHC)**

It indicates access to equitable health services by all citizens globally, without running into any financial difficulty.

### Priority setting by HITAP and NICE

**Priority setting**

This refers to the decision-making procedure regarding efficient allocation of available resources to safeguard public health

To enhance **priority setting** in LMICs in various continents, British HTA agency, “National Institute for Health and Care Excellence (NICE) International” and Thailand’s HTA program “Health Intervention and Technology Assessment Program (HITAP)” and their associate institutions forged collaborations around 15 years ago. The learnings from the work of NICE and HITAP will aid in implementing HTA at a national level and support evidence for the generation and application of research in decision-making in LMICs (Tantivess et al., 2017).

#### Institutionalizing HTA in Vietnam

NICE collaborated with Vietnam’s ministry of health to upgrade service quality and healthcare standards focusing on grade and performance based on certain factors. Vietnamese doctors initiated a process in close cooperation with NICE and NHS associates to aid in applying and learning from the evidence available globally at the national level. They implemented institutional steps by establishing stroke units and increasing patient awareness. Hospitals in Hanoi are adapting these practices to improve care standards, the aim is to further implement these services in different hospitals in the entire country. There was limited financial evaluation and lack of research on cost-effectiveness in Vietnam until efforts were initiated to institutionalize HTA in Vietnam. Thus, NICE and HITAP started a scheme for HTA institutionalization for priority setting in Vietnam, with the health department’s vision to implement UHC in the country. An evaluation was performed to acquire knowledge regarding the practices used in resource allotment, HTA requirements, practical potential, and political will to interlink research and policy. The initial steps included measures to increase stakeholder understanding of HTA as an instrument for priority setting. Vietnamese health department established the Vietnamese Health Strategy and Policy Institute (HSPI) to perform HTA-related tasks in association with stakeholders, to develop new action, strategic vision, and HTA institutional framework.

HITAP was approached six years ago, to guide the Vietnamese Benefit Package resulting in review of benefits package for expensive pharmaceutical medicines and health technologies under the ambit of Vietnamese social security scheme (VSS). This leads to reduced budget expenditure by around 147 USD without compromising on healthcare services and quality.

Despite disparities amongst the Vietnamese social, political and regional setup, compared with Thailand and the United Kingdom, the lessons from the HTA models, were instrumental in institutionalizing the HTA system in Vietnam. Vietnamese stakeholders were strengthened with the institutionalization of HTA in Vietnam, certain aspects from other HTA systems were duplicated. Fundamentals like clarity, technical competence, public accountability, importance of policy in developing HTA agencies, managing research, and social and public outreach for transforming evidence into policy. These steps were significant to encourage leadership and boost regional institutional initiatives of stakeholders. HTA-related capacity development in Vietnam is necessary to boost decision-making in healthcare, improve healthcare services, promote health equity and expand UHC across the country (Tantivess et al., 2017).

### Self-Check Questions

1. Please list three key lessons from HTA models, that were instrumental in institutionalizing the HTA system in Vietnam.

*Vietnamese stakeholders were strengthened with the institutionalization of HTA in Vietnam.*

*Fundamentals like clarity, technical competence, public accountability, importance of policy in developing HTA agencies, managing research and social and public outreach were adapted for transforming evidence to policy.*

*To encourage leadership and boost regional institutional initiatives of stakeholders.*

1. Please mark the correct statements.

* *The Asian regional initiative HTAsiaLink and South American associations like RedETSA, PAHO and IADB have close cooperation with each other A strategy is static and should not be changed within the timeframe it encompasses.*
* HTA institutional mechanisms are efficiently functioning in low- and middle-income countries.

1. Please complete the following sentence:

British HTA agency NICE and Thailand’s HITAP collaborated to support and guide HTA institutionalization in *Low- and Middle-Income Countries (LMIC countries)*.

## 5.2 Ethics, Rights, and Political Economy

Politics, ethics, and rights are core to designing health benefits package for UHC. Politically powerful people often make decisions which enormously impact on a huge population. They make decisions on budget expenditure, various sources of funding and modes of expenditure by allocating different resources for specific purposes. Based on the political will of the people, options and choices made have both moral and ethical implications. Due to funding shortage, any choices exclusively focusing on specific disease etiologies may lead to objections, and outrage. Any ethical, rights, or political problems may be sorted by establishing a robust governance model with fixed accountability. For instance, a clear and transparent strategy helps in informing stakeholders, maintaining communication and networking with the public allows for better public outreach and avoiding any conflict of interest. Any strategy adapted to perform cost-benefit analysis can sort ethical, social, and right issue. Cost-effectiveness plan will demonstrate how distinct hypothesis will influence the results, aiding decision-makers to keep in mind the standards of evidence or spectrum of results. Patient age may be a variable factor that can influence drug choice with reduced or minimal side effects. Political, ethics and rights issues need priority irrespective of governance and strategy choice (Glassman et al., 2017).

### Politics and Priority Setting

Health benefits package designing is complex and may give rise to political and economic problems. For example, the kind of services to be provided, under the kind of circumstances, and the monetary expenditure incurred are all open questions. Decision-making is becoming significant as countries are adapting UHC, as low-income countries are transforming to middle income countries and as population life span grows. Regarding LMICs, global agencies have recommended various priority-setting strategies like financial analysis, disease impact, and monetary budget to aid the method in determining the interventions to be used in health benefits package. Priority-setting in this sector focuses on technical aspects like analyzing disease load and training staff to implement cost-effectiveness plans. Limited focus has been given to the political economy around the health benefits package, especially the different spheres of political interest that shape decisions regarding funding accounts, the range of health services, and the level of health expenditure. Understanding the political economy of priority setting can aid in arranging more efficient resource allotment establishments, methods, and decisions, by identifying and regulating instead of entirely overlooking any conflicting interests (Glassman et al., 2017).

There are several examples of policy-related Political economy conflict which are difficult to comprehend. For example, Costa Rica adapted pneumococcal vaccine despite opposition from country’s top technical organization. The only supporting evidence was provided by a research student who was sponsored by the vaccine producing pharmaceutical company. Ghana’s and Mexico’s insurance programs are facing economic challenges, but they still cover high costs for country’s privileged subpopulation (Agyepong et al., 2008). The United Kingdom has mechanisms for ensuring cost-effectiveness in treatments from National Health Services (NHS). However, they include a Cancer Drugs Fund especially developed to supersede cost-effectiveness demands (Duerden, 2010). These examples demonstrate political subversion and politically motivated decisions in health benefit coverage and programs in different countries.

Comprehending political economy-related challenges to be encountered is itself a challenge for policy makers. Political economy is significant for evaluating the procedures that govern priority-setting in health, as there are conflicting interests. These are key areas for three reasons: limited resources and unlimited demand for health services, health policy-making is divided and scattered and is impacted by market failures, and federal decisions are mandatory to be implemented creating a competition amongst different stakeholders and parties involved due to conflicting interests (Glassman et al., 2017).

The political economy of health benefits package involves a diagnostic and illustrative framework and four stages of the political cycle as outlined below.

* **Agenda Setting –** Procedure in which requirement for a health benefits package gets interest, for expenditure and health equity objectives.
* **Formulation and Adoption –** Decision makers and concerned authorities decide on how to direct the issue via health benefits package.
* **Implementation –** Implementing the policy into action by applying a health benefits package policy.
* **Evaluation –** Evaluation of impact likeassessing the aftereffects of a health benefits package policy.

Understanding the policy cycle provides insight on how decisions aid in shaping the response of different players and stakeholders in the entire process of health benefits package designing and policy making.

### Ethics and Priority Setting

During the designing of health benefits package, policy makers face a series of difficult decisions and questions like the kind of services, products, and processes to be included, the population to be covered, which agencies will cover the expenditure and healthcare costs, and questions regarding budget sources need to be answered. All these challenges have ethical repercussions. At times, specific decisions lead to conflicts regarding selective bias for a specific group of people or bias toward overlooking interests of a particular disease group. Cultural factors, rights of patients, stakeholder engagement and lack of clarity regarding moral compliance may give rise to ethical issues. Thus, implications of any procedures and results need to be evaluated and analyzed based on ethically significant moral and fundamental values. Ethical evaluation is important for policy makers as it provides significant strategies and foresight for improved decision-making. Over the years, there is an increased demand to implement the implementation of concept of equity in health benefits package, it has also been recommended by the World Health Organization’s Committee on Equity and UHC.

#### Role of Ethics and Equity in Policymaking

Policy makers face a challenge to provide health benefits package policies addressing health equity, provide necessary health services and prevent the public from unnecessary treatment expenditure. A significant purpose of undertaking ethical evaluation while designing health benefits packages is to get a comprehensive knowledge about its objectives. A strong set of objectives provides a solid foundation for policy-based decision-making in healthcare. Thus core ethical elements of a health benefits package may include setting goals and criteria; implementing general criteria and defining methods for appraisal; choosing shape of health benefits package and selecting areas for further evaluation; collating existing evidence and collecting new evidence; undertaking appraisals and budget impact evaluation; deliberations around appraisals and evidence; making recommendations and taking decisions; transforming decisions into resource allotment and use; managing and applying health benefits package; reviewing, learning and revising. As some countries may design health benefits package considering health equity identical to providing human rights, in contrast other countries may prefer priority treatment based on treatment for specific diseases, or patient population. Primary goal of policy-making is to cover health costs and prevent healthcare-related expenditure. Health benefits package is considered as an instrument to upgrade healthcare infrastructure and facilities, frame better policies to have financial security and a transparent sustainable strategy. Thus, it is important to implement fair processes in health benefits package, to have equitable participation, equal representation and inclusion addressing the needs of all patient populations. For example, the South African National Health Insurance Scheme outlined in the report (2015) explains reasons for health system failures, funding strategies, unfair allotment of health staff, discrimination based on race and social status.

### Rights in Priority setting

Decision-makers have a tough task to make health packages transparent, fair, equitable and cost-effective, taking care of the needs and demands of the various stakeholders and patient groups. It is important for policy makers to determine whether implementing or removing a certain policy may impact or conflict with the patient’s right to health. Such conflicts commonly emerge in situations when patients do not have the right to access certain therapies, medicines, treatments, or healthcare benefits which is a fundamental component of UHC. Patients have the right to take legal course of action, seek legal assistance from the court of law and contest to receive the right to health via legal court (Glassman et al., 2017).

Right to health is not generally embedded in regional or national constitutions besides a few exceptions (like Brazil, Colombia, Latvia, Kenya, South Africa). However, the right to health is embodied in international laws as outlined below.

* Universal Declaration of Human Rights (Article 25) - Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including medical care and necessary social services. (United Nations, 1948, art. 25)
* The International Covenant on Economic, Social and Cultural Rights Article 12 recognizes the right of everyone to the enjoyment of the highest attainable standard of physical and mental health. (UN General Assembly, 1966, art. 12)
* The International Covenant on Economic, Social and Cultural Rights (General Comment 14) explains the three right-to-health obligations of states: to respect, to protect, and to fulfill.
* World Health Organization Constitution Preamble - The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being. (WHO, 1946)

It is important for policy makers to involve judiciary and international organizations like WHO to create public awareness regarding right based priority setting and to create a balanced health benefits package by prioritizing the interest of all stakeholders.

### Self-Check Questions

1. Please list any three core elements of health benefits package

*setting goals and criteria*

*implementing general criteria and defining methods for appraisal*

*choosing shape of health benefits package and selecting areas for further evaluation*

1. Complete the sentence

*Politics*, *Ethics*, and *Rights* are core to designing health benefits package for UHC.

1. Complete the sentence

*Agenda Setting* in political cycle refers to procedure in which requirement for a health benefits package gets interest, for expenditure and health equity objectives.

Summary

Primary goal of HTA is priority-setting, evidence-based guidance for safe and effective policy-based decision-making and to achieve UHC (UHC) and health-equity. HTA is identified by Low- and Middle- Income Countries (LMIC) as a competent instrument for shaping policies. Availability of evidence is essential to guide UHC Policies. These policies may encompass health insurance privileges, mechanisms for improving standards, health equity and health standards. Ethics, rights and politics are fundamental to shaping a well-balanced health benefits package for UHC. Political authorities taking decisions effect a big set of population, deciding on various aspects like cost analysis, funding sources, and resource allotment. Inclusion and Exclusion of specific disease groups from healthcare benefits may lead to conflicts. Thus, it is important to address any emerging issues by an equitable governance model benefitting all groups of population by maintaining communication with all stakeholders. Different assumptions may lead to distinct outcomes. A fair health benefits package complying to ethical and moral values, free of political maneuvering, and providing right to health to the patients will cover the tenets of UHC and will be in the interest of all stakeholders. Thus, Political, ethics and rights issue need priority irrespective of governance and strategy choice.

# Unit 6 – Institutionalizing HTA Mechanisms

**Study Goals**

On completion of this unit, you will be able to …

… identify institutional HTA mechanisms

… design institutional and governance arrangements.

… understand international initiatives NICE, IQWiG, EUnetHTA, INAHTA.

# 6. Institutionalizing HTA Mechanisms

## Introduction

To institutionalize HTA mechanisms, it is important to design an institutional arrangement, build institutional capacity, evaluate the risks involved, and create a governance and operational structure. To design an institutional system, different HTA systems should be assessed, and the most appropriate system should be adapted based on the country-specific demands and needs. Suitable location is chosen, and right public authority is nominated for taking reimbursement decisions. All the key stakeholders are identified. Institutional system is developed by assessing the existing bottlenecks and competence needed with that available. Create an action plan to learn about assessment models and exercises, state of the appraisal agency, resolution of any conflicts during assessment and appraisal, learn about regional law, legal compliances, and responsibilities. Risk assessment is conducted by recognizing institutional bottlenecks like data quality and access, resource supply and aid. A program should be drafted to overcome and quell any risks. An institutional structure needs to be created that encompasses all aspects (Bertram et al., 2021).

## 6.1 Institutional and Governance Arrangements

Institutional and legal frameworks are necessary for maintaining viable HTA mechanisms and systems. **Governance** structures establish institutional rules and regulations, which should be acknowledged and practiced. Governance is described as the procedure and structure by which HTA mechanisms are tailored. The foundation of good governance is based on the statutes of clarity, involvement of stakeholders and partners, logical and rational decision-making, accountability, and a steady equilibrium (Bertram et al., 2021).

**Governance**

It indicates the procedure of overseeing the operational control of the health system.

### Benefits of Good Governance

Effective governance has both intrinsic and extrinsic benefits. Intrinsic benefits to all stakeholders include participation of stakeholders in governance structures, a significant role in decision-making, questioning the rationale and relevance of specific policies. Extrinsically, a robust governance mechanism allows a healthy dialogue and exchange of views amongst all stakeholders on difference structures of governing principles.

### Designing an Institutional Arrangement

Different countries have distinct HTA models to fulfill their needs and adapt to the country-specific institutional arrangements. Institutional arrangement is designed based on the three key points: (a) the execution of the appraisal process, (b) if assessment process is to be performed internally or by an external agency, (c) the scale of the HTA function to be determined when developing the structure of the model, complying to the legal jurisdiction. Most of the HTA entities are multi-disciplinary involving stakeholder groups like pharma industries, and patients. Some of the institutions perform only appraisal like in Switzerland, dossiers are provided by pharma representatives. In contrast, other agencies manage both assessment and appraisal functions like NICE in the United Kingdom, it directs other agencies for assessment and perform appraisal themselves. HTA agency can review assessments and international regulations and provide customized guidance for their use. Thus, HTA institutions should take up the role of appraisal instead of performing assessments. In such a scenario, assessments can be partly or exclusively conducted by external agencies. Assigning assessments to external or contractual staff ensures efficient and timely completion of the task. Different considerations should be considered like budget and staff availability, appraisal of country specific HTA function. If there is an intention to establish HTA institution, the right organisation should be involved, and analysis should be conducted to identify the existing HTA mechanisms, and appropriate expertise. Public funding sources should be determined and authorities who should provide reimbursements should be identified complying with the national legal jurisdiction. Any necessary legal processes should be initiated, concerned authorities and stakeholders should be contacted to involve them in the process for designing HTA institutional framework (Bertram et al., 2021).

### Developing Institutional Capacity

HTA institutional capacity can be developed by acquiring necessary skills for assessment and appraisal and by identifying the right skillset and competent expertise which is already available. Public authorities, social non-governmental organizations and healthcare providers should be consulted to identify the existing HTA-related mechanisms and resources which can be used to build up institutional capacity. In local context it is significant to know how and where the health data can be accessed, which public authority should be approached and where the demographic, epidemiological and information on relevant costs in local markets is accessible. Human resources and staff with different skills and expertise are required to be included in the HTA process. Physicians, nurses, Biomedical engineers, Pharmacists, Health facility managers, epidemiologists, health economists, legal experts, ethicists, patients and civil society organizations, and communication officers are involved in the HTA process. HTA mechanisms and capacity development are performed as outlined and illustrated in the figure below.

Development of HTA Mechanisms During Institutional Reimbursement (adapted from Bertram et al., 2021)

**Assessment**

* Epidemiologists evaluate pros, cons and expected improvement in healthcare.
* Health economists develop cost effectiveness and fiscal impact of clinical and healthcare data.
* Ethical experts assess remaining aspects.

**Appraisal**

* Taking precautionary measures to avoid conflict of interest.
* Understanding of assessment results.
* Managing communication between various stakeholders.

**Recommendation**

* Communication of logic and concepts behind any advice or recommendations.
* Interpretation of legal compliance and responsibilities.

Legal and Institutional Arrangement

* Public procurement and contract management
* Understanding of the rule of law and legal responsibilities

### Conducting Risk Assessment

The challenges involved with specific drivers that develop hindrances to or enable development of HTA mechanisms within a national HTA system should be taken care of.

#### Drivers and associated risks

* **Data availability and quality –** Substandard assessment outcome results in bad decision-making and disregards the impact of HTA.
* **Cultural scenario –** Stakeholders unwilling to accept transformation in decision-making and HTA-related concepts like use of HTA for budget management.
* **Monetary support –** Lack of monetary support and sub-standard work disregards faith in and sanctity of the HTA system.
* **Healthcare infrastructure –** Challenges in providing and extrapolating substantial proof from global to local scenario. Application of HTA guidelines in different aspects of the healthcare system may be deemed risky and difficult. Buying technology may be challenging as sellers may or may not be following HTA recommendations. Adaptation of institutional mechanisms to a wider regional national scale may be another challenge.
* **Political assistance –** Lack of political will to support via federal funding may create a new series of challenges.
* **Knowledge of Stakeholders and their interests –** Stakeholders may try to dissuade and hinder implementation of HTA recommendations.
* **Communication –** Communication and networking amongst the HTA players may help to overcome any challenges.
* **Other challenges –** Changing priorities, too ambitious plans, management of conflict of interest.

A risk mitigation plan should be carried out to avoid these challenges. A well-planned communication mechanism should be developed to counter these risks and staff should be appointed to deal with various associated aspects.

### Establishing Operational System

After evaluating the system and mapping the available institutional capacity, it is important to determine and allocate necessary human resources and financial support required for establishing and executing the institutional operations. The table below reports operational structure implemented in different countries.

**Table. HTA Structure, Budget, and Expenditure in specific countries**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Country | Purpose | Members and Staff | Time required | Cost per HTA (USD) | Budget |
| Australia | Pharma Advisory council | 18 members, >40 staff, 5 external | 8-9 wks | 60000 | 15 million |
| Brazil | Science & Technology Department | 30 | 3 m-2 yrs | 15000-150000 | - |
| Germany | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen | 122 | 3-18 m | 65000-650000 | 19 million |
| Poland | Agency for Health Technology Assessment in Poland | 55 | 2-3 m | 28000-43000 | 3.8 million |
| Thailand | Health Intervention and Technology Assessment program | 50 | 9-12 m | 17000 | 1 million |
| United Kingdom | NICE | 500 | 7-14 m | Upto 400000 | 90 million |

Uninterrupted monetary support is important for smooth functional of HTA systems. Participating industries and companies can be charged a specific amount for each dossier submission. Depending on the adapted assessment system, various countries may have different financial and staff necessities. In case of limited financial support, system prevalent in countries like Romania can be adapted. Romanian assessment model and criteria accepts HTA decisions from France, Germany and the United Kingdom, and reimbursement model from other EU nations. This enables them to examine more medicines and technologies compared with other nations in limited budget (Bertram et al., 2021).

### Self-Check Questions

1. Please list three key points based on which the institutional arrangements are designed:

*The execution of the appraisal process.*

*If assessment process is to be performed internally or by an external agency.*

*The scale of the HTA function to be determined when developing the structure of the model, complying to the legal jurisdiction.*

2. Please mark the correct statements.

* *Communication and networking amongst the HTA players may help to overcome any challenges.*
* Substandard assessment outcome results in good decision-making and disregards the impact of HTA.
* *Lack of political will to support via federal funding may create new series of challenges.*

3. Please complete the following sentence:

*Risk assessment* is conducted by recognizing institutional limitations like data quality and access, resource supply and aid.

## 6.2 Country Case Studies and International Initiatives (NICE, IQWiG, EUnetHTA, INAHTA)

Country case studies focusing on characteristics of certain schemes and various grades of priority setting are elaborated below.

### Development of Mother and Child Health Development Program in Myanmar

Healthcare vaccination program ‘Global Alliance for Vaccination and Immunization’ funded a voucher initiative to upgrade mother and child health standards was implemented in Myanmar almost a decade ago. Thailand’s HTA agency HITAP was approached by WHO to seek assistance in guiding financial plan and budgeting strategy for priority setting of health issues. In co-ordination with Myanmar’s Ministry of Health, voucher scheme was introduced to enable mother and child health-related treatment and service access. Various aspects like financing strategy, voucher benefits, voucher distribution, funding mechanisms, and population intended to benefit were discussed and mutually agreed upon by the agencies and establishments involved. Cost-benefit evaluation revealed the advantages of the implementation of this scheme and benefit in reducing mother-child mortality rates. Thus, this scheme was practically started as a pilot model in 2013 in a small region of the country.

The objective of this initiative was to seek support from HITAP and improve evidence-based decision- and policy-making in Myanmar, instead of institutionalizing HTA in Myanmar. This is expected to strengthen evidence-based policy framing capacity in Myanmar with the aid of external partners (Glassman et al., 2017).

### Institutionalizing HTA in Colombia

Colombian health ministry with financial seed support from WHO, through a 5-year program (2008-2013) sponsored by Inter-American Development Bank (IDB), NICE International, Academic and Research Institutions working with Colombian agencies collaborated to institutionalize and develop a fundamental system in Colombia with a focus on technology. This initiative was spearheaded by court directions to the political authorities to integrate two benefit packages, i.e., a more generous and a less subsidized one. The technical challenges and strategies issues in merging the two systems was the major challenge to overcome by this collaboration. This consortium coordinated their action plan by a knowledge exchange and meetings between different international partners and research organizations including Argentina’s Institute for Clinical Effectiveness and Health Policy (IETS), support from Colombian agencies like IDB, NICE international and IECS supported development of an institutional framework and an executional action plan, which led to the enactment of a legal regulation and establishment of Institute for Health Technology Evaluation (IETS). A comprehensive assessment and evaluation of the Latin American and Western HTA systems was performed and price listing by judiciary.

Local capacity development and skill training was performed in close cooperation with academic institutions and universities, by training programs in UK in collaboration with NICE and by providing secondment options for Colombian members. However, in the current scenario IETS is facing several challenges like financial sustainability, and court rulings superseding and undermining policy decisions. Legal proceedings are continuing in court of law to address these emerging challenges and institutional mechanisms in Colombia despite political will (Glassman et al., 2017).

### International Initiatives

International initiatives including NICE, IQWiG, EUnetHTA, INAHTA are shaping policy-making and influencing healthcare related decision-making globally. Features of some of these initiatives are described below.

### NICE

NICE stands for National Institute for Health and Care Excellence (NICE) and performs HTA for National Health Service (NHS) in the United Kingdom. NICE is responsible for recommending specific technologies for funding to the NHS (Charlton, 2020).

#### Purpose and Development of NICE

The British government in 1997, realized the patients being treated at NHS do not have easy access to expensive medicines. Postal-code lottery system was employed for allocation of costly medicine to patients. Limited financial support was granted by the federal government to the NHS. Therefore, the government created a ‘National Institute for Health and Clinical Excellence’ in 1999. This new center was commissioned with the task to guide NHS for application of single or a set of identical therapeutic medicines, products, and systems (technology appraisal), and to prepare guidelines for clinical care by healthcare workers to improve the standards of care provided by NHS. Thus, the purpose was to guide the NHS with respect to the clinical efficacy and cost effectiveness of a new health technology (Bertram et al., 2021). The development of NICE was based on certain fundamentals like involvement of multiple stakeholders, clarity, no overlapping interests, and open debate. NICE has expanded its scope by making decisions on advanced and latest drugs and technologies implemented by the NHS and recommending benchmark guidelines for various clinical and public healthcare. Thus, NICE played a key role in transforming scientific and clinical evidence into policy in context of healthcare (Tantivess et al., 2017).

#### NICE International

Due to increasing prominence of NICE, international HTA agencies have approached NICE for support to improve and upgrade their own HTA systems, to help in decision-making and effective resource allocation. To support international HTA community, NICE established ‘NICE International‘ in the year 2008 to guide on capacity development for assessment and transforming evidence to policy. NICE International is currently serving in seven countries across Asia, Africa, Latin America and Europe (Tantivess et al., 2017).

### IQWiG

The German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) is a technically independent research institute with legal capacity within the German statutory health insurance. As the “HTA institute”, it provides evidence to the Federal Joint Committee (G-BA), the main decision-making body within the system.. IQWiG generates autonomous proof-based reviews on pharmaceutical drugs, medical interventions and clinical examinations. The IQWiG has a key role in the so-called early benefit assessment of innovative medicines. It conducts health economic evaluations. IQWiG is funded by grants and allowances from the **statutory health insurance** and may get financial support from the Federal Ministry of Health (IQWIG, n.d.).

**Statutory Health Insurance (SHI)**

German statutory health insurance (SHI) covers healthcare of all beneficiaries and provides a comprehensive coverage that comprises of treatment at the hospital, consultation with General Practitioners and clinicians, rehabilitation, physiotherapy, health examination, oncological screening and scanning, medicines, therapies, aids like hearing aid or wheelchairs, dental checkups, orthodontic treatment up to 18 years of age. Thus, bulk of SHI expenditure is spent on curative services and not only on chronic diseases. This includes inpatient services (about a third of total expenditure), prescription medicines.

#### Purpose of IQWiG

IQWiG has played an important role in the German health system since its inception in 2004. The purpose of IQWiG is to participate in advancing and improving healthcare services in Germany. IQWiG performs and publishes evaluations by efficacy, standard, and competence of health services. IQWiG impacts certain aspects like assessment of pros and cons of drug and non-drug treatment and therapies, assessment of clinical evidence-based regulations for epidemiology of a disease and providing knowledge to the public regarding standard and efficiency of healthcare. Further two new reforms in 2007 and 2010 were implemented to broaden the scope of IQWiG. The reform in 2007, known as the Act to Promote Competition of SHI (GKV Wettbewerbsstärkungsgesetz 2007), IQWiG can be instructed to compare the cost-effectiveness of drug interventions with the earlier treatment option. Other reform in 2010, the Law on the Reorganization of the Pharmaceutical Market (Arzneimittelmarktneuordnungsgesetz AMNOG, 2011), it is the liability of the Federal Joint Committee to evaluate the pros of the recently authorized drugs. If new benefits are noted, the cost of a new drug will be worked out amongst the Federal Association of the Health Insurance Funds and the relevant organisation. The evaluation is conducted depending on the dossiers provided by the producers to the Federal Joint Committee (G-BA), which then instructs the IQWiG with dossier evaluations.

#### Functioning of IQWiG

IQWiG compiles reports on subjects commissioned by the G-BA or the Federal Ministry of Health or on matters conceptualized by the IQWiG itself. The internal employees are supported by the temporary contractors for specific projects by open calls. All the reports are developed employing the strategies used in routine practice by the institute. Different organisations who are the Stakeholders can also be requested to participate in the functioning of the institute in different capacities. Reports compiled by IQWiG are available online and any recommendations can be indicated, which may result in modifications in the final version.

### EUnetHTA

To establish a robust and a balanced HTA system, the HTA Core Model was established by the European Network for Health Technology Assessment (EUnetHTA) (Kristensen et al., 2017). The task of Work Package 4 (WP4) of the European network for Health Technology Assessment (EUnetHTA) Project was to produce a multidisciplinary common core of HTA evidence (EUnetHTA, WP4, 2008).

#### Purpose of EUnetHTA

The strategic aim of the EUnetHTA was to decrease any overlap and duplication of work and use the available resources efficiently, enhance HTA to recommend or impact decisions in associated member states within the EU, focus on the association between HTA and healthcare policy making within EU and guide countries with limited knowledge and HTA experience. The two key issues of the existing HTA system were differences in the degree and scope of analysis, and variability in describing the outcome.

#### Purpose of HTA Core Model

The purpose of HTA Core Model was to develop a framework that allows useful association and knowledge exchange to avoid and overcome the afore-mentioned issues. This will increase global acceptance, relevance, and usefulness of international, national, or regional HTA reports (Lampe et al., 2009). HTA Core Model was developed based on views of members from twenty-four institutions belonging to seventeen different nationalities. This model evaluates medical and surgical interventions and assesses diagnostic technologies.  These assessments formed the basis of the Core HTAs (Lampe et al., 2009). The core HTA was developed together with the medical and diagnostic assessments to improve the HTA model based on the assessment feedback.

The validation of the HTA Core Model and pilot assessments allowed each domain participant to implement modifications to the model. The validation was performed by EUnetHTA and INAHTA (International Network of Agencies for Health Technology Assessment) members via an online questionnaire. Participants were asked to respond to the questionnaire encompassing three domains they had not worked on earlier and to compare the model with an existing model or with a completed HTA. Percentages were evaluated based on the questionnaire and ideas from these comments were taken. Public feedback was collected using a standard protocol and pros and cons in developing HTA Core Model were outlined (Lampe et al., 2008, 2009).

#### Elements and Domains of HTA Core Model

Elements of HTA Core Model include ‘Ontology’ which refers to the problems and questions to be answered by an HTA, ‘Methodological Guidance’ includes how to answer the question, and ‘Reporting Structure‘ refers to how the problem should be addressed (Lampe et al., 2009). The HTA Core Model encompasses around nine domains of HTA as illustrated below.

Health Technology Assessment Core Model

The four domains of the HTA Core Model, including the health problem and current use of technology, description and technical characteristics of technology, safety, and clinical effectiveness, influenced the generation of access evidence tools (EUnetHTA, WP4, 2009). The primary objective of evidence generation included the following: scoping disease and indication-specific evidence required for HTA agencies and patients, assessing the existing evidence creation plan, and finding gaps that may lead to threat in market access, assessing diverse options regarding evidence gaps and providing supplementary evidence, summarizing access evidence for application in HTA guidelines. Exclusive access evidence tools were developed to address each of the objectives.

The EUnetHTA WP4 project was led by the Finnish office of Health Technology Assessment. Germany and Belgium shared the Quality Management (QM) responsibility, while the HTA Core model fell under the Belgian’s Activity Center B under QM Scientific Guidance and Tools (EUnetHTA-WP4, 2009). A handbook has been developed for users of the online HTA Core Model detailing the basic principles of the HTA Core Model, practical guidelines on applying the model and methodological instructions for identifying answers to research questions of the core HTA (Lampe & Pasternack, 2009).

### INAHTA

INAHTA stands for International Network of Agencies for Health Technology Assessment.

#### Purpose

The purpose of this network was to allow mutual coordination and sharing of knowledge from various sources of HTA. Another objective was to decrease the burden on various national and international agencies working on identical topics (Hailey, 2009).

#### Structure and Function

INAHTA was formed by thirteen founding organizations from Australia, Canada, France, The Netherlands, Spain, Sweden, Switzerland, the United Kingdom, and the United States of America and currently involves around 50 agencies impacting health of people in around 31 nations. The functions and tasks of INAHTA were structured and outlined in 1994. Institutions running HTA initiative, giving consultation to governments, compiling HTA records and accepting half of the allowances from public were open for INAHTA memberships. All the members will contribute to incorporate a council and a three-member committee at the Canadian office for HTA (Hailey, 2009).

### Development

INAHTA has included members on a yearly basis. Some of the members opted out of the network due to changes in their scope and objective, or due to sponsorship crunch. INAHTA secretariat relocated to SBU (Swedish Council for Technology Assessment in Health Care) Sweden in the year 1996, and the executive council was expanded to facilitate smooth functioning of the network. A website was incorporated (http://www.inahta.org) as a platform for knowledge exchange for all members of the network. Network has been actively working to develop HTA reports, guidelines, abstracts, HTA frameworks, and members collaborate on projects. Even with a limited financial budget, INAHTA has been a success in establishing communication between different institutions. INAHTA is continuously attracting members from different parts of the world and is actively working on HTA-related projects.

### Self-Check Questions

1. Please list four domains of the HTA Core Model.

*Social aspects*

*Legal aspects*

*Clinical effectiveness*

*Costs and Economic evaluation*

2. Please mark the correct statement.

* *INAHTA was formed by thirteen founding organizations from Australia, Canada, France, The Netherlands, Spain, Sweden, Switzerland, the United Kingdom, and the United States of America.*
* INAHTA was formed by ten founding organizations from Australia, Canada, France, The Netherlands, Spain, Sweden.
* INAHTA was formed by three founding organizations from Australia, Canada, France.

3. Please complete the following sentence:

Elements of the HTA Core Model include *‘Ontology’* which refers to the problems and questions to be answered by an HTA, *‘Methodological Guidance’* includes how to answer the question, and *‘Reporting Structure‘* refers to how the problem should be addressed.

Summary

To institutionalize HTA mechanisms, it is important to design an institutional arrangement, build institutional capacity, evaluate the risks involved, and create a governance and operational structure. To design an institutional system, different HTA systems should be assessed, and the most appropriate system should be adapted based on the country-specific demands and needs. Suitable location is chosen, and right public authority is nominated for taking reimbursement decisions. All the key stakeholders are identified. Institutional system is developed by assessing the existing bottlenecks and competence needed with that available. Create an action plan to learn about assessment models and exercises, state of the appraisal agency, resolution of any conflicts during assessment and appraisal, learn about regional law, legal compliances, and responsibilities. Risk assessment is conducted by recognizing institutional bottlenecks like data quality and access, resource supply and aid. A program should be drafted to overcome and quell any risks. An institutional structure needs to be created that encompasses all healthcare-related aspects of the country. Several international initiatives like INAHTA, NICE, EUnetHTA and IQWiG are influencing development of HTA-related institutional mechanisms and policy-making in Lower- and Middle- Income Countries.

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Appendix 2 – List of Tables and Figures

**The Six-stage Model for Health Technology Assessment Impact**

Source: [Author] based on [Millar et al], (2021)

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**Impact of Health Technology Assessment**

Source: [Author] based on [Bowen et al], (2009)

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**Five-step Model for Evidence Based Medicine**

Source: [Author]

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**Flowchart Depicting Various Stages Involved in Literature Search**

Source: [Author] based on [Cooper et al], (2018)

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**Evidence Based Medicine Pyramid (EBM)**

Source: [Author]

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**Table. GRADE Recommendations and Evidence Levels**

Source: Author

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**PRISMA 2020 Flow Diagram Format for Systematic Reviews**

Source: [Author] based on [Page et al.], (2021)

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**Overview of HTA Functions**

Source: [Author] adapted from (Bertram et al., 2021)

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**Association Between Assessment, Appraisal and Recommendations**

Source: [Author] (adapted from Bertram et al., 2021)

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**HTA Components Assessment and Appraisal**

Source: [Author] adapted from [Teutsch et al., 2005]

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**Overview of Pricing Policies**

Source: [Author] adapted from [WHO collaborating center from pharmaceutical pricing and reimbursement policies]

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**Steps Involved in Horizon Scanning**

Source: [Author] adapted from [Grossman et al., 2019]

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**Flowchart Depicting Multistep Decision Analytic Modelling Criteria**

Source: [Author] adapted from [Goetghebeur et al., 2012]

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**Decision Tree for Breast Cancer Screening Options**

Source: [Author] adapted from [Sun et al., 2008]

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**HRQOL Conceptual Framework**

Source: [Author]

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**HRQOL Data Pyramid for Population health**

Source: [Author] adapted from [Fryback, 2010]

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**Contextual Model for HRQOL**

Source: [Author] adapted from [Ashing-Giwa, 2005]

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**RWD Challenges**

Source: [Author] adapted from [Grimberg et al., 2021]

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**Monitoring and Evaluation of Health Benefits Package Design**

Source: [Author], adapted from [Glassman et al.,] (2017)

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**Development of HTA Mechanisms During Institutional Reimbursement**

Source: [Author], adapted from [Bertram et al.,] (2021)

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**HTA Core Model**

Source: [Author], adapted from [Lampe et al.,] (2009)