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Systems for Improved Access to Pharmaceuticals and Services

Applying Principles of Pharmacoeconomics to Improve Medical Product Selection and Use in Low- and Middle-income Countries:

AUGUST 2017

Trainer's Guide

DEPARTMENT OF GLOBAL HEALTH
UNIVERSITY of WASHINGTON

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About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to ensure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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This version of the guide is intended for field-testing.
Once implemented, it will be revised and refined as needed.

Key Words

Pharmacoeconomics, health economics, essential medicines, training, cost, health outcome, cost effectiveness, decision analysis, health technology assessment

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This set of pharmacoeconomics training materials builds on an earlier draft based on pharmacoeconomic training programs conducted in Namibia, South Africa, and Kenya in 2007, 2012, and 2013, respectively. Those trainings were supported by the USAID-funded Strengthening Pharmaceutical Systems and the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) programs and were delivered in collaboration with the University of Washington (UW).

In addition to drawing on the above courses, this final training set incorporates information from other sources, including:

- Lecture materials of UW faculty members
- Essentials of Pharmacoeconomics, a book authored by Dr. Karen Rascati from the University of Texas at Austin
- Case study exercises from a World Health Organization (WHO) training course on pharmacoeconomics (http://www.who.int/selection_medicines/pharmacoeconomics/en/)
- Pharmacoeconomics-related materials developed by SIAPS for pharmacy students at the Universities of Limpopo and Kwa Zulu Natal in South Africa

Several individuals from UW contributed to the development of the earlier version of the materials, particularly Louis P. Garrison, Gillian A. Levine, and Joseph B. Bbigumira. We also acknowledge the support provided by other colleagues at UW—David Veenstra, Beth Devine, Cindy Watts, Will Hollingworth, Josh Carlson, Brian W. Bresnahan, and Catherine-Waweru Corbell—who shared their materials used in the UW course on economic evaluation in health and medicine. Andy Stergachis also provided thoughtful review to the earlier version of the training materials.

Jude I. Nwokike and Hye Lynn Choi (previously with SIAPS), Patricia Paredes (MSH/PHT), and Maura Soucy Brown (SIAPS) all contributed by reviewing and commenting on the earlier version of the training materials.

In 2017, SIAPS consultant Millidhashni Reddy substantially updated the earlier draft to develop this revised final version of the pharmacoeconomic training materials. SIAPS Principal Technical Advisor and Lead for Pharmaceutical Services Mohan P. Joshi reviewed and provided substantive feedback during the revision process. Finally, SIAPS Technical Deputy Director Sameh Saleeb managed the overall process and reviewed the final version of the materials.

TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS

CBA	cost benefit analysis
CCA	cost consequence analysis
CEA	cost effectiveness analysis
CMA	cost minimization analysis
CUA	cost utility analysis
DDD	defined daily dose
DALY	disability adjusted life year
EML	essential medicines list
FEV	forced expiratory volume
GDP	gross domestic product
HbA1c	glycosylated hemoglobin
HRQOL	health related quality of life
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
IRR	internal rate of return
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LMICs	low and middle-income countries
QALY	quality adjusted life year
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
STG	standard treatment guidelines
UNICEF	United Nations Children's Fund
UW	University of Washington
WHO	World Health Organization
WTP	willingness to pay

BACKGROUND

Tools and materials are needed for pharmacoeconomic evaluation and health technology assessment (HTA) training to strengthen health systems and increase and support their capacity to perform HTA in resource-limited countries. Training on how to apply pharmacoeconomics to essential medicines selection should focus on equipping health care workers, regulatory authorities, public health program personnel, and academic researchers with the skills and knowledge to strengthen pharmacoeconomic decision making as part of HTA within their health systems.

This guide provides a template for use, adaptation, or adoption in many settings. It is intended that these materials will be adapted and supplemented to meet the needs and contexts of individual countries.

In addition to this trainer's guide, the curriculum package includes presentation slides, case studies, and other resources. The package is meant to provide resources and information to help trainers and facilitators conduct in-person trainings and develop local capacity for evidence-based medical product selection. Included in this curriculum are nine training modules with notes for facilitators and guidance for each module, as well as workgroup activities and case studies to accompany the presentations. The modules are:

1. Introduction to Pharmacoeconomics
2. Essential Medicines Lists and the Role of Pharmacoeconomics
3. Health Outcomes
4. Costs
5. Cost Minimization Analysis
6. Cost Effectiveness Analysis
7. Cost Utility Analysis
8. Cost Benefit Analysis
9. Advanced Pharmacoeconomic Analyses and Budget Impact Analyses

In addition to being a guide and basic platform that can be adapted for different settings, this material can serve as the basis for developing delivery formats beyond in-person trainings, such as distance or online training, to meet local stakeholder needs. Resources and materials for further reading are included to help enhance knowledge and prepare facilitators.

HOW TO USE THE TRAINER'S GUIDE

The *Trainer's Guide on Applying Principles of Pharmacoeconomics to Improve Medical Product Selection and Use in Low- and Middle-income Countries (LMICs)* is accompanied by training slides. Products referred to in the guide include medicines, vaccines, diagnostics, and other medical commodities. The guide provides additional information to clarify and expand on the content of the slides. The slides can be used to guide the trainer in the classroom, and they include notes from the trainer's guide. The slides have been inserted into the trainer's guide to assist trainers when preparing for workshops.

Each module is accompanied by time allocation guidelines. Guidelines on preparing for a module and resources that may be required in the classroom are also provided.

Activities are provided. Participants are encouraged to complete the activities either individually or in groups. Some activities are discussion based to promote sharing best practices in a group setting, and only a sample response is provided in a separate document. Depending on the structure and time allocated to the training and case studies, activities can be given to participants as take-home assignments and discussed at the next meeting. Discussion points are provided as a guide to the trainer to assist in promoting discussion and sharing during group activities. *Trainers must remember not to share solutions with participants prior to participants attempting/completing the exercises.*

The trainer's guide contains a list of references used to develop the guide. Trainers and participants are encouraged to use these resources to obtain more information on the topic.

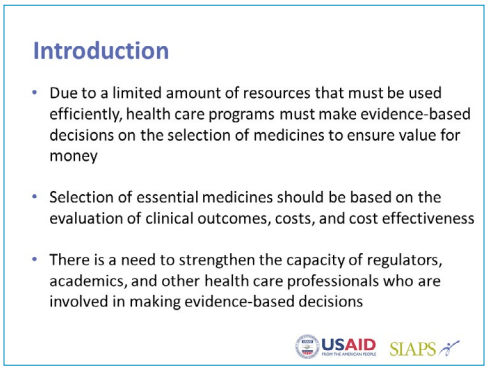
A short pre- and post-assessment survey is available to test participants' knowledge before and after the training (annex A). In addition, an evaluation sheet is available for participants to rate the quality of training (annex B). The evaluation form can be customized and administered to reflect the material covered.

At the end of the guide, a summary of concepts covered in the course is provided for facilitators/trainers to review the material covered in the modules. The topics can be reviewed in a question-and-answer format.

WORKSHOP INTRODUCTION AND OVERALL OBJECTIVES

Notes to the instructor

Time Allocation:		**1.5 hrs**
	Administering the preworkshop survey	30 min
	Introduction	10 min
	Workshop aim and objectives	10 min
	Brief synopsis of the modules covered in the course	10 min
	Discussion questions/comments	30 min
Preparation:	Read through the curriculum guide and corresponding slide deck	
Presentation:	Prior to the introduction and objectives, allow time for participant introductions: ▪ Ask participants to share their reasons for attending the pharmacoeconomics training, what they hope to take away from the training, and how they plan to use the information in their work duties. Depending on the size of the group, ask each participant why he or she signed up for the training. If group is too large, ask a random selection of participants.	
Optional:	Administer the preworkshop survey to determine participants' existing knowledge (annex A).	



Introduction to the Workshop

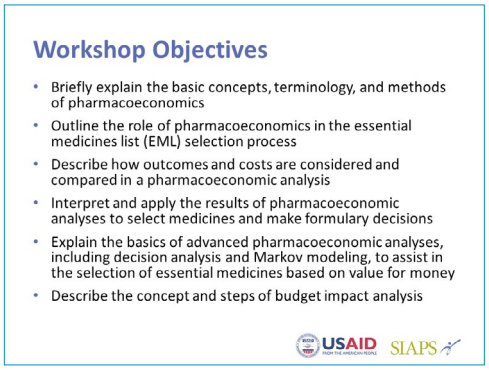
Medicines, including new ones, have the potential to greatly improve health outcomes, but health care programs across the globe are faced with the challenge of making evidence-based decisions on medicine selection to ensure value for money. Value for money is not the same as affordability. Value for money relates to the outcome relative to the money that you spend on a product or service. For example, you might spend $5 more on a hypertensive medicine, but the drop in blood pressure it produces is equal to or less than that produced by a less expensive item. In this case, the more expensive item is not providing value for money spent. Selection of essential medicines should be based on the evaluation of clinical outcomes, cost, and cost effectiveness. Many countries, including South Africa, Brazil, Taiwan, and China, now have pharmacoeconomic guidelines, indicating a growing country-level recognition of the value of pharmacoeconomics. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) offers a collection of pharmacoeconomic guidelines from around the world (https://www.ispor.org/PEguidelines/index.asp).[1] With the implementation of national guidelines for pharmacoeconomic evaluation of medicines, there is a greater need to strengthen the capacity of regulators, academics, and other health care professionals who are involved in making evidence-based decisions on essential medicines selection, medical product and device selection, pricing regulation, reimbursement, and review of clinical trials.

This is a basic pharmacoeconomics curriculum presented at an undergraduate level for use by health practitioners who have limited understanding of general and health economics.

The course was developed for implementation in LMICs to help incorporate economic evaluation into resource-limited settings that cater to the health needs of most of the population. Many LMICs do not have pharmacoeconomic guidelines. This course is designed to help participants understand the basics of pharmacoeconomics and how economic evaluation can be incorporated into the essential medicines selection process. The course can be adapted for use in diverse settings.

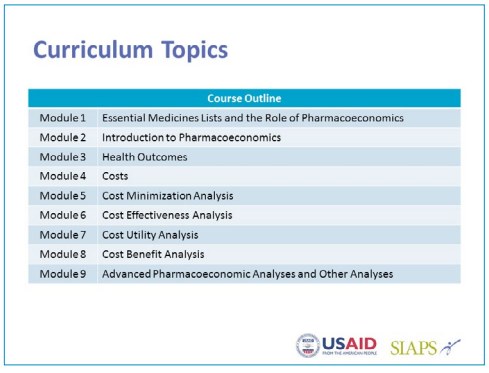
This course will empower academics and health care professionals to become pharmacoeconomic facilitators for further training programs in their own settings and incorporate pharmacoeconomic principles and methods into preservice training courses and in-service or continuing professional development courses in pharmacy and medicine and other disciplines.

Underuse of generic products and higher than necessary prices for medicines are among the top 10 leading causes of health resource inefficiency and waste.[2] While many resource-limited settings promote the use of generic medicines and reference medicine pricing, incorporating pharmacoeconomic principles, an up-and-coming discipline in LMICs, into the decision making process would reduce inefficiencies and waste in health-related expenditures and serve as a complementary long-term cost containment strategy.[2,3]



Workshop Objectives

- Briefly explain the basic concepts, terminology, and methods of pharmacoeconomics
- Outline the role of pharmacoeconomics in the essential medicines list (EML) selection process
- Describe how outcomes and costs are considered and compared in a pharmacoeconomic analysis
- Interpret and apply the results of pharmacoeconomic analyses to select medicines and make formulary decisions
- Explain the basics of advanced pharmacoeconomic analyses, including decision analysis and Markov modeling, to assist in the selection of essential medicines based on value for money
- Describe the concept and steps of budget impact analysis



The curriculum includes nine modules:

1. Introduction to Pharmacoeconomics
2. Essential Medicines Lists and the Role of Pharmacoeconomics
3. Health Outcomes
4. Costs
5. Cost Minimization Analysis
6. Cost Effectiveness Analysis
7. Cost Utility Analysis
8. Cost Benefit Analysis
9. Advanced Pharmacoeconomic Analyses and Budget Impact Analyses

In this course, each module builds the foundation for an improved understanding of the next module. We incrementally add concepts to help build a complete picture of the concept and processes of pharmacoeconomics. We start the course by sharing a brief introduction to pharmacoeconomics and economic evaluation. Basic economic principles are shared in this first module to provide a foundation for pharmacoeconomic analyses and discussions later in the course. During the introduction, we consider concepts such as opportunity cost; define pharmacoeconomics; list the four main types of pharmacoeconomic analyses; and define other analyses, such as a cost consequence analysis (CCA). We also review the definition of HTA and the role pharmacoeconomics plays in HTA.

In module 2, we review the concepts of essential medicines and explore how cost fits into the essential medicines selection process. It is important for us to explore the essential medicines concept because many LMICs use it in the provision of services through their public/government-funded health sector.

In module 3, we look at the health outcomes that form part of the denominator in a pharmacoeconomic analysis. We learn about the types of outcomes that form part of the four basic pharmacoeconomic analyses, such as natural health units in a cost effectiveness analysis (CEA) or Quality Adjusted Life Years (QALYs); its derivation using instruments such as the rating scale, standard gamble, and time trade off; and the use of QALYs in a cost utility analysis (CUA).

In module 4, we address what usually forms the numerator in pharmacoeconomic analyses, costs, looking at types of health care costs with examples, and addressing why it is important to consider "perspective" (whose cost) in an analysis. In addition, we learn that past costs must be adjusted or standardized while future costs and savings should be discounted to account for the differential timing for costs.

In modules 5–8, we take a detailed look at each of the four main types of pharmacoeconomic analysis, including the input (cost) and output (health outcome) measures we learned about in modules 3 and 4, and the advantages and disadvantages of each analysis. While the basic pharmacoeconomic analyses described in modules 5–8 provide very useful information/data on comparative costs and outcomes, they alone may not be enough from a public health perspective; these analyses sometimes need to be complemented by advanced decision or budget impact analyses when making public health choices and decisions based on evidence and affordability.

In module 9, we review the steps in a decision analysis through an example, look at when a Markov model is appropriate, and study the steps in a budget impact analysis to determine affordability.

This course is designed to highlight the basic concept of pharmacoeconomics so that participants can review pharmacoeconomic literature and understand when an evaluation is appropriate in the selection of essential medicines.

Questions and Comments

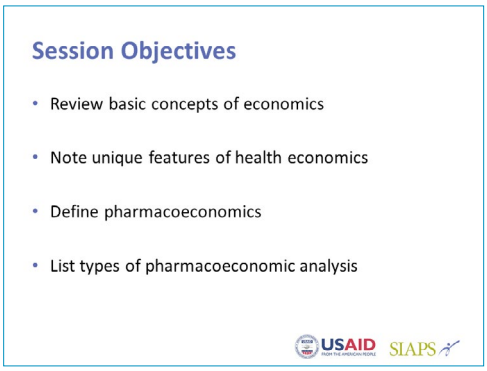
- Take a few minutes during the question and comments section to determine whether participants have had any previous pharmacoeconomic training or attempted to use pharmacoeconomic principles in their daily work. Ask participants:
  - Did you receive pharmacoeconomics training during your undergraduate training?
  - Have you attended any pharmacoeconomics continuing professional development workshops/trainings?
  - Have you used pharmacoeconomics principles in research?
  - Have you had continuing education or in-service training on pharmacoeconomics?
  - Have you found the need to use pharmacoeconomic principles in your daily work or research activities?
  - Have you read any articles related to pharmacoeconomics?

The information gathered can be used to enhance subsequent sessions. These questions give an idea about participants' levels and degrees of pre-existing knowledge and experience. This knowledge can be kept in mind while making subsequent presentations, and the facilitator can tap into specific participants' work/experiences at appropriate times to enhance interactive discussion and experiential learning.

MODULE 1 : INTRODUCTION TO PHARMACOECONOMICS AND ECONOMIC EVALUATION

Notes to the instructor

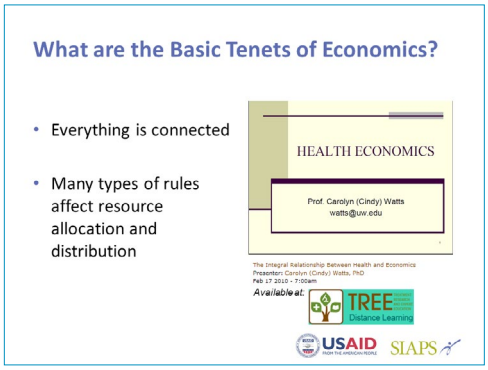
Time Allocation:		**60 min**
	Economic principles	20 min
	Introduction to pharmacoeconomics	20 min
	Pharmacoeconomics as a tool to complement HTA	20 min
Preparation:	Read through the curriculum guide and corresponding slide deck	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	



Session Objectives

The purpose of this session is to:

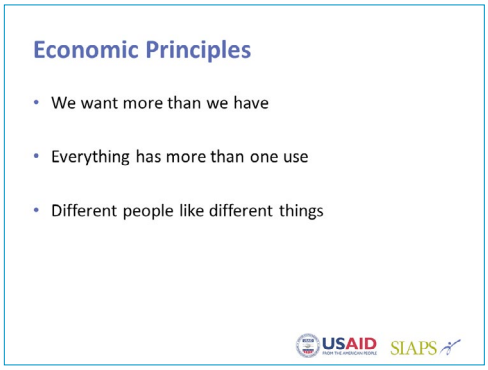
- Review basic concepts of economics
- Note unique features of health economics
- Define pharmacoeconomics
- List types of pharmacoeconomic analysis



Basic Concepts of Economics

The basic belief of an economist is that everything in life is connected and that many types of rules affect resource allocation and distribution.[4]

With regard to resource allocation, the principles of economics state that humans want more than they have, every resource has more than one use, and different resources appeal to different people.[4]



General Observations about Economic Realities

- "Cost" and "value" often have little meaning unless we know what alternative use the resources could be put to (opportunity costs)
- Most economic decisions are characterized by uncertainty before and (sometimes) after the decision (risk aversion)
- Many economic decisions are made subconsciously (implicitly) rather than consciously (explicitly)

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General Observations about Economic Realities

The true cost of a resource that is purchased or used can be judged by its opportunity cost (i.e., what was given up to obtain the item). For example, a medical doctor might work overtime in an emergency room. The opportunity cost is the time that person could have spent writing up his or her thesis for a postgraduate degree. We always give up something to get something else.

Opportunity Cost

- Definition: The value of the best-forgone option; the value of the "next best option".

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Opportunity Cost

Opportunity cost can be defined as the value of the best-forgone option.[5,6] In other words, it is the value of the best alternative that was given up by taking another course of action.[7] Regardless of the decision that is made, there is a certain degree of risk that accompanies that decision. Most economic decisions are made without thinking too deeply about it (i.e., the decision is made subconsciously rather than consciously).[4]

Economics vs. Health Economics

	Economics	Health Economics
Resources	Economics is the study of how societies allocate their inherently scarce resources to satisfy the demands of their citizens.	Health economics focuses on how these scarce resources are allocated to produce health and provide the medical services needed.
Markets	Economics posits that private markets are generally an "efficient" mechanism for allocating resources, maximizing the benefits received from the limited resources.	In the case of health care markets, a number of special circumstances occur that require special interventions and adaptations to improve efficiency.

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Economics vs. Health Economics

The unique features of health economics are related to how resources are allocated in a market. While economics is the study of how societies allocate their inherently scarce resources to satisfy the demands of their citizens, health economics focuses on how these scarce resources are allocated to produce health and provide the medical services needed.[4]

In economics, private markets are generally considered an "efficient" mechanism for allocating resources and maximizing the benefits of limited resources. However, in the case of health care markets, circumstances occur that require special interventions and adaptations to improve efficiency.[4]

Economic Perspective: Premise and Implications

- **Key Behavioral Premise:**
  - Individuals act to maximize their happiness (i.e., well-being or "welfare") by choosing among economic goods (or allocating resources so as to best satisfy wants); economists refer to this as maximizing "**utility**."
- **Important Implications:**
  - Health can be thought of as an economic good. Individuals have a demand for health, but the producers/suppliers of health include both the individual and medical care providers.
  - Health is not the only good; people are willing to trade off some health for other pleasures.

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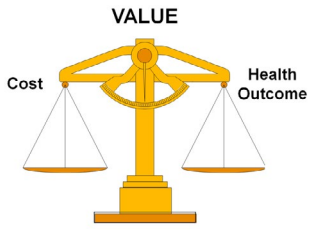
Premise and Implications of the Economic Perspective

Individuals act to maximize their happiness by choosing among economic goods (or allocating resources to best satisfy wants). Economists refer to this as maximizing "utility." Later, we will learn about CUA as a type of pharmacoeconomic analysis. Health can be thought of as an economic good.[4]

Individuals have a demand for health, but the producers/suppliers of health include both the individual and medical care providers. People are willing to trade off some health for other pleasures.[4]

Economics: Trade-offs and Balance



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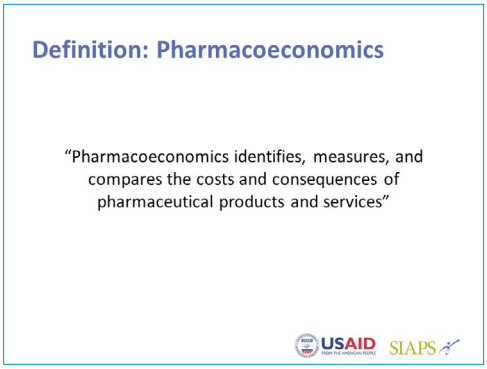
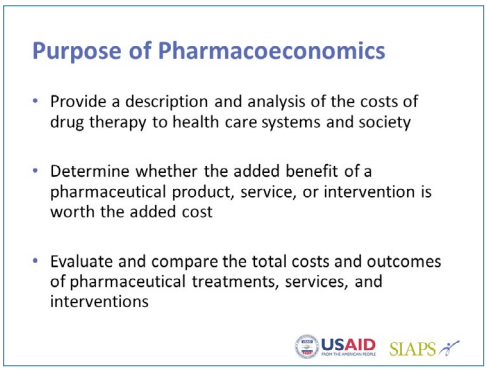
Economics: Trade-off and Balance

Pharmacoeconomics helps us determine whether the additional benefit a product or service provides is worth the additional cost. In so doing, we allocate scarce resources more efficiently.[5]



Definition of Pharmacoeconomics

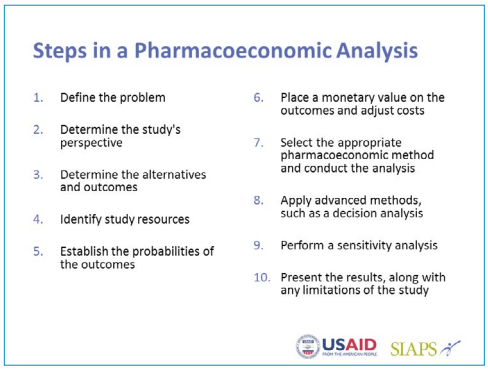
"Pharmacoeconomics identifies, measures, and compares the costs and consequences of pharmaceutical products and services."[5]



Purpose of Pharmacoeconomic Analysis

The purpose of pharmacoeconomic analyses is to:[5]

- Provide a description and analysis of the costs of drug therapy to health care systems and society
- Determine whether the added benefit of a pharmaceutical product, service, or intervention is worth the added cost
- Evaluate and compare the total costs and outcomes of pharmaceutical treatments, services, and interventions



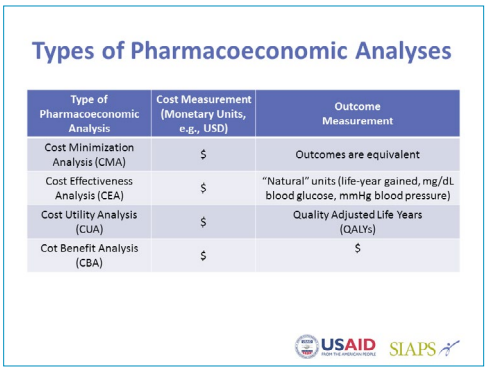
A well-designed pharmacoeconomic analysis will involve the following steps:[8]

1. Defining the problem
2. Determining the study's perspective
3. Determining the alternatives and outcomes
4. Identifying study resources
5. Establishing the probabilities of the outcomes
6. Placing a monetary value on the outcomes and adjusting costs
7. Selecting the appropriate pharmacoeconomic method and conducting the analysis
8. Applying advanced methods, such as a decision analysis
9. Performing a sensitivity analysis
10. Presenting the results, along with any limitations of the study

First, the problem or research question needs to be defined. For example, you might want to compare the cost-effectiveness of the standard treatment and of adding a new medicine to a formulary for the management of diabetes mellitus. The perspective of the study (whose cost) must be set to determine what costs to include in the study (module 4). The alternatives that will be compared to the new diabetes medicine must be defined (e.g., the treatment can be compared to current/standard treatment, lifestyle modification, or a combination of alternatives). Once the alternatives are determined, the outcomes of the study must be outlined (module 3). Outcomes might include quality of life outcomes; morbidity; or clinical outcomes, such as degree of glycemic control as measured by HbA1c (glycosylated hemoglobin). Probabilities for outcomes and costs will be required in pharmacoeconomic calculations, regardless of the type of analysis selected, and systematic reviews, meta-analyses, and other types of studies will be useful in comparing efficacy- and safety-related

outcomes. Once estimates are obtained for costs, from the perspective that was decided on, the total cost for each alternative must be determined. This might include medicine, diagnostic, and other costs (e.g., cost of productivity loss) as defined in module 4. Additional steps that might be required are adjustment of costs for differential timing (module 4).
A pharmacoeconomic method must be selected and analysis conducted following the appropriate rules and methodology. Sometimes advanced pharmacoeconomic methods, such as decision analysis or Markov model, might be required (module 9). After the analysis, a sensitivity analysis (module 4) will have to be employed to determine whether the results are robust to changes in estimates. Finally, the analysis must be presented, keeping limitations of the approach in mind.

Depending on the context of the problem, it may be appropriate to apply one of the following four basic types of pharmacoeconomic analysis.



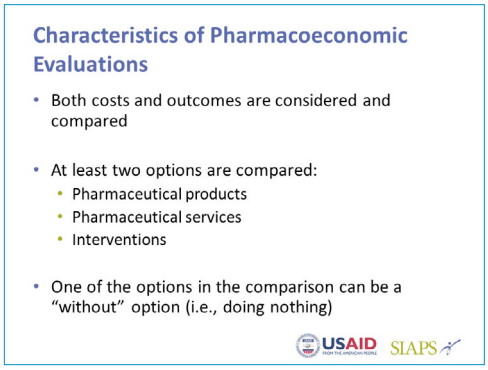
Types of Pharmacoeconomic Analysis

There are four basic types of pharmacoeconomic analysis. In each type, costs are measured in monetary units. The difference lies in how the outcomes are handled. The four types of pharmacoeconomic analysis are:[5,9]

1. *Cost Minimization Analysis (CMA):* Outcomes of two alternatives are identical, so it is only necessary to compare the costs.
2. *Cost Effectiveness Analysis:* Outcomes in a CEA are presented in natural health units, such as life years saved, blood pressure, blood glucose, successful treatment, cure, forced expiratory volume (FEV) (for asthma control), or symptom-free days. A single outcome must be chosen for a CEA.
3. *Cost Utility Analysis:* Like a CEA, a CUA uses natural units, usually life years saved, and adjusts them for the quality of life patients experience in those added life years.
4. *Cost Benefit Analysis (CBA):* A CBA converts all outcomes to monetary units and can combine multiple outcomes in one analysis.

Each analysis will be explained in detail in modules 5–8.

Question: The facilitator can ask participants to give examples of interventions they think could be compared in a pharmacoeconomic analysis.

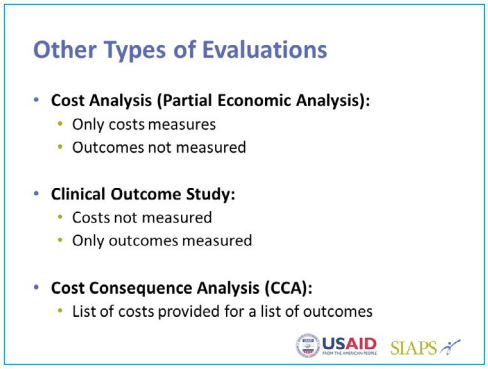


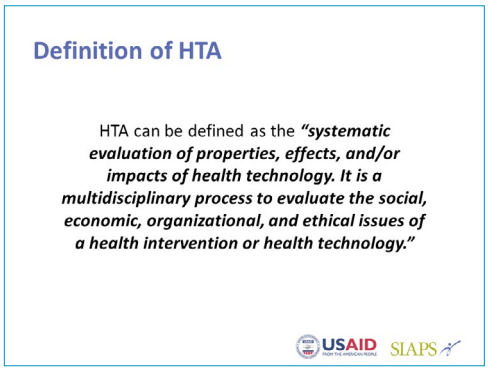
Characteristics of Pharmacoeconomic Evaluations

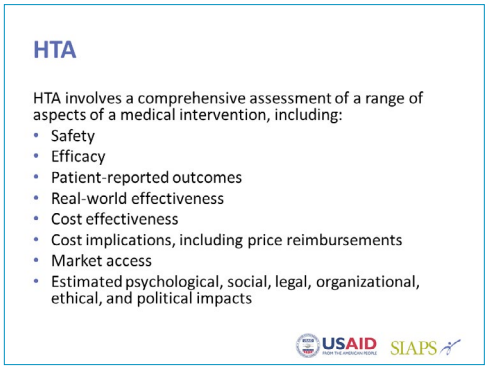
Both costs and outcomes are considered and compared in a pharmacoeconomic evaluation. At least two options are compared, for example:[5]

- Pharmaceutical products
- Pharmaceutical services
- Interventions

One of the options in the comparison can be a "without" option (i.e., comparing a treatment to doing nothing).[5]







Other Types of Evaluations

There are other types of evaluations linked to economics and pharmacoeconomics that are not considered full economic or pharmacoeconomic evaluations. These include:[5]

- Cost analysis (partial economic analysis)
- Clinical outcome study
- CCA

In a cost analysis, also known as a partial economic analysis, only costs are measured, not outcomes. In a clinical outcome study, only health outcomes are measured and not costs. In a CCA, a list of costs is provided for a list of health outcomes. In a CCA, all outcomes are listed with the corresponding total cost. That differs from a CEA, where a single outcome is studied, while in a CCA, several outcomes are listed.[5]

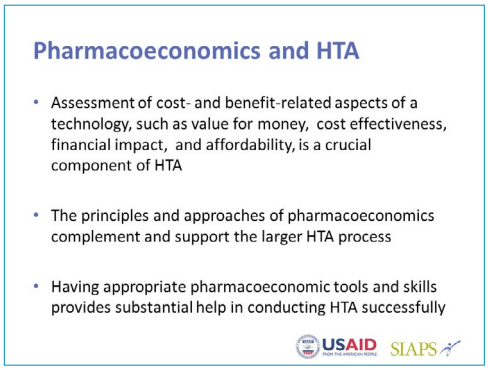
Resources: The International Society for Pharmacoeconomic and Outcomes Research

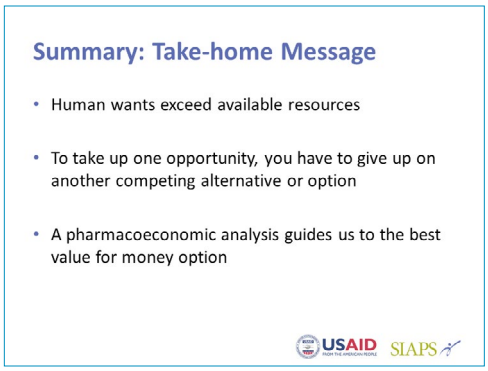
ISPOR (www.ispor.org) is a global nonprofit professional society founded in 1995. ISPOR advances the policy, science, and practice of pharmacoeconomics (health economics) and outcomes research (the scientific discipline that evaluates the effect of health care interventions on patient well-being, including clinical, economic, and patient-centered outcomes). ISPOR provides resources for health economics and outcomes research and its membership comprises researchers, academicians, decision and policy makers, consultants, payers, and patient representative groups.[10]

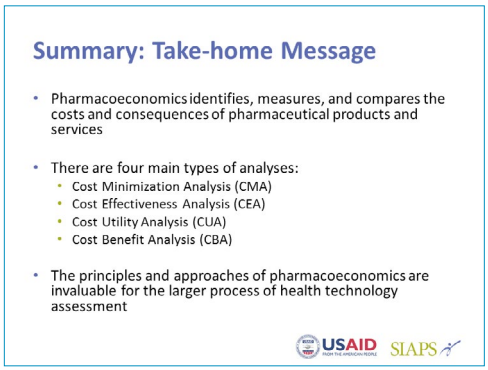
Pharmacoeconomics as a Tool to Complement HTA

HTA is the "systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology."[11] HTA may be used to assess technologies that are new or those that are old and already in use. It is important to stress that health technology relates not only to medicines but also to medical devices, diagnostic medical or surgical procedures, health services and organization, and prevention and rehabilitation. HTA is often regarded as the "bridge between research and decision making."[12]

The purpose of HTA is to provide evidence-based information and input to assist in making decisions about health care prioritization, policies, and practice. With universal health coverage high on the global health agenda, governments of many LMICs have pledged to increase health investments in the scale-up of essential health services to meet the needs of their people. This has led to the recognition of HTA as a necessary tool for setting priorities.[13]







References for the slides used in this module

HTA should be a systematic, transparent, unbiased, and robust process that aims to inform safe and effective health policies that are patient focused and seek to achieve the best value for the money invested.[12]

HTA can facilitate shaping a reimbursement or benefit packages; developing best practices and standard treatment guidelines (STGs); providing guidance on how best to organize service provisions; making decisions on market licensure of a technology; investing in further research; and informing investment decisions, including acquisition of new technologies.[14,15] It can also inform decisions to discontinue ineffective or cost inefficient technologies.

HTA is typically a comprehensive process and involves the assessment of a range of aspects or domains of a medical technology, including:[16]

- Description of the technology
- Burden of disease
- Safety
- Efficacy
- Patient-reported outcomes
- Real-world effectiveness
- Cost effectiveness
- Cost implications, including price reimbursements
- Market access
- Estimated psychological, social, legal, organizational, ethical, and political impacts

Because assessing cost- and benefit-related aspects of a technology, such as value for money, cost effectiveness, financial impact, and affordability, is a crucial component of HTA, the principles and approaches of pharmacoeconomics complement and support the larger HTA process. Therefore, having appropriate pharmacoeconomic tools and skills provides substantial help in conducting HTA successfully.

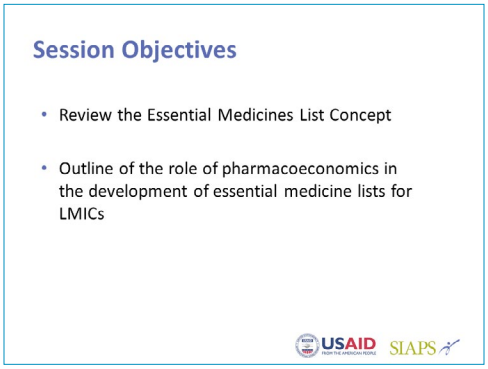
Take-home Message

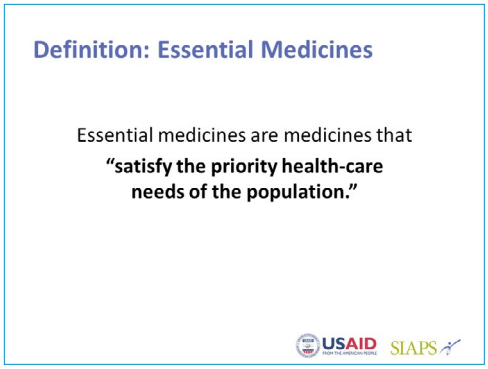
The principles of economics state that human wants exceed available resources. In addition, to take up one opportunity, you must give up a competing alternative or option. This is regarded as an opportunity cost. Every decision in life has a tradeoff. In health care, we have a limited number of resources available and usually have to choose one medical intervention over another. A pharmacoeconomic analysis may be required to guide us to the best value for money option. Pharmacoeconomics identifies, measures, and compares the costs and consequences of pharmaceutical products and services.[5] In all types of analyses (CMS, CEA, CUA, and CBA), the input measure is cost, but the analyses differ in how the outcomes are measured. The principles and approaches of pharmacoeconomics are invaluable for the larger process of HTA.

MODULE 2 : ESSENTIAL MEDICINES LISTS AND THE ROLE OF PHARMACOECONOMICS

Notes to the instructor

Time Allocation:		**2 hrs**
	WHO and essential medicines selection	20 min
	Role of pharmacoeconomics in the selection of essential medicines	10 min
	Group activity	1.5 hrs
Preparation:	Read through the curriculum guide and corresponding slide deck	
	Download and print the latest WHO Model List of Essential Medicines for an interactive question-and-answer session during the lecture	
Presentation:	Prior to presenting the module, allow time for the following questions: ▪ How many participants work in the selection of medicines for their country's EML and formulary? ▪ Are participants engaged in selecting medicine lists for health insurance companies?	
Resources:	Flip chart/white board for group activity discussion	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	





Session Objectives

The purpose of the **Essential Medicines Lists and the Role of Pharmacoeconomics** module is to:

- Review the EML concept for LMICs
- Outline of the role of pharmacoeconomics in the development of essential medicines lists for LMICs

The details regarding pharmacoeconomic concepts and the methods employed in pharmacoeconomic analyses will be explained in detail in the sessions to follow.

Definition and Rationale of Essential Medicines

WHO defines essential medicines as medicines that "satisfy the priority health-care needs of the population."[17]

Selection of Essential Medicines

The selection of essential medicines is one of the core principles of a national drug policy because it helps to set priorities for all aspects of the pharmaceutical system. This global concept can be applied in any country, in both the private and public sectors, and at different levels of the health care system.[17]

According to WHO: "Essential medicines are intended to be available within the context of functioning health systems at all times:

- in adequate amounts,

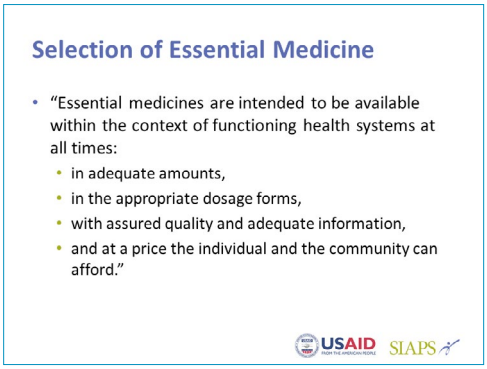
- in the appropriate dosage forms,
- with assured quality and adequate information,
- and at a price the individual and the community can afford."[17]

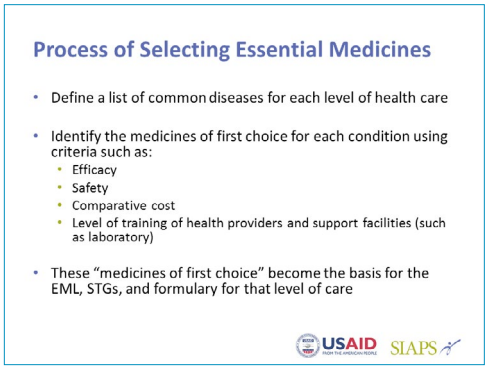
According to WHO, essential medicines "are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness."[17]

Relative cost effectiveness is a major consideration when choosing medicines within the same therapeutic category. For example, let's assume two steroid inhalers are available on the market for the management of asthma, and both reduce asthma symptoms. However, the higher priced product provides more symptom-free days, leading to fewer emergency room visits. Emergency room visits cost additional money. Although one product costs more, it provides additional value/savings by reducing the number of emergency room visits. Therefore, when comparing medicines, the overall cost of treatment (not just the cost of the medicine alone) must be calculated and compared to the treatment with an alternative medicine for the same condition.[17] Cost effectiveness is a type of pharmacoeconomic analysis and will be explained in detail later in this course.

Pharmacoeconomics is only one part of the decision making process.[5] In addition to costs, affordability, and value for money, the selection of items for medicine formularies or EMLs should be based on public health relevance, efficacy, and safety of the medicine.

In this course, apart from understanding how pharmacoeconomics is used in the selection of essential medicines and assessing the value for money a medicine or product can offer, we will learn about budget impact analyses and how they are used to assess affordability.





WHO Model List of Essential Medicines and Model Formulary

The WHO Model List of Essential Medicines consists of:[17]

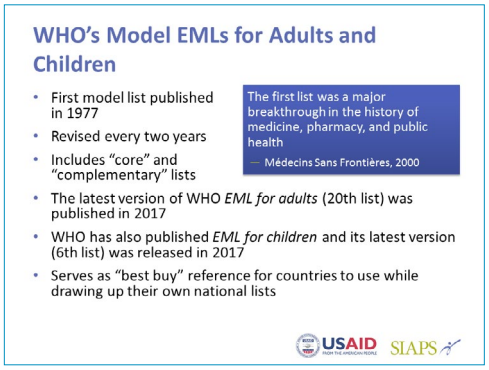
- A core list
- A complementary list

The core list is a list of minimum medicine needs for a basic health care system that is based on efficacy, safety, and affordability. The complementary list presents essential medicines for priority diseases for which specialized diagnostic or monitoring facilities, specialist medical care, and/or specialist training are needed. The complementary list can also include medicines based on consistent higher costs or less attractive cost effectiveness in a variety of settings.[17] For example, digoxin is indicated as a core medicine for heart failure in adult patients, while dopamine appears on the complementary list.

Question Session: To increase active learning and participation, the facilitator should ask participants:

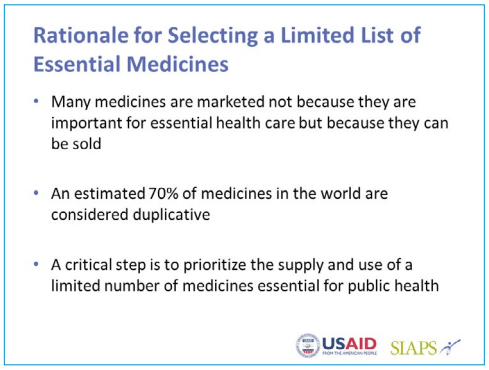
- How often does WHO update the Model EML?
- Which editions are the latest adult and pediatric lists and when were they published?

Note to facilitator: If possible, bring copies of the WHO Model EML to share with participants during the session.



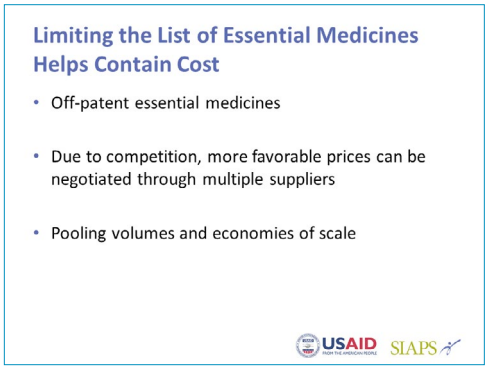
The WHO Model EML can be used as a starting point for countries as they develop their own EMLs.[17]

In 1995, the WHO Expert Committee on the Use of Essential Drugs recommended that WHO develop a Model Formulary that would complement the WHO Model List of Essential Medicines. The Model Formulary adds indications, usage, and other information to the EML. It was thought that such a Model Formulary would be a useful resource or starting point for countries wishing to develop their own national formulary or STGs.[17]



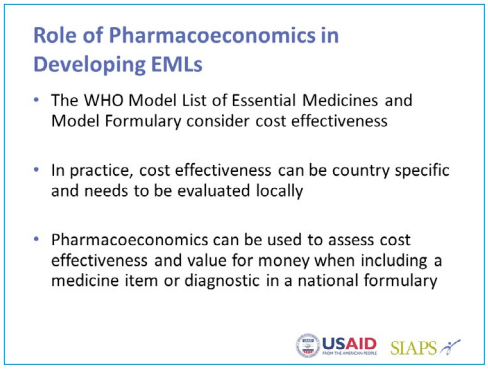
Rationale for Selecting a Limited List of Essential Medicines

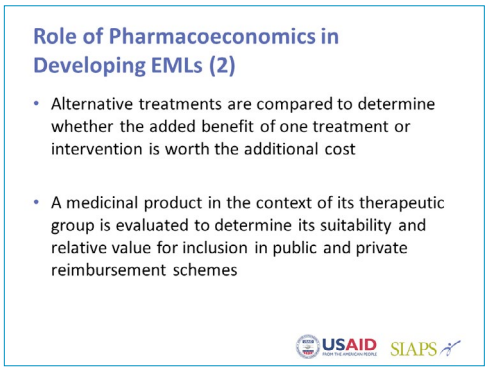
Many medicines are marketed not because they are important for essential health care, but because they can be sold. An estimated 70% of medicines in the world are considered duplicative. Therefore, a critical step is to prioritize the supply and use of a limited number of medicines that are essential for public health. This is the main rationale for developing an EML.[18]



Limited List of Essential Medicines Helps Contain Cost

Most of the medicines in an EML are off-patent and relatively inexpensive. Essential medicines are available from multiple suppliers, and more favorable prices can be negotiated through competition. By narrowing the list of medicines to essential ones, larger volumes of these selected medicines are likely to be procured, providing opportunities for economies of scale and improved pricing.[18]





Role of Pharmacoeconomics in Developing Essential Medicines Lists

Because of limited resources, governments in LMICs may limit procurement of medicines for the public health sector only to items listed on the EML. With the tendency toward universal health coverage, countries may ensure that only medicines listed on the EML are included as pharmacy benefits in a social health insurance program.

In developed countries, health insurance entities use similar lists (usually stipulated by the insurance companies) to limit pharmaceutical reimbursements to medicines on these specified lists or formularies.

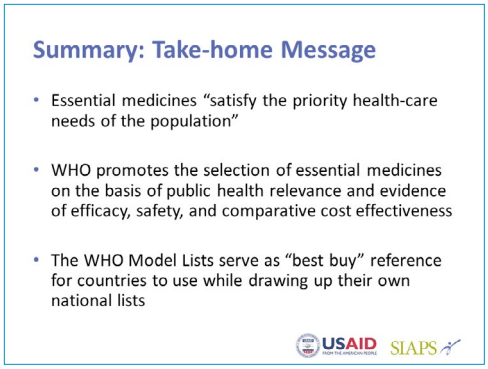
In summary, a medicinal product in the context of its therapeutic group is evaluated to determine its suitability and relative value for inclusion in public and private reimbursement schemes.

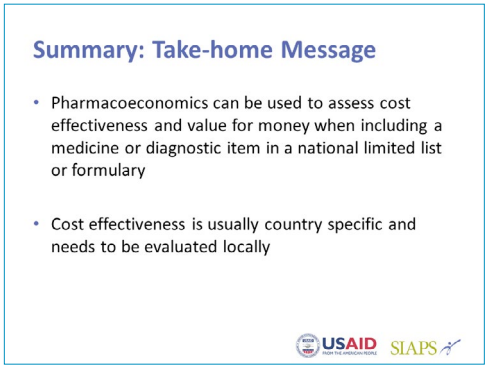
This assessment provides prescribers with additional information on the therapeutic value of the medicine. In pharmacoeconomics, alternative treatments are compared to determine whether the added benefit one treatment or intervention offers (i.e., fewer side effects, better efficacy, shorter treatment duration, less invasive procedure) is worth the higher cost.

The WHO Model List of Essential Medicines and Model Formulary consider cost effectiveness in determining whether to include an item on the list and formulary. In practice, cost effectiveness can be country specific and needs to be evaluated within the context of the country.[17]

This course provides a basic understanding about pharmacoeconomics—a tool that can be used by countries to assess cost effectiveness and value for money by including a product on a national EML or formulary.

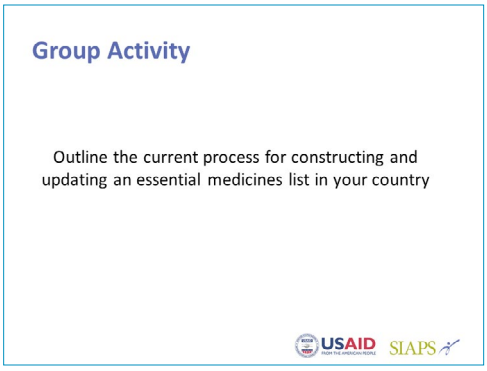
The addition of the first-line antiretroviral triple fixed dose combination tablet, which contains 300 mg tenofovir, 200 mg emtricitabine, and 600 mg efavirenz, is an example of an addition of a formulation to an EML to enhance cost effectiveness in the treatment of patients. The single tablet reduced pill burden, encouraged adherence, simplified procurement and supply chain processes, and reduced overall cost with no impact on efficacy or safety.[19] In short, a transparent selection was made based on evidence and cost effectiveness. Other examples of how pharmacoeconomic principles were used in the selection of essential medicines in South Africa by the National Essential Medicines List Committee are included in annex C.[20]





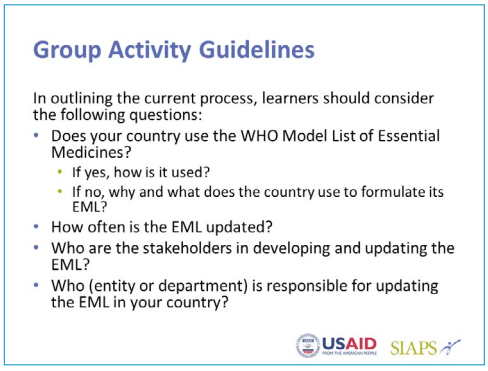
Take-home Message

In this module, we learned that essential medicines "satisfy the priority health-care needs of the population."[17] WHO promotes the selection of essential medicines based on public health relevance and evidence of efficacy, safety, and comparative cost effectiveness.



Group Activity

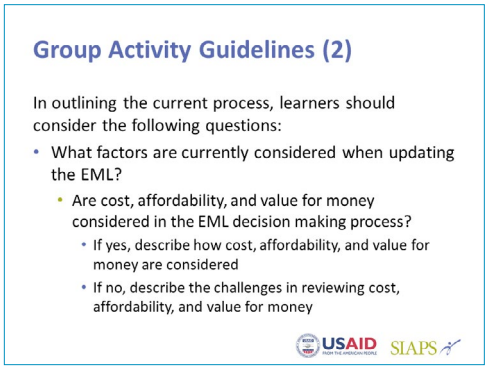
Objective of the Group Activity: To encourage learners to think about how the essential medicines process can be strengthened in country and to determine the extent to which pharmacoeconomics is used in the decision making process. In groups, participants should discuss and outline the current process for developing and maintaining an EML in their country.



Group Activity Guidelines

In outlining their current processes, participants should consider the following:

- Does your country use the WHO Model List of Essential Medicines?
  - If yes, how is it used?
  - If no, why and what does the country use to formulate its EML?
- How often is the EML updated?
- Who are the stakeholders in developing and updating the EML?
- Who (entity or department) is responsible for updating the EML in your country?
- What factors are currently considered when updating the EML?
  - Are cost, affordability, and value for money considered in the EML decision making process?
    - If yes, describe how cost, affordability, and value for money are considered
    - If no, describe the challenges in reviewing cost, affordability, and value for money



References for the slides used in this module

Facilitator Guidelines

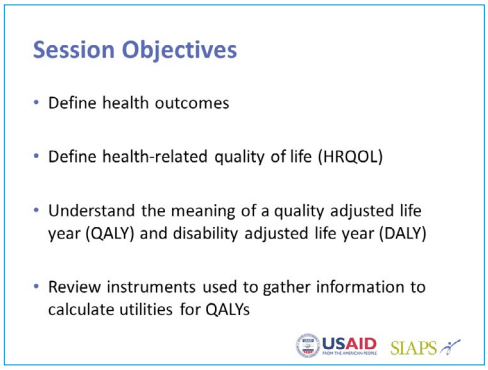
- If applicable, group participants by country or in pairs (for countries with single participants). Attempt to mix public- and private-sector participants.
- After group discussion, allow each group to provide feedback using the questions noted above.
- The facilitator should focus on summarizing for each country:
  - Governance structures for the selection of essential medicines in each country (e.g., a clear process set by the Ministry of Health for the selection of essential medicines in the country)
    - Regular review of the EML to ensure that essential medicines of the highest quality, efficacy, safety, and affordability have been included
    - Stakeholders in the selection of essential medicines for a country, such as:
  - STG committees, including expert clinicians appointed by the Ministry of Health to summarize STGs for each level of care (e.g., primary health care, district, provincial, and national levels) within the country. The medicines of first choice for STGs should be included in the EML so that medicines recommended in the STGs and included in the EMLs are consistent.
    - From a pharmacoeconomics perspective:
  - Is the country already using pharmacoeconomic methods?
  - What are the challenges experienced in incorporating pharmacoeconomic methods?
    - Limited awareness of and attention to pharmacoeconomic methods
    - Lack of pharmacoeconomics expertise

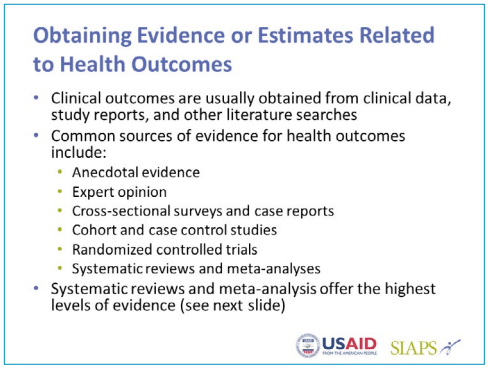
The facilitator should reassure participants that this course will provide a basic understanding of pharmacoeconomic concepts for participants to use in the selection of essential medicines.

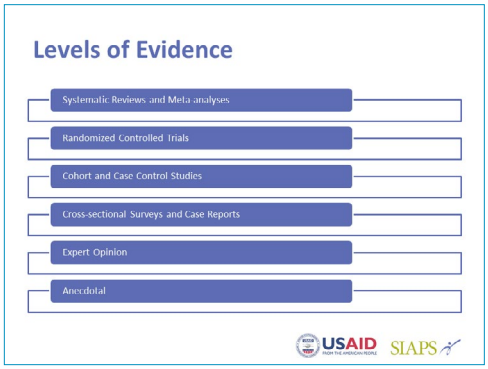
MODULE 3 : HEALTH OUTCOMES

Notes to the instructor

Time Allocation:		**3 hrs**
	Introduction and examples of health outcomes	10 min
	Health-related quality of life	20 min
	Quality adjusted life years	1 hr
	Group activity and report back	1.5 hrs
Preparation:	Read through the curriculum guide and corresponding slide deck	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	







Session Objectives

The purpose of this session is to:

- Define health outcomes
- Define health-related quality of life (HRQOL)
- Understand the meaning of a QALY and disability adjusted life year (DALY)
- Review instruments used to gather information to calculate utilities for QALYs

Introduction

Every medical product or intervention has an outcome of its use. The outcomes of a medicinal product or intervention include both benefits (positive effects) and adverse effects (negative effects). In a pharmacoeconomic analysis, the cost of acquiring the treatment or intervention is measured against the outcome the treatment or intervention provides. In this module, we review health outcomes with a focus on how outcomes are measured and fit into a pharmacoeconomic analysis.

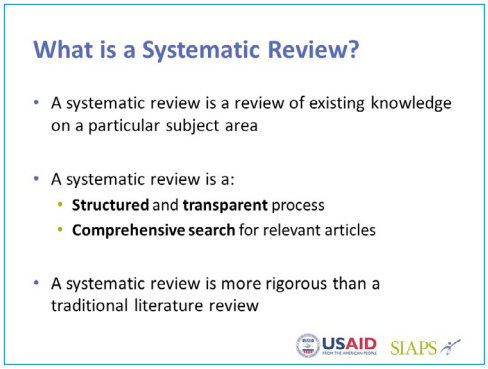
Examples of Health Outcomes

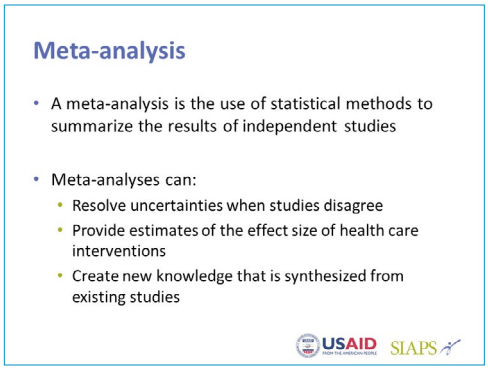
The input measure in any of the four basic pharmacoeconomic analyses is cost. The analyses differ in how the outcomes are measured and handled. Examples of output or health outcome measures included in pharmacoeconomic analyses include number of cases cured/number of successful outcomes; number of deaths; number of symptom-free days; percentage drop or increase in a clinical parameter (e.g., reduction in tumor size); or HRQOL achieved in the patient after use of the product or service.[5]

Where Do We Obtain the Evidence or Estimates Related to Health Outcomes Associated with a Medicinal Product or Service?

Health care publications are important resources in obtaining estimates of health outcomes related to medical products and services.

Clinical outcomes are usually obtained from clinical databases, randomized control trials, or literature searches. Outcomes can also be





assumed, estimated, or collected through survey research. Experts can also be asked to comment on assumed or estimated outcomes.

There are several levels of evidence regarding estimates for health outcomes. From least precise to most precise, levels or types of evidence include anecdotal evidence, expert opinion, cross-sectional surveys and case reports, cohort and case control studies, randomized control trials, and systematic reviews.

Anecdotal evidence could be something a colleague told you. Expert opinion refers to a consensus of experience from respected scientific professionals. Cross-sectional surveys refer to a survey of a sample of the population at a cross section or point in time. Case reports can be compiled for individual patients or a group of patients. Cohort studies follow patients prospectively (from present to future) for specific outcomes. Case control studies match cases to controls to determine the differences that exist between two groups of patients. A randomized control trial randomly allocates patients to treatment or control.

A systematic review is a structured, transparent, comprehensive literature search of existing knowledge on a subject area with clear inclusion and exclusion criteria. A systematic review is usually conducted to obtain summary measures for health outcomes linked to a medical intervention or medicine.[21, 22]

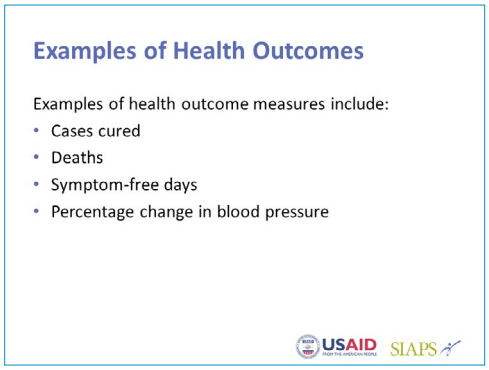
Meta-analyses, which use statistical methods to summarize the results of independent studies, can resolve uncertainties when studies disagree, provide estimates of the effect size of health care interventions, and create new knowledge that is synthesized from existing studies. The steps in a meta-analysis are similar to those in a systematic review: statement of purpose, data definition, data extraction, data analysis, and interpretation of results. An analysis is then performed to obtain one summary measure as an estimate of the effect size of the health care intervention that was reviewed.[22]

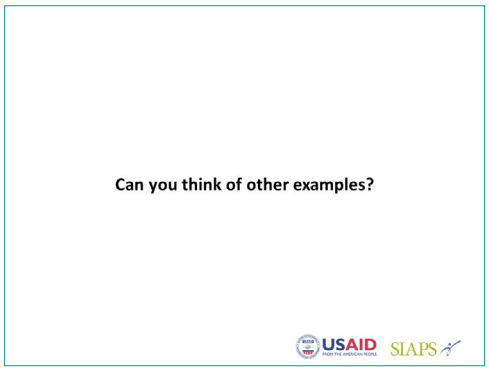
Types of Pharmacoeconomic Analysis

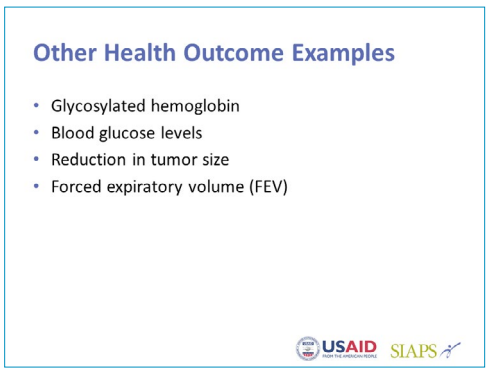
There are four basic types of pharmacoeconomic analysis. In a CMA, the outcomes produced by the products or interventions compared are assumed to be equal. In a CEA, the difference in outcomes produced by two or more products is compared against the difference in costs between the products and services. In a CBA, a monetary unit is attached to the outcome achieved. Finally, in a CUA, which is a subset of a CEA, the health outcomes are viewed in terms of quality of life (QALYs or DALYs) achieved by the product or intervention.

Health outcomes from a product or intervention tested in a randomized control trial usually differ from those achieved when the product or service is used in a heterogeneous group of people in everyday life.

Examples of Outcomes in the Four Basic Pharmacoeconomic Analyses







In a CMA, two generic glucose-lowering products can be compared. Because the generic products produce "identical" outcomes (i.e., the generics are assumed to drop blood glucose by the same percentage in patients with all other factors being equal), the products are compared only by price. Another example of a CMA is the administration of the same product in different settings (e.g., the administration of heparin for blood thinning in an inpatient vs an outpatient setting). The same product is administered in different settings to achieve the same level of outcome in reducing blood coagulation. However, the costs incurred in the outpatient and inpatient settings might differ. The outcome achieved, International Normalized Ratio, may be assumed to be equivalent in both settings.

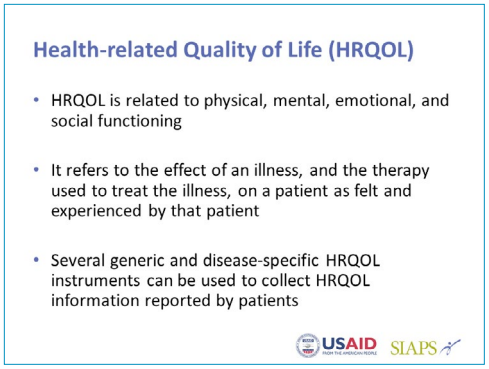
In a CEA, two treatment alternatives are compared by computing an incremental cost effectiveness ratio (ICER). The cost difference in the ICER is calculated as part of the numerator of the ICER, while the difference in outcomes constitutes the denominator. A CEA could be used to calculate the difference in average glycosylated hemoglobin percentage achieved by two glucose lowering agents (e.g., insulin and metformin). The outcome in question could be the percentage glycosylated hemoglobin (long-term glucose control) obtained with each item.

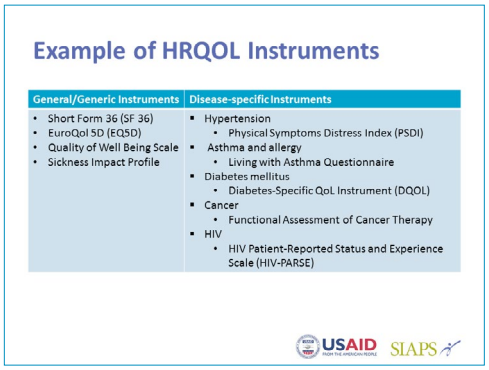
In a CUA, the studied outcome is a combination of the length of life (life expectancy) and the quality of life obtained in the years that the product or service extended the patient's life. For example, a cancer medicine might increase a patient's life expectancy by three years. The CUA helps attach a quality of life utility to the years of life gained. This utility is a combination of morbidity and mortality. The QALY and how it is calculated will be explained in detail later in this module.

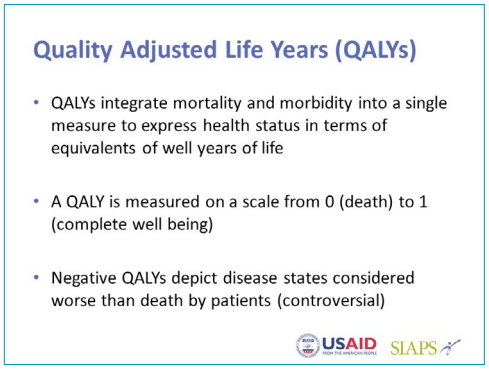
In a CBA, the outcome of a program could be the reduction in wait time for a health service through the implementation of a mail order pharmacy at a public service clinic. Wage rate calculations can be used to attach a monetary unit to the outcome (i.e., number of hours saved waiting in line at the clinic could be valued in terms of hourly wage rate because the mail order pharmacy allowed the patient to work rather than wait in line.

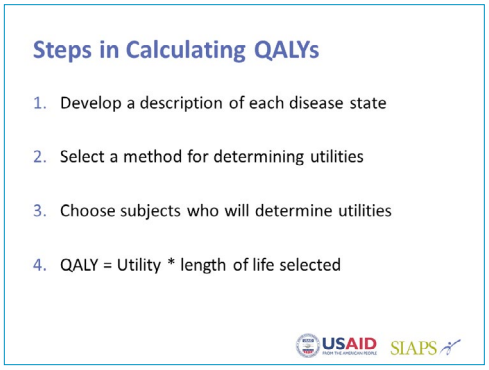
Note to Facilitator: Facilitators should reassure participants that concepts will become much clearer in the subsequent modules as the four methods of analysis are explained in detail.

Ask participants to discuss and provide examples of other research questions for a pharmacoeconomic analysis. Participants can also be encouraged to conduct literature searches to review the pharmacoeconomic analyses conducted on health outcomes.









Health-related Quality of Life

HRQOL is related to physical, mental, emotional, and social functioning.[23] It refers to the effect of an illness and the therapy used to treat that illness as felt and experienced by the patient.[5] Several instruments can be used to report HRQOL or patient-reported outcomes. Some HRQOL instruments are generic, while others offer disease-specific questions. Later we will look at QALYs, which differ from other HRQOL assessments in that QALYs provide a single index measurement that incorporates quantity of life in addition to HRQOL.[24]

Generic instruments include short-form health surveys, such as SF 36, EQ5D, Quality of Well Being Scale, and Sickness Impact Profile (annex D).[25] Disease-specific instruments exist for hypertension, cancer, asthma, and HIV/AIDS, among other conditions (annex E).[5]

The EQ5D is a relatively short instrument that covers mobility, self-care, daily activities, pain/discomfort, and anxiety/depression and is not specific to a condition. Patients are generally not asked to link to a specific disease or recall over a period of time. The Living with Asthma Questionnaire, a disease-specific instrument, asks questions that specifically relate to the disease state, such as "I check all the time that I have my inhaler with me", which are then linked to a score based on responses.[25]

Participants can be encouraged to research and review instruments.

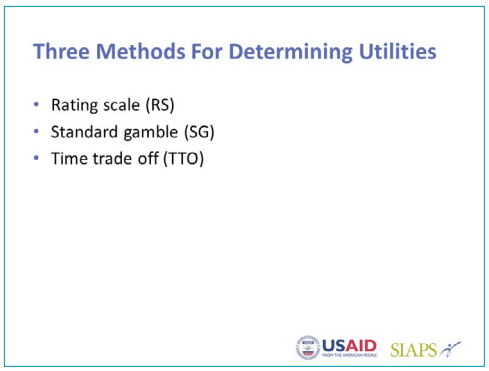
Quality Adjusted Life Years

QALYs measure the usefulness or utility of a health state and the quality of life lived in the health state. A QALY helps us present the value of a health outcome. The QALY assumes that health is a function of length of life (quantity) and quality of life, and it combines these values into a single index number. In other words, QALYs integrate mortality and morbidity into a single measure to express health status in terms of equivalents of well years of life. A QALY is calculated by multiplying the utility value (how we obtain utility values will be described later in this module) associated with a health state by the years lived in that health state. A year of life lived in perfect health is worth 1 QALY (1 year of life × 1 utility value). A QALY is measured on a scale from 0 (death) to 1 (perfect health or 1 year of optimal or healthy life). Controversially, some argue that there are health states that might be worse than death (e.g., a coma), represented by a negative QALY.[5]

Use of QALYs in an analysis will be shown in module 7.

QALYs are calculated as follows:[5]

- Describe a disease state to a patient
- Select a method to determine a utility (quality of life score):
  - Rating scale
  - Standard gamble
  - Time trade off



- Ask the patient to select a utility based on the description of the disease
- Multiply the utility by the number of years selected to live in the disease state

A year of life lived in a health state of less than perfect health is worth less than 1 QALY. For example, in the cancer example mentioned earlier in this module, 3 years of life lived in a situation with utility 0.1 (e.g., bedridden cancer patient, 3 years × 0.1 utility) is assigned 0.3 QALYs. Similarly, half a year lived in perfect health is equivalent to 0.5 QALYs (0.5 years × 1 utility). Death is assigned a value of 0 QALYs, and as mentioned earlier, in some circumstances, it is possible to accrue negative QALYs to reflect health states deemed "worse than dead".

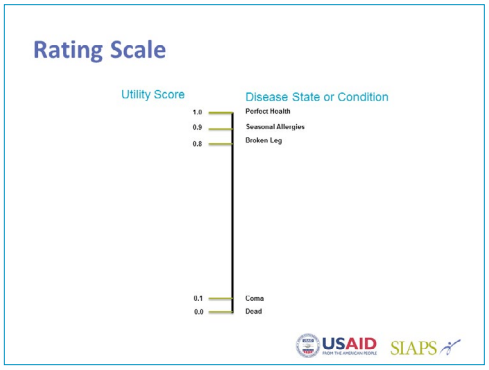
We can also compare QALYs among medicines using standard of care as a baseline measure and review the additional QALYs that will be provided with alternative competing treatments (table 1).

Table 1. Comparison of QALYS between Treatments

	Standard of Care	Alternative Medicine Treatment
Number of Life Years Gained on Treatment	3	3
Utility Value Assigned	0.5	0.7
QALY	3x0.5=1.5	3x0.7=2.1

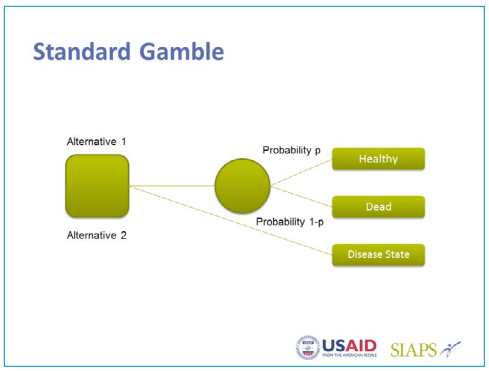
Alternative medicines can be compared to the current standard of care in terms of QALYs gained. In other words, the current standard of care is taken as the baseline, and the QALYs gained from the alternative intervention are compared to the standard of care. In the example in table 1, the standard of care provides 1.5 QALYs. Alternative treatment provides 2.1 QALYs for the same period (i.e., 0.6 QALYs more than the standard of care (2.1-1.5=0.6)).

The utility values are usually selected by the patient (respondent) using the rating scale, standard gamble, or time trade off method. The number of years to live in the disease state can be assumed or extracted from research studies and clinical trials. The standard gamble and time trade off also include time in the responses, which are used to calculate the QALY. The three methods used to determine utilities are described in detail below. QALY estimations can also be extracted from the literature.



Rating Scale

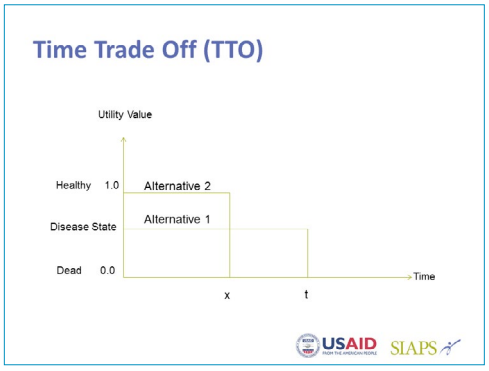
The rating scale looks like a thermometer, with increments marked on a line from 0.0 to 1.0. Several disease states can be described to a patient and the patient is asked to rank the disease states on the line. It is simple to use and can be self-administered. However, in the rating scale different treatment options cannot be offered to the patient; moreover, time is not incorporated in the instrument. Standard gamble and time trade off do incorporate time into the calculations.[5]



Standard Gamble

Using the standard gamble method, an alternative intervention to living with a chronic disease state is presented to the patient with a probability of two outcomes (death or healthy life) following the alternative intervention. The probability of death or living in a health state for a period is varied until the patient/responder finds it difficult to choose between the two options. For example, a patient might be living with a chronic heart condition. The patient is offered a surgical procedure that could return the patient to normal health. However, there is a risk that the patient could die during the surgical procedure. In the standard gamble, the probability of death is varied against the probability of healthy living for a period; for example, 99% chance the patient would continue living a healthy life after the surgery for X period vs 1% chance of death; followed by 90% chance that the patient will continue living a healthy life after the surgery vs 10% chance of death. If the patient is indifferent at 80% chance of death versus 20% change of life, then the utility score used is 0.8 (or 80%). Depending on the type of chronic condition presented, respondents would want to gamble chance of death to a different extent. For example, for a condition that is not limiting, people are less likely to choose a risky surgery and therefore the utility score would likely be higher.[5]

Standard gamble is considered the gold standard instrument for obtaining utilities. However, it is more labor intensive and can take time to administer because the concept might be difficult for patients to grasp. The other challenge that the standard gamble presents is that there are few disease states that can be "cured" with an intervention.[5]

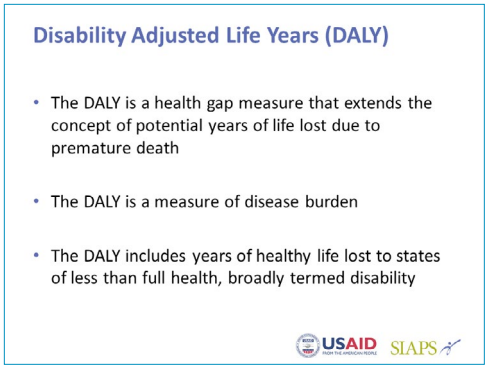


Time Trade Off

In a time trade off scenario, the patient is given two alternatives: living in a chronic disease state for a period *t* or living in a healthy state for a shorter period than time *t* (x). The time x in a healthy state is decreased until the patient is no longer willing to trade any more healthy years of life. For example, if the patient is told he or she could live with the chronic condition for 30 years but is willing to live in a healthy state for 15 years, the utility score would be x over *t,* which in this example is 15/30 or 0.5.[5]

The time trade off incorporates time into the utility score. However, like the standard gamble, it is time intensive to administer.[5]

Results produced by the three methods can differ for the same chronic disease state. Advanced modeling and calculations can be used to address these limitations.[5]

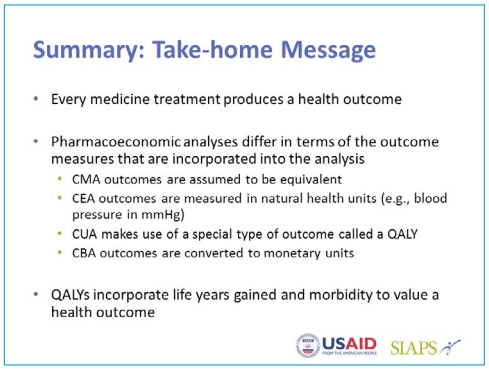


Disability Adjusted Life Years

The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death. The DALY is a measure of disease burden and includes years of healthy life lost to states of less than full health, broadly termed disability.[6] This course explains the use of the QALY because the QALY is the more frequently presented of the two outcome units in the literature.

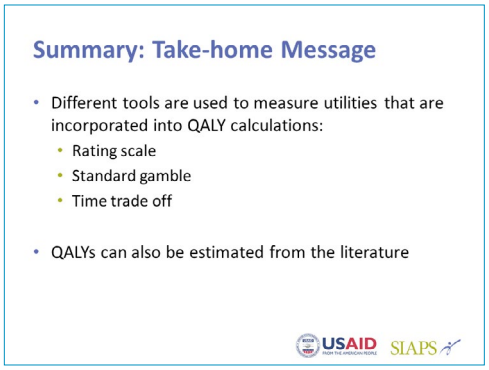
Detailed literature is available on QALYs and DALYs that can provide further insight into the concept and calculations.[26] QALYs can be calculated using the methods above, which are time consuming and the instruments would need to be administered to many respondents. QALYs can also be obtained or estimated from the literature.

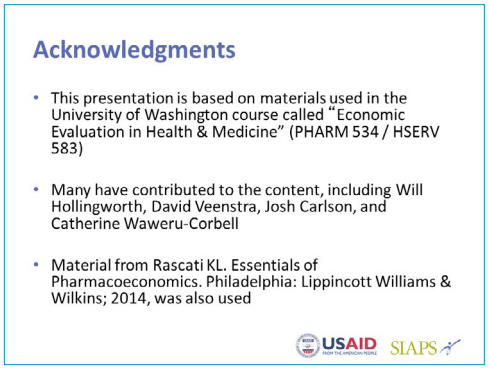
QALY calculations in a CUA are included in module 7. Suggestions for handling health outcomes that fall into the denominator of a CEA are provided in module 6.



Take-home Message

Every medicine treatment produces a health outcome. Pharmacoeconomic analyses differ in terms of the outcome measures that are incorporated into the analysis and the handling of the outcome measures. In a CMA, the outcome measures between the alternatives are assumed to be equivalent. In a CEA, the outcomes are measured in natural health units (e.g., blood pressure (mmHg) or blood glucose (mmol/l)). In a CUA, a special type of outcome measure called a QALY is used, which incorporates life years gained and morbidity to value a health outcome. Finally, in a CBA, the outcomes are converted to monetary units. Different tools are used to measure utilities that are incorporated into QALY calculations. These include the rating scale, standard gamble, and time trade off. QALYs can also be assumed or estimated from the literature. Details of how these outcomes are included in the four main types of pharmacoeconomic analysis will be discussed in future modules.





Activity

The activity is designed to help participants gain practical experience in using the rating scale and time trade off methods. The activity was adapted from the WHO Workshop on "Evidence, money and drug selection."[27]

Participants can discuss each example in groups but should answer the questions independently.

Step 1: Read the three health states
- Anne, a 60-year-old woman in full health for someone her age
- Elizabeth, a 60-year-old woman who has a hip fracture
- Mary, a 60-year-old woman who has a fear of falling

Step 2: Complete the rating scale exercise for Elizabeth

Step 3: Read the three health states again if necessary and perform the time trade off exercise for Elizabeth

Step 4: Read the three health states again and repeat steps 2 and 3 for Mary

Step 5: Score your exercises using the scoring sheets

There are no right or wrong answers in these exercises. What counts is how you feel about living in each of these health states.

Anne: Full health state

Anne is 60 years old. She lives in her own home and cares for herself. Anne is active in her local community and is out and about with friends quite a bit. She swims regularly and enjoys visiting with her children each weekend. Anne walks without any aids and can manage her 12 steps at home without any problems. She enjoys shopping and cooking for herself. Anne does not need any help with the housework and derives pleasure and relaxation from gardening.

Mary: Fear of falling

Mary is 60 years old. She lives alone in her own home and cares for herself. Mary is involved in community fundraising and enjoys playing bridge. Mary recently had a fall. She did not break any bones, but was badly cut and bruised. She fears falling. Mary continues to walk without aids. She still looks after herself and does her own housework. Mary has been a bit depressed since her fall. She has returned to her bridge group but is anxious when she is outside the home because she fears falling again.

Elizabeth: Hip Fracture

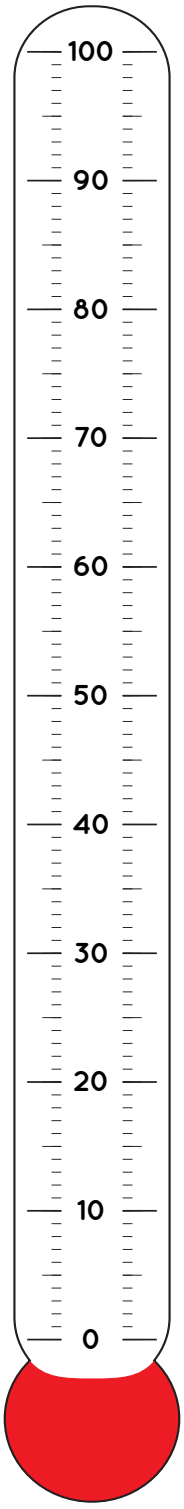
Elizabeth is 60 years old. Until her recent fall, she lived in her own home and managed to care for herself. She was active in her local community. Elizabeth broke her hip when she fell and it has been very slow to heal and has required surgery. She is now unable to live alone as she requires a great deal of help to do most things. Elizabeth now lives in a nursing home near her family but away from her friends. She is limited in where she can walk because of the frame and is unable to walk for long distances. She is unable to shower or dress without help from the nurse. She is unable to pursue her gardening or community involvement. Her leg aches sometimes at night. She has become anxious and is easily upset.

Activity: Elizabeth

Rating scale

Imagine that you are 60 years of age and that you are Elizabeth. You will continue to live in this chronic health state for 20 years and then die. If zero represents the worst possible health state and 100 represents Anne (normal good health for a 60 year old), where would you place living in Elizabeth's health state on this scale from 0 to 100?

The Health Thermometer



Time Trade Off

Imagine that you are 60 years of age and have a life expectancy of 20 years. Imagine that you are Elizabeth. You will continue to live in this chronic health state for 20 years and then die. You will now be given some choices. Circle the letter corresponding to your preference for each choice until you are prompted to stop.

Circle A, B, or C for each choice

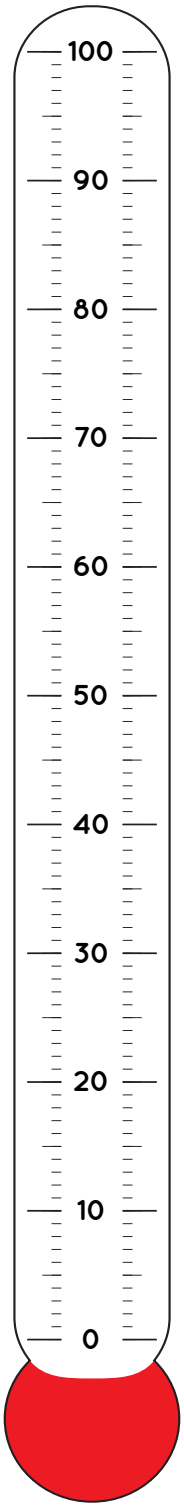
Choice 1	A	Live 20 years in good health [***Go to Choice 2***]
	B	Live 20 years as Elizabeth [***Error!***]
	C	Indifferent between A & B [***Stop***]
Choice 2	A	Live 2 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Go to Choice 3***]
	C	Indifferent between A & B [***Stop***]
Choice 3	A	Live 18 years in good health [***Go to Choice 4***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
Choice 4	A	Live 4 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Go to Choice 5***]
	C	Indifferent between A & B [***Stop***]
Choice 5	A	Live 16 years in good health [***Go to Choice 6***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
Choice 6	A	Live 6 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Go to Choice 7***]
	C	Indifferent between A & B [***Stop***]
Choice 7	A	Live 14 years in good health [***Go to Choice 8***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
Choice 8	A	Live 8 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Go to Choice 9***]
	C	Indifferent between A & B [***Stop***]
Choice 9	A	Live 12 years in good health [***Go to Choice10***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
Choice 10	A	Live 10 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]

Activity: Mary

Rating scale

Imagine that you are 60 years of age and that you are Mary. You will continue to live in this chronic health state for 20 years and then die. If zero represents the worst possible health state and 100 represents Anne (normal good health for a 60 year old), where would you place living in Mary's health state on this scale from 0 to 100?

The Health Thermometer



Time Trade Off

Imagine that you are 60 years of age and have a life expectancy of 20 years. Imagine that you are Mary. You will continue to live in this chronic health state for 20 years and then die. You will now be given some choices. Circle the letter corresponding to your preference for each choice until you are prompted to stop.

Circle A, B, or C for each choice

Choice 1	A	Live 20 years in good health [***Go to Choice 2***]
	B	Live 20 years as Elizabeth [***Error!***]
	C	Indifferent between A & B [***Stop***]
Choice 2	A	Live 2 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Go to Choice 3***]
	C	Indifferent between A & B [***Stop***]
Choice 3	A	Live 18 years in good health [***Go to Choice 4***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
Choice 4	A	Live 4 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Go to Choice 5***]
	C	Indifferent between A & B [***Stop***]
Choice 5	A	Live 16 years in good health [***Go to Choice 6***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
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	B	Live 20 years as Elizabeth [***Go to Choice 7***]
	C	Indifferent between A & B [***Stop***]
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	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
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	B	Live 20 years as Elizabeth [***Go to Choice 9***]
	C	Indifferent between A & B [***Stop***]
Choice 9	A	Live 12 years in good health [***Go to Choice10***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]
Choice 10	A	Live 10 years in good health [***Stop***]
	B	Live 20 years as Elizabeth [***Stop***]
	C	Indifferent between A & B [***Stop***]

Scoring

For some of the methods we have used (the thermometer, for example), your own numerical value for the health state is obvious. For others, you need to calculate a score. Here's how.

Time trade off scoring sheet

The table below contains the answers (utility weights) to the time trade off questions. To calculate your utility weight, match your response to each question (A, B, or C).

Start with choice number 1 and work your way towards choice number 10.

Choice number 1

If you chose 'A' for choice number 1, proceed to choice number 2 (and repeat the exercise). If you chose 'B' for choice number 1 then you record 'error'. You have then completed the scoring exercise. If you chose 'C', you record a utility weight of 1. You have then completed the scoring exercise.

Choice number 2

If you chose 'A' for choice number 2, you record a utility weight of 0.05. You have then completed the scoring exercise. If you chose 'B' for choice number 2, proceed to choice number 3 (and repeat the exercise). If you chose 'C', you record a utility weight of 0.1. You have then completed the scoring exercise.

Choice numbers 3–10

Proceed through each choice question until you record a utility weight.

Choice Number	A	B	C
1	Go to Choice 2	Error	1
2	0.05	Go to Choice 3	0.10
3	Go to Choice 4	0.95	0.90
4	0.15	Go to Choice 5	0.20
5	Go to Choice 6	0.85	0.80
6	0.25	Go to Choice 7	0.20
7	Go to Choice 8	0.75	0.70
8	0.35	Go to Choice 9	0.40
9	Go to Choice 10	0.65	0.60
10	0.45	0.55	0.50

Once you have calculated the value that you obtain for each method, enter it in the table below. You may want to consider why your results are the same or different from those of your colleagues. You may also want to think about the different results from each of the different methods.

Your scores

Scale	Elizabeth	Mary
Rating scale		
Time trade off		

Class scores

Scale	Elizabeth	Mary
Rating scale		
Time trade off		

Your name

Discussion

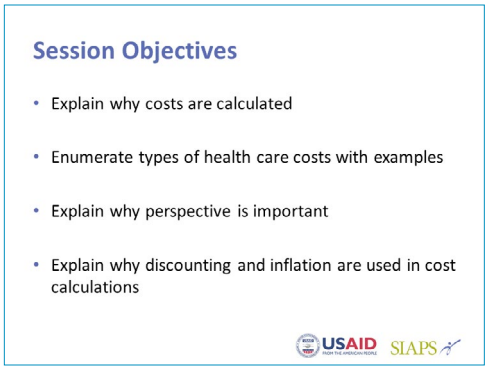
Encourage participants to discuss their scores as a group.

1. Why did some participants rate the condition higher or lower? (Remember that no score is right or wrong.)
2. Ask participants to consider how scores might differ if the exercise is complete by a caregiver rather than a patient.
3. Calculate the QALY value if the respondent scored Mary's utility as 0.4 on the rating scale and Mary's life expectancy is 10 years (assuming the utility value does not change over 10 years).

MODULE 4 : COSTS

Notes to the instructor

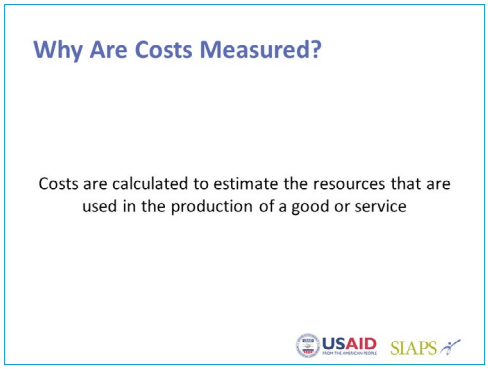
Time Allocation:		**3.5 hrs**
	Types of health care costs: ▪ Group activity 1	5 min 20 min
	Perspective	20 min
	Allowance for differential timing: ▪ Group activity 2, adjustment/standardization ▪ Group activity 3, discounting	15 min 30 min 30 min
	Sensitivity analysis	30 min
	Group activity 4	1 hr
Preparation:	Read through the curriculum guide and corresponding slide deck	
Resources	Flip chart/white board for presenting calculations during the activity session	
	Calculators	
Optional:	Ask participants to rate the module evaluation sheet (annex B)	



Session Objectives

The purpose of this session is to:

- Explain why costs are calculated
- Enumerate types of health care costs with examples
- Explain why perspective is important
- Explain why discounting and inflation are used in cost calculations



Why Are Costs Measured?

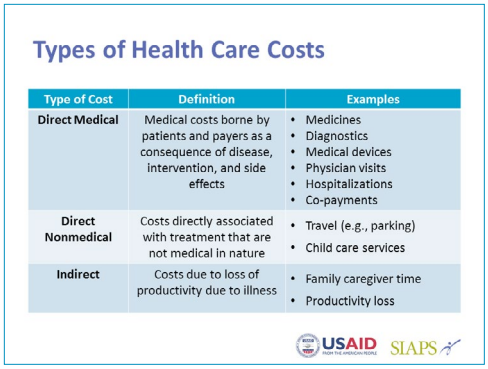
Costs are calculated to estimate the resources used in the production of a good or service. According to economic theory, the true cost of an item is equal to the opportunity cost (i.e., the value of the resources if those resources had been used for another productive purpose or the next best alternative).[6]

Types of Health Care Costs

There are four types of health care costs:[5]

- Direct medical costs
- Direct nonmedical costs
- Indirect costs
- Intangible costs

Direct medical costs are costs borne by patients and payers because of disease, intervention, and side effects. Examples include medicines, devices, diagnostics, physician visits, hospitalizations, and co-payments. Direct nonmedical costs are costs directly associated with the patient's

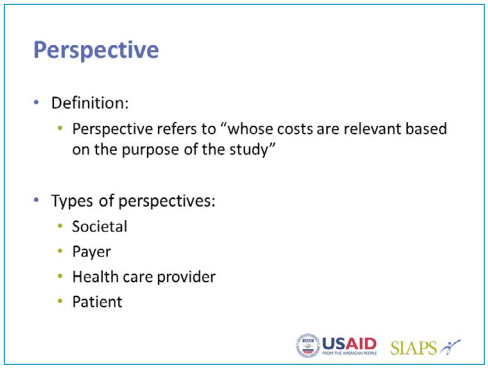


treatment but not medical in nature. Examples include travel costs to obtain treatment (e.g., fuel costs and parking) and child care services. Indirect costs are costs due to loss of productivity due to illness (e.g., family caregiver time and productivity loss). A fourth type of cost is referred to as an intangible cost, which includes the cost of suffering due to an illness. Examples of intangible costs include pain, fatigue, and anxiety.[5] Intangible costs are difficult to measure or convert into monetary units because they include subjective descriptions by patients.

Often, we think only of direct medical costs. However, other costs are also important to reach valid conclusions. If we neglect to include all applicable costs, we could underestimate the costs associated with a disease and the value for money an intervention could provide.

Group Activity 1

Before sharing examples with participants, ask them to think of examples of costs in each cost category



Perspective

Perspective can be defined as "whose costs are relevant based on the purpose of the study".[28] Perspectives can include those of the society, payer, health care provider, and patient. The health care costs taken into consideration will depend on the perspective of the study. It is essential to specify the perspective because an item that may be a cost from one perspective may not be from another. For example, from the societal perspective, all medical and nonmedical costs are relevant. However, from the health care insurer perspective, certain categories of costs may not be relevant, such as patient productivity loss, caregiver time, travel costs, and other indirect costs.

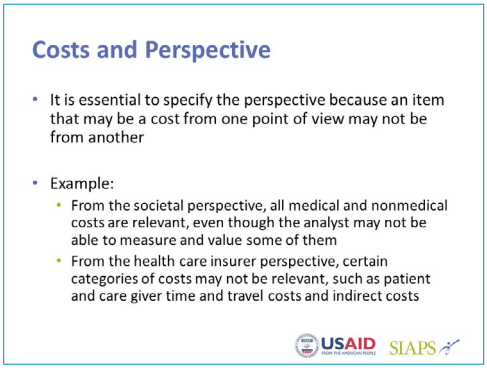


Table 2 provides examples of perspectives and the types of health care costs that might be measured from each perspective.[29]

Note to facilitator: Ask participants what costs are relevant from which perspective prior to sharing the table. The facilitator should encourage thought and discussion on relevant costs by perspective.

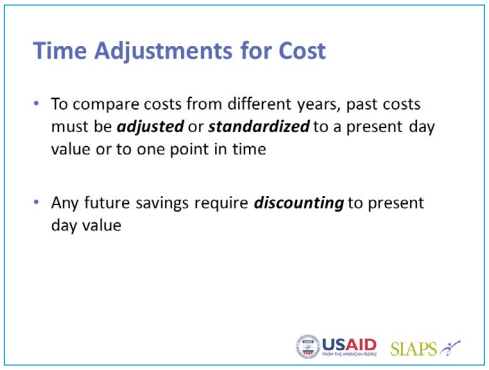
Table 2. Types of Health Care Costs by Perspective

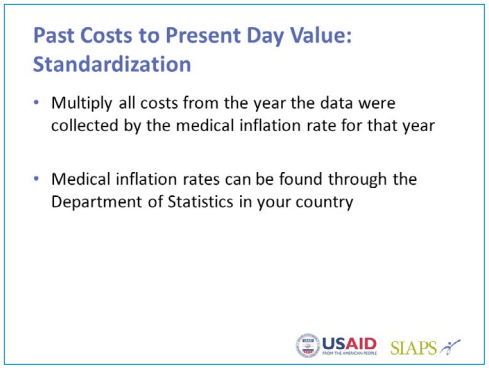
Panel 1: Inclusion and exclusion of costs, dependent on perspective for economic analysis

Examples of costs	Include (+) or not (–) dependent on perspective (*a*) Patient(*b*)	Physician(*c*)	Hospital	Payer(*d*)	Society(*e*)
Direct medical					
Physician time	Yes	Yes	Yes	Yes	Yes
Other medical personnel time (eg, nurse, technician)	No	Yes	Yes	Yes	Yes
Drugs	Yes	No	Yes	Yes	Yes
Medical devices (eg, syringes, ultrasound)	No	No	Yes	Yes	Yes
Laboratory tests	No	No	Yes	Yes	Yes
Direct non-medical					
Administration(*f*)	No	No	Yes	Yes	Yes
Physical facility (eg, clinic, office)	No	No	Yes	No	Yes
Utilities (eg, telephone, electricity)No	No	Yes	No	Yes	Yes
Patient's travel costs	Yes	No	No	No	Yes
Temporary hired care-giver(*g*)	Yes	No	No	No	Yes
Indirect					
Time off from work to visit physician	Yes	No	No	No	Yes
Time off work while ill and recuperating	Yes	No	No	No	Yes
Hire temporary household help while ill(*h*)	Yes	No	No	No	Yes

(*a*) Inclusion of cost item will depend upon chosen perspective; four perspectives (societal is the sum) do not cover all possible perspectives.
(*b*) Assumes patient is covered by health-care insurance; physician time and drug costs will involve co-payments.
(*c*) Perspective assumed to be that of a physician employed by health-care provider such as hospital.
(*d*) Third-party payer who reimburses physician for services rendered that are covered by an insurance scheme (private or public).
(*e*) Sum of all perspectives.
(*f*) Physician's practice and health insurer might each have separate administration costs.
(*g*) Hired to look after family members while adult visits physician.
(*h*) Might be hired to do household chores and look after family while an adult is ill, or to allow an adult to concentrate on nursing a sick child.
Source: adapted from Meltzer MI. Economic consequences of infectious diseases. In: Lederburg J, ed. Encyclopedia of microbiology: vol II, 2nd edn. San Diego: Academic Press, 2000: 131-55.

Taken from: Meltzer M. Introduction to health economics for physicians. The Lancet. 2001. 358:993–997.[29]





Allowance for Differential Timing

Even with zero inflation and no financial interest available for investment, there is inherent benefit to receiving benefits and money earlier than later. The value of money today is not equal to the value of money yesterday or tomorrow. This means that when we determine cost, we must also consider difference in cost over time.[5]

To illustrate the point in class discussion, use an example of what a chest x-ray might have cost in 1970 vs 2017.

Therefore, past costs and future savings must be adjusted for differential timing. *Past costs are adjusted or standardized to present value, while future costs and savings are discounted to present value*. Formulas are used for the adjustment/standardization and discounting. Examples of these calculations follow in a group activity.[5]

Past Costs to Present Day Value: Standardization

To standardize past costs to present day value, a medical inflation rate is used. Inflation refers to an increase in the cost of products in combination with a decreasing value of money. The costs from the year the data were collected are multiplied by the medical inflation rate for that year. Medical inflation rates can be found through a country's Department of Statistics.

Past Costs to Present Day Value: Standardization

- The formula used is:
  - Cost * (1+Medical Inflation Rate for Year 1) * (1+Medical Inflation Rate for Year 2)…etc.

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Past Costs to Present Day Value: Example

Resources Used to Diagnose and Treat Tuberculosis	Cost	Year
Physician Visits	$50	2015
Diagnostic Tests	$25	2016
Medication Cost	$30	2017

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Past Costs to Present Day Value: Example (2)

Resources Used to Diagnose and Treat Tuberculosis	Cost	Year	Medical Inflation (Example)	Standardization Calculation
Physician Visits	$50	2015		
Diagnostic Tests	$25	2016		
Medication Cost	$30	2017		

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Past Costs to Present Day Value: Solution

Resources Used to Diagnose and Treat Tuberculosis	Cost	Year	Medical Inflation (Example)	Standardization Calculation
Physician Visits	$50	2015	4%	50*1.04*1.05 =$54.6
Diagnostic Tests	$25	2016	5%	25*1.05 = $26.25
Medication Cost	$30	2017	Year of Study	$30
TOTAL	$105			$110.85

Current Year = 2017. Therefore, no inflation rate is applied to the Current Year.

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Future Costs/Savings to Present Day Value: Discounting

- Future health care costs/savings (money) is valued at a lower rate than present day health care savings (money)
- Therefore, future health care costs/savings must be discounted
- An accepted discount rate is usually between 3% and 5%

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In South Africa, for example, inflation rates, including medical inflation rates, can be obtained from Statistics, South Africa (http://www.statssa.gov.za/).[30] Present day/year costs are generally not standardized.

The formula used is:[5]

- Cost * (1+Medical Inflation Rate for Year 1) * (1+Medical Inflation Rate for Year 2)…etc.

The inflation percentage must be expressed as a fraction in the calculation. For example, 5% is 0.05 (i.e., 5 divided by 100) and 4% is 0.04 (i.e., 4 divided by 100) before using the formula to complete the calculation.

Group Activity 2

Purpose of the Activity

The activity gives participants an opportunity to conduct adjustment and standardization calculations.

Adjust or standardize physician visits, diagnostic tests, and medication costs for tuberculosis treatment from 2015, 2016, and 2017 (the current year), respectively. Assume that the medical inflation rates (from the Department of Statistics for the country) for 2015 and 2016 were 4% and 5%, respectively; the physician cost in 2015 was $50, the diagnostic test cost in 2016 was $25, and the medication cost in 2017 was $30.

What do the participants notice about the values with and without standardization?

Resources Used to Diagnose and Treat Tuberculosis	**Cost**	**Year**	**Medical Inflation (Example)**	**Standardization Calculation** Cost * (1+Medical Inflation Rate for Year 1) * (1+Medical Inflation Rate for Year 2)…etc.
Physician Visits	$50	2015	4% (2015)	
Diagnostic Tests	$25	2016	5% (2016)	
Medication Cost	$30	2017	Year of Study (2017)	
TOTAL	**$105**			

Future Costs/Savings to Present Day Value: Discounting

Future health care costs/savings (money) is valued at a lower rate than present day health care savings (money). Therefore, any future health care costs/savings must be discounted to present day value. An accepted annual discount rate is usually between 3% and 5%.[5]

The formula[5] used is: $x/(1+r)^t$

- x is the future savings
- r is the discount rate (time preference rate)
- t is the number of years into the future

Discounting is not required in the present year (i.e., only future costs/savings must be discounted).[5]

Future Costs/Savings to Present Day Value: Discounting

- The formula used is: x /(1 +r)t
  - x is the future costs/savings
  - r is the discount rate (time preference rate)
  - t is the number of years into the future
- Discounting is not required in the present year

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Future Savings to Present Day Value: Example

Years into the Future	Savings	Calculation	Savings after Discounting
Year 1	$50		
Year 2	$25		
Year 3	$30		

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Future Costs to Present Day Value: Solution

Years into the Future	Savings	Calculation	Savings After Discounting
Year 1	$50	50/1	$50
Year 2	$25	$25/(1.04)^1$	$23.07
Year 3	$30	$30/(1.04)^2$	$27.73
	$105		**$100.08**

Discount Rate = 4%

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Marginal and Incremental Costs

- When comparing treatment alternatives (A vs B):
  - If treatment A offers a better outcome at a higher cost than treatment B:
    - It is important to determine if the added benefit that treatment A offers is worth the added cost
- Marginal and incremental costs are used to describe this change in cost between the two alternatives

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Marginal and Incremental Costs

- Marginal cost refers to the cost of producing one extra unit of outcome
- Incremental cost refers to the difference in cost between the two treatment options

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Group Activity 3

Discount the savings for each year shown in the table. Year 1 is the current year. Year 2 and Year 3 are 1 and 2 years in the future.[5] Use a discount rate of 4%.

What do the participants notice about the values with and without discounting?

Years into the Future	**Savings**
Year 1	$50
Year 2	$25
Year 3	$30

Years into the Future	**Savings**	**Calculation** $x/(1+r)^t$	**Savings After Discounting**
Year 1	$50		
Year 2	$25		
Year 3	$30		
	$105		

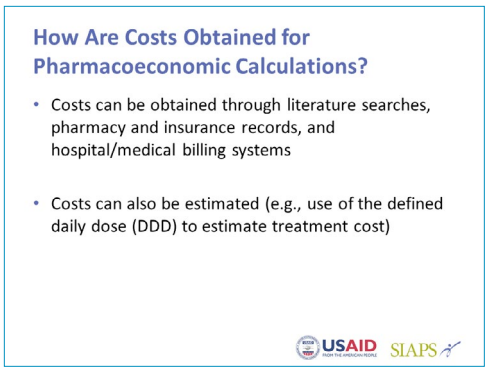
Using the discounting equation, the Year 2 and Year 3 savings are discounted to present day value. The total savings after discounting ($100.08) is less than the total savings without discounting ($105).

These examples clearly illustrate that if the costs were included in a pharmacoeconomic calculation without adjustments for time, the results obtained would be skewed.

Marginal and Incremental Costs

When comparing two or more treatment alternatives, if treatment A offers a better outcome at a higher cost than does treatment B, it is important to determine whether the added benefit that treatment A offers is worth the added cost. *Marginal and incremental costs describe this change in cost between the two alternatives.*[5]

Marginal cost refers to the cost of producing one extra unit of outcome. An example of this would be the cost of metformin needed to decrease HbA1c by 1%. Incremental cost refers to the difference in cost between the two treatment options. An example of this would be the difference in the cost of metformin versus sitagliptin to decrease HbA1c by 1%. The ICER is the difference in the cost divided by the difference in outcomes of the two interventions being compared.[5] This ratio can be used to determine which medication should be selected for use, due to better value for money. This will be discussed in detail in module 6.



How Are Costs Obtained for Pharmacoeconomic Calculations?

There are various sources for costs. Costs can be obtained through literature searches, pharmacy and insurance records, and hospital/medical billing systems. Costs can also be estimated. An example of this is the use of the defined daily dose (DDD) to estimate treatment costs. The DDD is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults."[31] The monthly cost of the drug can be "estimated" by using the DDD to calculate a monthly total requirement and multiplying the unit price of the medicine by the quantity of medicine required to meet the total monthly need.[32] Participants should be encouraged to collect costs in a systematic manner, by year, and with adequate referencing so that information can be tracked easily, especially for calculation of a sensitivity analysis (described below).

Sensitivity Analysis

A *sensitivity analysis* is encouraged when dealing with estimates. In economic models or pharmacoeconomic analyses, assumptions are often used when data are not available. A sensitivity analysis helps determine how sensitive the results are to changes in the economic model or pharmacoeconomic calculation.

A base-case model uses the best estimates in the analysis. In a base-case scenario, several one-way or two-way sensitivity analyses can be conducted on the estimates. In a one-way sensitivity analysis, one variable is tested on a range of alternative values, holding all other values constant. In a two-way sensitivity analysis, two key variables can be varied simultaneously (e.g., the effect size of the product and the cost of the product or service).[5]

In a sensitivity analysis on cost, the costs are varied to determine whether the change in cost alters the outcome of the calculation. If varying the cost does not change the result in a pharmacoeconomic analysis, the results are said to be "robust" to changes in cost. However, if a sensitivity analysis adjusts the result, then the results are said to be "sensitive" to changes in cost.[5] Conducting sensitivity analyses can be complex, and advanced Microsoft Excel skills are required for complex models. The following article outlines how a sensitivity analysis is conducted and displayed:

Hoerger TJ, Harris R, Hicks KA, Donahue, K, Sorensen S, Engelgau M. Screening for Type 2 Diabetes Mellitus: A Cost-Effectiveness Analysis. Ann Intern Med. 2004; 140(9):689–699. The abstract is provided for background and context. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15126252.

An example of a sensitivity analysis in a group activity is included in module 9.

Summary: Take-home Message

- Costs are calculated to estimate the resources that are used in the production of a good or service
- Types of health care costs include:
  - Direct medical costs
  - Direct nonmedical costs
  - Indirect costs
  - Intangible costs

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Summary: Take-home Message

- Perspective refers to "whose costs are relevant based on the purpose of the study"
- To compare costs from different years, costs must be ***adjusted*** or ***standardized*** to a present day value or to one point in time
- Marginal cost refers to the cost of producing one extra unit of outcome
- Incremental cost refers to the difference in cost between the two treatment options

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Acknowledgments

- This presentation is based on materials used in the University of Washington course called "Economic Evaluation in Health & Medicine" (PHARM 534 / HSERV 583)
- Many have contributed to the content, including Will Hollingworth, David Veenstra, Josh Carlson, and Catherine Waweru-Corbell
- Material from Rascati KL. Essentials of Pharmacoeconomics. Philadelphia: Lippincott Williams & Wilkins; 2014, was also used

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Take-home Message

Costs are calculated to estimate the resources used in the production of a good or service. Types of health care costs include direct medical costs, direct nonmedical costs, indirect costs, and intangible costs. Perspective refers to whose costs are relevant based on the purpose of the study. To compare costs from different years, we require adjustment or standardization to a present-day value or to one point in time. Any future savings require discounting to present day value. Definitions that are important to understanding future modules include marginal cost, which refers to the cost of producing one extra unit of outcome, and incremental cost, which refers to the difference in cost between two treatment options. A sensitivity analysis is conducted on costs to determine whether changes in cost estimates bring different results.

Group Activity 4[27]

Exercise

Rambosarten for Heart Failure

You are a member of a formulary committee that is assessing applications for additions to your hospital formulary. Among the new applications is:

- A new angiotensin II receptor antagonist (rambosarten)

You have been provided with costs and estimates of effects to assess. In this case, the drug's manufacturer claims that not only is the drug effective, but also that it will generate cost savings to the hospital, the national health system, and the community. These arise from expected cost offsets, including fewer hospitalizations and less time off work.

The claim is that rambosarten decreases the frequency and duration of hospital admission for management of heart failure, which saves money, and also reduces the cost of care required in the home and of care giver time off work. The cost information that you have been provided is shown in the table below. It is from an Australian pharmacoeconomic analysis, commissioned by the company as part of a submission to the Pharmaceutical Benefits Advisory Committee.

Costs	Rambosarten			Standard treatment		
	No. units	Unit price	Total cost	No. units	Unit price	Total cost
Drug	6 months	$800/ month	$4,800	6 months	$300/ month	$1,800
Hospitalization	10 days	$800/day	$8,000	18 days	$800/day	$14,400
Home care	20 visits	$80/visit	$1,600	35 visits	$80/visit	$2,800
Care giver time	20 days	$150/day	$3,000	35 days	$150/day	$5,250

Answer the following questions.

1. Which perspective (point of view) do you think is most appropriate for an economic analysis?
2. Which costs are included? Whose pays the cost? Where could they be potentially obtained from (i.e., sources)? Discuss the reliability of the sources.

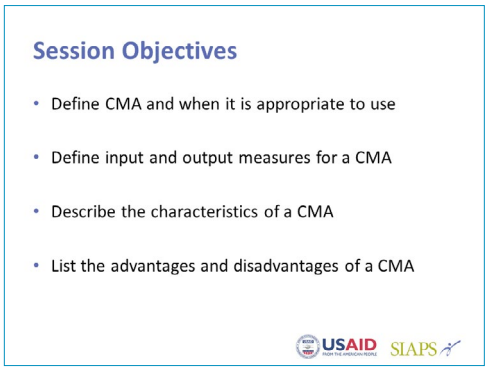
3. Do you think that all relevant costs have been identified? Have they used appropriate units to measure and value the costs?
4. Can the costs be categorized in some way?
5. How might you examine the impact of over or underestimates of costs?
6. What is the difference in net costs between the two treatments

Suggested reading on costing for a disease state: Pooran A, Pieterson E, Davids M, Theron G, Dheda K (2013) What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa? PLoS ONE 8(1): e54587. doi:10.1371/journal.pone.0054587

MODULE 5 : COST MINIMIZATION ANALYSIS

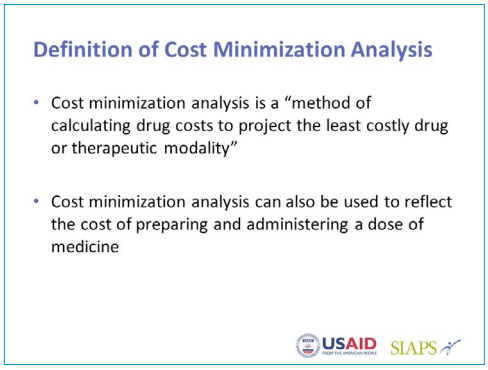
Notes to the instructor

Time Allocation:		**3.5 hrs**
	CMA Lecture:	30 min
	Group activities 1, 2, and 3 (breakout sessions):	90 min (30 min per activity)
	Group activities 1, 2, and 3 (report back/discussion):	90 min (30 min per activity)
Preparation:	Read through the curriculum guide and corresponding slide deck	
Resources Required:	Flip chart/white board for group activity discussion	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	



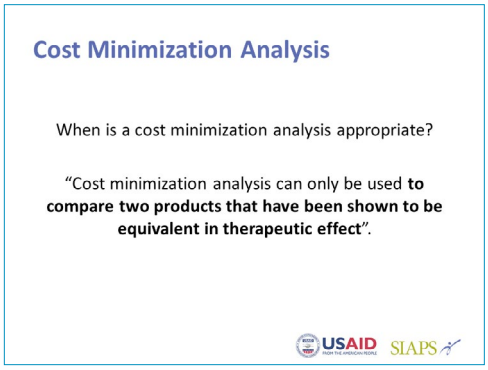
Session Objectives

- Define CMA and when is it appropriate to use
- Define input and output measures for a CMA
- Describe the characteristics of a CMA
- List the advantages and disadvantages of a CMA



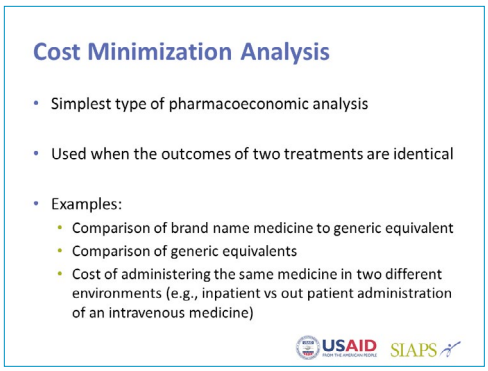
Definition of Cost Minimization Analysis

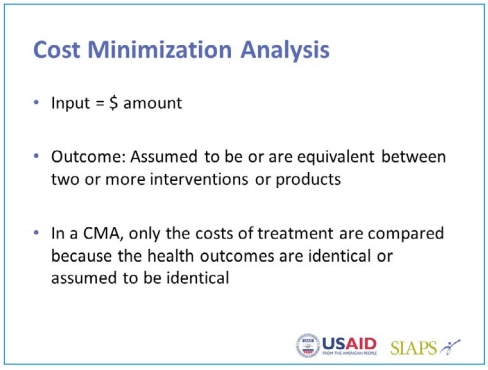
CMA is a "method of calculating drug costs to project the least costly drug or therapeutic modality".[33] A CMA is used to compare products that have been shown to be equivalent in therapeutic effect. A CMA can also be used to reflect the cost of preparing and administering a dose of a medicine or the cost of administering a medicine in different settings. Because products compared in a CMA must be shown to be equivalent in therapeutic effect, the CMA method is most useful for comparing generic equivalents. A CMA may also be used to compare therapeutic equivalents. However, because absolute equivalence is difficult to demonstrate between two non-generic products, some argue that a CMA may not be appropriate in comparing anything but generic equivalents or the administration of the same medicine in different settings.[33]

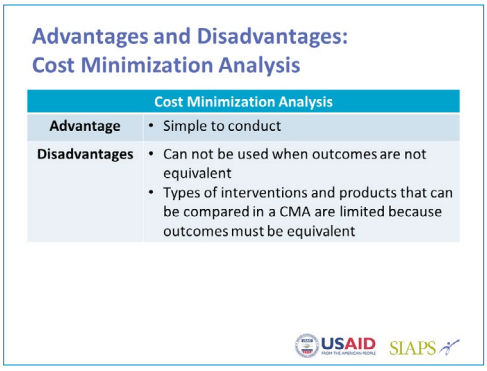


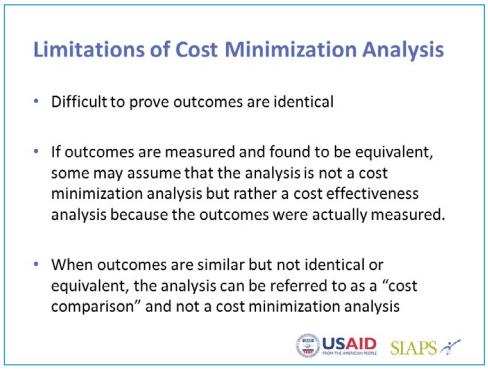
Characteristics of a Cost Minimization Analysis

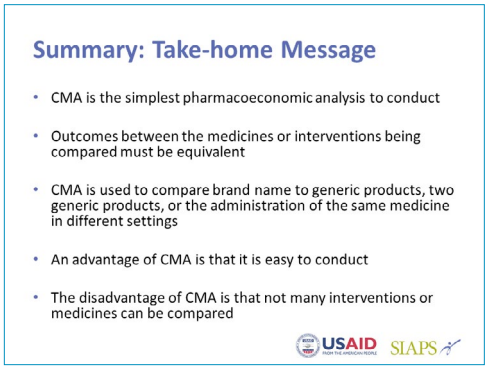
A CMA is the simplest type of pharmacoeconomic analysis. In a CMA, only the costs of treatment are compared between two or more interventions or products, because the health outcomes are identical or assumed to be identical. The input measure for a cost minimization analysis is cost, and the outcomes are assumed to be equivalent.[5]











A CMA can be used to compare a brand name item to a generic equivalent, two generic equivalents, or the administration of the same medicine in different settings (outpatient versus inpatient).[5]

If outcomes are measured and found to be equivalent, some argue that the analysis is not a true CMA because outcomes were measured. Similarly, if the outcomes of the products being compared are similar but not identical, costs should be compared in a CCA (an analysis where only product costs are compared and no outcomes are considered) and not a CMA.[5]

Note to facilitator: Using the descriptions given in the lecture, ask participants to list the potential advantages and disadvantages of a CMA.

Advantages and Disadvantages

An advantage of a CMA is that it is simple to conduct. Disadvantages include the fact that it cannot be employed when outcomes of the products are not equivalent. Types of interventions and products that can be compared in a CMA are limited because the outcomes must be equivalent.[5]

Take-home Message

CMA is the simplest pharmacoeconomic analysis to conduct. To use a CMA, the outcomes of the medicines or interventions being compared must be equivalent. Therefore, a CMA is used to compare brand name to generic products, two generic products, or the administration of the same medicine in different settings. The simplicity of a CMA is one of its advantages. The disadvantage of a CMA is that not many interventions or medicines can be compared.

Group Activity 1

Take-home Exercise

The purpose of the activity is to understand when a CMA is appropriate and how it is approached.

Suggested Resources

- Paper copies of O'Brien B, Levine M, Willan A, et al. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. Arch Intern Med 1999; 159: 2298–2304, from which this exercise is adapted
- Flip charts to illustrate calculations

Suggested Approach to the Activity

- Project the case study/activity question
- Provide participants with copies of the articles or at a minimum the costing activity (table 3)
- Participants can be allowed to work in groups

Time Allocation

- Allow participants approximately 30 minutes to complete the activity alone or in groups
- Allow 30 minutes for sharing solutions and discussion
- Participants/groups can be requested to lead the discussion

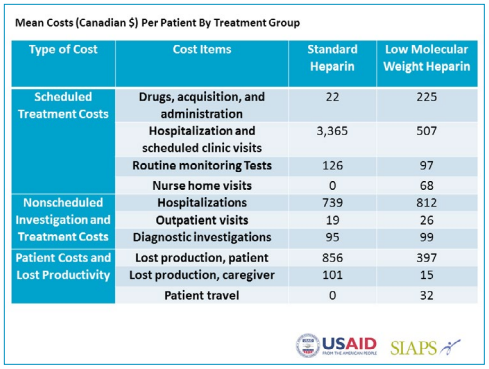
Case Study[34]

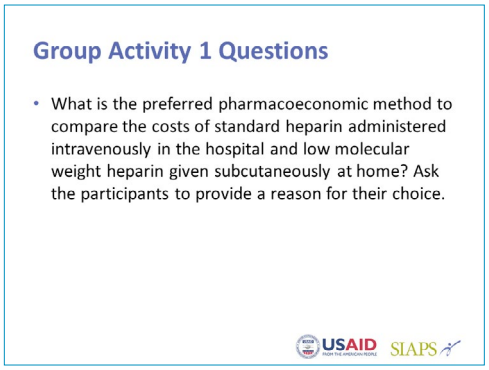
The **safety and efficacy** of taking subcutaneous **low molecular weight heparin at home** compared to **standard intravenous heparin in a hospital setting** was demonstrated to be **equal in a randomized control trial** in patients with deep vein thrombosis. Researchers are interested in comparing the costs of administering heparin in the home and in a hospital setting from the perspective of society. Costs studied include health care costs, patient costs, and lost productivity because of days off work.

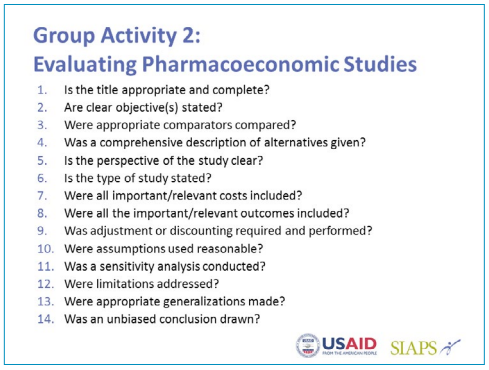
Review table 3 and answer the questions that follow.

Table 3. Mean Costs (Canadian $) per Patient by Treatment Group

Type of Cost	Cost Items	Standard Heparin	Low Molecular Weight Heparin
Scheduled Treatment Costs	Drugs, acquisition, and administration	22	225
	Hospitalization and scheduled clinic visits	3,365	507
	Routine monitoring tests	126	97
	Nurse home visits	0	68
Nonscheduled Investigation and Treatment Costs	Hospitalizations	739	812
	Outpatient visits	19	26
	Diagnostic investigations	95	99







Type of Cost	Cost Items	Standard Heparin	Low Molecular Weight Heparin
Patient Costs and Lost Productivity	Lost productivity, patient	856	397
	Lost productivity, caregiver	101	15
	Patient travel	0*	32**

O'Brien B, Levine M, Willan A, et al. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. Arch Intern Med 1999; 159: 2298–2304.34

*Patient travel costs for administration of standard heparin while hospitalized were assumed to be zero

** Travel for patients to obtain routine laboratory tests

Questions

1. What is the preferred pharmacoeconomic method to compare the costs of standard heparin administered intravenously in the hospital vs. low molecular weight heparin given subcutaneously at home? Ask participants to provide a reason for their choice.
2. Is there is a difference in *scheduled treatment costs* between standard heparin and low molecular weight heparin in these settings? Please show all calculations and explain your answer.

Group Activity 2

Pharmacoeconomic Article Critique/Review

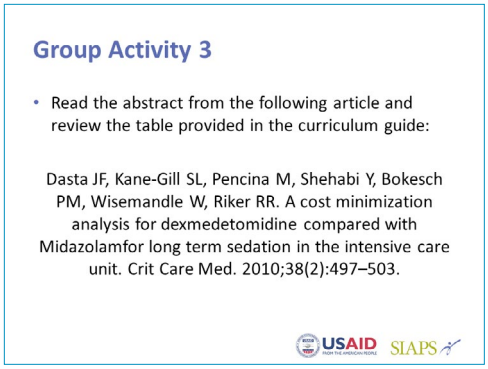
Now that elements of pharmacoeconomic analyses, such as health outcomes and costs, have been addressed and one pharmacoeconomic analysis (CMA) discussed, participants should be encouraged to review pharmacoeconomic literature.

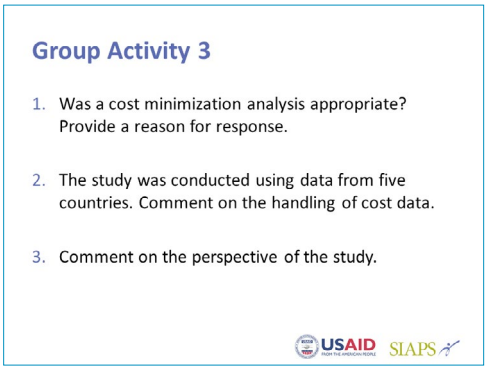
Purpose of the Activity: To encourage participants to read articles on pharmacoeconomics

Time Allocation: 15 minutes

Suggested Approach to the Activity: Ask participants to consider the information discussed in the modules that have been completed (1 to 5), including CMA, and consider what components would be included in a pharmacoeconomic article. Expected answers might include cost, perspective, and health outcomes.

Use a flip chart to document participants' responses.





Group Activity 3

Take Home

The purpose of the activity is to stimulate discussion around critiquing a cost minimization article.

Read the following abstract and study the table from the full article.[35]

Abstract: Dasta JF, Kane-Gill SL, Pencina M, Shehabi Y, Bokesch PM, Wisemandle W, Riker RR. A cost minimization analysis for dexmedetomidine compared with midazolam for long term sedation in the intensive care unit. Crit Care Med. 2010;38(2):497–503.

Objective: To compare the intensive care unit costs and determine factors influencing these costs in mechanically ventilated patients randomized to dexmedetomidine or midazolam by continuous infusion.

Design: Cost minimization analysis of a double-blind, multicenter clinical trial randomizing patients 2:1 to receive dexmedetomidine or midazolam from the institutional perspective.

Setting: Sixty-eight intensive care units in the United States, Australia, New Zealand, Brazil, and Argentina.

Patients: A total of 366 intubated intensive care unit patients anticipated to require sedation for >24 hours.

Measurements and Main Results: Intensive care unit resource use was compared within the two treatment arms, using the U.S. representative costs for these resources. The analyses characterized patient costs from start of study drug until intensive care unit discharge including costs associated with the intensive care unit stay, costs during mechanical ventilation, study drug acquisition cost, and costs of treating adverse drug reactions probably or possibly related to study drugs. Blinded to treatment group, costs were calculated using Medicare reimbursement schedules, average IMS drug costs, expert opinion, and peer-reviewed literature. Censored lengths of intensive care unit stay and mechanical ventilation were imputed, using a nonparametric adjustment algorithm. Crude and multivariate median regressions were performed to relate intensive care unit cost and treatment. Including drug acquisition cost, sedation with dexmedetomidine was associated with a median total intensive care unit cost savings of $9679 (confidence interval, $2314–$17,045) compared with midazolam. The primary cost drivers were reduced costs of intensive care unit stay (median savings, $6584, 95% confidence interval, $727–$12,440) and reduced costs of mechanical ventilation (median savings, $2958, 95% confidence interval, $698–$5219).

References for the slides used in this module

Conclusions: Continuous sedation with dexmedetomidine results in significantly lower total intensive care unit costs compared with midazolam infusion for intensive care unit sedation, primarily due to decreased intensive care unit stay costs and reduced mechanical ventilation costs.

Table 4. Median (1st–3rd Quartile) Costs for Study Arms (part of table shown from article)

Cost Driver	Dexmedetomidine (n=244)	Midazolam (n=122)	p
Adjusted Method			
Total ICU Cost	40,365	50,149	0.010
ICU Component	36,571	40,501	0.028
Mechanical Ventilation	7022	10,855	0.010
Adverse Drug Reaction Treatment Component	507	810	0.013

Taken from: Dasta JF, Kane-Gill SL, Pencina M, Shehabi Y, Bokesch PM, Wisemandle W, Riker RR. A cost minimization analysis for dexmedetomidine compared with Midazolam for long term sedation in the intensive care unit. Crit Care Med. 2010;38(2):497–503.

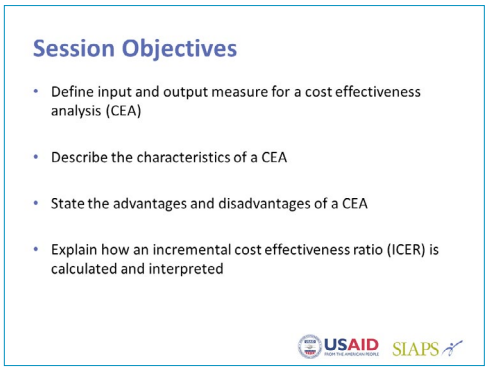
Questions/Points to consider:

1. Was a CMA appropriate? Why or why not?
2. The study was conducted using data from five countries. Comment on the handling of cost data.
3. Comment on the perspective of the study.

MODULE 6 : COST EFFECTIVENESS ANALYSIS

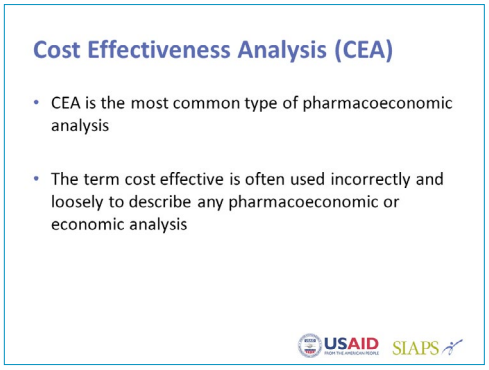
Notes to the instructor

Time Allocation:		**2.5 hrs**
	Background to CEA	10 min
	Group Activity 1, outcomes	10 min
	Advantages and disadvantages of CEA	10 min
	ICER	10 min
	Group activity 2, ICER (breakout session and discussion)	40 min
	Cost effectiveness grid and cost effectiveness plane	10 min
	Group activity 3, calculation	60 min
Preparation:	Read through the curriculum guide and corresponding slide deck	
Resources Required:	Flip chart/white board for group activity discussion	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	



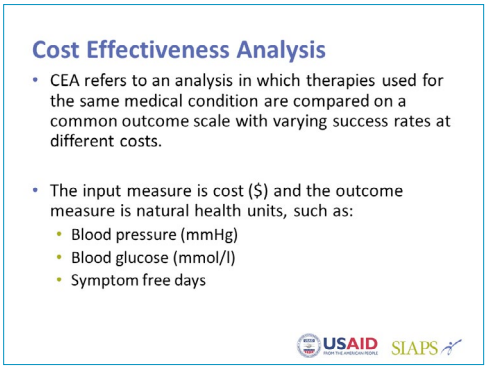
Session Objectives

- Define input and output measures for a CEA
- Describe the characteristics of a CEA
- List the advantages and disadvantages of a CEA
- Explain how an ICER is calculated and interpreted



Characteristics of a Cost Effectiveness Analysis

In a CEA, the input measure is cost and the output measure is measured in natural health units. Examples of natural health units include mmol/l (for blood glucose levels); mmHg (for blood pressure); and symptom-free days (e.g., asthma or ulcer treatment). In a CEA, treatment alternatives for the same medical condition measured in the same natural health units can be compared. A CEA cannot be used to compare treatments or interventions used for different conditions with different outcomes.[5]



A CEA is the most common pharmacoeconomic analysis. CEA and CMA are likely to be reviewed in the literature or frequently used in the selection of essential medicines in LMICs, depending on the availability of data. However, the term cost effectiveness is sometimes used incorrectly and loosely to describe any pharmacoeconomic or economic analysis. CEA refers to an analysis in which therapies used for the same medical condition are compared on a common outcome scale with varying success rates at different costs. For example, in a CEA, an oral hypoglycemic agent and insulin—both treatments used to reduce blood

Example of a CEA

- Oral hypoglycemic agent versus insulin treatment used to reduce blood glucose levels in type II diabetes mellitus
- The outcome measure = drop in blood glucose level:
  - Drop in blood glucose in mmol/l
  - Percentage drop in glycosylated hemoglobin level/HbA1c

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glucose levels—can be compared. The outcome measure would be a drop in blood glucose levels (i.e., a drop in blood glucose in mmol/l or a percentage drop in HbA1c).[5]

Group Activity 1

Can you think of other examples of where a CEA could be conducted using two drug treatments and natural health units as the outcome?

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Group Activity 1

The facilitator should encourage participants to give other examples of CEA

Advantages and Disadvantages

An advantage of a CEA is that medical practitioners are familiar with the natural health units (outcomes) used in a CEA comparison, which makes it easy to explain the concept of cost effectiveness. A disadvantage is that the treatments/alternatives must have outcomes that are measured in the same natural health units (i.e., a hypertensive treatment cannot be compared to a diabetic agent). If treatments for the same condition are compared, the same natural health units must be compared in the analysis (e.g., for asthma medication, treatments can be compared based on symptom-free days or FEV). If both comparisons (FEV and symptom-free days) are needed, two separate cost-effectiveness calculations must be performed. The CEA cannot be summarized for different types of outcomes for one treatment. A CUA, which is considered a subset of a CEA, uses a QALY to summarize different outcomes into one measure; this will be discussed later. Finally, a disadvantage of a CEA is the subjectivity that surrounds an ICER calculation. Estimates might be used in the calculation that limit the analysis. Furthermore, once the ICER is calculated, it may be unclear whether the intervention or medicine should be adopted, based on the ICER, because many countries do not have a threshold or willingness to pay (WTP) ratio to which the ICER can be compared.[5]

Advantages and Disadvantages: Cost Effectiveness Analysis (CEA)

Cost Effectiveness Analysis	
Advantages	• Outcomes are routinely measured • Medical practitioners are familiar with natural health units as an outcome measure
Disadvantages	• Treatments/alternatives must have outcomes that are measured in the same natural health units (i.e., a hypertensive treatment cannot be compared with an antidiabetic agent) • CEA cannot be summarized for different types of outcomes for one treatment • Subjectivity as to whether the added benefit is worth the extra cost

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Incremental Cost Effectiveness Ratio

The ICER is the ratio of the difference in costs divided by the difference in outcomes.[5] In other words, it is the change in cost divided by the change in outcome. The ICER is calculated in a CEA. The equation used to express an ICER is shown below:

ICER = (Cost of Drug B - Cost of Drug A)/(Effectiveness of Drug B - Effectiveness of Drug A)

Incremental Cost Effectiveness Ratio (ICER)

- Ratio of difference in costs divided by the difference in outcomes
- ICER = (Cost of Drug B – Cost of Drug A) ÷ (Effectiveness of Drug B – Effectiveness of Drug A)
- Several ICERs will have to be calculated when a number of different outcomes are important (e.g., when comparing asthma medications, ICERs for symptom free days and forced expiratory volume (FEV) can be calculated)

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The costs and effectiveness measures can be collected from the literature, estimated, or assumed. Module 4 showed that there are different types of costs (direct medical, indirect medical, indirect nonmedical, and

intangible). Because the costs and effectiveness can change depending on where the information is collected, the costs and outcomes are usually varied in a *sensitivity analysis*. A sensitivity analysis involves varying the estimates in the calculation by a certain percentage to determine whether the ICER that is calculated changes significantly.

Group Activity 2

ICER Calculation

The following scenarios serve as a guide on why and when we calculate an ICER. The scenarios have been adapted from *Essentials of Pharmacoeconomics* by Dr. Karen Rascati.[5] In these examples, the input measure is the cost of the medicine and the outcome measure is the success rate.

The facilitator can use these examples in a group activity to provide clarity on the ICER.

Scenario A

Two antibiotic treatments are available to treat a chest infection. Both treatment A and treatment B are used to treat 100 people in a randomized control trial. Treatment A cured 85 people while Treatment B cured 90 people (i.e., 85 out of 100 people (a treatment success rate of 85%) were cured with treatment A and 90 out of 100 people (a treatment success rate of 90%) were cured with treatment B). The cost of the two treatments is equal. Treatment A is $400. Side effect profile and duration and convenience of treatment do not differ according to the results from the randomized control trial.

In this scenario, treatments A and B cost the same and there is no difference in side effect or convenience profile. **Which treatment should be used?**

Answer: It would be ideal to select treatment B. It has a higher success rate at the same cost. The decision can be made without any advanced pharmacoeconomic analysis.

Scenario B

Two antibiotic treatments are available to treat a chest infection. Both treatment C and treatment D are used to treat 100 people in a randomized control trial. Treatment C cured 85 people while treatment D cured 90 people (i.e., 85 out of 100 people (a treatment success rate of 85%) were cured with treatment C and 90 out of 100 people (a treatment success rate of 90%) were cured with treatment D). **The cost of treatment C, $400, is higher than the cost of treatment D**. The side effect profile and duration and convenience of treatment do not differ according to the results from the randomized control trial.

In this scenario, treatment D costs less than treatment C and provides better outcomes with no difference in side effect or convenience profile. Which treatment should be used?

Answer: It would be ideal to select treatment D because it costs less and is more effective. The decision can be made without any advanced pharmacoeconomic analysis.

Scenario C

Two antibiotic treatments are available to treat a chest infection. Both treatment E and treatment F are used to treat 100 people in a randomized control trial. Treatment E cured 85 people while treatment F cured 90 people (i.e., 85 out of 100 people (a treatment success rate of 85%) were cured with treatment E and 90 out of 100 people (a treatment success rate of 90%) were cured with treatment F). **The cost of treatment F is $100 more than the cost of treatment E.** Treatment E is $400. The side effect profile and duration and convenience of treatment do not differ according to the results from the randomized control trial.

Which treatment should we select?

Calculation of the ICER and Discussion

In scenario C, treatment F costs more but also provides more benefit in that it has a higher success rate. To determine whether the treatment is cost effective, we need to calculate an ICER.

At first glance, the choice appears to be simple. If an individual is faced with the decision of choosing between treatment E and treatment F and could afford the extra $100, he or she would choose treatment F. However, a government must make decisions for its people. In cases where resources are limited and everyone in the country should have equal access to the treatment, a difference of $100 per patient may not provide value for money. The ICER can be used to determine whether the alternative treatment (treatment F) is cost effective.

After all costs and effectiveness measures have been gathered, it is useful to summarize the information in a table (example provided in table 5). This is a simple example. Complex tables can be produced when several costs are included (e.g., cost of adverse effects and hospitalizations). **The facilitator should encourage participants to review pharmacoeconomic articles and the ways that costs and outcomes are presented**.

Table 5. Summary of Treatment Costs and Effectiveness Measures

	Treatment E	**Treatment F**
Cost	$400	$500
Success Rate	85%	90%

Step 1: Calculate the average cost effectiveness for each treatment

- Treatment E: Average cost effectiveness = 400/0.85 = $470
- Treatment F: Average cost effectiveness = 500/0.90 = $555

What does the average cost effectiveness ratio tell us?

- For treatment E, the average cost effectiveness was $470, meaning that each additional success costs $470
- For Treatment F, the average cost effectiveness was $555, meaning that each additional success costs $555

Step 2: Calculate the ICER

ICER = (Cost of Treatment F-Cost of Treatment E)/(Effectiveness of Treatment F-Effectiveness of Treatment E)
= (500-400)/(0.90-0.85)
= 100/0.05
= $2000

What Does the ICER Mean?

The ICER reflects that the "true difference in cost" of using treatment F vs treatment E is $2,000 per successful treatment. Treatment F cured five more people than treatment E. The cost to achieve these five additional cures was not $500 ($100 x 5 cures). It was $10,000 ($2,000 per successful outcome x 5 successful outcomes). The ICER means that the "true difference in cost" of using treatment F vs treatment E is $10,000. The ICER allows us to review the cost for each successful outcome.

When a country has limited resources, those resources must be used efficiently. The ICER helps determine whether the addition of treatment F to the formulary will be cost effective. These three scenarios provide examples as to how the ICER can be used by decision makers to incorporate pharmacoeconomics into the formulary decision making process.

Once the ICER is calculated, the difficulty is that the decision on whether to adopt the alternative treatment is subjective. Many countries do not have a clear or set cost-effectiveness cut off (i.e., at what point do we decide that the alternative treatment is cost effective?). For developing countries, three times the Gross Domestic Product (GDP) per capita is sometimes used as a cut off to determine whether the addition of the higher-priced item is cost effective. If the ICER is less than three times the GDP per capita of the country, the new treatment at the higher cost and effectiveness is deemed to be cost effective.[36]

Participants should be urged to consider their country's GDP. The GDP in some countries is high and most items would be deemed cost effective if three times the GDP per capita is used. Ideally, in a CEA, quality of life should be taken into consideration when making cost-effectiveness decisions. It is often difficult to include quality of life measures in the analysis because the information is not always readily available for certain groups of patients and assumptions must be made, which can make reaching a decision on whether the item is cost effective difficult.[36]

Cost-effective Grid and Cost-effectiveness Plane

A cost-effectiveness grid or cost-effectiveness plane can provide definitions related to cost effectiveness when two treatments (e.g., current treatment compared to an alternative for the formulary) are being compared.

Table 6. Cost-effectiveness Grid[5]

	Lower Cost	**Same Cost**	**Higher Cost**
Lower Effectiveness	A Conduct ICER	B	C Dominated
Same Effectiveness	D	E Arbitrary	F
Higher Effectiveness	G Dominant	H	I Conduct ICER

If the "alternative" treatment has a higher cost and higher effectiveness or a lower cost and lower effectiveness, an ICER should be calculated to determine whether the "alternative" option is cost effective (cells A and I).

If the "alternative" treatment has a higher cost and lower effectiveness, the alternative is referred to as dominated (cell C).

If the "alternative" treatment has a lower cost and higher effectiveness, the alternative is referred to as dominant (cell G).

If the "alternative" treatment has the same cost and lower effectiveness or a higher cost but the same effectiveness, it should not be selected (cells B and F).

If the "alternative" has a lower cost but the same effectiveness or the same cost but higher effectiveness, it should be selected (cells D and H).

If the "alternative" has the same cost and the same effectiveness, other factors can be considered before selecting the treatment for the formulary (e.g., ensuring a continuous supply chain).[5]

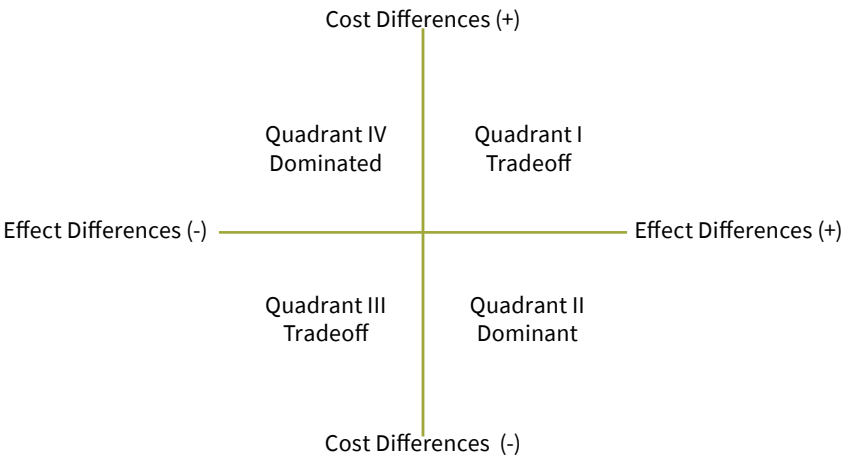

Figure 1. Cost-effectiveness plane

- Quadrants I and III: an ICER would need to be calculated because the "alternative" has a higher price for a higher effectiveness or a lower cost for lower effectiveness
- Quadrant II: the "alternative" is the dominant option and should be selected because it provides higher effectiveness at a lower price
- Quadrant IV: the "alternative" is the dominated option and should not be selected because it provides lower effectiveness at a higher price.[5]

Summary: Take Home Message

- In a CEA, the input measure is cost and the output measure is a natural health unit or clinical outcome
- An ICER is calculated in a CEA and compared to a willingness to pay measure or three times the GDP per capita of a country
- Only medicines with the same clinical outcome can be compared in a CEA

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Take-home Message

A CEA involves the calculation of an ICER. To calculate an ICER, costs of competing therapies or interventions and their clinical outcomes (in natural health units), such as blood pressure measurements or glucose control measures, are compared. The benefit of using natural health outcomes in a CEA is that many clinicians work with these measures daily. The disadvantage of a CEA is that only medicines or interventions with the same outcome measures can be compared (e.g., one can compare two antihypertensive medicines in a CEA but cannot compare a diabetes medicine to an antihypertensive medicine). The ICER is compared to a WTP threshold or, in the absence of a WTP measure, to three times the GDP per capita of a country to determine whether the proposed intervention is cost effective. The results of a CEA are sometimes displayed in a cost-effectiveness grid or plane to illustrate the point of dominance (where one treatment may be more effective but cost less) or to indicate when an ICER calculation would be required (e.g., where one treatment might cost more but offer a better clinical outcome).

Group Activity 3

Compare two treatments for the prevention of kidney transplant rejection (treatment A and treatment B) with a CEA using the following information:

One hundred patients are treated with each agent to prevent organ rejection after transplant. Among those patients, 48 rejections occur with treatment A and 32 rejections occur with treatment B. The total costs to treat 100 patients with treatment A and treatment B are $2,890,000 and $2,930,000, respectively.

Group Activity 4

Cost Effectiveness Analysis of Two Antimalarial Treatments [37]

The Pharmaceutical Therapeutics Committee is considering adding artemisinin-based combination therapy for the treatment of uncomplicated malaria. There are two options: artesunate+lumefantrine (A+L) or artesunate+mefloquine (A+M).

The effectiveness of both medicines was summarized in a systematic review:

- A+L, 6 doses: 11 of 289 patients (4%) had parasitemia at 28 days
- A+M, 3 days: of 100 patients, none had parasitemia at 28 days

References for the slides used in this module

The A+L dosage in adults is six doses of four tablets (20 mg + 120 mg). The A+M dosage in adults is four tablets of artesunate daily for three days (200 mg per day) and 500 mg of mefloquine on day 2 and 250 mg on day 3 (for a 50 kg adult).

The cost of one pack of 24 A+L tablets is $5.00. The cost of A+M (two separate packets) is $1.54 for 12 artesunate 50 mg tablets and $4.57 for six mefloquine 250 mg tablets.

1. Evaluate the cost effectiveness of A+M compared to A+L. *Assume the cost is current day costs*.
2. Conduct a simple sensitivity analysis by reducing the effectiveness of A+M to 5% lower than that of A+L. What other important criteria should be considered when adding such a medicine to the formulary?
3. Which of these two medications is the preferable product for the formulary?

Group Activity 5

Take-home Activity

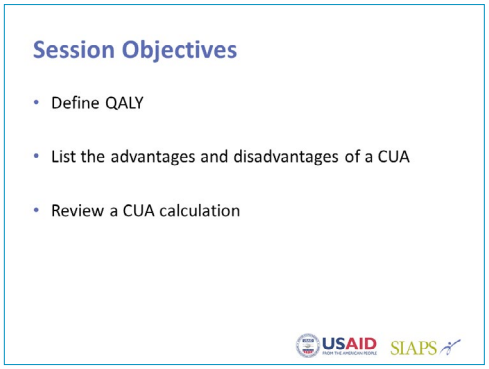
Participants should be encouraged to read and critique the following article using the critique questions outlined in module 5, as suggested by Rascati in *Essentials of Pharmacoeoncomics*. **This can be a take-home activity, with time provided at follow up sessions to review responses if desired**.

Chen JG, Ferrucci L, Moran WP, Pahor M. 2006. A cost-minimization analysis of diuretic-based antihypertensive therapy reducing cardiovascular events in older adults with isolated systolic hypertension. Open Access. Cost Effectiveness and Resource Allocation 2005, 3:2.

MODULE 7 : COST UTILITY ANALYSIS

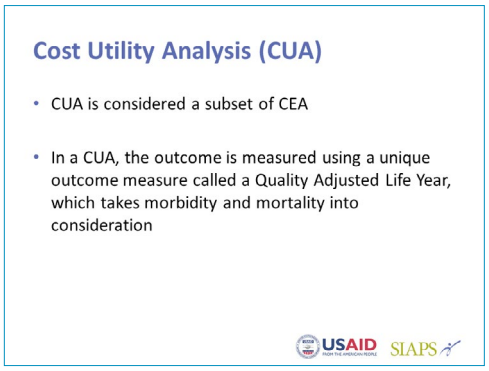
Notes to the instructor

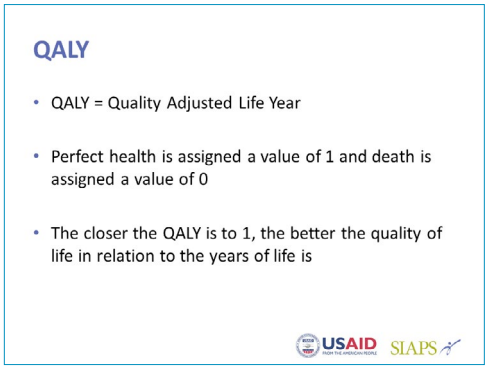
Time Allocation:		**1 hr**
	Introduction and recap of QALY	10 min
	Advantages and disadvantages of CUA	20 min
	Group activity	30 min
Preparation:	Read through the curriculum guide and corresponding slide deck	
	Encourage participants to quickly recap module 3	
Resources Required:	Flip chart/white board for group activity discussion	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	



Session Objectives

- Define QALY
- List the advantages and disadvantages of a CUA
- Review a CUA calculation

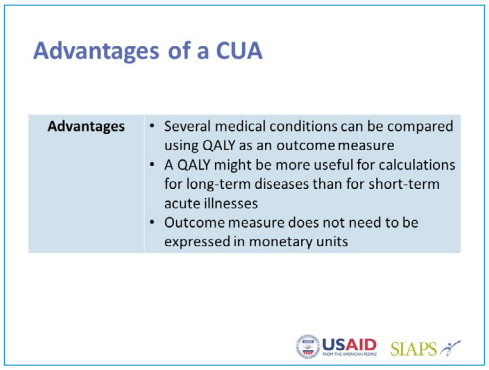


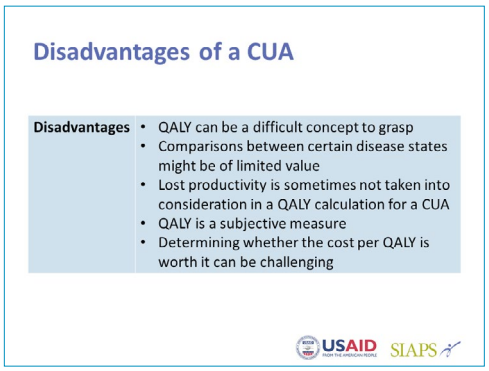


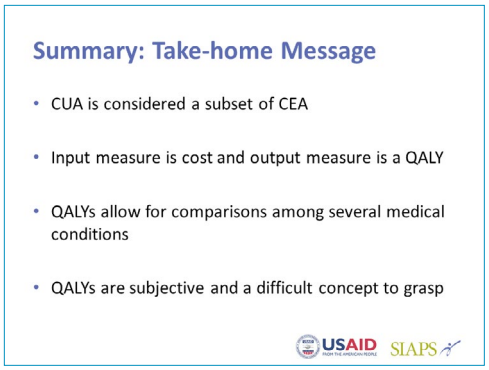
Introduction

CUA is considered a subset of CEA in which the outcome is measured using QALY, a unique outcome measure that takes morbidity and mortality into consideration. The length of life saved is measured against the patient's quality of life. This is important because many treatments can extend a patient's life but produce very poor quality of life due to side effects of the medication or other factors. The outcome measure in a CUA can also be a DALY, where the number of years lived with the disability plus the number of years lost is taken into consideration. The QALY is more commonly used in a CUA.[5]

The definitions of QALY and DALY and methods for calculating QALYs are discussed in module 3. In summary, perfect health is assigned a value of 1 and death is assigned a value of 0. Using various methods (e.g., rating scale, time trade off, standard gamble), utilities are calculated and used to generate a QALY between 0 and 1. The closer the QALY is to 1, the better the quality of life in relation to the years of life. For example, dealing with seasonal allergies might be assigned a value of 0.9 while being diabetic on dialysis with diminishing eye sight might be given a QALY of 0.4.[5]







Advantages and Disadvantages of a CUA

The advantage of a CUA compared to a CEA is that in a CEA, one ICER is calculated for two or more medicines for the same medical condition, while in a CUA, several medical conditions can be compared using the QALY as an outcome measure. Compared to the CBA, an advantage of the CUA is that the outcome measure does not need to be expressed as a monetary unit.[5]

One major disadvantage of a CUA is that the QALY can be a difficult concept to grasp and is not used frequently by clinicians and decision makers. Lost productivity may not be taken into consideration as part of the morbidity aspect of a QALY and might limit the CUA.[28] Determining whether the cost per QALY is worth it can be challenging. Ethically, it is difficult to set a WTP value for a cost per QALY. The QALY is a subjective unit, derived from reports from several groups of patients, compared to for example the natural health units that are used in a CEA.[5]

CUA Calculations

The CUA calculation is similar to a CEA calculation. The numerator outlines the differences in cost and the denominator outlines the difference in QALYs, resulting in a cost per QALY.

Take-home Message

CUA is a subset of CEA in which the input measure is cost and the outcome measure, a QALY, combines morbidity and mortality. Several medical conditions can be compared using the QALY as an outcome measure. Although the CUA allows for several conditions to be compared, a major disadvantage of this type of analysis is that the concept of the QALY is subjective and difficult to grasp.

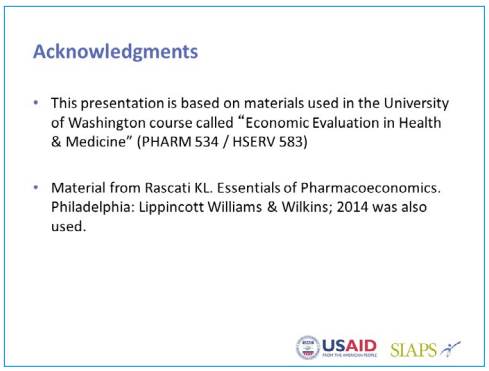
Group Activity

Review the following abstract and table from *Round J, Leurent B, Jones L. A cost-utility analysis of a rehabilitation service for people living with and beyond cancer. BMC Health Services Research 2014, 14:558 and complete the CUA calculation.*

Abstract[38]

Background: We conducted a wait-list control randomized trial of an outpatient rehabilitation service for people living with and beyond cancer, delivered in a hospice day care unit. We report the results of an economic evaluation undertaken using the trial data.

Methods: Forty-one participants were recruited into the study. A within-trial stochastic cost-utility analysis was undertaken using Monte-Carlo simulation. The outcome measure for the economic evaluation was quality adjusted life years (QALYs). Costs were measured from the perspective of



the NHS and personal social services. Uncertainty in the observed data was captured through probabilistic sensitivity analysis. Scenario analysis was conducted to explore the effects of changing the way QALYs were estimated and adjusting for baseline difference in the population. We also explore assumptions about the length of treatment benefit being maintained.

Results: The incremental cost-effectiveness ratio (ICER) for the base-case analysis was £14,231 per QALY. When QALYs were assumed to change linearly over time, this increased to £20,514 per QALY at three months. Adjusting the estimate of QALYs to account for differences in the population at baseline increased the ICER to £94,748 per QALY at three months. Increasing the assumed length of treatment benefit led to reduced ICERs in all scenarios.

Conclusions: Although the intervention is likely to be cost-effective in some circumstances, there is considerable uncertainty surrounding the decision to implement the service. Further research, informed by a formal value of information analysis, would reduce this uncertainty.

Table 7. Cost and QALY measures for Control and Intervention

Base Case Results	Control		Intervention	
	Cost (£)	**QALY**	**Cost (£)**	**QALY**
	1,193	0.112	1,928	0.164

1. For the base case, calculate the incremental cost per QALY.
2. Comment on the calculation based on the abstract.

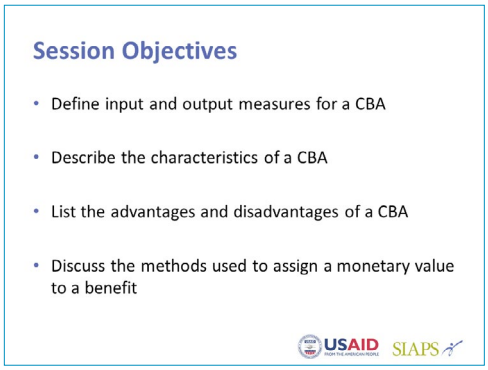
Suggested Reading

- Paltiel AD, Fuhlbrigge AL, Kitch BT, Liljas B, Weiss ST, Neumann PJ, ScD D, Kuntz KM. Cost-effectiveness of inhaled corticosteroids in adults with mild-to moderate asthma: Results from the Asthma Policy Model. Allergy Clin Immunol 2001; 108:39-46.
- Howard K, White S, Salkeld G, McDonald S, Craig JC, Chadban S, Cass A, MBBS. Cost-Effectiveness of Screening and Optimal Management for Diabetes, Hypertension, and Chronic Kidney Disease: A Modeled Analysis. Value in Heath (13):2.

MODULE 8 : COST BENEFIT ANALYSIS

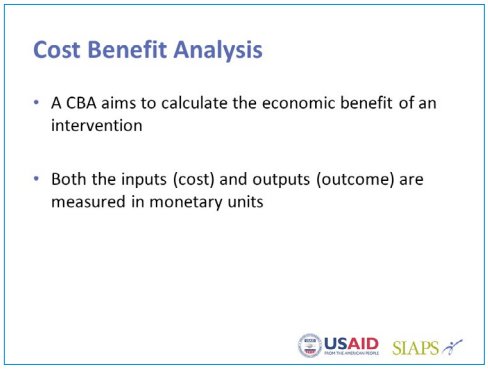
Notes to the instructor

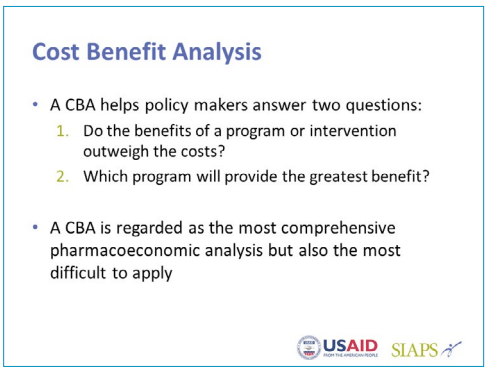
Time Allocation:		**3.5 hrs**
	Characteristics, advantages, and disadvantages of a CBA	20 min
	Methods to monitor the monetary value of health benefits	40 min
	Steps in a CBA with example	30 min
	Group activities 1 and 2 (activity and report back)	2 hrs (1 hr each)
Preparation:	Read through the curriculum guide and corresponding slide deck	
Resources required:	Flip chart/white board for group activity discussion	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	



Session Objectives

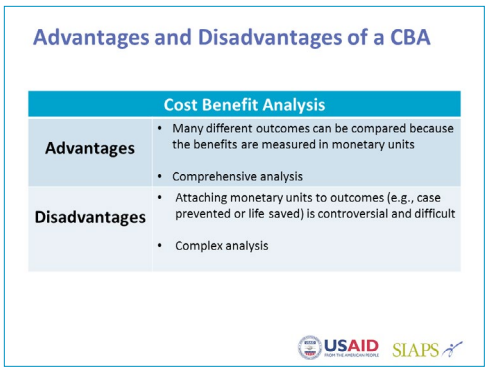
- Define input and output measure for a CBA
- Describe the characteristics of a CBA
- List the advantages and disadvantages of a CBA
- Discuss the methods used to assign a monetary value to a benefit

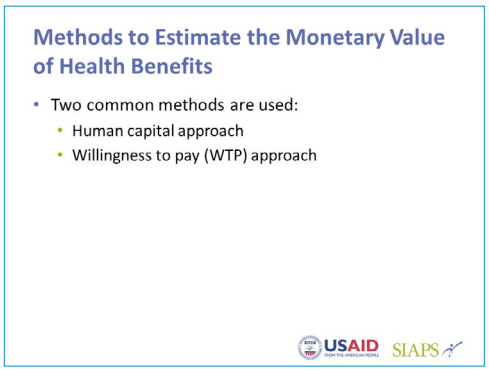


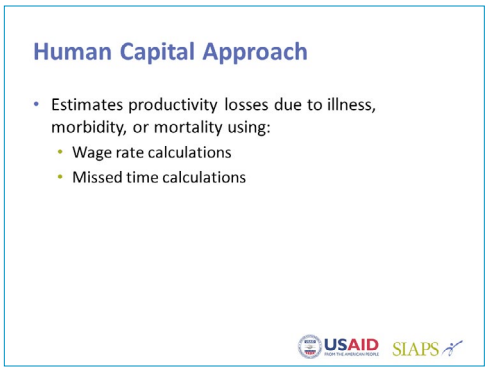


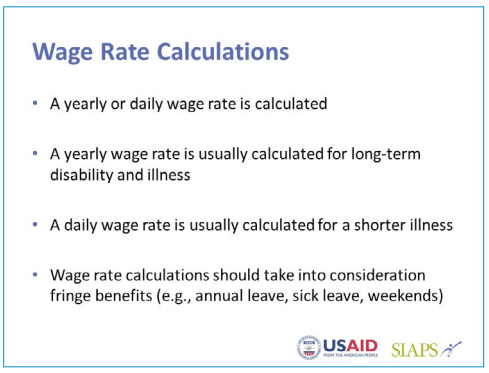
Characteristics of a Cost Benefit Analysis

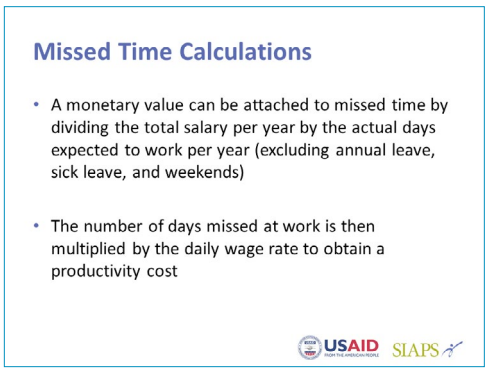
A CBA aims to calculate the economic benefit of an intervention.[28] In a CBA, both the inputs (cost) and outputs (outcome) are measured in monetary units. A CBA helps policy makers answer two questions: Do the benefits of a program or intervention outweigh the costs? Which program will provide the greatest benefit?[5] Benefits can be viewed as cost savings or costs avoided. For example, the cost benefit of a mail order pharmacy service for stable chronic patients that is designed to decrease waiting times at clinics could be assessed in a CBA. The benefit of the mail order service is that a patient's medicines are delivered at home and the patient does not need to take time off from work. The hours saved by not waiting in line at the clinic can be spent at work. The indirect benefit of the intervention (mail order pharmacy) is increased productivity. In a CBA, we attach a monetary value to the hours saved by not waiting in line at the clinic, and thereby to the indirect benefit of increased productivity. The monetary value that is attached to the increased productivity is the wage rate per hour that would have been lost if the patient could not work due to the long waiting time at the clinic. A CBA is regarded as the most comprehensive pharmacoeconomic analysis but also the most difficult to apply.[28]











Advantages and Disadvantages

An advantage of a CBA is that, unlike a CEA, many different outcomes can be compared because the benefits are measured in monetary units. If conducted correctly, it is a very comprehensive analysis. If interventions for different disease states are compared (e.g., an asthma clinic compared to a diabetes clinic), the intervention with the highest benefit to cost ratio would most likely be selected to maximize resources. This advantage can also be viewed as a disadvantage because it is difficult to attach monetary value to some types of outcomes (e.g., lives saved), making the analysis complex to conduct.

Methods to Estimate the Monetary Value of a Health Benefit[5]

Two common methods are used:

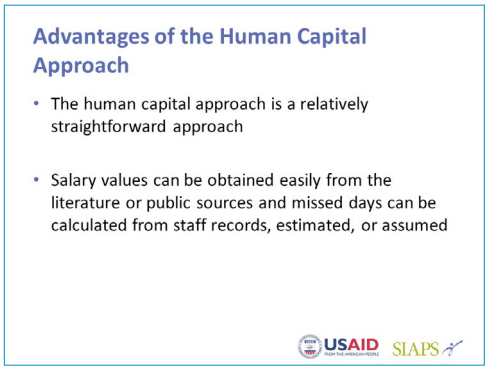
- Human capital approach
- Willingness to pay approach

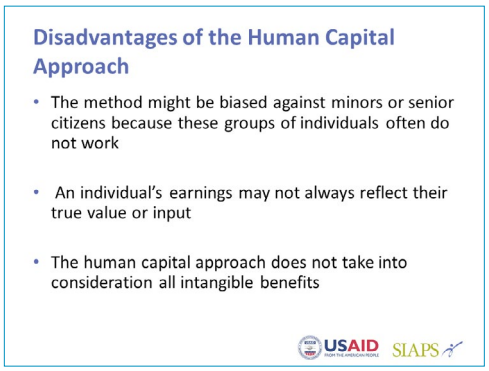
Human Capital Approach[5]

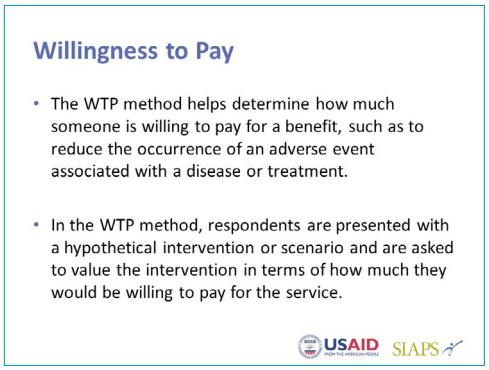
The human capital approach estimates productivity losses due to illness, morbidity, or mortality. Wage rate calculations and missed time because of illness are used.

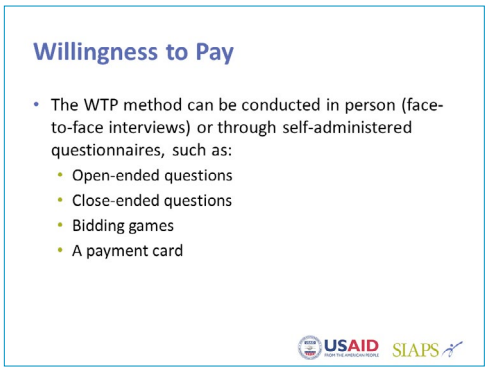
In a wage rate calculation, a yearly or daily wage rate is calculated. An annual wage rate is usually calculated for long-term disability and illness, while a daily wage rate is usually calculated for a shorter illness. Wage rate calculations should consider fringe benefits, such as annual leave, sick leave, and weekends.

A monetary value can be assigned to missed time days by taking the total salary per year divided by the actual days expected to work per year (excluding annual leave, sick leave, and weekends) to provide a daily wage rate. The number of work days missed is then multiplied by the daily wage rate to obtain a productivity cost.[5]









Group Activity 1

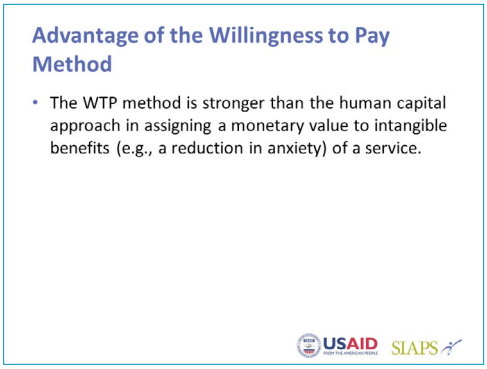
The purpose of the activity is to show how productivity benefits are calculated.

A diabetes clinic intervention decreased the average waiting time for patients at a clinic from eight hours to three hours per month. Calculate the indirect benefit/productivity saving per year for a patient who earns $12,000 per year without weekend work. Annual leave and sick leave are each 12 days per year. Assume an eight-hour workday.

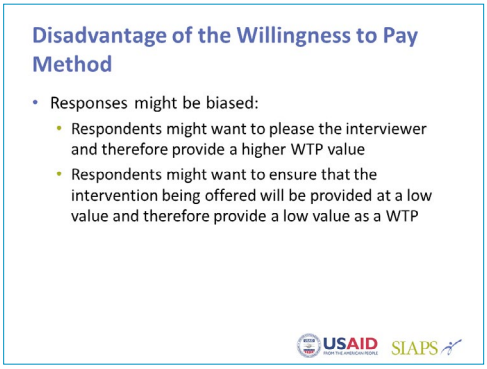
The human capital approach is relatively straightforward. Salary ranges can be easily obtained from the literature or public sources, and missed days can be calculated from staff records, estimated, or assumed. A disadvantage of the human capital approach is that the method might be biased against groups of people who are not employed (e.g., minors or senior citizens). In addition, Rascati points out that an individual's earnings may not always reflect their true value or input. Therefore, average wages for the population should be used in the calculations if possible. The human capital approach does not take into consideration all intangible costs that may impact productivity (e.g., hot flashes, which are associated with menopause, can affect a person's quality of life but not necessarily causes missed time from work).[5]

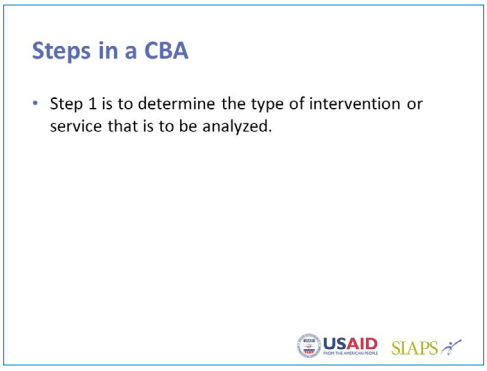
Willingness to Pay Method[5]

The WTP method helps determine how much someone is willing to pay for a benefit, such as to decrease the frequency of an adverse event associated with a disease or treatment. In the WTP method, respondents are presented with a hypothetical intervention or scenario and are asked to value the intervention in terms of how much they would be willing to pay for the service. The WTP method can be conducted in person (face to face interviews) or through self-administered questionnaires. Open-ended questions, close-ended questions, bidding games, or a payment card are then used to determine the respondents' WTP for the intervention or service described in the hypothetical scenario. In an open-ended question, the respondent is asked how much he or she would be willing to pay for a product or service. In a close-ended scenario, the respondent is asked to answer yes or no, in terms of willingness to pay a stipulated price for a product or service. In a bidding game, the respondent is asked if he or she is willing to pay a certain amount for a product or service. If the answer is yes, the price increases. If the answer is no, the price decreases and the respondent is asked the question again. Using a payment card system, the respondent is given several options on a price for a product or service, all at once, and has to pick one option.[5]



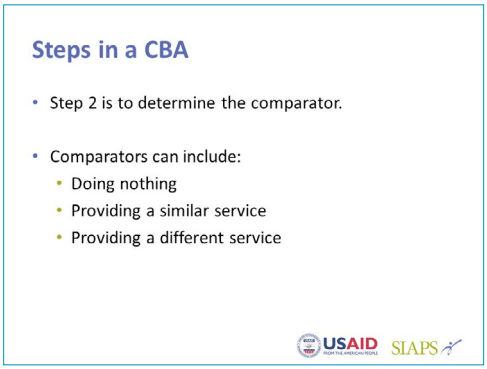
The WTP method is stronger than the human capital approach in assigning a dollar value to intangible benefits (e.g., a reduction in anxiety) of a service. A disadvantage of this method is that responses might be biased in that respondents might want to please the interviewer and therefore provide a higher WTP value. Other respondents might want to ensure that the intervention being offered will be provided at a low value and gives a low value for WTP.[5]



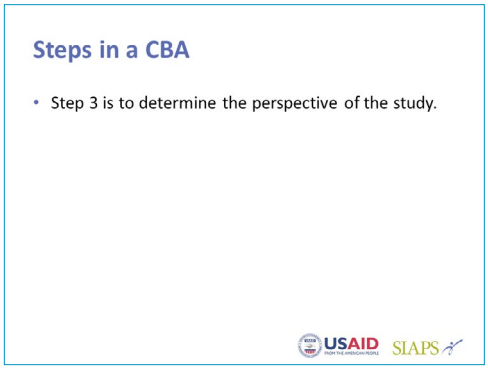


Steps in a CBA[5]

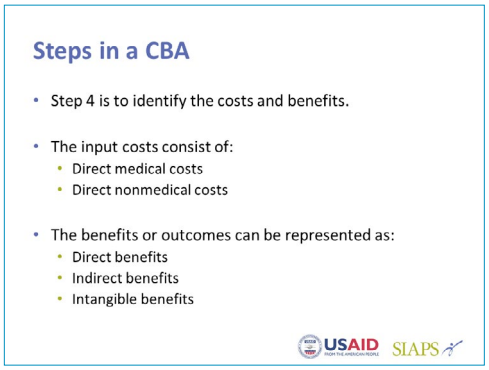
- **Step 1** is to determine the type of intervention or service that is to be analyzed, such as the implementation of a diabetes service.



- **Step 2** is to determine the comparator. Comparators can include doing nothing, providing a similar service, or providing a different service.

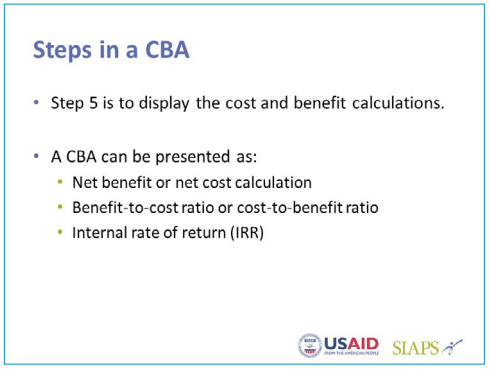


- **Step 3** is to determine the perspective of the study (i.e., whose cost are you measuring?).



- **Step 4** is to identify the costs and the benefits.
  The input costs usually consist of:
  - Direct medical costs
  - Direct nonmedical costs

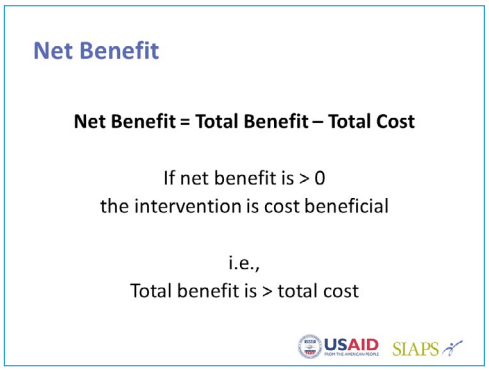
  The benefits or outcomes can be represented as:
  - Direct benefits (medical and nonmedical)
  - Indirect benefits (productivity costs)
  - Intangible benefits (e.g., reduction in anxiety associated with illness)



- **Step 5** is to display the cost and benefit calculations.
  A CBA can be presented as:
  - Net benefit or net cost calculation
  - Benefit-to-cost ratio or cost-to-benefit ratio
  - Internal rate of return

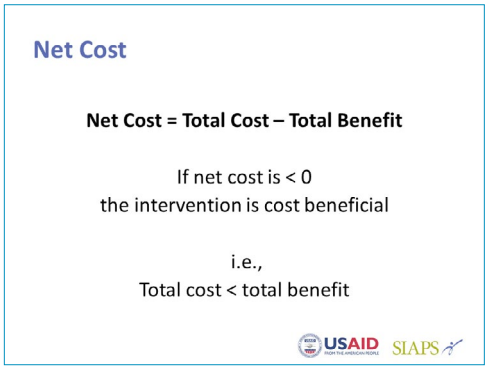
Once the overall benefits and total costs are totaled (i.e., a monetary value is attached to benefits and costs), a net benefit or net cost is calculated. Alternatively, the benefits and costs can be displayed as a benefit-to-cost or cost-to-benefit ratio.

Equations:



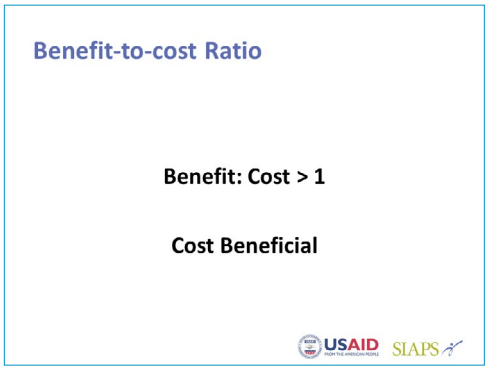
Net Benefit = Total Benefit – Total Cost

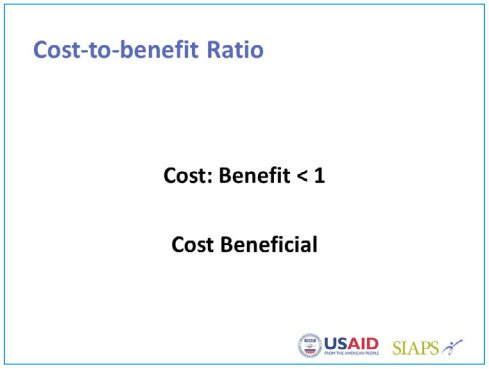
If the net benefit is > 0, the intervention is cost beneficial.



Net Cost = Total Cost – Total Benefit

If the net cost is < 0, the intervention is cost beneficial.





Benefit-to-cost OR Cost-to-benefit Ratio

For an intervention or program to be cost beneficial, the monetary value (e.g., savings produced from the intervention) attached to the benefits should be greater than the costs incurred.

Therefore, if we divide the benefits by the costs, we want the numerator (benefits) to be greater than the denominator (costs) so that the benefit-to-cost ratio is greater than 1.

Similarly, if we divide the costs by the benefits, we would want the denominator (benefits) to be greater than the numerator (costs) so that the cost-to-benefit ratio is less than 1.

Sample CBA

A CBA can be illustrated to participants using the following article: Behrens RH, Roberts JA. Is travel prophylaxis worthwhile? Economic appraisal of prophylactic measures against malaria, hepatitis A, and typhoid in travelers. 1994. BMJ: 309.

The article should be used for an illustrative purpose only to highlight the process and value of CBA. Participants should be encouraged to review the paper as a take-home activity to understand the process of a CBA.

The primary aim of the study was to "estimate the costs and benefits of prophylaxis against travel acquired malaria, typhoid fever, and hepatitis A in United Kingdom residents during 1991".[39]

The study describes the research as follows:

"For a cost-benefit analysis it is necessary to assess the costs of the prophylaxis and compare these with the gains that are attributable to its use. To do this it is necessary to trace the costs and benefits to all those concerned-namely, the public sector, including the public health service, community services, hospital services-and costs to individuals and society in terms of loss of productive capacity and, occasionally, life. The researchers used the cost of avoided diseases estimated from prophylaxis use in 1991 and costed prophylaxis provision to derive a cost-benefit ratio."[39]

The main outcome measures studied and used in the CBA were:

- "Incidence of travel associated infections in susceptible United Kingdom residents per visit
- "Costs of prophylaxis provision from historical data
- "Benefits to the health sector, community, and individuals in terms of avoided morbidity and mortality based on hospital and community costs of disease".[39]

The table below summarizes how the cost and benefit components of the CBA were derived. Participants should be encouraged to read the full article as a take-home activity.

Table 8. Description of Cost and Benefits[39]

Incidence of Disease in Travelers	▪ Estimated the incidences of hepatitis A, typhoid fever, and malaria in United Kingdom residents who returned from disease endemic regions ▪ Based on immunization and effectiveness of prophylaxis	
Costs	▪ Health Sector Costs	– Hospital costs – General practitioner costs – Prescription charges and expenses
	▪ Costs to Travelers and Society	– Costs to the traveler and society include estimated lost productivity time and lost income based on average earnings plus costs of employment in 1991 for non-manual employees. – Costs of travel to the general practitioner's surgery and to hospital for diagnosis and treatment and obtaining prescriptions
Loss of Life	▪ Reported case fatality rates for typhoid, hepatitis A, and malaria were used to provide the number of lost lives, which was used to calculate the value of these lives by the incurred costs of avoidance. This is regarded by some as controversial as it involves placing a dollar value on life.	

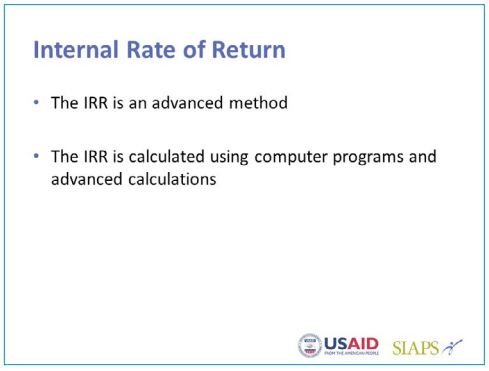
Table 9 summarizes the findings. We see that the cost-to-benefit ratio for malaria prophylaxis is between 0.19 and 0.57 (depending on treatment), indicating that malaria prophylaxis is cost beneficial. The cost-to-benefit ratios for typhoid prophylaxis and hepatitis prophylaxis are both greater than one. Participants should be reminded that this is a cost-to-benefit ratio rather than a benefit-to-cost ratio, and therefore a ratio of less than 1 is desired for an intervention to be cost beneficial.[39]

Table 9. Estimated Costs and Prophylaxis and Illness Prevented by Regimen in 1991 with Cost Benefit Ratios[39]

TABLE V – Estimated costs ofprophylaxis and illness prevented iy, regimen in 1991 with cost-benefit ratios

	No of cases prevented	Cost of intervention (£)	Avoided expenditure on illlness (£)	Expenditure avoided per case (£)	Prophylaxis cost per avoided case (£)	Cost-benefit ratio	Cost-benefit sensitivity range
Malaria prophylaxis for three months							
Chloroquine+proguanil	2 653	3 607 308	19 116 709	7 205	1 360	0·19	0·18–0·21
Mefloquine	3 144	12 822 363	22 656 840	7 205	4 078	0·57	0·51–0·67
Typhoid, single journey	183		1 676 747	9 182			
Ty 21a vaccine		36 925 695			202 207	22·0	14·1–26·1
Typhoid Vi vaccine		30 247 947			165 639	18·0	11·6–21·4
Whole cell killed monovalent typhoid vaccine		30 343 095			166 160	18·1	11·6–21·5
HepatitisA, single joumey	291		3 451 187	11 857			
Human normal immunoglobulin		20 145 455			69 210	5·8	4·7–6·3
Hepatitis A vaccine		54 471 134			187 137	15·8	12·7–17·0
Hepatitis A, four journeys	291		12 061 666	41 438			
Human normal immunoglobulin		70 407 014			241 885	5·8	4·7–6·3
Hepatitis Avaccine		54 471 134			187 137	4·5	3·6–4·9

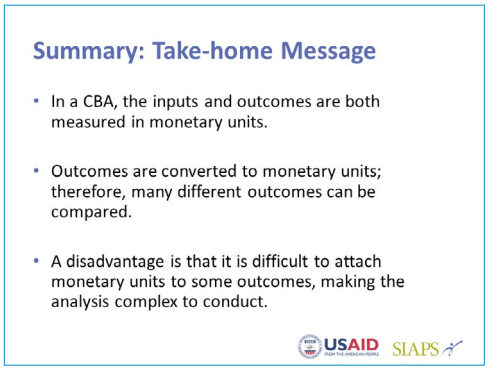
For multiple joumeys costs were discounted at 6% annually. Cost-benefit ratio was derived from morbidity cost avoided by 1991 levels ofprophylaxis use against cost ofprophylaxis provision.

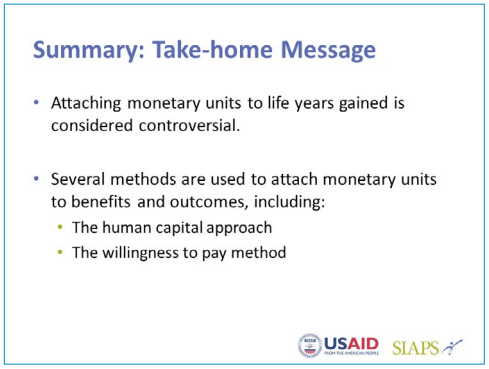


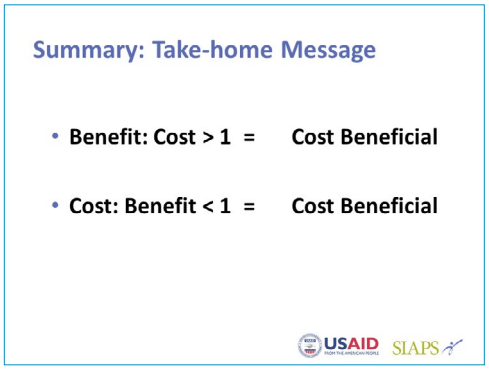
Internal Rate of Return[5]

Internal rate of return (IRR) is an advanced method and is calculated using computer programs and advanced calculations. IRR is the rate at which the present value of benefits equals the present value of costs. The point at which costs and benefits are equal is calculated and then compared to a hurdle rate or minimum rate of return. To calculate the point at which the costs and benefits are equal, discount rates that are used in the calculations can be increased or decreased until the calculation results in a zero value. The discount rate at which the benefits equal the costs is the IRR. If the IRR is greater than the hurdle rate, the intervention or program is accepted as cost beneficial (i.e., it will yield a higher rate of return than another option). This is an advanced CBA analysis.[5]

The IRR is introduced here as a method to present a CBA. Facilitators should reiterate to participants that there is no expectation for participants to master this advanced CBA method. There are experts in the field who should be consulted for countries that require this type of analysis and support.







Take-home Message

In a CBA, the inputs and outcomes are both measured in monetary units. Because outcomes are converted to monetary units, many different outcomes can be compared. However, a disadvantage is that it is difficult to attach monetary units to outcomes, which makes the analysis complex to conduct. In addition, attaching monetary units to life years gained is considered controversial. Several methods are used to attach monetary units to benefits and outcomes, including the human capital approach (where productivity losses are measured) and the WTP method. For an intervention or program to be cost beneficial, benefits divided by costs should be greater than 1 or costs divided by benefits should be less than 1.

Group Activity 2

The purpose of this activity is to understand and interpret the net benefit and net cost calculations and the benefit and cost ratios.

For the following two interventions, calculate and compare the:

- Net benefit calculation
- Net cost calculation
- Benefit-to-cost ratio
- Cost-to-benefit ratio

	Benefits ($)	**Costs ($)**
Intervention 1	10,000	7,000
Intervention 2	15,000	13,500

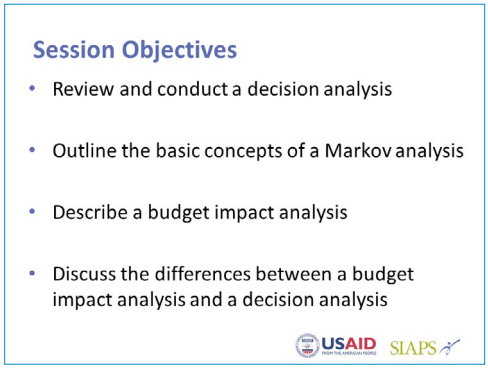
Discussion Questions

1. Which intervention is cost beneficial?
2. Which intervention would you select?

MODULE 9 : ADVANCED PHARMACOECONOMIC ANALYSES AND BUDGET IMPACT ANALYSES

Notes to the instructor

Time allocation:		**5.5 hrs**
	Decision analysis	1 hr
	Markov analyses	30 min
	Group activity 1	1 hr
	Group activity 2	1 hr
	Budget impact analyses and group activity 3	1 hr
	Group activity 4, article critique	1 hr
Preparation:	Read through the curriculum guide and corresponding slide deck	
Resources required:	Flip chart/white board for group activity discussion	
Optional:	Ask participants to rate the module using the module evaluation sheet (annex B)	



Session Objectives

- Review and conduct a decision analysis
- Outline the basic concepts of a Markov analysis
- Describe a budget impact analysis
- Discuss the differences between a budget impact analysis and a decision analysis

Introduction

The selection of essential medicines in LMICs can usually be supported by simple pharmacoeconomic methods, including CMA and CEA. However, there might be occasions where more advanced pharmacoeconomic analyses are required. Advanced pharmacoeconomic analyses usually require expert input as there may be complicated calculations associated with these methods.

In this module, we introduce the basic concepts of advanced pharmacoeconomic methods, such as decision analyses and the Markov model. Facilitators should reiterate to participants that there is no expectation for participants to master advanced pharmacoeconomic analyses through this training. There are experts in the field who are available to consult on advanced pharmacoeconomic analyses for countries that require this type of analysis and support.

The purpose of this module is to provide the broad details of advanced pharmacoeconomic methods so that participants will recognize these advanced forms of analyses in the literature, understand when advanced methods might be suitable, and know when to contact an expert for support.

Decision Analysis

- Decisions analysis:
  - Analytical/quantitative method
  - Systematically compares the relative costs and consequences of different treatment options
  - Assesses the value of one or more medical options

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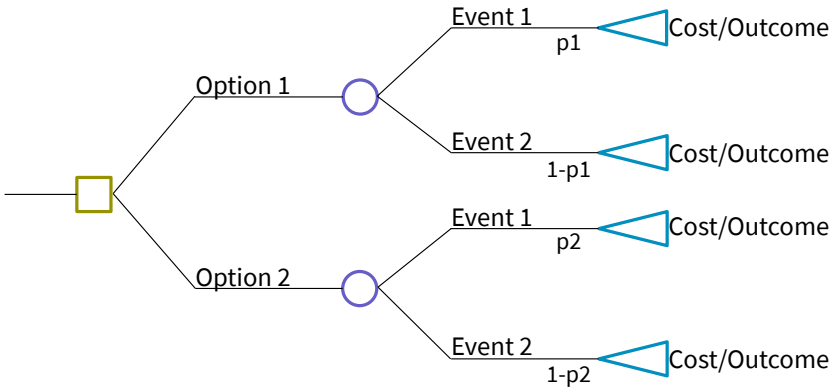
What Is a Decision Analysis?

A decision analysis is a systematic approach for assessing the relative costs and consequences of different treatment options. It is appropriate if a problem involves chance or potential events that occur over a short time horizon. Examples of potential events include the probability of a treatment cure or failure with or without an adverse event. In a decision analysis, we structure a problem using a decision tree. This is a diagram that begins with a treatment decision and then branches out to explore all potential health outcomes and costs arising from the treatment alternatives.[9]



(p1 and 1-p1 are probabilities linked to event 1, while p2 and 1-p2 are probabilities linked to event 2). Option refers to the pharmacotherapeutic/treatment alternatives/ interventions.

Figure 2. Outline of a decision tree

Software Programs for Conducting Decision Analysis

- Computer programs such as TreeAge can be used to conduct a decision analysis
- TreeAge. Available at: https://www.treeage.com/
- Calculations can also be conducted manually or completed in Microsoft Excel

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There are sophisticated computer programs that can be used to conduct a decision analysis, such as TreeAge.[40] Calculations can also be conducted manually or completed in Microsoft Excel.

In a decision tree, lines or branches connect chance, choice, and terminal nodes. The square denotes a choice node, or the point at which different treatment options could be selected. The circles represent a chance node, or the probability of an event over another event. The branch terminates in a terminal node.

Steps in a Decision Analysis

1. Identify the specific decision
2. Specify the alternatives
3. Draw the decision tree
4. Specify possible costs, outcomes, and probabilities
5. Perform calculations
6. Conduct a sensitivity analysis

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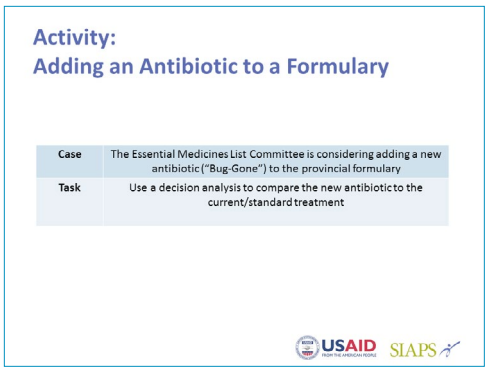
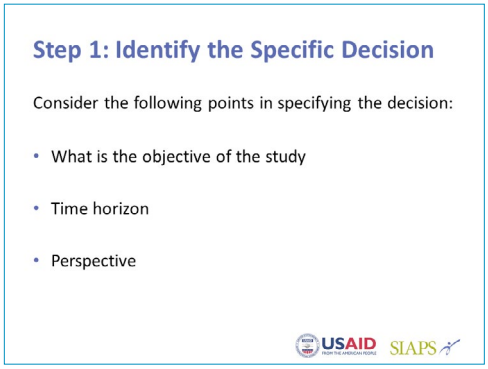
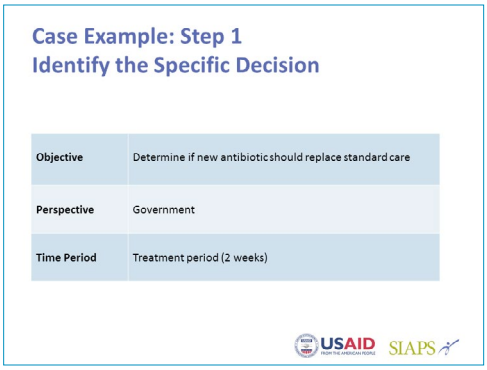
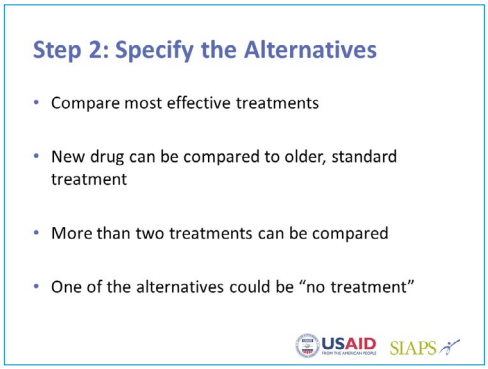
Steps in a Decision Analysis

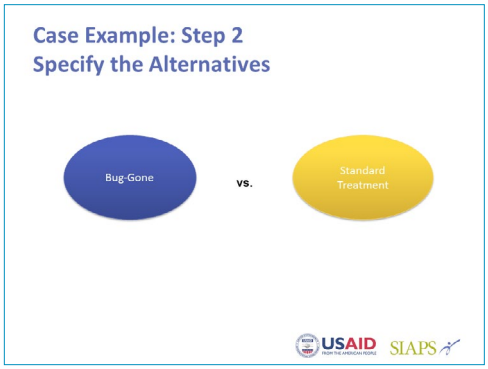
There are six steps in a decision analysis: (1) identifying the specific decision; (2) specifying the alternatives; (3) drawing the decision tree; (4) specifying the possible costs, outcome, and probabilities; (5) performing the analysis; and (6) conducting a sensitivity analysis. Each step will be explained using an example adapted from *Essentials of Pharmacoeconomics*.[5] As a hypothetical example, an essential medicine selection committee within a provincial department of health in South Africa is considering adding a new antibiotic, "Bug-Gone" to an STG. Currently, a standard of care option is being used for the same indication. The new antibiotic promises reduced adverse effects at a higher cost. The essential medicine selection committee requests a decision analysis as part of the selection process. The analysis is conducted in South African Rand Value.









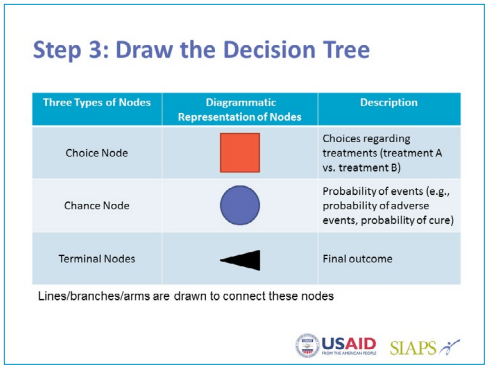


Step 1: Identify the Specific Decision

The task that is being undertaken is to determine whether a new antibiotic should be added to the STG or whether the standard of care option should be retained. The two options are being compared on their outcome (success and failure rates) relative to cost and adverse drug reactions. Before we proceed, you will recall from the cost section that we also need to specify the perspective of the study. In this case, the essential medicine committee is a government body; therefore, the perspective of the study is that of the government/public health sector. Another aspect that is important to consider is the time over which the treatment will be used. In this example, we are conducting an evaluation of an antibiotic, and therefore the dosing period and period over which side effects might occur (e.g., one to two weeks) would cover the time horizon.

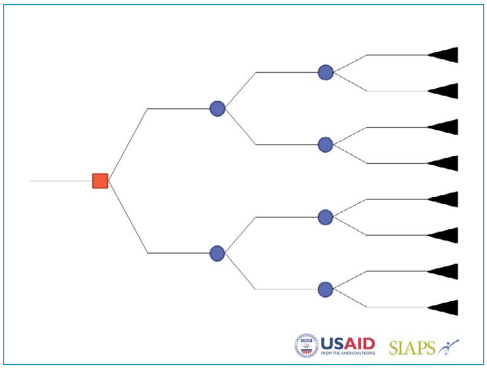
Step 2: Specify the Alternatives

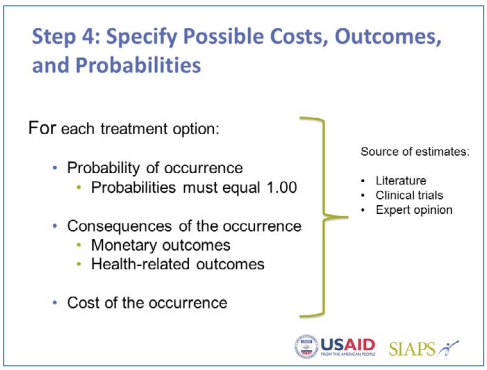
In this example, the new treatment will be compared to the standard treatment. In a decision analysis, two or more treatments are compared; ideally, the most effective treatments should be compared. A decision analysis can include a "no action"/"no treatment" option.



Step 3: Draw the Decision Tree

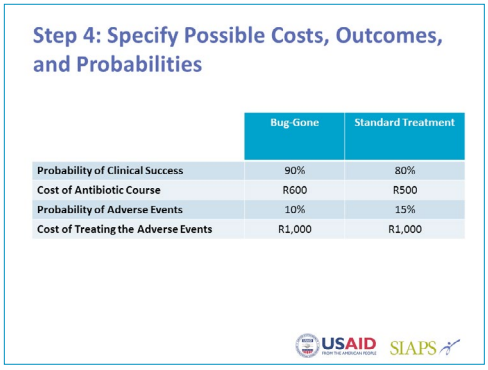
In a decision tree, the choice node represented by a square indicates the point at which alternatives are an option. The circles represent the chance nodes or the probability of an event (e.g., death, cure, or adverse events with or without cure). The decision tree terminates in a terminal node (represented by a "backward" triangle). In this example, there are two antibiotic treatment options. Both can lead to a successful outcome with adverse effects, a successful outcome with no adverse effects, a failure with adverse effects, or a failure with no adverse effects.

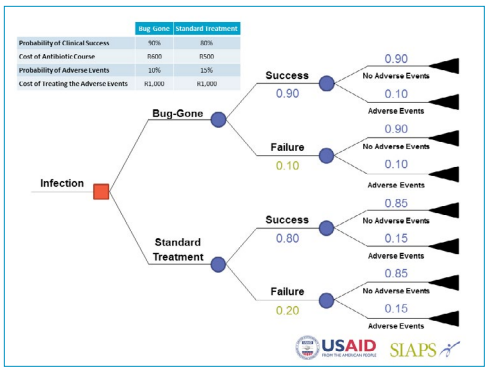


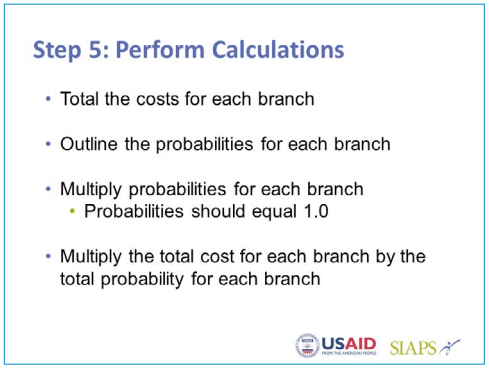


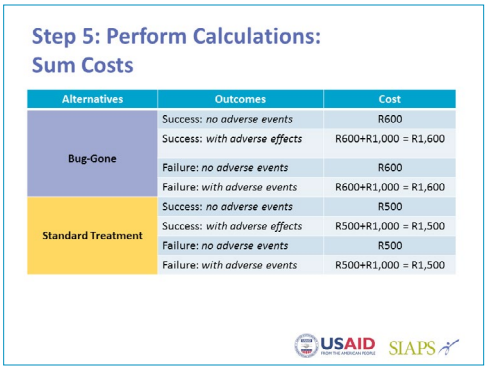
Step 4: Specify Possible Costs, Outcomes, and Probabilities

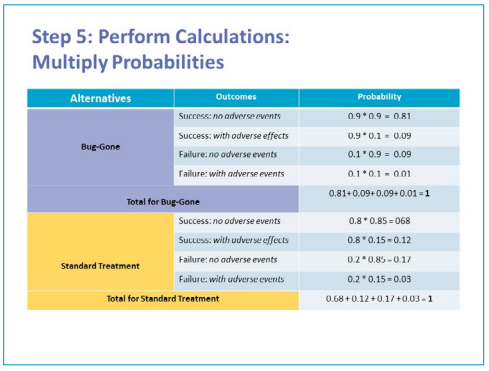
This could be the most time intensive portion of the analysis because the costs, outcomes, and probabilities will have to be obtained from the literature, randomized control trials, claims information, historical prices, other estimations/assumptions, and expert opinion. The costs, outcomes, and probabilities should ideally be outlined in a table. It is important to arrange the information in a systematic manner, with reference, which will help during step 6, conducting the sensitivity analysis. The information can be stored in a Microsoft Excel spreadsheet.

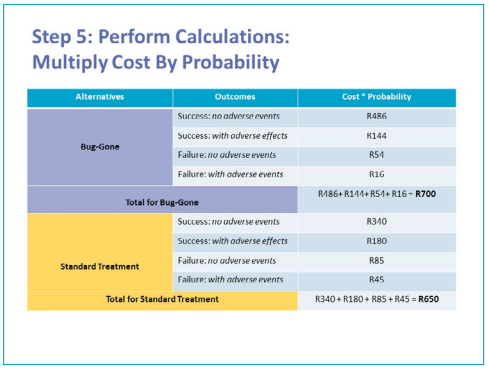








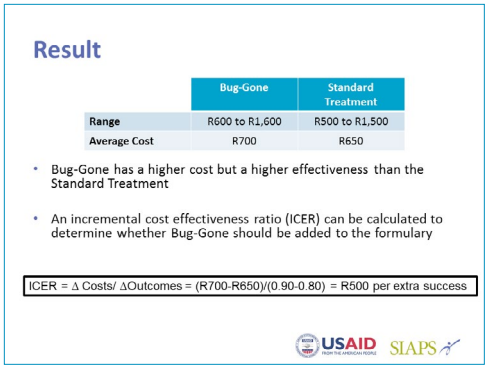


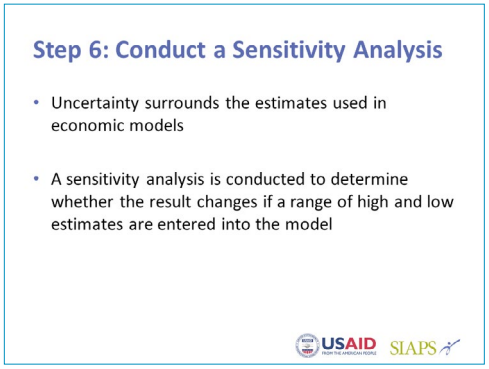


Step 5: Conduct the Calculations

- For each branch, sum up the costs. For Bug-Gone, costs for successful treatment with adverse effects would include the cost of the drug and the costs of the adverse effects.
- Outline the probabilities. *Probabilities for an outcome should equal 1*. In this example, if the probability of successful treatment with Bug-Gone is 90%, then the probability of failure on Bug-Gone is 10% (i.e., 100%-90%=10% or 1-0.9=0.1).
- All probabilities along a branch should be multiplied. For example, the probability of successful treatment with Bug-Gone is 0.9 and the probability of an adverse effect occurring while obtaining successful treatment on Bug-Gone is 0.1; therefore, 0.9 is multiplied by 0.1. This must be conducted along each branch.
- Finally, multiply the total cost (summed earlier) by the total probability (the product of the multiplied probabilities along a branch, obtained in c above) for each branch.
- Sum the answers for each alternative. This final sum produces an average cost per branch, which can be included in a CEA to obtain an ICER.

The calculations can be displayed on the decision tree.



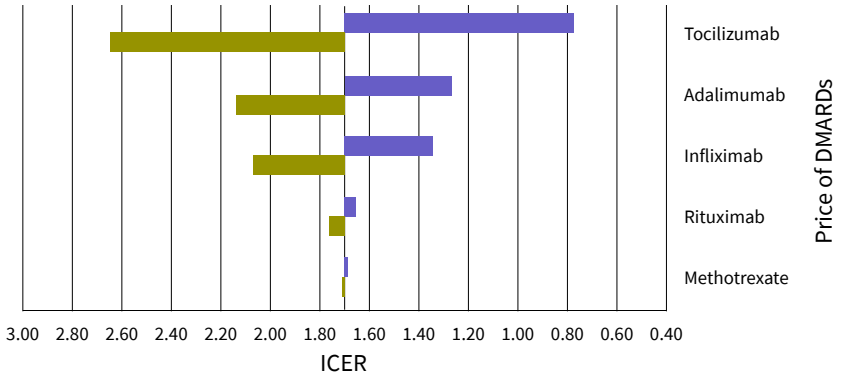


Step 6: Conduct a Sensitivity Analysis

In module 4, a brief explanation on sensitivity analyses was provided.

A sensitivity analysis, where estimates in the model are varied, is necessary because in economics there is always uncertainty surrounding estimates. Probability and cost estimates can be varied in the model to determine whether the ICER changes in relation to the willingness to pay threshold.

Several graphs can be used to depict the results of a sensitivity analysis, including a tornado diagram, which is used to show the impact of varying several variables on a range of values (figure 3).



Tornado diagram of sensitivity analysis. The effect of the price of to tocilizumab on the ICER was more than that of other medicines in both treatment sequences. DMARDs, disease-modifying antirheumatic drugs; ICER, incremental cost-effectiveness ratio.

Hashemi-Meshkini A, ShekoufehNikfar S, Glaser E, Jamshidi A, Hosseini SA. Cost-Effectiveness Analysis of Tocilizumabin Comparison with Infliximab in Iranian Rheumatoid Arthritis Patients with Inadequate Response to DMARDs: A Multistage Markov Model. Value in Health Regional Issues. 9C (2016):42-48.

Figure 3. Example of a Tornado Diagram[41]

The variable that had the greatest impact on the model is usually shown at the top of the tornado graph, in this case tocilizumab, where the price of tocilizumab on the ICER was more than that of the other medicines. The variable that had the lowest impact on the ICER in the sensitivity analysis is shown at the bottom of the tornado graph (with a smaller bar). In this example, the variation in the price of methotrexate had the smallest impact on the ICER.[41]

Group Activity 1

Pair participants to conduct a sensitivity analysis.

Participants will change out one or even two numbers in the example of "Bug-Gone" discussed in class to see how the decision analysis results change. Both participants should obtain the same answer at the end of the calculation and should be allowed to compare work to troubleshoot any problems. Allow the group to discuss what numbers were changed and how the results changed depending on how the estimate was adjusted in the sensitivity analysis (i.e., a higher or lower estimate was used).

The purpose of the activity is to give participants the opportunity to practice the steps of a decision analysis while also conducting a simple sensitivity analysis.

For example, participants may choose to increase the price of Bug-Gone, which will increase the average cost per successful treatment. Alternatively, if the effectiveness of the standard treatment decreases compared to Bug-Gone, the average cost per successful treatment for standard treatment will also increase, likely increasing the chance of Bug-Gone being cost effective depending on the WTP threshold.

Group Activity 2

What to do about Measles Vaccination (based on an exercise from Pettiti (2000))[42]

In 2000, WHO, the United Nations Children's Fund (UNICEF), and the Centers for Disease Control and Prevention co-sponsored a technical working group meeting to review the status of global measles control and regional elimination efforts and to formulate recommendations to accelerate control activities. Participants concluded that vaccination coverage of greater than 90% is required to achieve measles control and that a one-dose measles policy is insufficient to achieve and sustain measles control targets. The average seroconversion rate of 85% following one dose at age 9 months, which is the recommended strategy for routine vaccination in developing countries, leaves many children susceptible. The routine delivery system in many countries also fails to reach many children with a dose at 9 months. Therefore, in addition to the first dose at age 9 months, meeting participants recommended that a second opportunity for measles immunization is essential to protect those children previously missed by routine services and for those who failed to respond to their first dose of measles vaccine.

Your Minister of Health is now being lobbied to implement the recommendations of the technical working group without delay. As your country has a measles vaccination rate of 100%, he feels that your one-dose measles policy is sufficient to protect your country's children. He asks you for advice. You decide to perform a decision analysis to explore

the question. You begin by conducting a literature search. You have no country-specific epidemiological data on annual measles exposure rates, but from the literature, rates from similar countries range from 20% to 50%. You decide to use the average value (35%), and test the range in sensitivity analyses. From the literature, the probability of getting measles if exposed is 0.33 in a child who has had one vaccination and 0.05 in a child who has been revaccinated. UNICEF estimates the complete cost of a revaccination campaign is $1.25 per child (UNICEF. Measles: The Urban Challenge. UNICEF, New York. 1998).

Please respond to the following questions/points to consider in relation to the measles scenario. Be prepared to present your group's answers to the larger group.

1. What are the treatment options that you are being askedto consider?
2. List the possible events andoutcomes.
3. Based on the above information, construct a decision tree forthe problem, using cases of measles as your outcome and enter the probabilities of chance events into your decisiontree.

Do you agree that after constructing the decision tree, the data components required (probabilities, health outcomes, and costs) are more easily identifiable? These data may be derived from a literature review, primary data collection, and/or consultation with experts.

To analyze your decision tree, calculate the expected value of each relevant outcome for each decision option. This is a two-step process.

4. For each branch, or row, find the expected value of the branch by multiplying all of the branch's probabilities. Do this for both treatment options by filling out the following tables.

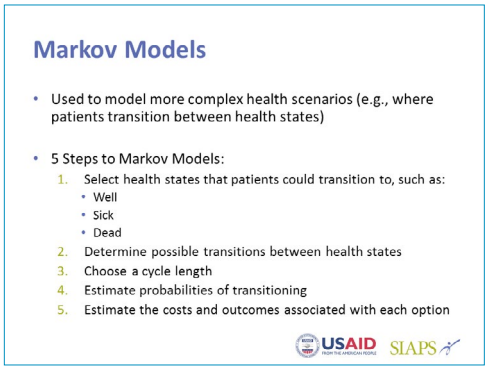
Revaccinate

P(exposed/not exposed)	P(get/don't get measles)	Multiplication	Expected value	Outcome
				Measles
				No measles
				Measles
				No measles

Don't revaccinate

P(exposed/not exposed)	P(get/don't get measles)	Multiplication	Expected value	Outcome
				Measles
				No measles
				Measles
				No measles

5. Add the measles outcomes for each decision option. What is the probability of measles for each of the twooptions?
6. What is the difference in the expected probability ofmeasles between revaccination and norevaccination?
7. How many cases of measles would be prevented if 100,000 eligible children wererevaccinated?
8. What is the total cost of revaccinating all eligiblechildren?
9. What is the cost per case of measles prevented of therevaccination program compared with doingnothing?
10. How do your results change if you use the lower rate of exposure to measles?
11. Based on the ICERs calculated in questions 9 and 10, would you implement the two-dosevaccination schedule? Why?



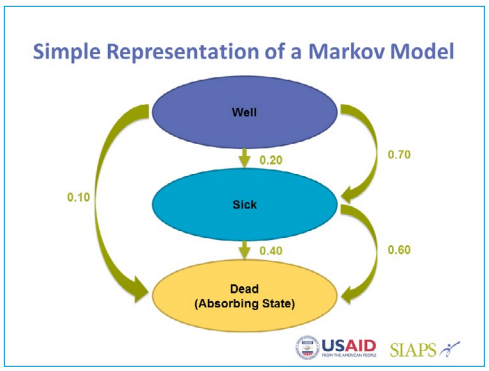
Markov Modeling

A Markov analysis is a more advanced analysis. In real-life scenarios, patients often transition between different states in their disease. For example, a cancer patient might go into remission before having a relapse. The Markov analysis allows for simulation in these different states. It is more complicated than a decision analysis because probabilities of transitioning in and out of disease states must be determined until finally the patients that run through the model move into an absorbing state, which is usually death (i.e., cannot transition back to other states). Sophisticated computer programs can be used to simulate these scenarios.[5]

These analyses are complex and usually require a computer program like TreeAge or advanced Microsoft Excel skills. For the purposes of this course, it is important for participants to list the steps in a Markov analysis and understand that the distinct difference compared to a decision analysis is that patients can transition between health states before progressing to an absorbing state (e.g., death).

There are five steps to a Markov analysis:

1. Determine the health states that the patient can transition among. For example, in the cancer example, the states could be active disease, remission, relapse, and death.
2. Determine transitions among health states. For example, from the state of death, a patient cannot return to active disease, but from relapse a patient could transition to remission or death. Transition probabilities can be constant (i.e., remain the same between cycles) or variable (vary between cycles or over a period of cycles depending on the disease state).
3. Select a time over which the model will run (i.e., cycle length).
4. Estimate probabilities of transition (i.e., the percentage of patients who will cycle from one health state to the next after each cycle).
5. Estimate the costs and outcomes of each transition using a decision analysis.



For example, in a Markov analysis, patients transition through several cycles:

In *Essentials of Pharmacoeconomics*, Dr. Rascati outlines a simple representation of a Markov model in which "constant" probabilities are used for transitions. We see that in cycle one, 100% of patients start in a "well" state. Among those patients, 70% remain in the well state, 20% develop the disease, and 10% die. In the second cycle, 70% of the 70% of patients (depicted by a thick black arrow) who are well remain well. Among those who were well in cycle one, 20% develop the disease, 10% of the 70% of patients who were well in cycle one die, and 40% of the 20% who had the disease in cycle one die.

In the first cycle:

- 70% (70 ÷ 100) remain well
- 20% (20 ÷ 100) develop the disease
- 10% (10 ÷ 100) die without developing the disease

In the second cycle:

- 70% of 70% stay well = 70% * 70% = 49% well
- 20% of 70% (i.e., 20% * 70%) develop the disease = 14% develop the disease + (60% of 20%) remain sick (i.e., 60% * 20% = 12%) = 14% + 12% = 26% in the disease state
- 10% of 70% die (i.e., 10% * 70%) = 7% are dead + (40% of 20%) who had the disease in cycle 1 die (i.e., 40% * 20% = 8%) + 10% remain dead from cycle 1 = 7% + 8% +10% = 25%

In the third cycle:

- 70% of 49% remain well (i.e., 70% * 49%) = 34% remain well
- 20% of 49% develop the disease (i.e., 20% * 49%) = 10% develop the disease + (60% of 26%) remain sick (i.e., 60% * 26% = 16%) = 10% + 16% = 26% in the disease state
- 10% of 49% die (i.e., 10% * 49%) = 5% die + (40% of 26%) who had the disease in cycle 2 die (i.e., 40% * 26% = 10%) + 100% of the 25% from cycle 1 remain dead (i.e., 100% * 25% = 25%) = 5% + 10% + 25% = 40% dead

In this same complex method, QALYs can be estimated and attached to each cycle.

Markov models are complex, requiring many transition probabilities that are often not available and have to be estimated. Even when a model is finished, it becomes difficult to show all steps in the analysis, making the analysis difficult to understand. The calculations require expert understanding. For the purposes of this course, it is important to know that the option of a Markov analysis exists, but participants should reach out to an expert on Markov analysis for input when such an advanced analysis is necessary.

Group Activity 3

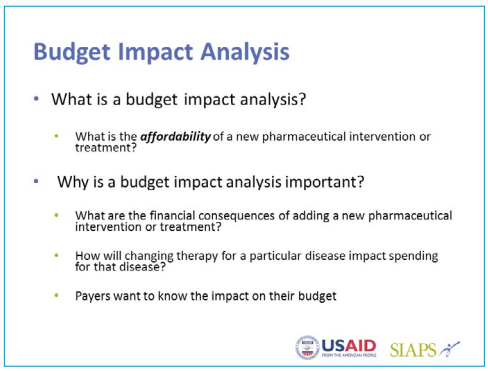
Ask participants to read Kim SW, Kang GW. Cost-Utility Analysis of Screening Strategies for Diabetic Retinopathy in Korea. Korean Med Sci 2015; 30: 1723–1732 and answer the 14 pharmacoeconomic critique questions.

The purpose of this activity is to help participants connect pieces covered in the modules. The Kim and Kang article outlines:

- CUA in a decision analysis (Markov model) using a hypothetical cohort
- A decision tree
- The costs included in the model
- How the QALYs were derived through literature searches where time trade off and standard gamble were used (participants will recall these methods from module 3)
- Why sensitivity analyses were conducted in their research

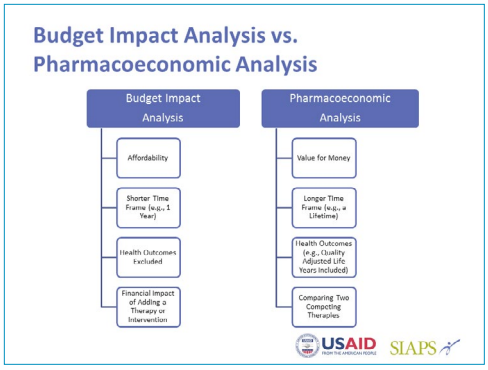
Other Analyses

Budget Impact Analysis



The pharmacoeconomic methods and advanced methods that we have touched on give us an indication of value for money (i.e., a certain cost is incurred to obtain a certain health outcome). Value for money does not translate to affordability. Affordability is gauged through a budget impact analysis (i.e., can we afford the new medicine, intervention, service, or diagnostic?). A budget impact analysis does not tell us if we are getting value for money. It only helps us determine what the total cost would be for the new medicine, intervention, service, or diagnostic to be adopted. From there, decision makers must review the budget and see if the funds are available.

Differences between a Budget Impact Analysis and a Pharmacoeconomic Analysis



There are four basic differences between a budget impact analysis and a pharmacoeconomic analysis:

1. A budget impact analysis allows us to determine affordability, while a pharmacoeconomic analysis is conducted to determine value for money
2. Budget impact analyses are usually conducted for shorter time periods (e.g., review of an annual budget) while a pharmacoeconomic analysis can be conducted using a longer time horizon (e.g., a calculation using lifetime variables)
3. A budget impact analysis does not consider health outcomes (i.e., no value for money consideration is made), while a pharmacoeconomic analysis considers health outcomes
4. In a budget impact analysis, the financial impact of adding a therapy is considered, while in a pharmacoeconomic analysis competing therapies are compared on cost and outcomes

Example of a Budget Impact Analysis

The EML Committee would like to consider adding a new treatment to the formulary that offers fewer adverse effects at a higher cost. To proceed with the budget impact analysis, the total cost of medicine treatment (including the cost of adverse effects) and the estimated number of patients who would require treatment would be needed.

Consider that the current cost of care per patient per annum for treating the condition is $1,000, broken down as:

- Medication: $900
- Adverse drug reaction: $100

A new agent on the market, which comes at higher cost, has fewer adverse effects. The annual cost per patient per year for the newer agent is $1,500, broken down as:

- Medication: $1,450
- Adverse drug reaction: $50

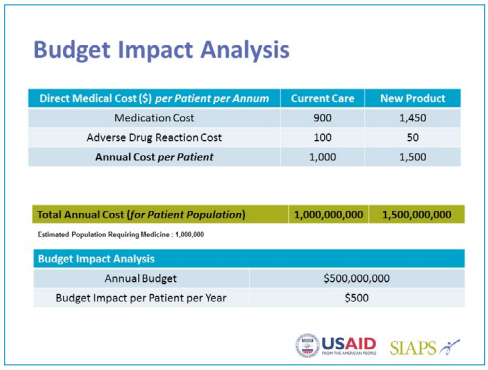
If it is estimated that 1,000,000 people would need treatment, the cost to treat with the standard of care vs the newer agent is:

- Standard of care: $1,000 * 1,000,000 = $1,000,000,000
- Newer agent: $1,500 * 1,000,000 = $1,500,000,000

The budget impact is the difference between the total cost for the two treatments:

$1,500,000,000 – $1,000,000,000 = $500,000,000

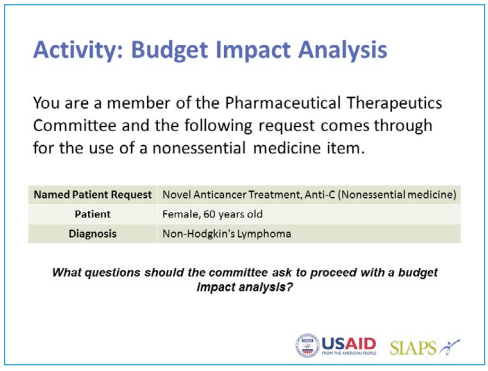
The budget impact per patient per annum = $500,000,000 /$1,000,000 = $500



What Does this Mean?

Discussion Tips

Use this opportunity to ask participants what they would do if they were deciding for their own health versus deciding for the health of 57 million citizens of a country. It is easier to decide to choose the newer treatment at an additional cost of $500 per person per annum when decisions need to be made for one person versus 57 million people.



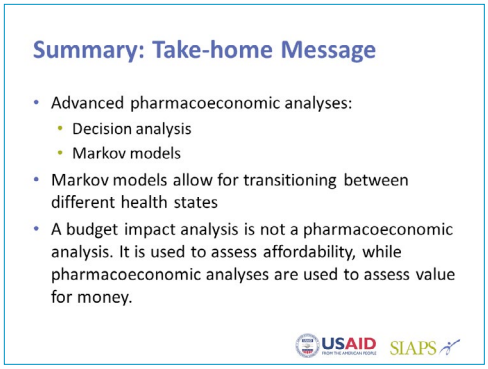
Group Activity 4

Provide the following case study to participants to discuss, and draw up a list of questions to consider when conducting a budget impact analysis.

The purpose of the activity is to encourage thought around the steps that would be required in conducting a budget impact analysis.

The drug and therapeutics committee receives a request for a nonessential medicine list item, a novel anti-cancer item called Anti-C, to be used for a patient. The patient is a 60-year-old female diagnosed with non-Hodgkin's lymphoma, and extensive therapy has already been administered.

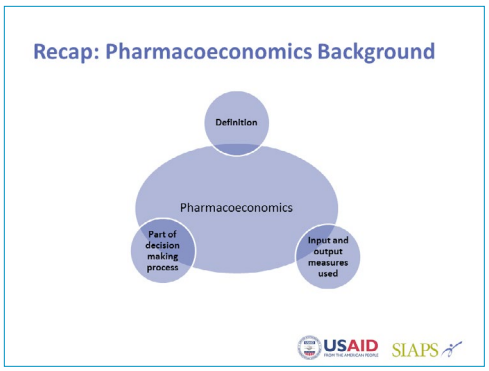
It is important to consider questions related to the medicine treatment when conducting a budget impact analysis because the true impact on your budget may be over or underestimated if all variables are not considered. It is important to consider whether therapy is added on because if the current medication is not stopped, the cost includes the cost of current treatment. Doses are important because quantity to be purchased should be considered. If only a portion of a dose in a pack is used but the shelf life of the product is not long, a new pack might be required at each administration. If we do not take shelf life into consideration, we might underestimate the volume that would need to be purchased for the patient, thereby underestimating the budget impact. If a decision must be made in the middle of a budget period, one must consider what portion of the budget has already been used. Equity is an important factor to consider, particularly in resource-limited LMICs. Therefore, decision makers will have to ensure that if more patients require the treatment, an adequate budget is available. Although controversial, when limited resources must be used efficiently, payers must prioritize their needs, so comparing the cost of one item for one patient and treatment that covers millions of patients may help decision makers prioritize their budgets. In an LMIC, economies of scale and price reduction might also help contain cost and should be considered in parallel to adding an item to a formulary.

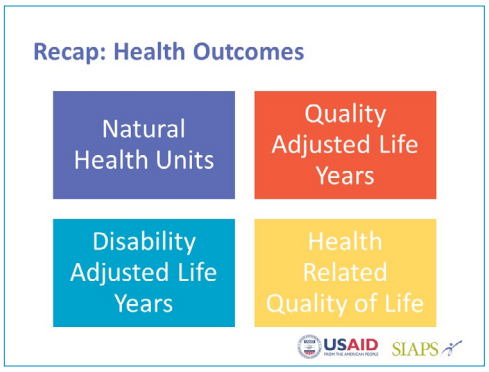


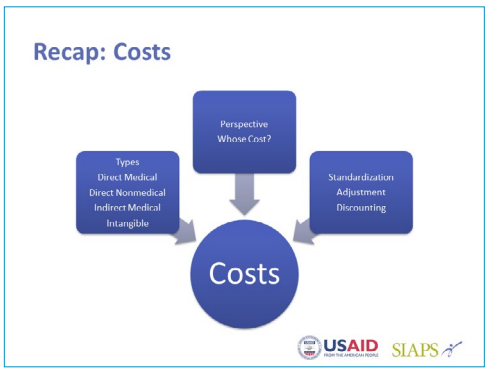
Take-home Message

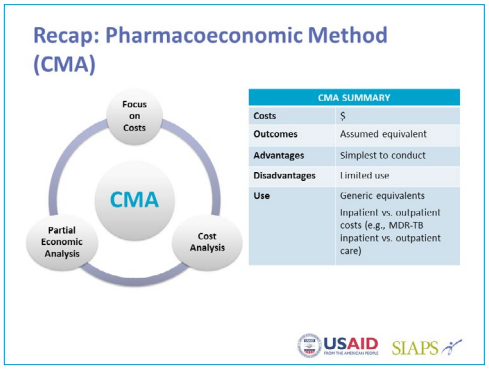
Advanced pharmacoeconomic analyses include decision analyses and Markov models in which probabilities and costs for several outcomes are reviewed following specific calculation steps. In a Markov model, patients can transition in and out of health states. In this module, we also reviewed budget impact analyses. A budget impact analysis is not a pharmacoeconomic analysis. It is used to assess affordability, while a pharmacoeconomic analysis is used to assess value for money.

Reference for the slides used in this module









CONCLUSION

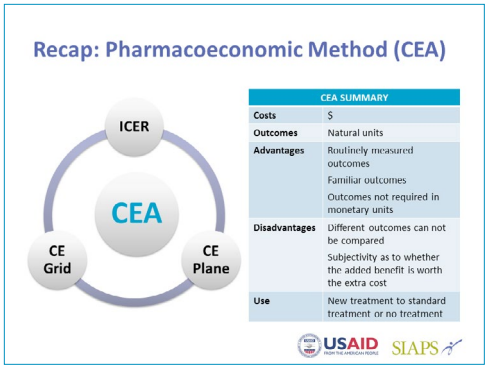
Review Topics Covered in the Pharmacoeconomics Course

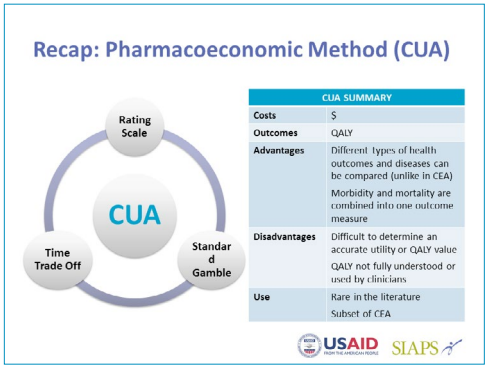
For the instructor: Now that all nine modules have been covered, recap or revisit the take-home or key message of each module with participants to piece together the important components of the overall field of pharmacoeconomics.

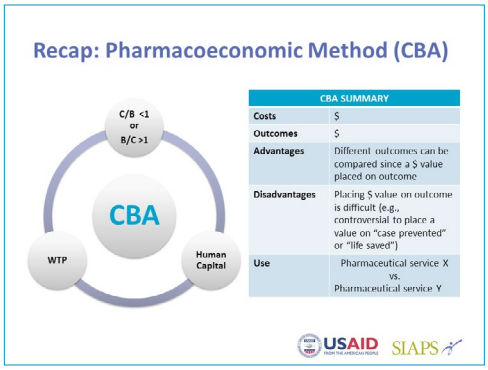
The slides on "Summary of Concepts Covered in the Pharmacoeconomics Course" highlight topics covered in the course and can be used by the instructor to review topics in a question-and-answer format. For example, present the recap slide on costs and ask participants to provide examples of health care costs. The instructor could go around the room asking each participant/group a question. These slides are there to ensure that the take-home message—the basics of pharmacoeconomics—is understood.

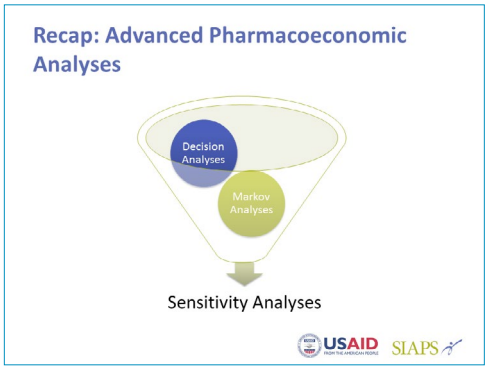
In this course, we have covered the basics of pharmacoeconomics and its use in the selection of essential medicines in LMICs. In summary, the course included:

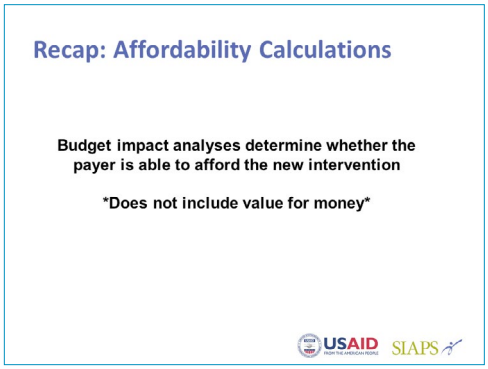
- A brief introduction to the economic principles relevant to pharmacoeconomics
- The essential medicines selection process and the factors used in the selection of medicines for a country formulary
- The denominator in a pharmacoeconomic analysis, which is the output/outcome measure:
  - Effectiveness measures, such as clinical outcomes or a special type of outcome measure that is commonly used in a cost utility analysis known as a QALY
  - Instruments such as the rating scale, standard gamble, and time trade off are used to calculate utilities for QALYs
- The numerator in a pharmacoeconomic analysis, which is cost:
  - Types of health care costs
  - Adjusting/standardizing and discounting past and future costs respectively
  - Considering perspective (whose cost) in the analysis
  - Sensitivity analyses
- Four types of pharmacoeconomic analyses:
  - CMA:
    - The input ($) and output (clinical outcomes assumed to be equivalent) measures of the analyses
    - Advantages and disadvantages of CMA
  - CEA:
    - The input ($) and output (natural health units) measures of the analyses
    - Advantages and disadvantages of CEA
    - Calculation of an ICER











  - CUA:
    - The input ($) and output (QALY) measures of the analyses
    - Advantages and disadvantages of CUA
  - CBA:
    - The input ($) and output ($) measures of the analyses
    - Advantages and disadvantages of CBA
    - Concepts of the WTP and human capital approaches
- Advanced pharmacoeconomic analyses, such as decision analysis and Markov model
- Budget impact analysis for affordability calculations

Now that the course is over, participants should also be able to pick up a pharmacoeconomics article and understand the concepts discussed. Participants should also be able to review the pharmacoeconomics literature using the 14 questions that are described in module 5 and outlined in *Essentials of Pharmacoeconomics*.[5]

Facilitators can end the review by asking students to read through Walley and Haycox's 1997 article.[28] This short article provides an overview of pharmacoeconomics concepts. Depending on the size of the group, the class could read through the article together, pausing after each heading to review and discuss the concepts learned. The article outlines in a concise and easy-to-read manner all of the basic pharmacoeconomic concepts outlined in this course. The students will recognize the concepts that they have learned, and the reading will highlight where further review is required.

Revisit Participants' Expectations

For the instructor: In this session, the facilitator/trainer should revisit the expectations expressed by participants at the beginning of the course. See how many were met and which remain unresolved. Now that participants have gained a reasonable level of knowledge and understanding of the overall concept of pharmacoeconomics, they should be able to search the literature in a more focused and appropriate manner to find additional information or answers to the remaining topics/expectations that could not be covered in this basic course.

If possible, the facilitator should have follow-up communications with the participants to determine whether and how participants apply the knowledge/skills gained during the basic pharmacoeconomics course once they are back in their in-country work settings.

ANNEXES

Annex A

Pre-Post Workshop Survey

Choose One Correct Answer

1.1 What are potential sources to obtain probability and cost estimates for a cost-effectiveness analysis?

a) Expert opinion
b) Clinical trials
c) National Department of Health Tender Contracts with Pharmaceutical Suppliers
d) All of the above

1.2 What is an incremental cost effectiveness ratio (ICER)?

a) Difference in costs divided by difference in outcomes
b) Difference in outcomes divided by difference in costs
c) A calculation used in a cost minimization analysis
d) a and b

1.3 Which of the following pharmacoeconomic analyses are considered a subset of cost-effectiveness analysis (CEA)?

a) Cost benefit analysis (CBA)
b) Cost minimization analysis (CMA)
c) Cost utility analysis (CUA)
d) None of the above

1.4 Which of the following pharmacoeconomic analyses is considered the simplest to conduct?

a) Cost benefit analysis (CBA)
b) Cost minimization analysis (CMA)
c) Cost utility analysis (CUA)
d) None of the above

1.5 Interventions are usually considered to be *cost beneficial* if:

a) Net benefit > 0
b) Net cost > 0
c) Benefit-to-cost ratio > 1
d) a and c

1.6 In a decision analysis tree, at a chance node the following occurs:

a) Choices regarding treatments (e.g., treatment A vs. treatment B)
b) Probability of events (e.g., probability of adverse events, probability of cure)
c) Final outcome or decision made
d) a and c

1.7 Which of the following is **not a characteristic of a budget impact analysis**?

a) Helps determine affordability and value for money of adding a therapeutic intervention/ pharmaceutical service
b) Patient/health outcomes are generally excluded from budget impact analyses
c) Compared with pharmacoeconomic analyses, budget impact analyses cover a shorter time frame
d) Unlike pharmacoeconomic analyses, "discounting" is not required in a budget impact analysis

1.8 In which of the following pharmacoeconomic analyses is the outcome measure of the products being compared assumed to be equivalent?

a) Cost benefit analysis (CBA)
b) Cost minimization analysis (CMA)
c) Cost utility analysis (CUA)
d) None of the above

1.9 Patient travel to receive treatment is regarded as a:

a) Direct medical cost
b) Indirect medical cost
c) Direct nonmedical cost
d) Intangible cost

1.10 Using the information in the table below (Diabetes Mellitus Education Program and reduction of days with glycemic events for six months), what is the ICER per patient per day of glycemic symptoms avoided?

	Intervention	**Control**
Cost ($)	415	70
Days with glycemic symptoms avoided	10.5	3.3

a) $-48 for each day without glycemic events
b) $48 for each day without glycemic events
c) $-287.5 for each day without glycemic events
d) $287.5 for each day without glycemic events

Annex B

Evaluation Sheet of Module

Number of Module:

Name of Module:

Please circle the number that best reflects your evaluation of each educational aspect as indicated on the scale below

Outstanding: Greatly exceeded my expectations
Satisfactory: Met my expectations
Poor: Below my expectations

	Outstanding			**Satisfactory**				**Poor**		
Achievement of stated objectives	10	9	8	7	6	5	4	3	2	1
Relevance of content for my job	10	9	8	7	6	5	4	3	2	1
Effectiveness of training techniques	10	9	8	7	6	5	4	3	2	1
Effectiveness of trainer	10	9	8	7	6	5	4	3	2	1
Usefulness of module materials	10	9	8	7	6	5	4	3	2	1

Was the length of the module (*please tick*)?

☐ Too Long ☐ Too Short ☐ Just Right

What was the best thing about the module?

What was the worst thing about the module?

Suggestions for improvement

Would you recommend this training to other work colleagues? ☐ Yes ☐ No

How will you use this training in your work?

Annex C

Examples of the Use of Pharmacoeconomic Principles in the Selection of Essential Medicines in South Africa

(Courtesy of the National Essential Medicines List Committee, National Department of Health, South Africa)

National Essential Medicines List Cost-Effectiveness analysis
Primary Health Care
Component: Mental health conditions

Date: 22October 2014
Medication: Risperidone vs. haloperidol, oral
Indication: Schizophrenia

Background: During the review of the 2008 Primary Healthcare Standard Treatment Guidelines, comments from external stakeholders recommended that risperidone be considered for the management of psychosis as it had a better safety profile than the current recommendation of haloperidol. In addition, the National Department of Health Contract Circular, HP09-2014SD was awarded and it was noted that there was a price reduction of risperidone (30-40%) compared to the previous HP09-2012SD contract circular.

Aim: Costing analysis was performed to compare cost-effectiveness of haloperidol versus risperidone for treatment of schizophrenia at primary level of care, based on available good quality evidence published in the literature.

Method: A search of the literature was performed to source evidence comparing safety and efficacy of risperidone to first generation antipsychotics. Utilising statistically significant and clinically appropriate outcomes and the current contract circular prices, the incremental cost effectiveness ratio was calculated. A sensitivity analysis was performed, incorporating the upper and lower limits of the confidence intervals; and an additional cost comparison was performed using expert opinion on dosing to determine the real life experience in local context.Direct costs (medication costs) were only considered for the purpose of this analysis.

Results: A meta-analysis, funded by the National Institute of Mental Health (Germany) was quality checked using the PRISMA checklist. Risperidone was shown to be have better overall efficacy than first-generation antipsychotic (FGAs) medicines, −0·13 (−0·22 to −0·05, p=0·002). In addition, NNT for one additional responder was 15 (9–36) for risperidone and relapse was reported to be significantly better than FGAs, RR 0·74 (0·63–0·87), NNT: 11 (7–33). Extrapyramidal side effects (EPSE) associated with risperidone compared to FGAs were less, RR (95% CI): 0·61 (0·52 to 0·72). However, not all patients that experience EPSE would require an anticholinergic. It was assumed that 45.8% of patients on haloperidol and 30.8% of patients on risperidone that developed EPSE would require an anticholinergic, based on 1 year data from a RCT by Crespo-Facorro*et al* (2011).
The daily dose ranges for risperidone and haloperidol determined from the meta-analysis was 4-6 mg and 3-20 mg, respectively.
There is a paucity of evidence supporting orphenadrine dose for neuroleptic induced tardive dyskinesia. However, guidelines provided a daily dose of 150 mg daily.
Discounting rate was not factored into this analysis, as short-term studies were analysed in the meta-analysis (duration of 4 to 108 weeks).
The meta-analysis listed a number of studies on risperidone were industry-sponsored. Excluding these studies reduced risperidone's effect size (overall symptoms) to -0.04 which was not significantly different from FGAs.

Limitations:

i. Details of anticholinergic medicines used for EPSE was not described in the meta-analysis; dose and indication for orphenadrine derived from BNF(2013) and SAMF(2012).

Assumptions:

ii. Doses used in this study were reflective of doses used for maintenance therapy.
iii. Haloperidol was deemed to represent total class effect of all FGAs in this meta-analysis (comparator drug in 95 studies)
iv. Orphenadrine 150 mg oral, daily considered as safe and effective dose for neuroleptic induced EPSE [Paucity of good quality data; recommendations as per guidelines]

v. Direct costs (medication costs) were considered relevant for the purpose of this analysis.
vi. Patients with EPSE that would require anticholinergic medication was extrapolated from randomised, open label study by Crespo-Facorro *et al* (2011): 1 year data - haloperidol = 45.8% vs risperidone = 30.8%, p < 0.0001.

From a provider perspective, the ICER for the meta-analysis and respective sensitivity analyses (comparing risperidone to haloperidol) were as follows:

Evidence-based cost analysis:

Effect	ICER	Sensitivity analysis (lower limit)	Sensitivity analysis (upper limit)
i. Overall efficacy	R8.64 to R117.63	R5.40 to R73.52	R21.60 to R294.07
ii. One additional responder	-R16.20 to -R220.56	-R9.72 to –R132.33	-R38.89 to –R529.33
iii. Relapse improved	- R11.88 to –R161.74	-R7.56 to –R102.93	-R35.65 to –R485.22

As it was noted that higher doses of risperidone (4-8 mg) is used in clinical practice, a further cost analysis was performed by extrapolating the efficacy data to these doses. However, it is important to note that this analysis does not adhere to the principles of evidence-based medicine.

Extrapolated cost analysis:

Effect	ICER	Sensitivity analysis (lower limit)	Sensitivity analysis (upper limit)
i. Overall efficacy	-R4.35 to R101.89	-R2.72 to R63.68	-R10.88 to R254.71
ii. One additional responder	R8.16 to –R191.04	R4.90 to to –R114.62	R19.59 to –R458.49
iii. Relapse improved	R5.99 to –R140.09	R3.81 to –R89.15	R17.96 to –R420.28

The meta-analysis showed that risperidone effect size was relatively small (-0.13 in terms of overall symptoms), so an additional costing analysis using the minimum effective dose method was used (Leucht *et al*, 2014). Comparative dose of risperidone: haloperidol was considered to be 2 mg: 5 mg based on the minimum effective dose method.

Risperidone	vs	Haloperidol
R 5.13		R 6.13

Conclusion:

Different scenarios were analysed to provide modeled cost-effectiveness of risperidone compared to haloperidol for management of psychosis at primary level of care. It is important to note the limitations and assumptions of this model during the decision-making process.

References:

[1]Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009 Jan 3;373(9657):31-41
[2] Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr Bull. 2014 Mar;40(2):314-26.
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[4] BNF for adults, volume 65, 2013.
[5]Crespo-Facorro B, Pérez-Iglesias R, Mata I, Ramirez-Bonilla M, Martínez-Garcia O, Pardo-Garcia G, Caseiro O, Pelayo-Terán JM, Vázquez-Barquero JL. Effectiveness of haloperidol, risperidone and olanzapine in the treatment of first-episode non-affective psychosis: results of a randomized, flexible-dose, open-label 1-year follow-up comparison. J Psychopharmacol. 2011 Jun;25(6):744-54.
[6] PHC STG, 2008.
[7] Adult Hospital level STG, 2012.
[8] Contract circular HP09-2014SD.
[9] Contract circular HP14-2013PM.

National Essential Medicines List Pharmacoeconomics and Budget impact analysis Adult Hospital Level Component: Cardiovascular conditions

Date: 11 December 2015
Medication: Rivaroxaban
Indication: Treatment of recurrent deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thrombolic events (VTE)

1 INTRODUCTION

A motivation was received for rivaroxaban to be added to the EML for the following conditions;

- Post hip and knee surgery prophylaxis
- Treatment of DVT and pulmonary embolism
- Stroke prevention in treatment of non-valvular atrial fibrillation

This report deals with the pharmacoeconomics and budget impact analysis for the use of rivaroxaban in the treatment of DVT or PE and the prevention of recurrent VTE

2 PHARMACOECONOMICS MODEL - METHODS

A cost-minimization approach was used but with differences in bleeding rates and hospitalization costs taken into consideration. The perspective was that of a third-party payer – i.e. Department of Health/Government and therefore only direct costs were included. The costs were modeled for 3, 6 and 12 months and therefore no discounting was required.

A decision tree structure was used as per the figure below;

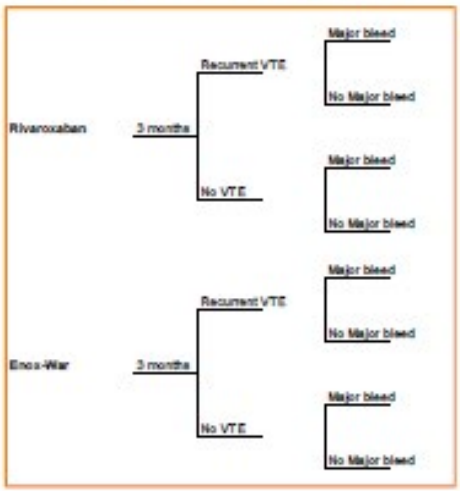

Figure 1. Diagram of decision analysis model for rivaroxaban vs enoxaparin-warfarin

3 CLINICAL INPUTS AND COSTS

The clinical input variables for the cost-effectiveness analysis were obtained from a number of sources, predominantly the EINSTEIN-DVT and EINSTEIN-PE studies (1) (2) which showed a statistically significant non-inferiority in the primary efficacy endpoint (incidence of symptomatic recurrent VTE) in both trials at 3, 6 or 12 months and therefore a base-line event rate of recurrent symptomatic VTE was selected at 2.1%

The risk of first major bleeding was significantly reduced with rivaroxaban from 1.7% to 1% in the EINSTEIN pooled analysis (3).

The initial length of stay for treatment was based on 1 day in ICU followed by a general ward stay of 4 days and 5 days for rivaroxaban and enox/war respectively. Analysis of the EINSTEIN PE and DVT studies shows a reduction in initial length of stay for patients treated with rivaroxaban compared to standard of care (4).

The average length of stay for hospitalization for a recurrent VTE was taken from a review of the cost of VTE (5) in 18 published studies. The length of stay varied considerably between countries with ranges from 4.9-7 days and 5.8-7.7 days for DVT and PE respectively in the US. In Germany and Belgium the length of stay increased to around 14-24 days. Therefore a baseline LOS of 6 days was selected and a sensitivity analysis carried out to determine the impact.

The unit costs for in-patient admissions and consultations were taken from the UPFS Tariffs from April 2015. The medication costs for rivaroxaban were obtained from the SEP database and for warfarin/enoxaparin, the costs were obtained from the most recent contract database. INR monitoring costs were obtained from the 2015 NHLS Costing Tables.

The medicine costs used in the model are as follows;

Medicine Costs

Medicine	Strength	Dosage form	Pack	Price/pack	Price /unit	SEP packsize	SEP (+VAT)	SEP (incl VAT)/unit
Rivaroxaban	10 mg	tab	30	n/a	n/a	30	795.29	23.79
Rivaroxaban	15 mg	tab	42	n/a	n/a	42	1113.40	26.51
Rivaroxaban	20 mg	tab	28	n/a	n/a	28	742.27	26.51
Warfarin	5 mg	tab	100	29.19	0.29	100	125.1495	1.25
Enoxaparin	40mg	inj	1	20.21	20.21			

Table 1. Medicine pricing for rivaroxaban, enoxaparin and warfarin

A number of assumptions were made for the model including the following;

- Hospitalisations included 1 day in ICU or HC followed by the balance of the days in general ward
- The patient was consulted by an ICU specialist once on the day in ICU followed by general medical consultations in the general ward per day thereafter. Only general ward or no hospital stay was also modelled.
- All patients were treated at a Level 2 facility in terms of costs
- Both DVT and PE patients were included together in the model even though it is acknowledged that they have different outcomes and prevalence.
- Recurrent VTEs were similar in terms of treatment regardless of whether the patient was on rivaroxaban or enoxaparin-warfarin and therefore accumulated the same costs
- Efficacy of rivaroxaban and standard of care is the same (proven by non-inferiority) based on EINSTEIN trials and only bleeding outcomes differ
- Only one further event occurred per time period (ie only one recurrent VTE regardless of whether in 3 6 or 12 months)
- Bleeding outcomes of rivaroxaban and standard of care differs (proven by pooled EINSTEIN data)
- All patients were admitted for treatment of recurrent DVT or PE

4 RESULTS

At a base case pricing of full SEP for rivaroxaban (R743 per month for 20mg), the incremental cost of treating a patient for 12 months with rivaroxaban would be approximately R2 500. The outcomes of the model were as follows;

Total cost per patient	*3 months*	*6 months*	*12 months*
Rivaroxaban	8 923.23	11 895.66	17 787.50
Enox-War	7 505.44	8 628.57	9 554.24
Incremental Cost	1 417.79	3 267.09	8 233.26

Table 2. Incremental cost of treating DVT and PE over a period of 3, 6, and 12 months

If the price of rivaroxaban was reduced by 80%, the 3 and 6 month treatment periods would become cost-saving at -R66.75 and R-168.56 respectively.

The model was most sensitive to changes in LOS and then the price of rivaroxaban (Table 3). If patients did not need an ICU stay when on rivaroxaban, the model became cost-saving for at 3 months. However, if both rivaroxaban and enox-war had the same LOS, then the incremental cost increased quite substantially. Changing the efficacy event rate did not impact the model as much as varying the major bleed rate. Changing the LOS of a recurrent VTE did not impact the model at all as it was assumed to be the same for both arms (rivaroxaban and enox-war).

		Incremental Cost		
Range		**3 months**	**6 months**	**12 months**
Event Efficacy (VTE)	*2.10%*	*1417.79*	*3267.09*	*8233.26*
Lower (Riv)	1.75%	1390.52	3238.90	8203.22
Upper (Enox-war)	3.00%	1347.68	3194.60	8156.02
Event Bleed riv	*1%*			
Lower	0.5%	1365.01	3214.31	8180.48
No Diff	1.7%	1491.68	3340.98	8307.15
Upper	2.5%	1576.13	3425.43	8391.60
Event Bleed enox-war	*1.70%*			
Lower	1.00%	1491.68	3340.98	8307.15
Upper	3.00%	1280.56	3129.86	8096.03
LOS_riv	*5*			
Lower	4	939.79	2789.09	7755.26
Upper	10	3807.79	5657.09	10623.26
No ICU stay	5	-1525.21	324.09	5290.26
LOS_enox-war	*6*			
Lower	5	1895.79	3745.09	8711.26
Upper	10	-494.21	1355.09	6321.26
No ICU stay	5	4838.79	6688.09	11654.26
LOSre	*8*			
Any value	5	1417.79	3267.09	8233.26
Rivaroxaban (per unit)	*26.51*			
20% reduction	21.21	1046.65	2408.18	6409.40
50% reduction	17.23	768.30	1763.99	5041.50
65% reduction	9.28	211.60	475.62	2 305.70

80% reduction	5.30	-66.75	-168.56	937.81
Major bleed Cost	*5278.00*			
Lower	3000	1449.68	3298.98	8265.15
Upper	12000	1323.68	3172.98	8139.15

Table 3. Sensitivity Analysis of key parameters for the model at 3, 6, and 12 months

5 Published Health Economics

There are a number of published cost-effectiveness studies on this subject (6). All used efficacy data from the EINSTEIN DVT and PE studies and reported ICERS as cost/LYG and cost/QALY. Rivaroxaban was found to be dominant (ie cost less with greater benefit) in all 3 of the US based studies, as well as in the model submitted by the manufacturer to NICE in the UK. The Evidence Review Group (ERG) of NICE presented their own analysis for DVT and PE and found that for DVT rivaroxaban dominated standard of care in the 3 month treatment arm but showed an ICER of £3,200 and £14,900 for the 6 and 12 month treatment groups respectively. For PE, the ERG produced an ICER of £11,590/QALY for 12 months treatment and £35,909 for lifelong treatment. An analysis carried out in 2015 which evaluated the cost-effectiveness of treatment of VTE with rivaroxaban compared to LMWH/WAR for lifelong treatment showed ICERs of £8677 and £7072 for DVT and PE respectively which is still well below the cost-effectiveness threshold (around £20 000/QALY) for the UK (7).

6 Budget Impact Analysis

It is challenging to determine the incidence of DVT and PE as well as rate of recurrence in the South African population. According to the South African guidelines, the DVT prevalence appears to be similar in medically ill patients compared to moderate risk surgery patients (around 10-20%) (8) however little information is available as to the actual numbers of DVTs or PE in the total population in order to be able to assess the total and incremental budget impact of treating patients with rivaroxaban compared to standard of care.

The total medicine cost per patient of treating DVT and PE with rivaroxaban compared to enoxaparin-warfarin (including INR monitoring) is shown in Table 4 below;

Rivaroxaban	**Cost Rx**		**Total Cost (including initial Tx and INR)**
Initial phase (15mg bd x 21 days)	1 113.40		
3 months (20mg daily)	1 855.68		2 969.08
6 months (20mg daily)	4 294.56		5 407.96
12 months (20mg daily)	9 119.32		10 232.72
Enoxaparin+Warfarin		**INR**	
Initial phase (enox 160mg x 8 days)	646.72		
Initial phase (warfarin 5mg x 26 days)	7.59	245.46	
3 months (5mg daily)	17.81	81.82	999.40
6 months (5mg daily)	44.66	204.55	985.34
12 months (5mg daily)	97.79	450.01	1 283.93

Table 4. Medicine cost of treating DVT and PE for 3, 6, and 12 months

The absolute medicine cost difference per patient is R1 969 (3 months), R4 422 (6 months) and R8 948 (12 months) assuming 6 INR in the initial treatment phase followed by 1 INR per month thereafter.

Making some broad assumptions around number of patients eligible for treatment, the possible incremental budget impact could be as follows;

Per patient	Medicines only	Medicines + INR	Overall cost
3 months	2 297	1 970	1 418
6 months	4 709	4 423	3 267
12 months	9 481	8 949	8 233
1000 patients			
3 months	2 296 959.70	1 969 679.70	1 417 787.70
6 months	4 708 992.04	4 422 622.04	3 267 090.04
12 months	9 480 621.24	8 948 791.24	8 233 259.24
15 000 patients			
3 months	34 454 395.50	29 545 195.50	21 266 815.50
6 months	70 634 880.64	66 339 330.64	49 006 350.64
12 months	142 209 318.64	134 231 868.64	123 498 888.64
25 000 patients			
3 months	57 423 992.50	49 241 992.50	35 444 692.50
6 months	117 724 801.07	110 565 551.07	81 677 251.07
12 months	237 015 531.07	223 719 781.07	205 831 481.07

Table 5. Incremental cost (Rands) of treatment for rivaroxaban compared to enoxaparin-warfarin

However, the pharmacoeconomics model shows that whilst there is an increase in medicine costs when rivaroxaban is used, in a number of instances, rivaroxaban becomes cost-saving compared to warfarin, especially when the price of rivaroxaban is reduced by 80% and when the LOS of rivaroxaban is reduced compared to standard of care and even more so if no ICU stay is required. Therefore it is possible that the introduction of rivaroxaban at a negotiated price reduction could be cost-neutral or even cost-saving from a budget impact perspective.

7 Conclusion

There is an incremental cost per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE, however, if the price of rivaroxaban is reduced, the incremental cost can be neutralized. A price reduction should be negotiated.

The initial budget impact will be considerable and it is recommended that a follow-up study is carried out to assess whether the projected cost savings from reduction in hospital stay and reduction in long-term outcomes (fewer bleeds, possibly fewer recurrent VTEs) materialize.

There is a risk that if rivaroxaban becomes available on the EML for the treatment of VTE, it will also be used in other clinical indications for anticoagulation, such as atrial fibrillation, where the cost-effectiveness is not proven.

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Annex D

EQ5D Health Related Quality of Life Instrument (Youth)[25]

EQ-5D-Y

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY.

Mobility *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

Looking after myself

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

Doing usual activities *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

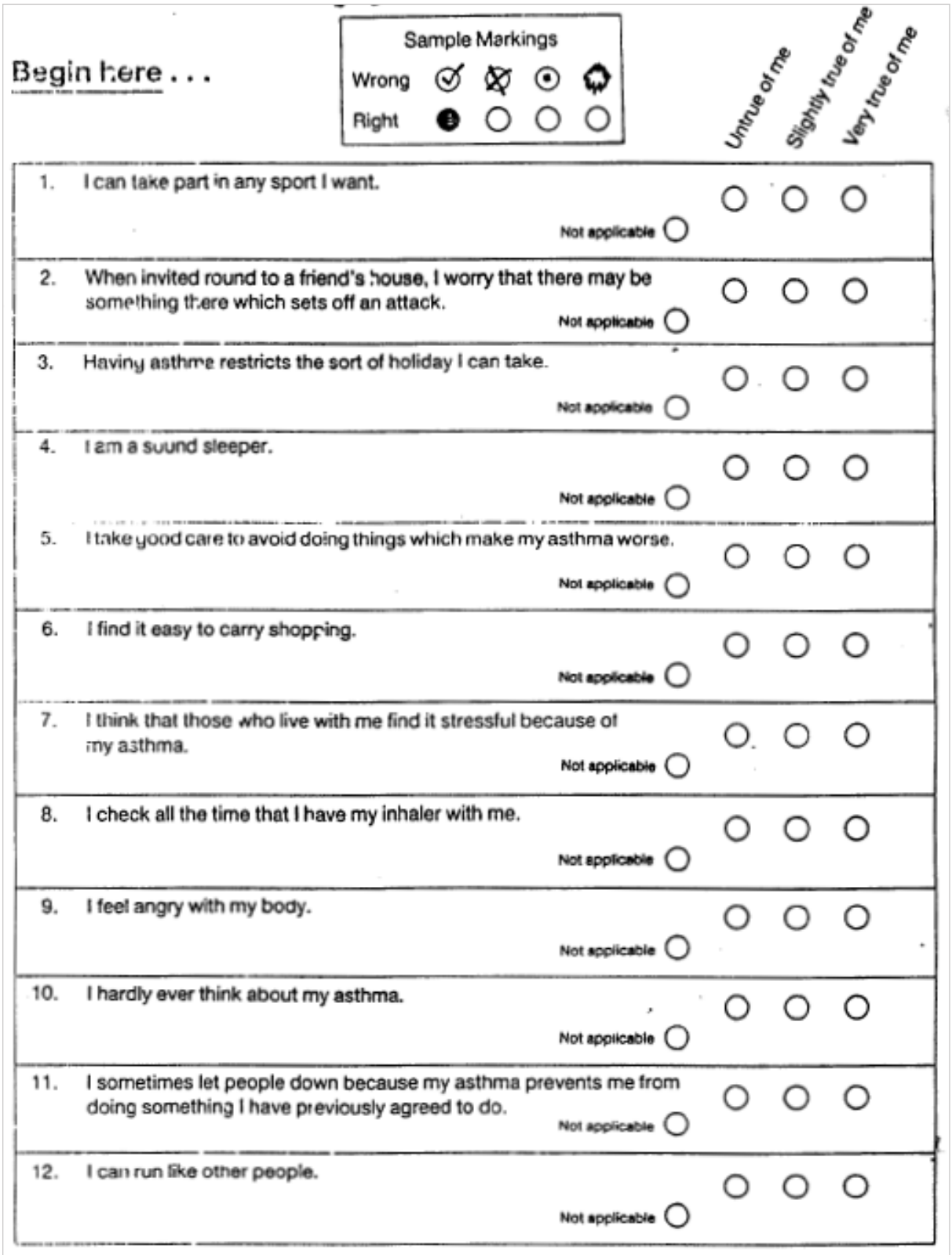
I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

Annex E

Excerpt from the Living with Asthma Questionnaire[43]



Begin here . . .

Sample Markings

Wrong ✓ ✗ ● ●

Right ● ○ ○ ○

	Untrue of me	Slightly true of me	Very true of me
1. I can take part in any sport I want. Not applicable ○	○	○	○
2. When invited round to a friend's house, I worry that there may be something there which sets off an attack. Not applicable ○	○	○	○
3. Having asthma restricts the sort of holiday I can take. Not applicable ○	○	○	○
4. I am a sound sleeper. Not applicable ○	○	○	○
5. I take good care to avoid doing things which make my asthma worse. Not applicable ○	○	○	○
6. I find it easy to carry shopping. Not applicable ○	○	○	○
7. I think that those who live with me find it stressful because of my asthma. Not applicable ○	○	○	○
8. I check all the time that I have my inhaler with me. Not applicable ○	○	○	○
9. I feel angry with my body. Not applicable ○	○	○	○
10. I hardly ever think about my asthma. Not applicable ○	○	○	○
11. I sometimes let people down because my asthma prevents me from doing something I have previously agreed to do. Not applicable ○	○	○	○
12. I can run like other people. Not applicable ○	○	○	○

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