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Pharmacoeconomic Analysis Methods

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Abstract

In the last years, the growing interest of healthcare professionals, policy-makers, and other stakeholders in enlarging the role of economic evaluations was driven by several factors such as evidence-based healthcare culture, patient-centered actions, and quality-linked incentives, associated with an important increase of financial constraints and pressures on healthcare budgets. Pharmacoeconomics, as a branch of health economics, focuses on balancing the costs and benefits (i.e., consequences) of an intervention towards the use of limited resources, aiming at maximizing value to patients, healthcare payers, and society. These concepts are part of the Health Technology Assessment process that informs clinical and governmental players about medical, social, and economic implications of development, diffusion, and use of health technologies. This chapter aims to provide an overview of the important concepts in pharmacoeconomic analysis methods, including studies classification (e.g., budget-impact analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis), types of costs and outcomes, modeling approaches (e.g., decision trees or state transition models), and new trending analysis (e.g., value of information and value-based healthcare analyses), and additionally discuss some recommendations for future studies towards evidence synthesis and practical application.

Keywords

Pharmacoeconomics · Economic evaluations · Costs

Introduction

Health Technology Assessment (HTA) is a multidisciplinary, evidence-based, and systematic process aiming at informing interested players about medical, social, and economic implications of the development, diffusion, and use of health technologies (e.g., drugs, vaccines, medical procedures, services). These assessments intend to provide a

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bridge between scientific research and decision-making processes, including setting priorities in healthcare or guiding the selection or incorporation of new treatments. In the past years, the growing awareness of the importance of HTA worldwide also highlighted the need of using well-designed and standardized studies and tools to support these reports, especially considering the economic component. This is because studies of costs and related economic implications comprise a major group of methods used in HTA (Rabarison et al. 2015; Clement et al. 2009).

The World Health Organization (WHO) passed a resolution for HTA in 2014, recognizing the importance of HTA in supporting countries to make cost-effective resource allocation decisions. Many high-income countries and an increasing number of middle-income countries worldwide have established HTA systems to support priority-setting decisions. Since economic evaluation is one of the mainstays of HTA, several countries have developed guidelines that address the design and conduct of these evaluations (Allen et al. 2017; Sharma et al. 2021).

Pharmacoeconomics is a branch of health economics that usually focuses on balancing the costs and benefits of an intervention towards the use of limited resources, aiming at maximizing value to patients, healthcare payers, and society (Walley and Haycox 1997; McIntosh and Luengo-Fernandez 2006). This is important as cost containments are common for the management of healthcare systems worldwide, yet the development of innovative and cheaper interventions is scarce. However, although most of the newer technologies are costlier than the existing ones, they also usually provide added benefits over previous interventions. In this scenario, decisions-makers (e.g., healthcare professionals, politicians, and other stakeholders) have to consider whether or not the new intervention is affordable and result in an efficient use of resources. Additionally, full pharmacoeconomic evaluations, defined as analyses that identify, measure, and compare the outcomes (i.e., relate the costs with the respective consequences) among available interventions, are key studies to inform pricing and reimbursement decisions in several countries (McIntosh and Luengo-Fernandez 2006; Murphy et al. 2003).

In recent years, there is a general trend on the increase in number of the pharmacoeconomic studies on different levels of complexity worldwide. These studies can involve attributes of either or both primary data collection and integrative methods. That is, cost data can be collected, for example, as part of randomized controlled trials and other clinical studies, as well as from administrative databases used in healthcare payment. Cost data from one or more sources are often combined with data from primary clinical studies, epidemiological studies, and other sources to conduct one (or more) economic evaluations (e.g., cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis) that involve weighing health and economic impacts of health technology (Goodman 2014; Drummond et al. 2005).

The suitability of any of this variety of approaches to economic analysis depends on the purpose of an assessment and the availability of data and other resources. It is rarely possible or necessary to identify and quantify all costs and all outcomes (or benefits), and the units used to quantify these may differ. Thus, our aim is to provide an overview of the main pharmacoeconomic analysis methods that should be used during evidence-synthesis and for the assessment of healthcare technologies and additionally discuss some recommendations for future studies and practical applications.

Guidelines for Economic Evaluations

Economic evaluations of healthcare interventions pose a particular challenge for conduction and reporting because substantial information must be conveyed to allow scrutiny of study findings. Globally, several countries have developed guidelines that describe the design and conduct of economic evaluations as part of HTA or pharmacoeconomic analysis for decision-making (Eccles and Mason 2001; Nixon et al. 2000; McGhan et al. 2009; Fenwick et al. 2020).

A recent scoping review summarized the recommendations made on methods of economic evaluations by the national healthcare economic evaluation (HEE) guidelines. A total of 31 national HEE guidelines, published between 1997 and August 2020, were evaluated. Almost half of them (45%) targeted the evaluation of pharmaceuticals. The nature of the guidelines was either mandatory (31%), recommendatory (42%), or voluntary (16%). There was a substantial consensus among the guidelines on several key principles, including the primarily or preferable type of economic evaluation (cost-utility analysis), time horizon of the analysis (long enough to capture the benefits from the intervention), health outcome measure (quality-adjusted life-years – QALY), and use of sensitivity analyses. The recommendations on study perspective, comparator, discount rate, and type of costs to be included varied according to the country given the differences in the health systems and financing mechanisms, capacity of local researchers, and data availability (Sharma et al. 2021).

The Professional Society for Health Economics and Outcomes Research (ISPOR), for instance, is responsible for creating guidelines in the pharmacoeconomic field to be used worldwide. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement is one of the most well-known checklists that can help during the process of performing and reporting a health economic study. It provides examples and explanations for each of the 24 items and accompanying recommendations, with some specific recommendations for single study-based and model-based economic evaluations. The final recommendations are subdivided into six main categories: title and abstract, introduction, methods, results, discussion, and others (Husereau et al. 2013). Overall, a well-designed pharmacoeconomic analysis usually involves 10 main steps (Husereau et al. 2013; Jolicoeur et al. 1992):

- Define the problem.
- Determine the study's perspective.
- Determine the alternatives and outcomes.
- Select the appropriate pharmacoeconomic method.
- Place monetary values on the outcomes.
- Identify study resources.
- Set the probabilities of the outcomes.
- Apply decision analysis.
- Discount costs or perform a sensitivity or incremental cost analysis.
- Present the results, along with any limitation of the study.

Key Attributes in Economic Evaluations

A health economic evaluation usually involves a comparative analysis of at least two health interventions used to assess both the costs and consequences of the different technologies in a given population, providing a decision framework. In most cases, the two main components of the analysis are "costs" and "outcomes."

Table 1 presents the main inputs and definitions of pharmacoeconomic evaluations as a brief summary of the CHEERS statement. The design of the study should be considered in the same way as a clinical study (e.g., population, intervention, comparator, outcome, and timing – PICOT). The target population refers to the individuals with the health condition under study and who can benefit from the health technology. The intervention is the technology of interest. The identification and measurement of outcomes and costs will depend on the intervention characteristics and perspective adopted. The appropriate expression of the time horizon is important because interventions costs and benefits vary with time. All assumptions made (for clinical or cost parameters) should be clearly described to guarantee the transparency of the analysis (Ademi et al. 2013).

The concept of opportunity cost refers to the loss of potential benefits from other options when one option is chosen. This concept is based upon the idea that the scarcity of resources leads players to expend capital on one healthcare activity by sacrificing services elsewhere. Thus, understanding the potential missed opportunities foregone by choosing one technology over another allows for better decision-making (Danzon et al. 2018).

Pharmacoeconomic Analysis Methods, Table 1 Main parameters that should be covered in economic evaluations

	Brief definition
Target population	The group or subgroup of patients who will benefit from the health intervention
Target intervention	Intervention under assessment (e.g., drugs, vaccines, medical procedures, services)
Comparator	Other intervention, standard of care (current best practice), minimum practice, or no intervention that is being compared to the target intervention
Setting	The context in which the intervention will occur (e.g., hospital, community pharmacy, outpatients)
Perspective	The different viewpoints from which outcomes and costs are being assessed (e.g., patient, provider, payer, society)
Costs	The monetary component of the economic analysis. It can be broadly divided into direct, indirect, and intangible costs
Outcomes	Also called "benefits" or "consequences," the outcomes are the expected healthcare or humanistic results from an intervention
Time horizon	The duration over which costs and outcomes are calculated in an economic analysis. This time should be long enough to reflect the effects of the intervention on a given disease or health-related condition
Data capture method	The methods and sources used to identify, collect, and estimate the costs and outcomes
Discounting	Cost analyses should account for the effect of the passage of time on the value of costs and outcomes. Discounting is used to account for individual's time preference (i.e., most individuals have a positive rate of time preference whereby benefits are preferred sooner rather than later, and costs incurred later rather than sooner)
Modeling	Decision analyses from economic evaluations can be operationalized through modeling processes such as decision trees or state transition models
Sensitivity analysis	Estimation of data stability; a means of representing uncertainty in the results of economic evaluations (e.g., one-way simple sensitivity analysis, multiway sensitivity analysis, threshold sensitivity analysis, probabilistic sensitivity analysis)
Findings	Final report and recommendations suitable for the healthcare decision-making

Types of Costs and Costing Methods

One of the firsts steps in any cost analysis is the identification of the various possible costs types that are usually classified into the following (Goodman 2014; Drummond et al. 2005):

- **Direct costs** represent the value of all goods, services, and other resources consumed in providing health care or dealing with side effects or other current and future consequences of healthcare. They are paid directly to healthcare service (i.e., associated with patients' treatment). These costs can be additionally classified into fixed or variable (according to the changes in the volume of services provided) and medical or non-medical direct costs, depending on their nature. Medical costs include, for instance, staffing (e.g., physicians, nurses), consumables (e.g., drugs, treatments), consultations, exams, procedures, hospital and intensive care admissions, equipment and installations, and ambulance services. Non-medical costs include extra expenses from treatments, travel costs, and temporary residence.
- **Indirect costs**, sometimes referred to "productivity losses" represent the costs experienced by patients', family, or society, as the loss of earnings or productivity resulting from patients' illness. These include the costs of lost work due to absenteeism or early retirement, impaired productivity at work (sometimes known as "presenteeism"), and lost or impaired leisure activity. Indirect costs also include the costs of premature mortality.
- **Intangible costs** are attributed to the amount of suffering that occurs due to illness or healthcare intervention. This cost is usually difficult to measure in monetary terms yet is being increasingly included in utility assessments. They include costs related to pain, suffering, and grief.

The cost can be measured as cost/unit, cost/treatment, cost/person, cost/person/year, cost/case prevented, cost/life saved, cost/DALY (disability-

adjusted life year), cost/QALY (quality-adjusted life year), and cost/LYG (life years gained) (Walley and Haycox 1997; McIntosh and Luengo-Fernandez 2006).

The validity of a cost-related study depends on the sources of the data for costs and outcomes. The costing methods generally fall on a spectrum between a bottom-up (micro-costing) and a top-down (gross costing) approach, each with trade-offs between accuracy, precision, and the burden research. The bottom up is a more detailed approach, in which all individual resources are accounted for. An example is the activity-based costing (ABC), which considers costs that go beyond the direct medical costs, such as administrative indirect costs. On the other hand, the top-down approach is easier to implement, as resources are treated in bundles, for example, the hospitalization cost per day in the intensive care unit (Chapko et al. 2009). Commonly, hybrid approach is found to be appropriate under given feasibility restraints.

Additionally, increased attention is being given to collection of cost data in rigorous, prospective clinical studies, for example, the so-called piggy-back trials, in which additional economic cost and outcome data are collected, but the trial is still designed according to traditional clinical aspects. The closer integration of economic and clinical studies can promote more informed resource allocation for new technologies and generate reliable cost and outcomes data during the early part of a technology's lifecycle (Graves et al. 2002; Briggs et al. 2003). There is also a growing interest in using observational data to assess the safety, effectiveness, and cost-effectiveness of medical technologies. However, operational, technical, and methodological challenges may limit its widespread use. Common data models and federated data networks offer a potential solution to many of these problems. For instance, the open-source Observational and Medical Outcomes Partnerships (OMOP) common data model standardizes the structure, format, and terminologies of otherwise disparate datasets, enabling the execution of common analytical code across a federated data network in which only code and aggregate results are shared. The use of open-source and standardized analytics improves transparency and reduces coding errors, thereby increasing confidence in the results (Kent et al. 2020).

Assessments should also make clear whether average costs or marginal costs are being used in the analysis. Whereas average cost analysis considers the total (or absolute) costs and outcomes of an intervention, marginal cost analysis considers how outcomes change with changes in costs (e.g., relative to the standard of care or another comparator), which may provide more information about how to use resources efficiently. Marginal cost analysis may reveal that, beyond a certain level of spending, the additional benefits are no longer worth the additional costs (Drummond et al. 2005; Epstein and Sutton 2011).

Outcome Measures

The second component of any economic analysis is the outcome or consequence to be measured that is defined as the expected benefits from an intervention. "Benefit" measurement aims to be equally comprehensive by incorporating all of the impacts upon the patients' life that arise as a consequence of the use of a healthcare technology. The benefits derived from an intervention might be measured in (i) natural units (e.g., years of life gained, events prevented, avoided medical procedures) and (ii) utility units that attempt to evaluate the quality of a state of health (and not just its quantity) or the satisfaction derived from moving from one state of health to another as a consequence of the application of an intervention. Such utility estimates are frequently informed by some measurement of "quality of life" in different disease states (McIntosh and Luengo-Fernandez 2006; Brazier et al. 2019).

Healthcare-related quality of life (HRQoL) measures attempt to incorporate into the analysis the physical, social, and emotional aspects of the patient's well-being, which are not directly measurable in clinical terms. One of the most common summaries of quality and quantity of life is the quality-adjusted life year (QALY) measure. In order to generate QALYs, health utilities

(or HRQoL weights) are needed. Utilities are preference weights, where preference can be equated with value or desirability. Utilities are usually measured on a cardinal scale of 0 to 1, where 0 indicates the worst health possible (usually represented by death) and 1 indicates full health. States worse than death can also be accounted for, with such states taking a negative value (Whitehead and Ali 2010). The QALY is able to combine the effects of health interventions on mortality and morbidity into a single index thereby providing a "common currency" to enable comparisons across different disease areas. QALYs are calculated simply by multiplying the duration of time spent in a given health state by the HRQoL weight (i.e., utility score) associated with that health state. For instance, if an individual is in a health state for 10 years, where the health state has an associated utility of 0.7, this would generate 7 QALYs (Whitehead and Ali 2010; Torrance and Feeny 1989).

Many different methods have been proposed to value HRQoL based upon widely different techniques and value systems that are broadly divided into direct or indirect methods (also called generic preference-based measures). Authors may also use imputed data from literature or expert opinion.

The direct methods that tend to be used most regularly for eliciting preferences include the visual analogue scale (VAS), the time trade-off (TTO), and the standard gamble (SG). The VAS (a form of rating scale) involves the use of a scale shown on a single line. The top of the scale indicates the "best imaginable health," whereas the bottom of the scale indicates the "worst imaginable health." The TTO method presents individuals with two alternative scenarios and asks which they would prefer: the choice is between living for the rest of their life in an impaired health state or living in full health for a shorter period of time. Then, participants are asked how much time they would be willing to sacrifice to avoid an impaired health state. Finally, the SG involves an element of risk in the decisions faced by participants. The choice is between the certainty of remaining in a particular health state or taking a gamble of either being in full health or risking death. Indirect methods involve the use of pre-scored generic preference-based measures (also called "off-the-shelf" questionnaires or generic multi-attribute systems), which are routinely used in healthcare trials. In this context, health states are described using standardized generic utility questionnaires, which cover general aspects of health. The most commonly generic questionnaires are the EuroQol (EQ)-5D, the Short Form 6D (SF-6D), and the Health Utilities Index (HUI). The measures of these tools differ in terms of aspects such as the dimensions of health (attributes) that are included, the number and description of levels defined for each dimension, and the population on which the preferences are based. The instruments also differ in terms of the valuation method: the TTO was used to value the EQ-5D, whereas the SF-6D and HUI were grounded on SG. Once completed, the questionnaires generate a score using an algorithm based on values that have been obtained from a sample of the general population (Whitehead and Ali 2010; Torrance and Feeny 1989).

However, many controversies in using QALY approach exist, especially considering its limitations in terms of capturing health benefits, its blindness towards equity concerns, the underlying theoretical assumptions, and the most appropriate generic preference-based measure of utility. Additionally, there is growing debate relating to whether a QALY is the same regardless of who accrues it and also the issue as to who should value health states (Sharma et al. 2021; Whitehead and Ali 2010; Schwarzer et al. 2015).

In this context, other approaches such as DALY may be used. Disability-adjusted life year (DALY) was created by the World Health Organization (WHO) in the 1990s and is routinely used in the Global Burden of Disease (GBD) study (healthdata.org/gbd/2019), which quantifies the burden on human populations of more than 350 diseases and injuries in 195 countries. The DALY considers years lost due to ill-health, disability, or early death into a single measure. Different from QALY, DALY measures the total burden from the disease and has a societal perspective. One DALY represents the loss of the equivalent of 1 year of full health. DALY is a universal metric that allows different conditions

and populations to be compared across time. For example, a disease that causes premature death can be compared to a non-fatal chronic condition (Drummond et al. 2005).

Another approach that can be used to assess benefits in economic evaluations is the willingness to pay (WTP) analysis, which the main feature is to value health outcomes in monetary terms. In this analysis, individuals are asked the maximum they are willing to pay ("sacrifice") to achieve a given benefit of an intervention. For this, players must consider all the important attributes of the technology/service under evaluation. Using WTP to estimate the benefits of healthcare allows individuals to value both health outcomes, non-health outcomes, and process attributes. WTP can be estimated using techniques such as open-ended, bidding, payment card, and closed-ended (Clement et al. 2009; Berger 1998).

Perspective, Time Horizon, and Discounting

The economic evaluations have another important component, called "perspective," that represents the point of view adopted when deciding which types of costs and health benefits are to be included in the analysis. Typical viewpoints are those of the patient, health insurance companies, and employer (e.g., payers), hospital/clinic or healthcare professionals (e.g., providers), healthcare systems, or society (Walley and Haycox 1997; Stahl 2008). The most comprehensive perspective is societal as it includes the perspectives of all stakeholders in healthcare, aiming at reflecting a full range of social opportunity costs associated with different interventions. In particular, this includes productivity losses arising from patients' inability to work and changes in these losses associated with a new technology. The UK NICE (The National Institute for Health and Care Excellence), an important HTA agency, recommends that any pharmacoeconomic analyses submitted to the regulators should include a societal perspective – called the "reference case." Other perspectives may be also evaluated (McIntosh and Luengo-Fernandez 2006). However, in practice, the usually adopted perspective is that of the payer, for example, the government in the case of a public health system or the hospital in the case of a private facility.

Interpretation of cost analyses must consider that the time horizon (or time-frame) of a study is likely to affect the findings regarding the relative magnitudes of costs and outcomes. The choice of time horizon is an important decision for economic modeling and depends on the nature of the disease, the intervention under consideration, and the objectives of the analysis. It should be long enough to capture the effects in health and economic outcomes (including significant intended and unintended ones). These could encompass a disease episode, patient life, or even multiple generations of life. For instance, longer time horizons are recommended for chronic conditions associated with on-going medical management, rather than a cure. A shorter time horizon may be appropriate for some acute conditions, for which long-term consequences are less important, highly uncertain, or marginal. HTA agencies usually recommend a lifetime horizon, although it may be useful in sensitivity analysis to test out intermediate time horizons (e.g., 5 to 10 years), for which there may be more robust data available. Additionally, it is important to consider that the use of long-term time horizon is likely to involve extrapolating clinical outcomes into the future and making assumptions about the continued efficacy of interventions and costs of care, as well as discounting of future inputs, which can add important uncertainty into the analysis (Basu and Maciejewski 2019; Kim et al. 2017).

The discounting is a method that accounts for individual time preference, considering that costs and outcomes can occur at different times when using a technology. Most individuals have a positive rate of time preference whereby benefits are preferred sooner and costs incurred later. That is to say, costs and outcomes that occur in the future usually have less present value than costs and outcomes realized today. In economic evaluations, the discount rates of costs and outcomes is performed if the costs and effectiveness outcomes are considered beyond 12-month time periods.

The present value of money, as well as better health, is higher than future costs and outcomes. Currently, the NICE recommends a discount rate of 3.5%, but overall rates of 1.5% until 5% per year can be used. Cost analyses should also correct for the effects of inflation (which is different from the time preference accounted for by discounting), such as when cost or cost-effectiveness for 1 year is compared to another year (Westra et al. 2011). This correction is especially important in development countries, which usually have higher inflation rates.

Type of Economic Analyses

Considering the abovementioned concepts, the main types of economic analyses used in HTA are as depicted in Table 2.

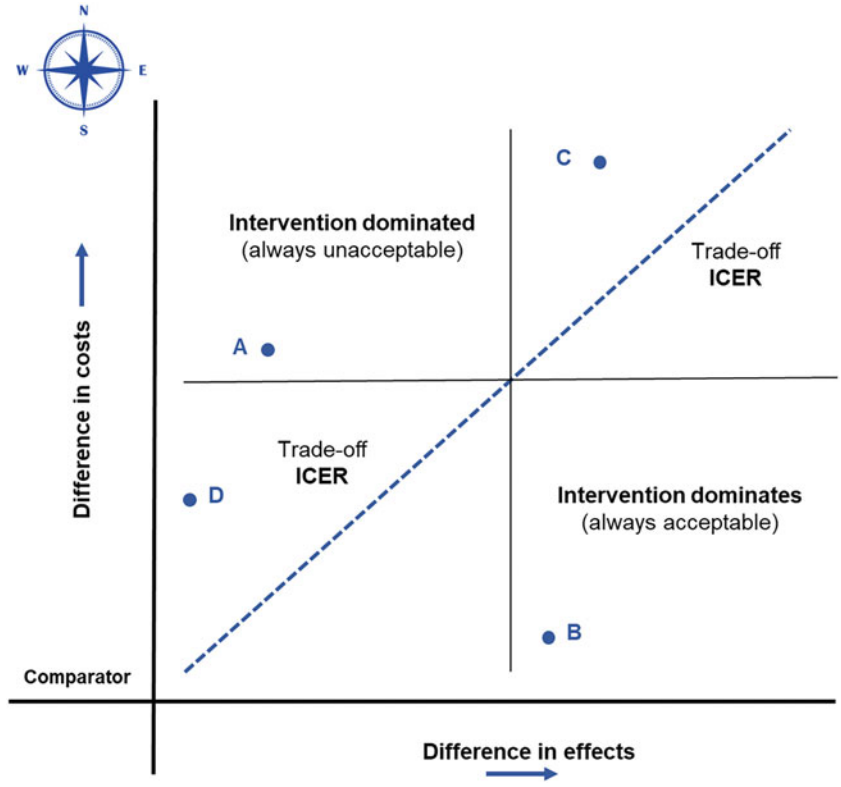
- *Cost-of-illness analysis (COI):* A determination of the economic impact (burden) of a disease or condition on a given population or region/country including the associated treatment costs (Goodman 2014). This analysis can be useful to prioritize between diseases. However, it is not sufficient to ground efficient healthcare allocation for coverage and reimbursement decisions of a particular intervention (e.g., a high-cost burden does not mean that treatments are available to reduce this burden) (Greenberg et al. 2014; Onukwugha et al. 2016). In this case, budget-impact analysis (BIA) is preferable, as affordability is also important for short-run economic purposes.
- *Cost-minimization analysis (CMA):* Aims to determine the least costly among alternative technologies that are assumed to produce equivalent healthcare outcomes (same efficacy/safety profiles). The evidence on the equivalence must be referenced by the author conducting the study and should have been done prior to the cost-minimization analysis (McIntosh and Luengo-Fernandez 2006; Goodman 2014).
- *Cost-effectiveness analysis (CEA):* One of the most used economic evaluation worldwide, it is defined by ISPOR as a comparison of interventions regarding costs in monetary units and outcomes expressed in quantitative non-monetary health units (e.g., reduced mortality or morbidity, symptom-free days gained, cases prevented, life years gained) (Brazier et al. 2019; Bertram et al. 2016). The CEA usually considers a long-term or lifetime time horizon applies discounting rates and the inputs considered the population average. Based on cost and effectiveness incremental results, an incremental cost-effectiveness plane can be built to better visualize the results and to demonstrate the meaning and use of the cost-effectiveness threshold (i.e., a defined maximum monetary value that can be spent for an additional unit of the effect, according to the payer) (Fig. 1).

In the incremental cost-effectiveness plane, usually the comparator is set at the zero axis (represented in Fig. 1 by "comparator"). Then, the alternative is being compared in plotted according to the incremental cost and effect. Costs are conventionally placed on the top-bottom (north-south) axis and effects on the right-left (east-west) axis. In both cases, these effects can be negative, zero, or positive. If the intervention lies in the top left quadrant (NW), as demonstrated by point A (Fig. 1), the costs of the intervention are higher than its alternative, and its benefits are lower. As this is unambiguously worse than its alternative, the intervention is considered "dominated" and should be rejected (unacceptable). Similarly, in the bottom right quadrant (SE), point B refers to a technology with lower costs and higher benefits than its alternative, so the new treatment "dominates" the previous one and should always be accepted. For both the top right (NE) and bottom left (SW) quadrants – represented by points C and D, respectively – neither alternative dominates. In these cases, the incremental cost-effectiveness ratio (ICER) should be calculated. For point C, the ICER represents the cost per unit of effect gained, while for

Pharmacoeconomic Analysis Methods, Table 2 Pharmacoeconomic analysis according to costs and outcomes

Type of analysis	Valuation of costs[a]	Valuation of health outcomes	Calculation
Cost of illness analysis (COI)	$	None	At disease level
Budget-impact analysis (BIA)	$	None or various[b]	Compare interventions
Cost-minimization analysis (CMA)	$	Assume same	Compare interventions
Cost-consequence analysis (CCA)	$	Natural units	Compare interventions
Cost-effectiveness analysis (CEA)	$	Natural units	Cost-benefit ratio
Cost-utility analysis (CUA)	$	Utility units	Cost-benefit ratio
Cost-benefit analysis (CBA)	$	$	Ratio or net costs and benefits

[a]Any currency
[b]It can determine the impact of a technology on a designated nonfixed budget or it can maximize some health outcome within a designated fixed budget
Adapted from the US National Information Center on Health Services Research and Health Care Technology (NICHSR) www.nlm.nhi.gov/nichsr/hta101/ta10107.html



Pharmacoeconomic Analysis Methods, Fig. 1 Summary of an incremental cost-effectiveness plan diagram. (Source: Courtesy of the authors)

point D, it refers to a cost saving per unit of effect lost (Eq. 1). If there are more than two alternatives, they are compared on a systematic pairwise basis using their ICERs (Brazier et al. 2019; Westra et al. 2011).

$$\textit{Incremental cost effectiveness ratio } (ICER) = \frac{Cost_A - Cost_B}{Effect_A - Effect_B} \quad (1)$$

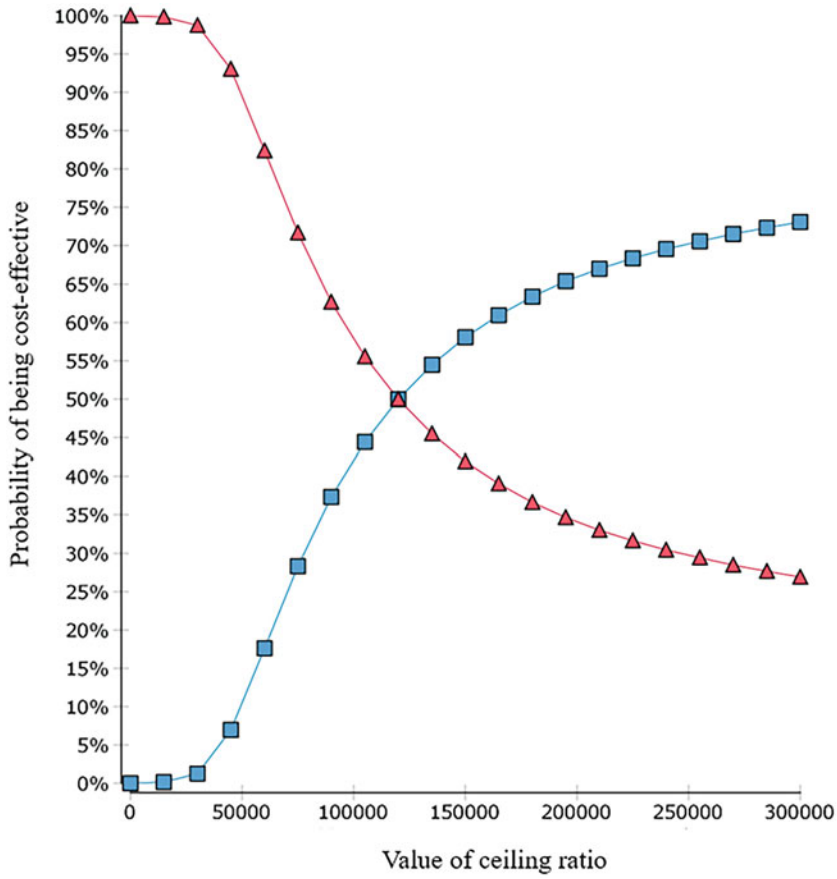
The dashed line in Fig. 1 represents the cost-effectiveness threshold. For the quadrant NE, which represents a typical case in CEA analyses (the proposed intervention in more effective but also more expensive), if the intervention falls under the line, it is considered cost-effective. If it falls above the line (such as the intervention represented by the letter C), it is not cost-effective, because the additional benefit costs more than what the payer has defined as the maximum value that can be spent for this incremental gain.

Many countries or private entities do not have a unique and defined cost-effectiveness threshold for multiple reasons, which may include equity and economic concerns. In these cases, a valuable alternative to explore the results is the cost-effectiveness acceptability curve (CEAC – see "Sensitivity Analysis" section). For this analysis, it is necessary that the model is run probabilistically rather than deterministically (i.e., several iterations will be conducted with values being sampled from distributions that represent parameters uncertainty). After that, a graph is plotted with different ceiling ratios in the x-axis (i.e., the range of cost-effectiveness threshold that is to be evaluated) and the probability of being cost-effective in y-axis (i.e., the percentage of iterations in which each alternative is cost-effective considering the given ceiling ratio). An example is shown in Fig. 2, where two alternatives are being compared. It is possible to see that as the ceiling ratio increases, the alternative represented by blue squares increases the probability of being cost-effective, while the alternative pictured by red triangles decreases it. Therefore, apart from exploring different cost-effectiveness thresholds at once, CEAC also allows for the assessment of the uncertainty around the results: when an alternative has 100% probability of being cost-effective, the uncertainty is low, meaning that the results are robust. On the other hand, if the probability of being cost-effective in a determined ceiling ratio is low (e.g., close to 50%), this indicate that the uncertainty is high at this threshold and the decision-making process based on this result should be cautious.

- *Cost-utility analysis (CUA):* A form of CEA that compares costs in monetary units with health outcomes regarding their utility and mortality, which is expressed in QALYs. This is the preferred type of economic evaluation as it allows the use of the same health outcome for all interventions and diseases and thus helps decision-makers to allocate resources efficiently (Brazier et al. 2019; Torrance and Feeny 1989; Bertram et al. 2016). Similar to CEA, the ICER in the CUA is calculated considering a ratio of costs over benefits, in this case over QALYs as follow (Eq. 2):

$$\textit{Incremental cost} - \textit{utility ratio} = \frac{Cost_A - Cost_B}{QALY_A - QALY_B} \quad (2)$$

- *Cost-consequence analysis (CCA):* A form of CEA that presents costs and health outcomes in discrete categories, without aggregating or placing weights on the costs and health outcomes (Walley and Haycox 1997; McIntosh and Luengo-Fernandez 2006).
- *Cost-benefit analysis (CBA):* Compares costs and health benefits (and risks), all of which are quantified in common monetary units (Walley and Haycox 1997; McIntosh and Luengo-Fernandez 2006). However, as it can be complex to convert a health outcome in a monetary value, this approach is not often applied.
- *Budget-impact analysis (BIA):* This type of analysis estimates the impact of implementing or adopting a new technology or technology-related policy or service on a designated healthcare budget, and it is usually

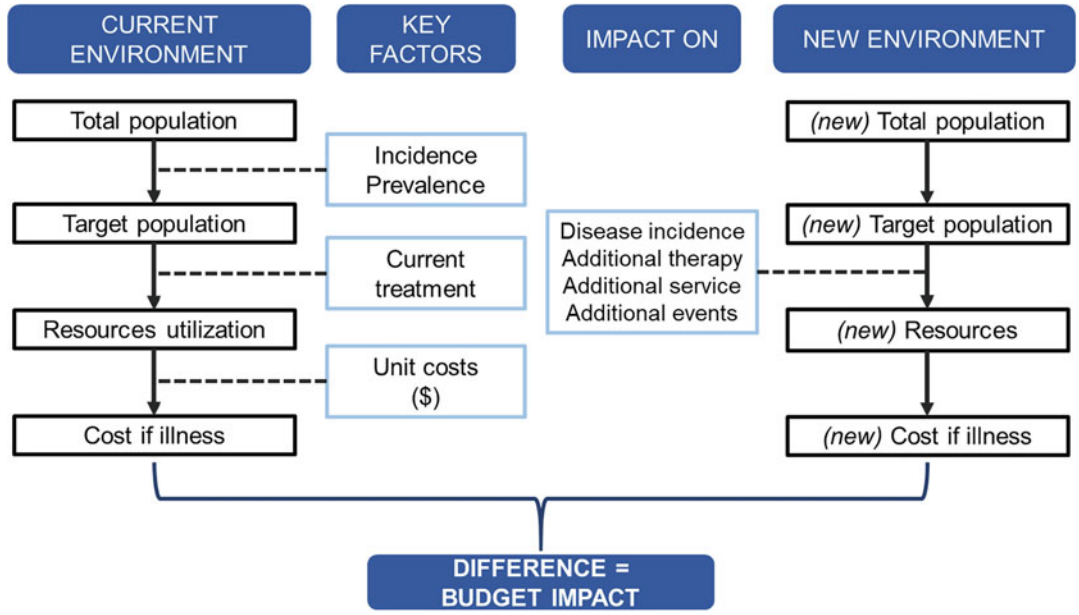


Pharmacoeconomic Analysis Methods, Fig. 2 An example of a cost-effectiveness acceptability curve (CEAC). (Source: Courtesy of the authors)

conducted in addition to a CEA. This method is able to assess the affordability of a healthcare intervention if the intervention is used within an environment as compared to not using it within that same environment (Rabarison et al. 2015; Sullivan et al. 2014) (see Fig. 3). The BIA is usually performed from the payer perspective, considers the size of the population, and has a short-term and steady time horizon (for instance, 3 to 5 years). Here, the only model output is the cost. BIA is especially important in cases where the target population is large and there is a monetary restraint: a technology can be cost-effective compared to the current scenario; however, if the number of patients who will consume this technology is large, it may not be an affordable strategy. For example, a new technology can be deemed cost-effective because it produces 1 additional QALY per additional $20,000. Yet, if the population who would use this technology consists of 50,000 people, the total budget impact would be of $1 billion, which may not be affordable.

Decision Modeling

Modeling is defined as the reproduction of events and possible consequences due to alternative policy options at the cohort or individual levels using mathematical and statistical frameworks. Models of costs and benefits are paramount in economic evaluations that are part of decision-making



Pharmacoeconomic Analysis Methods, Fig. 3 Basic framework of a budget impact analysis. (Source: Courtesy of the authors)

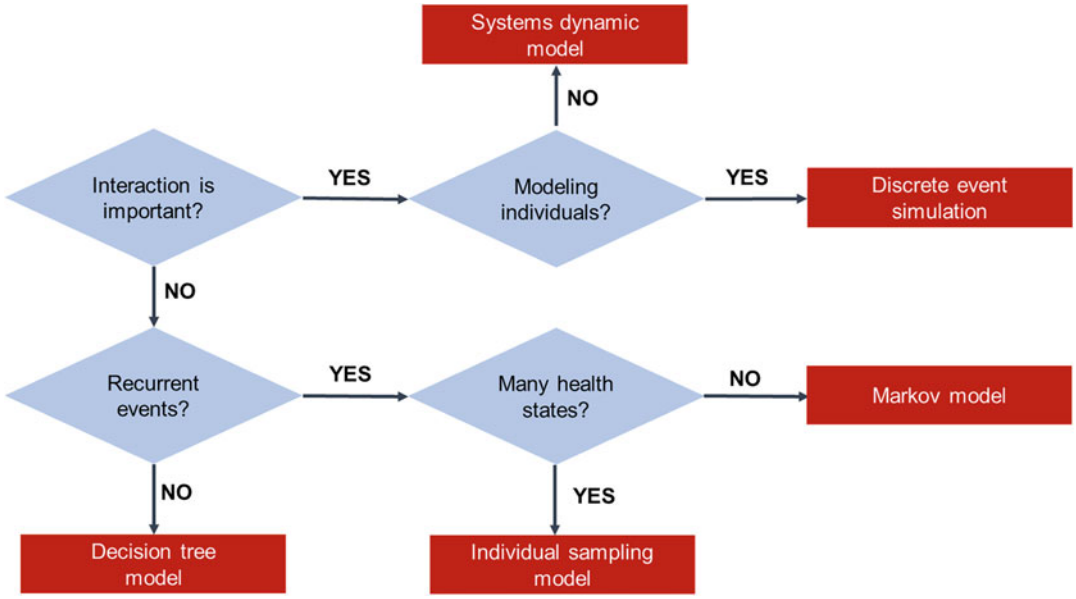
processes for incorporation and financing of technologies of healthcare systems. In health economics, the decision analyses can be operationalized through different analytic mathematical models that should be selected considering the context and available data (Epstein and Sutton 2011; Hay 1998; Annemans et al. 2000). To address uncertainty involved in estimations of costs, outcomes, and other variables used in a decision-model analysis, sensitivity analysis should be performed. This type of analysis may find that including variables such as indirect costs in the model or using a reasonable higher discount rate changes the cost-effectiveness of one intervention compared to another. The four main types of sensitivity analyses are one-way simple sensitivity analysis, multiway sensitivity analysis, threshold sensitivity analysis, and probabilistic sensitivity analysis (Epstein and Sutton 2011; Boshuizen and van Baal 2009).

Figure 4 summarizes the flowchart for deciding which model should be used. The model can be populated by a simulated cohort or individually and it can exist interaction between agents or not. Decision trees and Markov models are the most employed models in health economics decision analyses; however, other types exist and may be more appropriate depending on the decision problem. Beyond that, it is not rare the use of hybrid models.

Regardless of their structural form, several similarities across healthcare decision analyses exist:

- They require the clinical and policy relevant features of the problem, the time horizon of the analysis, and the description of the target population.
- They require information on the probability of experiencing a health state or a health event.
- They require data on the value associated with a health state or health event (e.g., cost, health effect, or both).
- Almost all healthcare decision analyses use inputs from multiple studies or sources given to limitations on data availability.

A decision tree is the simplest decision model, which outlines and quantifies the consequences of the two or more options. It can be represented by

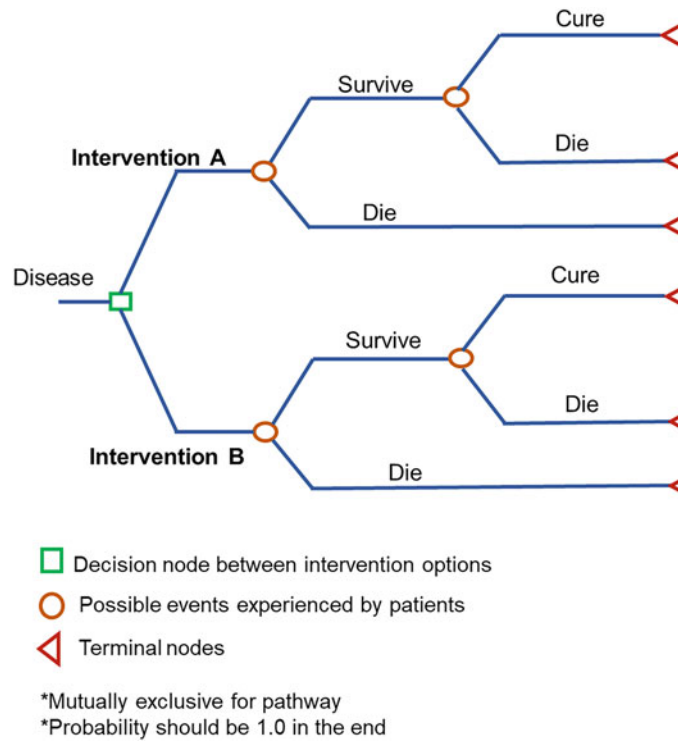


Pharmacoeconomic Analysis Methods, Fig. 4 Type of decision analytic models. (Source: Courtesy of the authors)

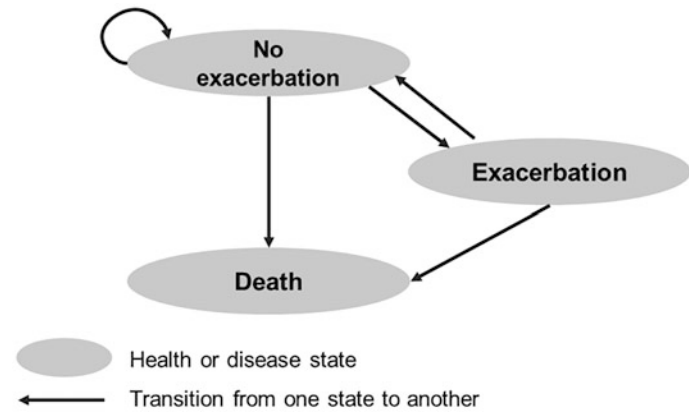
means of a tree diagram as demonstrated in Fig. 5 that is constituted by one decision node at the root, branches representing all the strategies that are to be compared, a series of chance nodes off every strategy branch from which emanate two possible consequences, and outcomes depicted at the end of each pathway. The cohort advances the model according to transition probabilities. The sum of all transition probabilities emanating from a chance node is always one, since the events must be mutually exclusive and exhaustive. Finally, the terminal nodes, also called payoff (e.g., utilities), are quantified in the analysis (e.g., health impact of each consequence) (Husereau et al. 2013; Ademi et al. 2013). Decision trees are usually employed for simple decision problems without recurrent events, such as acute and limited health conditions.

Markov models are used to represent more complex diseases, usually chronic health conditions in which different and recurrent health states exist. It can be used to model a cohort of patients (called Markov cohort model) or individuals (called microsimulation or first-order Monte Carlo model) (Epstein and Sutton 2011; Stahl 2008). These health states are mutually exclusive and exhaustive, and so each individual represented in the model can be in one and only one of these disease states at a specified or fixed period of time. Individuals move ("transition") between disease states as their condition changes over time. Time itself is considered as discrete time periods called "cycles" (e.g., number of weeks or months), and movements from one disease state to another (in the subsequent time period) are presented as "transition probabilities." At the end of each cycle, the individual can either stay in the same health state or move to another one. The time spent in each state for a single model cycle (and transitions between states) is associated with a cost and a health outcome, which will both be summed for the complete time horizon (Ademi et al. 2013; Stahl 2008).

In Fig. 6, an example of a Markov model is presented. This model includes three health states: "no exacerbation," "exacerbation," and "death." The arrows represent the direction that the patients can migrate at the end of each cycle (which can last for 1 day, 1 month, or 1 year, depending on the disease being modeled). Patients can transition to the death state from all states, which is applicable to any Markov model (a patient can always die, irrespective of the cause being the disease under study or not). However, the death state is



Pharmacoeconomic Analysis Methods, Fig. 5 Simple hypothetical example of a decision analysis tree. (Source: Courtesy of the authors)



Pharmacoeconomic Analysis Methods, Fig. 6 Simple hypothetical example of the Markov model. (Source: Courtesy of the authors)

absorptive, i.e., patients cannot exit from this state once they are there. In this example, patients in the "no exacerbation" state can migrate to the "exacerbation" state or continue in the "no exacerbation" state. On the contrary, the state "exacerbation" does not last for more than one cycle, as can be seen by the absence of a recursive arrow. This means that after that cycle, the patient will return to the "no exacerbation" state or will die. The analysis can last until all patients achieve the absorptive state (all patients die) or a fixed time horizon, for example, the estimated life expectancy of a given population.

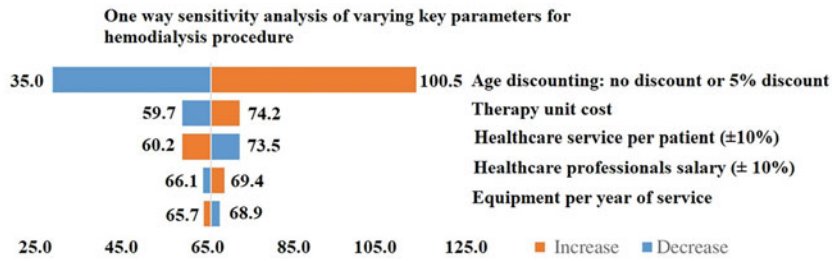
In the described Markov model, it is assumed that all patients will stay in the same health state until the end of the cycle, when finally will be able to migrate to another state according to transition probabilities. However, in the real practice, the transition between states is not fixed. For example, in a model with 1-year cycles of an aggressive

disease, some individuals can die after 3 months, others after 6 months or after 9 months, and not necessary at the end of the cycle (12 months). To take this behavior into account, approaches known as half-cycle and within-cycle corrections can be applied. In the half-cycle correction, the costs and outcomes are divided by two in the first and last cycles. In the within-cycle correction, half the costs and outcomes are granted at the beginning of the cycle and half at the end, considering the next state for the which the patients migrated (Elbasha and Chhatwal 2016). When there is interaction between individuals, other types of models can be employed. For example, in the case of infectious diseases, disease transmission can be included into the model, which can be simulated in dynamic models (Pitman et al. 2012). The dynamic model can be open, i.e., new patients can enter the model, or closed. This type of model is useful to study vaccines and treatments that can reduce risk of infection. Another model with flexible frameworks is the discrete event simulation (DES). DES relies on how long until the patient experiences the event (time to event), and it is individual based. DES is useful for decision problems where there is a list or waiting line, for example, in the case of queue for transplants. One important advantage of DES is the low analysis processing time, because time is not discrete as in Markov model (Ademi et al. 2013; Stahl 2008; Zhang 2018)..

Sensitivity Analysis

Sensitivity analysis is used to illustrate and assess the level of confidence that may be associated with the conclusion of an economic evaluation. It is performed by varying key assumptions made in the evaluation (individually or severally) and recording the impact on the result (i.e., output) of the evaluation. In model-based economic evaluations, this includes varying the values of key input parameters, as well as structural assumptions concerning how the parameters are combined in the model (Boshuizen and van Baal 2009; Elbasha and Chhatwal 2016; Vreman et al. 2021). These analyses are usually classified into the following:

- **One-way or simple sensitivity analysis**: Input parameters are varied one by one as demonstrated in Fig. 7 in a so-called tornado chart or tornado diagram. In this graph, the X-axis is the net present value (NPV) (i.e., total present value over a period). Longer bars indicate more sensitive variables.
- **Multiway sensitivity analysis**: More than one parameter is varied at the same time. It should be noted that multiway sensitivity analysis becomes more difficult to interpret as progressively more variables are varied in the analysis.
- **Threshold analysis**: The model is used to assess the tipping point for an input parameter (at what value of this parameter would the decision based on the output of the evaluation be altered?)
- **Probabilistic analysis**: A stochastic approach is taken to produce a distribution of output-based "n" distributions of input parameters. In this scenario, faced with the choice of whether or not to reimburse a new technology, the decision maker will likely be interested in the probability that the new technology is cost-effective compared to the existing alternative. This probability can be identified from ICER plane with reference to the decision-maker's defined maximum acceptable ceiling ratio (λ). This probability is simply the proportion of the scatter plot points that fall to the south and east of a ray with slope of λ drawn through the origin (i.e., proportion of incremental cost-effect pairs with a value below λ). Since the maximum acceptable ceiling ratio will generally not be stated explicitly, a sensitivity analysis should be undertaken with the probability determined for a range of λ s. The cost-effectiveness acceptability curves (CEAC) provide a plot of these probabilities (y-axis) against λ (x-axis) (see Fig. 2). CEAC were introduced as an alternative to calculating confidence intervals for ICERs with statistical methods. The CEAC indicates the probability that an intervention is cost-effective compared with the alternative, given the observed data, for a range of λ values. Given a specified value of this "acceptable" cost-effectiveness ratio (i.e., λ on the x-axis), the CEAC shows the probability



Pharmacoeconomic Analysis Methods, Fig. 7 Hypothetical example of a one-way sensitivity analysis. (Source: Courtesy of the authors)

(read off on the y-axis) that the data are consistent with a true cost-effectiveness ratio falling below that value.

Sensitivity analysis is an important part of the evaluation process and gives valuable information to decision-makers about the robustness of their decision based on the findings of an economic evaluation, as well as the potential value of collecting more information before making a decision (Vreman et al. 2021).

Trends in Pharmacoeconomics: Value of Information (VOI) and Value-Based Healthcare (VBHC) Analyses

The value of information (VOI) analysis is a broad term referring to the estimation of the value, in terms of cost and health outcomes, of collecting more data/information on key parameters influencing a decision, for instance, the reimbursement of a new technology. This analysis is useful where the output of an economic evaluation (e.g., ICER) is uncertain, yet close to a decision threshold (willingness to pay – WTP), and a key parameter on which the output is based is itself uncertain. In this scenario, new information reducing uncertainty in that parameter will increase the chance towards a more assertive decision, and the "value" of this information is a function of how likely it would enable a decision to be made or changed. VOI analysis may be performed using conventional economic models as long as they include probabilistic sensitivity analysis. Common outputs of VOI analysis are the Expected Value of Perfect Information (EVPI), Expected Value of Partially Perfect Information (EVPPI), and Expected Value of Sample Information (EVSI) (Fenwick et al. 2020; Tuffaha et al. 2014).

Value-based healthcare (VBHC) is nowadays a global trend in healthcare management and policy, as its purpose is to provide care grounded on "values." The framework, concepts, practices, theories, and tools of VBHC are coined by Harvard, Harvard Business School, and Harvard Medical School and Professors Porter, Teisberg, Kaplan, Bohmer, and Christensen. Although the framework is not completely "new," it does constitute a current challenge for a definitive commitment to standardize, systematize, and incorporate value-based thinking and functioning into the clinical and management practices. VBHC incorporates some relevant elements that have been hitherto absent or neglected in the daily management of organizations and healthcare systems. For instance, outcomes should be measured from a broad, plural perspective and not merely from a health economics or primary care scope. Patient-defined outcomes and patient-reported outcomes are the essential piece of this proposal. It involves breaking with the usual complacency of measuring activity, average stays, process indicators, and resources. The widespread acceptance of VBHC is thought to provide new opportunities for organizational innovation, benchmarking and benchlearning, value-based purchasing, shared decision-making, comparative effectiveness analysis, and competition for value creation (Nuno-Solinis 2019; Smith et al. 2020; Damman et al. 2020).

Further Applications and Challenges in Economic Evaluations

One of the primary applications of pharmacoeconomics in clinical practice today is to aid clinical and policy decision-making. Through the appropriate use of pharmacoeconomics, healthcare professionals, managers, and other stakeholders can make better, more informed decisions regarding the products and services they provide both for patient-level and for the entire healthcare system. Pharmaceutical manufactures also benefit from economic evaluations, as they provide inputs for the development of portfolios. HTA agencies worldwide highly recommend the performance of economic evaluations to ground approval of new technologies. Other scenarios, performance-based pricing and reimbursement agreements, also rely on pharmacoeconomics. This is important as in the foreseeable future, the economic burden of several diseases is likely to keep increasing – both in the case of infectious surges, like COVID-19, and chronic diseases, like cancer or diabetes (Tonin et al. 2021; Bridges 2005).

Currently, the main challenges for economic evaluations in healthcare continue to be establishing international guidelines or standards of practice to be strictly followed by researchers; creating a cadre of trained producers and consumers of economic evaluation analyses; continuing education on the relevant features of this field for healthcare professionals, government officials, and private sector executives; innovating on methods and integrating economic evaluation with other analyses (e.g., network meta-analysis, living systematic reviews, model-based meta-analysis); and stable funding to support applied pharmacoeconomic research worldwide.

Conclusion

In this chapter, a broad view on pharmacoeconomic analyses and methods alongside with major recommendations for the conduction and reporting of economics studies were presented. These concepts are paramount for evidence synthesis and should be properly applied in complete HTA or during clinical decision-making processes. Some important definitions and methods such as the cost and outcomes that can be used in health economics analyses, the type of economics analyses (cost-minimization, cost-effectiveness, budget impact analysis), and the available models to perform a simulation cost analysis were described. Beyond the concepts presented here, others may be of interest to readers, such as how to deal with uncertainty in the analysis, which is inherent to any health economics analysis and may encompass variability, heterogeneity, parameter, and structural uncertainty. Other topics which have gained attention are the value of information and value-based healthcare analyses. Finally, to achieve more robust results and decrease uncertainty, individual patient data and real-world evidence are increasingly being focus of research and incorporated into the economic evaluations. Authors should strictly follow international guidelines and checklists (e.g., CHEERS) to perform and report an economic evaluation and try to be updated on the new trend methods of this field.

Cross-References

► CHEERS Guideline

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