

## 2 Definitions and Basic Concepts

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### Abstract

Pharmacoeconomics describes and analyzes the costs of pharmaceutical products and services and their impact on individuals, healthcare systems, and society. In pharmacoeconomic analyses, direct, indirect, and sometimes intangible costs are generally considered. One or more than one perspective could be adopted (e.g., society, healthcare insurers, healthcare providers, healthcare system, patients) and analyzed separately. A variety of economic outcomes may be considered, such as monetary and non-monetary costs. Objective physiological endpoints, subjective humanistic endpoints, morbidity, and mortality are usually categorized as patient outcomes.

When designing a study, a time horizon should be set to specify a period of time during which the outcomes of an analysis will be considered.

Finally, a brief overview about discounting, that has to be applied to bring future costs to the same frame of reference as present costs, is provided.

### 2.1 Definitions

Pharmacoeconomics arises from a fusion of pharmacy and economics. Economics is defined as “a social science concerned chiefly with description and analysis of the production, distribution, and consumption of goods and services” [Merriam-Webster’s Collegiate Dictionary, Tenth Edition].

It comes of the set of analytical methodologies designed to identify, measure, and evaluate the costs and related consequences of two or more therapeutic alternatives.

Therefore, we may define “pharmacoeconomics” as a social science concerned with the description and analysis of the costs of pharmaceutical products and their impact on individuals, healthcare systems, and society. Pharmacoeconomics is a subset of health economics, which deals with healthcare services in general rather than being restricted specifically to pharmaceuticals.

Because pharmacoeconomics is a social science substantially concerned with events in clinical practice, it overlaps with a branch of medicine called “outcomes research”. Outcomes research is the study of the clinical (e.g., presence of disease), economic, or humanistic (e.g., patient quality of life) end results (“outcomes”) of providing healthcare services. Pharmacoeconomics is that subset of outcomes research that deals with pharmaceuticals and includes economic outcomes.

## 2.2 Costs

The cost is the expenditure necessary for someone (patient, National Health System, and society) to obtain something (health intervention). The definitions of some cost terms commonly used in pharmacoeconomics are given in Table 2.1.

Term	Definition
Average cost	Total cost divided by the number of units produced
Direct cost	The cost of the goods and services that are used in providing a treatment
Incremental cost	The increased cost of one treatment program relative to an alternative
Indirect cost	The value of the productivity loss resulting from an illness
Intangible cost	The value of psychosocial effects such as pain and suffering
Marginal cost	Change in total cost that results from the production of an additional unit
Mortality cost	The cost incurred due to death
Opportunity cost	The value of all costs when an alternative is chosen
Overhead cost	The cost of providing space, electricity, administrative services, etc.
Production cost	The total amount of resources used in producing goods
Productivity cost	Same as indirect cost

Table 2.1. Definitions of pharmacoeconomic costs.

### Example

The average cost of detecting a case of condition Y is the total cost of all the screening tests performed divided by the number of true positive cases of Y detected. If the screening only uncovers 75% of cases of condition Y and a program is applied to increase this to 85%, the cost of that program would be the marginal cost of increasing the detection rate by 10%.

First of all, economists distinguish **average cost** from **marginal cost**.

In practice, the marginal cost is often greater than the average cost.

Average costs can be distinguished from **incremental costs**. The incremental cost is the increased cost of one healthcare program relative to an alternative. The incremental cost differs from the marginal cost in that the former relates to treatment alternatives while the latter refers to more of the same treatment.

The distinction between **direct** and **indirect costs** is particularly relevant to cost-of-illness analysis. The direct cost of an illness, such as asthma, to society is the cost of providing all of the healthcare services to treat it, including the costs of medicines, physician visits, emergency room visits, and hospitalizations due to asthma. The indirect cost to society is the value of the productivity loss when asthma prevents people from working.

Most direct costs considered in pharmacoeconomic analysis are direct medical costs, i.e., the costs of physician visits, hospitalizations, laboratory tests, drugs, and medical supplies and equipment. Non-medical costs include a variety of out-of-pocket expenses, such as transportation to healthcare facilities, special foods, etc.

$$\text{Direct costs} = \text{Direct medical costs} + \text{Direct non-medical costs}$$

Indirect costs, i.e., productivity costs, arise from morbidity—when people miss work (absenteeism) or are less productive while at work (presenteeism)—and mortality.

$$\text{Indirect costs} = \text{Morbidity costs} + \text{Mortality costs}$$

In computing total costs, researchers may include not only the direct and indirect costs but also **intangible costs**. Intangible costs include the value placed on pain and suffering.

$$\text{Total costs} = \text{Direct costs} + \text{Indirect costs} + \text{Intangible costs}$$

## 2.3 Consequences

### **Economic Outcomes**

The word “cost” is taken to mean two different things in a pharmacoeconomic analysis, i.e., the non-monetary costs, referring to the healthcare and other resources consumed, and the monetary value of these resources.

#### *Monetary Costs*

The true monetary costs of the healthcare resources used are not necessarily easy to determine and in practice several surrogate measures are used. Charges by providers may be equated with cost. However, these charges are not necessarily the same as the true cost to the provider nor equivalent to the payments they actually receive. The cost of medical services and pharmaceuticals can be equated with the actual reimbursements that the healthcare insurer paid to the provider. The list prices for drugs and the fee schedules for medical services are available in different repositories according to each country.

#### *Non-monetary Costs*

Direct non-monetary costs are expressed as the healthcare resources consumed by a program or treatment alternative. These typically are the costs associated with time spent by healthcare professionals to perform visits, hospitalizations, and laboratory tests, for drugs and medical supplies. The numbers of these events are counted. The indirect costs may be expressed in terms of the number of work-loss days or the number of days off school.

### **Patient Outcomes**

#### *Physiological*

Patient outcomes may be expressed in terms of a physiological variable such as blood pressure, bone mineral density, or serum concentration of cholesterol, etc. In a cost-effectiveness analysis of a cholesterol-lowering drug, for example, the patient endpoint might be the average percentage reduction in serum cholesterol concentration. These kinds of variables can be measured

objectively using medical instrumentation. However, such “hard” endpoints are criticized as not being directly experienced by patients and thus not directly relevant to patients’ feelings of well-being.

### ***Mortality and Morbidity***

In between the objective physiological endpoints and subjective humanistic endpoints are mortality and morbidity. Death is both relevant to patients’ lives and objectively measurable. Morbidity—a diagnosis, e.g., heart failure, or pneumonia, and the effects on the patient’s ability to function—is also relevant to patients’ lives and may be based at least in part on objective data. Diagnoses, however, are usually based in part on patients’ symptoms, which are by definition subjective.

### ***Humanistic***

In outcomes research, endpoints more directly relevant to patients’ experience of their lives are often chosen. These “humanistic” endpoints include quality of life and patient satisfaction. While more relevant to patients’ expressed desires, humanistic endpoints are based on patients’ perceptions of their lives and are by definition subjective.

### ***Quality of Life***

The measurement of quality of life is an attempt to measure the totality of a person’s experience of life, including work, recreation, social activities, sex life, etc. In pharmacoeconomics, we are usually interested in the impact of a person’s health status on their quality of life, i.e., their health-related quality of life. Standardized questionnaires measure either health-related quality of life in general or quality of life in the context of a specific disease. The Medical Outcomes Study Short Form 36, or SF36, is a widely used generic health-related quality-of-life instrument. The SF36 has eight domains, including physical functioning, social functioning, role functioning, psychological distress, general health perceptions, bodily pain, vitality, and psychological well-being. It is worth citing also EQ-5D, which is a family of instruments used to describe and value health [EuroQol Group]. EQ-5D has been used worldwide for over 30 years and proved robust, reliable, and responsive on a wide variety of pathologies. It evaluates 5 dimensions, which are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

An example of a disease-specific questionnaire is a migraine quality-of-life questionnaire that measures migraine symptoms, work functioning, social

functioning, vitality, and the migraine sufferer's feelings or concerns about her or his migraine and its treatment [Hartmaier, 1995].

### ***Patient Preference and Satisfaction***

The same psychometric techniques that are used to measure quality of life can be applied to patients' satisfaction with the healthcare they receive. Patients might be asked to rate the healthcare provider's knowledge and skill, the quality of the interpersonal care, their degree of trust in the provider, etc.

## **2.4 Perspectives**

Since costs are seen differently from different points of view, the perspective of any pharmacoeconomic analysis must be explicitly stated. Society, healthcare insurers (payers), and healthcare providers all have different perspectives on costs. Furthermore, the organization of healthcare financing, and therefore the appropriate cost perspective, varies from country to country and within countries such as the United States that have mixed Healthcare Services. The usual perspectives in cost-effectiveness analysis are those of society and the Healthcare Service.

### **Example**

A science writer with coronary heart disease is hospitalized following an acute myocardial infarction that subsequently proves fatal. From the perspective of the science writer's healthcare insurer (the payer), the cost of hospitalization is the amount of money paid to the hospital under the terms of the health plan. From the perspective of the provider (the hospital), the cost is the true cost of providing the hospital services. From the perspective of the science writer's employer, which (in this fictional example) entirely subsidizes its employees' health plans, the cost is that part of the insurance premium designed to cover coronary heart disease, plus the indirect costs, i.e., the cost of the productivity lost while the science writer was incapacitated, and the cost of hiring a replacement.

## **2.5 Time Horizon**

The term "time horizon" is used to specify a period of time during which the outcomes of an analysis will be considered. The time horizon could be

expressed as a fixed number of years (or months or weeks) or relative to study variables (e.g., patients' lifetimes, or the amount of time that patients were enrolled in a clinical trial). More precisely, the time horizon is a point in the future up to which all costs and effects must be accounted for and beyond which everything can be ignored.

### Example

A cost-effectiveness analysis of parenteral nutrition with lipid emulsions with or without  $\omega$ -3 fatty acids in a variety of clinical settings (i.e., Intensive Care Unit—ICU or surgical/non-ICU) and in four European scenarios (Italy, France, Germany, and the UK) adopted a perspective of healthcare provider and a time horizon that was limited to patients' hospital stay [Pradelli, 2020b]. The clinical experience of patients was modeled over time in terms of the events that occur and the consequences of those events, which might be solved with patient discharge or lead to hospital death, according to the evidence-based medicine of a published meta-analysis [Pradelli, 2020a].

In another example, with the aim to assess the cost-effectiveness of obinutuzumab in comparison to rituximab in patients with untreated advanced follicular lymphoma from an Italian National Health Service perspective, a lifetime horizon was used to record all consequences of therapeutic choices, in terms of efficacy and costs [Bellone, 2021].

The lifetime analysis is a projection of events into the future, and lifetime horizon should be preferred to capture differences in outcomes across alternative technologies. A shorter time horizon may be appropriate for acute diseases or when long-term consequences are not relevant.

## Discounting

If the time horizon of a pharmacoeconomic analysis is several weeks or months, no adjustment for changes in costs over time is required. If the time horizon is several years, however, then costs that are incurred at different times must be brought to same reference time point.

The value of a dollar today is not what it was, say, twenty years ago. For example, the cost of a drug in 2012 must be expressed in dollars for the current year (or the reference year of the analysis) by increasing it according to the annual inflation rate for pharmaceuticals. Conversely, the value of a dollar twenty years from now will be less than its **present value**. In order to bring future costs to the same frame of reference as present costs, they must be discounted.

### Example

The cost of a medical service is \$1,000. The medical service will be utilized five years from now: What is its present value? The formula for discounting prices into the future is:

$$C_{\text{present}} = \frac{C_n}{(1 + r)^n}$$

where  $C_{\text{present}}$  is the current cost,  $n$  is the number of years,  $C_n$  is the cost  $n$  years from now, and  $r$  is the discount rate. If the discount rate is 5% per annum, the present cost of the medical service is:

$$C_{\text{present}} = \frac{1,000}{(1 + 0.05)^5} = \$784$$



## Questions

### 1 Tick the correct affirmation

- A. Productivity costs are synonymous of indirect costs
- B. Productivity costs are synonymous of direct costs
- C. Productivity cost is the total amount of resources used in producing something
- D. Productivity cost is the change in total cost that results from the production of an additional unit

### 2. Which is the difference between incremental and marginal cost?

- A. The incremental cost relates to treatment alternatives, while marginal cost refers to more of the same treatment
- B. The marginal cost relates to treatment alternatives, while incremental cost refers to more of the same treatment
- C. The incremental cost is the total cost of all the screening tests performed divided by the number of true positive cases of the condition detected, while the marginal cost relates to treatment alternatives
- D. The incremental cost of an illness is the cost of providing all of the healthcare services to treat it, while the marginal cost is the value of the productivity loss

### 3. Tick all that applies

- A. Morbidity costs have to be considered as a part of direct costs
- B. Intangible costs may be considered among total costs
- C. Hospitalization costs have to be considered as a part of direct costs
- D. Presenteeism doesn't affect indirect costs

### 4. Tick the correct affirmation

- A. Direct costs are related to the productivity loss
- B. The true monetary costs of the healthcare resources are always easy to determine
- C. The costs associated with time spent by healthcare professionals to perform visits, hospitalizations, and laboratory tests, for drugs and medical supplies are direct non-monetary costs
- D. Indirect costs take into account only the cost for drugs and medical supplies

**5. Tick the correct affirmation**

- A. Measurable “hard” endpoints include quality of life and patient satisfaction
- B. Patients’ symptoms are objectively measurable
- C. “Humanistic” endpoints are often chosen in outcome research
- D. The Medical Outcomes Study Short Form 36 has 36 domains

**6. Which of these is not a physiological patient outcome?**

- A. Blood pressure
- B. Hematocrit
- C. Bone mineral density
- D. Patient’s satisfaction

**7. What is  $C_{\text{present}}$ ?**

- A. The total cost
- B. The discount rate
- C. The current cost
- D. None of the above

## Answers

- 1. A
- 2. A
- 3. B, C
- 4. C
- 5. C
- 6. D
- 7. C

## References

- Bellone M, Pradelli L, Molica S, et al. Obinutuzumab Plus Chemotherapy Compared with Rituximab Plus Chemotherapy in Previously Untreated Italian Patients with Advanced Follicular Lymphoma at Intermediate-High Risk: A Cost-Effectiveness Analysis. *Clinicoecon Outcomes Res* 2021; 13: 661-71. <https://doi.org/10.2147/CEOR.S317885>
- EuroQol Group. EQ-5D. Available at <https://euroqol.org> (last accessed September, 2022)
- Hartmaier SL, Santanello NC, Epstein RS, et al. Development of a brief 24-hour migraine-specific quality of life questionnaire. *Headache* 1995; 35: 320-9. <https://doi.org/10.1111/j.1526-4610.1995>
- Merriam-Webster's Collegiate Dictionary, Tenth Edition. Available at <https://www.merriam-webster.com/> (last accessed July 2022)
- Pradelli L, Mayer K, Klek S, et al.  $\omega$ -3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis. *JPEN J Parenter Enteral Nutr* 2020; 44: 44-57. <https://doi.org/10.1002/jpen.1672> [a]
- Pradelli L, Muscaritoli M, Klek S, et al. Pharmacoeconomics of Parenteral Nutrition with  $\omega$ -3 Fatty Acids in Hospitalized Adults. *JPEN J Parenter Enteral Nutr* 2020; 44 Suppl 1: S68-S73. <https://doi.org/10.1002/jpen.1775> [b]