THE COMPLEX INTERFACE BETWEEN ECONOMY AND HEALTHCARE: AN INTRODUCTORY OVERVIEW FOR CLINICIANS

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ABBREVIATIONS:

EE, economic evaluation; OECD, Organization for Economic Co-operation and Development; CEA, cost-effectiveness analysis; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; WTP, willingness to pay; NICE, National Institute for Health and Clinical Excellence; CUA, cost-utility analysis; QALY, quality adjusted life year; HUI, Health Utilities Index; SF-6D, Short-form 6D; EQ-5D, Euro Quality of life 5 Dimensions.

ABSTRACT

In a period of generalized economic crisis, it seems particularly appropriate to try to manage a continuing growing sector such as healthcare in the best possible way. The crucial aim of optimization of available healthcare resources is obtaining the maximum possible benefit with the minimum expenditure. This has important social implications, whether individual citizens or tax-funded national health services eventually have to pay the bill. The keyword here is efficiency, which means either, maximizing the benefit from a fixed sum of money, or minimizing the resources required for a defined benefit. In order to achieve these objectives, economic evaluation is a helpful tool. Five different types of economic evaluation exist in the health-care field: cost-minimization, cost-benefit, cost-consequences, cost-effectiveness and cost-utility analysis. The objective of this narrative review is to provide an overview of the principal methods used for economic evaluation in healthcare. Economic evaluation represents a starting point for the allocation of resources, the decision of the valuable investments and the division of budgets across different health programs. Moreover, economic evaluation allows the comparison of different procedures in terms of quality of life and life expectancy, bearing in mind that cost-effectiveness is only one of multiple facets in the decision making-process. Economic evaluation is important to critically evaluate clinical interventions and ensure that we are implementing the most cost-effective management protocols. Clinicians are called to fulfill the complex task of optimizing the use of resources, and, at the same time, improving the quality of healthcare assistance.

Introduction

Inadequacy of resources is the base of economy. For this reason, the need for optimization of the available resources appears of primary importance, with the objective of obtaining the maximum possible benefit with the minimum expenditure. [1]. In a context characterized by frequent cuts to public spending, the introduction in the health-care field of economic evaluations represents another intent of reconsidering a sector that consumed 8.8% of Italian gross domestic product (GDP) in 2013, excluding capital expenditure, compared with an OECD (Organization for Economic Co-operation and Development) average of 8.9% [2]. As a reflection of the economic crisis, health spending continued to shrink in Greece, Italy and Portugal in 2013 [3]. On the contrary, in the last five years health spending has been growing with a medium rate of 2.5% per year outside Europe [3].

As a consequence, it seems appropriate to try to obtain the best allocation of the finite available resources at our disposal, in order to guarantee health assistance despite the negative effects of the economic crisis and to manage in the proper way a continuing growing sector. The keyword here is *efficiency*, which means either maximizing the benefit from a fixed sum of money or minimizing the resources required for a defined benefit [1]. This has important social implications, whether individual citizens or tax-funded national health services eventually have to pay the bill. Considering that the healthcare budgets are limited and spending in one area is unavoidably at the expense of investment in another, efficiency can be interpreted as ensuring that the benefits obtained exceed the benefits forgone [1]. The latter concept could be also express as "opportunity cost" [4].

The objective of this narrative review is to appraise the most recent evidence regarding economic evaluation and healthcare spending. In fact, the priority is to try to disseminate information and implement this model within the health community, with the aim of handling appropriately the financial resources, ensuring the wellbeing of the patient at the first place.

Methods

For this review, the best quality evidence was selected with preference given to the most recent and definitive original articles and reviews. Information was identified by searches of MEDLINE and references from relevant articles, using combinations of MESH terms “economic evaluation”, “cost-effectiveness analysis”, “cost-effectiveness threshold” “cost-utility analysis”, “efficiency”, “health economic evaluation”, “health care economic analyses”, “value based medicine”, “NICE” “utility” and “QALY”. The search was limited to peer-reviewed, full-text articles in the English language. For most issues, papers published between January 2003 and December 2015 were considered.

Two authors (FLO and LB) performed an initial screening of the title and abstract to exclude citations deemed inappropriate for the present narrative review (e.g., experimental studies or investigational health economic analyses relative to specific treatments). Articles describing the various approaches with an apparent didactic format were retrieved and assessed. A total of 22 articles that were deemed more informative and clear by both reviewers were eventually selected and analyzed in detail (1, 2; 5-24). No formal system was adopted to rate the quality of the evaluated articles. Four reviews (16-19), written by an ophthalmology research group, were excluded because they were analogous to a fourth included article (15). For a similar reason, we excluded one review (20) and included another one (1) previously published by the same author. Two articles (21, 22) were excluded as they explained how to conduct a specific economic analysis, rather then describe the general characteristics of the various methods. One article (23) was excluded because it focused on methodological and interpretative aspects of economic analysis. One article (24) was excluded as only cost-utility and cost-benefit analysis were addressed, but not cost-effectiveness analysis. A total of 13 articles were eventually included in the present review.

Types of economic evaluation

In the most commonly used economic evaluations, two interventions, a standard treatment and an experimental one are compared with the scope of assessing the value of the novel procedure. When

the latter is more cost-effective than the older one, the novel procedure is obviously chosen; on the other hand, if the new treatment is more expensive and less effective, the standard one is generally maintained. Uncertainty arises when the novel treatment is more effective but also more expensive than the traditional treatment [5]. The scenario becomes more complex when evaluations aim at a more comprehensive approach, i.e. the comparison between interventions of highly distinct medical areas.

Five different types of economic evaluations exist in the health-care field: cost-minimization, cost-benefit, cost-consequences, cost-effectiveness and cost-utility analysis [5] (Table 1):

- *Cost-minimization analysis:* in cost-minimization analysis, two or more interventions with equivalent consequences in terms of benefit are compared [1]. It should ideally be used only when comparing treatment of equal effectiveness, and it focuses on costs alone to help choosing the cheapest option [6].

- *Cost-benefit analysis:* it evaluates, in monetary terms, cost and consequences of an intervention [1]; if the monetary value of an intervention exceeds the cost of the intervention, then the intervention is acceptable. [7]. This analysis places money values on both inputs (costs) and outputs (general benefits) of health care and represents the best method to inform allocation decisions because it consents to compare interventions from highly heterogeneous areas and it is based on a more comprehensive economic vision of the society [4].

- *Cost-consequences analysis*: this analysis reflects how decisions are made in the real world. This approach is often used when various outcomes cannot be condensed into a single measure that summarizes benefits and costs. For example, in a cost-consequences analysis, the general practitioner and nurse's salaries as well as expenditures sustained by patients are considered as costs, whereas patient health state and satisfaction with treatment are considered as consequences [1].

- *Cost-effectiveness analysis (CEA)*: it is the most widely used analysis and it consents to compare interventions with a common health outcome. The outcomes could be measured using different ratios (for example, cost per life year gained or pain free days) [1]. This data should be obtained, when possible, from clinical trials [8]. CEAs provide a definite answer on a specific comparison, i.e. it concludes which of the compared options has a more favorable cost-effectiveness profile. However, a less cost-effectiveness procedure may still be of economic and clinical interest if it is more effective. To disentangle this possibility, one may rely on the incremental cost effectiveness ratio (ICER). Specifically, the cost effectiveness ratio (CER) expresses the ratio between the cost of an intervention (K) and the benefit endpoint gained (E). The ratio K/E describes a treatment's marginal costs per gained clinical benefit unit [9]. The ICER allows the comparison between different interventions for the same pathology. Considering respectively K_1 and K_2 as the costs of the standard treatment and the novel one, and E_1 and E_2 as the benefit endpoints of the two interventions, the ICER is calculated as [9]: $ICER= (K_2-K_1) / (E_2-E_1)$. This ratio permits to define the additional costs for unit of benefit gained with the new treatment with the possibility of drawing a "health economical ranking" of the different procedures [9].

Before comparing the ICERs, it's fundamental to estimate the cost-effectiveness benchmark, which expresses the insurer's maximum willingness to pay (WTP) additional treatment costs per gained benefit unit. The new treatment will be selected only if the ICER is inferior of the benchmark [9].

The objective is to establish the socially acceptable CER. As Noyes and Holloway [10] stated: "Is the additional effects of our new technology compared with the old technology worth the additional costs?". The most suitable cost-effectiveness benchmark to be used should be adapted to the local economical situation but remains highly debated. In the affluent Western world, the thresholds used are generally more or less equivalent to the gross domestic product (GDP) pro capita [11]. The National Institute for Health and Clinical Excellence (NICE) has established a cost-effectiveness threshold range between £ 20.000 and £ 30.000 per life year gained.[11] However,

this kind of analysis could be performed only if the compared interventions use a common unit of effectiveness, such as cost per life year gained [8]. In addition, a cost-effectiveness analysis might examine this intervention in terms of quantity and not of quality [8].

- *Cost-utility analysis (CUA):* represents an economic evaluation that aims at defining the patient's preference for being in a particular health-state [4]. In CUA all the outcomes analyzed are expressed in terms of QALY (quality adjusted life year). With this method it is possible to compare treatments used in different stages of a pathology and "opportunity cost" could be measured [4]. It consents to compare interventions from very different medical disciplines or interventional areas, such as, for instance a vaccine program and an ambulance referral system. CUAs thus represent a valuable instrument for taking decisions regarding the allocation of public health resources.

Contrary to CEA, which analyses a benefit of an intervention only in terms of quantity, CUA focuses also on quality and include also the preferences of the patient [8]. The effectiveness of an intervention is measured through its utility value [8] that is ranged between 0 (worst health) and 1 (best health). Then, by multiplying the utility value with the length of time in that state, QALYs are obtained [8]. Several direct methods exist to calculate the utility value. These include scaling methods, such as visual analogue system, and choice methods such as the time trade-off and standard gamble [7].

The visual analogue system is a linear scale that runs from 0 to 1, 10 or 100, with the higher values representing the perfect health and 0 the worst health state conceivable (or death) [7]. Strengths of this method include the easiness of use and the possibility of answering by postal survey. Moreover, the visual analogue system requires no "trade-off" or choice and the individual does not have to justify his preference based on monetary, time or health factors [7].

In the standard gamble, the individual chooses between remaining in the actual state of chronic health for the rest of his life or picking an uncertain gamble: the possibilities are of being healthy for the rest of their life, with a probability of *p*, or immediate death, with a probability of 1-*p* [10]. The amount of *p* range from 1.0 to 0.1 until a point of indifference is reached, which defines

the utility weighting [7]. Advantages of standard gamble are the combination of time, risk and quality. At the same time these characteristics could represent a weakness, in particular in those individuals who are time-sensitive and are not prone in taking risky decisions [7].

The time trade-off system is the method most frequently adopted in the calculation of QALYs. The individual has to make a choice between two different options: a diminished health state for a definite time or a full heath state for a shorter life span [7]. Choosing the second alternative means the sacrifice of a period of life span in exchange of a shorter period of full health state. For example, if the patient has a life expectancy of 30 years with a specific pathological condition and decides to reduce it to 15 years with a full health status, the value of his actual health state is 15/30, i.e. 0.5. This system involves a choice and balances both quality and quantity. Limitations include the reluctance of exchanging time for health due to personal, philosophical or religious beliefs [7].

Moreover, the utility value could be measured with indirect methods like questionnaires, such as Health Utilities Index (HUI), Short-form 6D (SF-6D), and Euro Quality of life 5 Dimensions (EQ-5D) [4].

Specific fields that require a CUA include the importance of quality of life as effectiveness outcome, when the intervention has an impact on both morbidity and mortality, when the intervention have a multiple range of different outcomes with the aim of producing a single general outcome for comparison, and when resources must be allocated from a fixed budget [4]. The main drawback of CUA is the use of measures (QALYs) obtained from population samples, which reflect the mean value of the general population, that, at the same time, could differ from the specific interests of the single individual [12].

Discussion

Key points correlated with the interpretation of the results of an economic evaluation include the perspective and time horizon, from which the lost and gained costs can be estimate [10]. It should

be underlined that multiple kinds of perspectives exist: “personal”, “health insurance”, “provider” and “societal”. The societal perspective takes account of all costs, and is the most suitable one. Moreover, the societal perspective considers not only the individual patient’s costs but also the disbursement of the insurance and the National Health System, obtaining a global analysis [10].

At the same way, the temporal definition of the time horizon, considering that same benefit could require several years to manifest, appears of fundamental importance [10].

Another aspect to consider is the possible creation of an inter-individual conflict of values. In fact, we have to take into account the impact of individual preferences even when general population preferences are used to value the benefits of interventions [12]. Furthermore, patient’s preferences have a rebound on efficacy outcomes, partly due to the inadequate compliance of the patient to therapy, and to personal psychological factors [12].

In clinical practice the patient alone is assumed to make the definitive treatment choice, after receiving all the technical information from the clinician. The figure of the clinician is located in the middle of this “conflict”, trying to reach a balance between the ideal treatment and the healthcare budget [12]. In order to overcome this situation, it could be advisable to adopt a two-part decision process [12]: the detection of the most cost-effective therapy according to mean population values, and the identification of those treatments that are cheaper than the most cost-effective therapy.

In the individual patient-doctor relationship, the clinician should describe in detail all the potential benefits and harms of the available therapeutic alternatives. Fully informed patients are more likely to choose treatments that show a net benefit [25]. In this regard, the inclusion of the extra cost for the net benefit of different treatments is fundamental in health care economic evaluation.

However, when prescribing a treatment or a procedure, doctors carry a responsibility also for future patients and for the society at large, especially within a tax-funded national health system. In fact, when a fixed budget is managed, the use of resources for a category of patients is unavoidably at the expense of another one. This is known as “opportunity cost”.

The main objective of any cost evaluation approach is the optimization of the use of finite resources. Economic evaluation allows a transparent and logical use of a predetermined budget according to an equity value. In fact, patients have different health conditions that require different expenditure of resources but, eventually, the result in terms of overall health benefit should be similar for all patient categories.

In order to achieve the above objectives, physicians should foster high-value interventions [26]. The introduction of the concept of value-based medicine in the health service daily practice appears of fundamental importance also from the economic perspective. Value-based medicine is obtained by matching the value of an intervention, in terms of QALYs, to evidence-based medicine. Healthcare providers should not only demonstrate the efficacy of a procedure, but also analyze its impact on quality of life and on financial resources. The final target of value-based medicine is maximizing the use of resources, and, at the same time, improving the quality of the healthcare assistance [15].

Value is a word that arouses skepticism, because it is often misunderstood and conceived as cost reduction [27]. Conversely, value-based medicine could represent the highest form of efficiency and social equity that health care providers and medical decision-makers could offer to individual patient and society as a whole, as it constitutes a balance between potential benefits, potential harms and cost of care, and takes into account patient priorities and preferences [28]. The medical educational training itself should be restructured with the objective of de-adopting low-value care. According to Schwartz, "medical students; interns; residents; and fellows must learn that their mentors and teachers are judging them not only by their ability to properly perform a procedure but also by their having the expertise in clinical decision making to know when and why that procedure is medically appropriate" [29].

An additional point to stress is the amount of money that the government is prone to pay to gain an extra unit of benefit. As previously stated in the United Kingdom, the NICE has established a cost-effectiveness threshold range between £20.000 and £30.000 with the aim of obtaining an

optimal allocation of limited resources [11]. This threshold should be periodically reassessed to guarantee that it captures the impact of modifications in efficiency and budget over time [11].

Maynard and Bloor [13] emphasize the bipolar role of the UK government, as both regulator and sponsor of the pharmaceutical industry. NICE approves only treatments that have shown to produce a QALY for an adequate cost, and commissioners are obliged to fund it. In order to obtain a reimbursement, pharmaceutical industries need to comply with a cost-QALY ratio inferior to £30.000 [13]. In recent years, pharmaceutical industries have lobbied NICE for the widening of the cut-off for reimbursement, especially for cancer treatments, that are particular expensive. The risk is the creation of an unequal logic, in which the cost-effectiveness of a specific treatment is placed in second line [13]. Moreover, this choice of reimburse only cancer treatments, which cost exceed the threshold of £30.000, discriminates against other disease which may be equally in need of additional funding [13].

The economic evaluation represents a starting point for the allocation of the resources, the decision of the valuable investments, and the division of the budget across different health programs. Moreover, economic evaluations allow the comparison of different procedures in terms of quality of life and life expectancy, remembering that cost-effectiveness is only one of multiple facets in the decision-making process. On the other hand, economic evaluations are seen as an insensible form of utilitarianism and mistrust due to the idea of a “rationing” of the health care resources. In reality, economic evaluations consent a rational and methodical partition of resources, in a process of transparency in the decision-making context [14].

Learning points

- Particularly in a period of economic crisis, maximizing the available health care resources in order to appropriately manage pre-determined financial budgets, and obtaining the greatest benefit with the minimum expenditure, according to efficiency, is essential.
- Economic evaluation is the starting point for allocation of finite health care resources.

- There are five different types of economic evaluation: cost-minimization analysis, cost-benefit analysis, cost-consequences analysis, cost-effectiveness analysis, cost-utility analysis.
- The main analysis is cost-utility, and the measure is cost per QALY; it focuses on patient's preferences and on quality of life.
- In economic evaluation analysis it is crucial to consider different perspectives, i.e., time horizon, patient compliance, and the extra amount of money that healthcare administrators are prone to pay with the aim of obtaining the extra benefits.
- The next frontier is value-based medicine, achieved by matching the value of an intervention with the evidence-based medicine.
- The end-result of economic evaluation in health care is not rationalization of resources but social equity, that is, providing the best possible medical care to as many as possible people.

Conclusion

Physicians represent a key figure in the management of resources for the wellbeing of patients, and they must learn how to allocate in the best possible way the finite budget they have. Therefore, the role of the physician and the ability in communicating with the patient are of utmost importance. In fact, the gold standard intervention (on the basis of economic evaluation) may not coincide with the one chosen by the patient, and the patient's compliance has a rebound on the effectiveness of the treatment [12].

Contrary to common belief, careful administration of resources does not mean transformation of physicians in economic managers more focused on budgets than on patient health. Conversely, the combination of available evidence and economic analysis into value-based medicine represents optimization of the efficiency of the system, supporting the use of a transparent decision process. The physician has to select the best intervention in terms of efficacy and effectiveness, using a different amount of resources from patient to patient, tailoring a specific

305 treatment for individual cases, respecting at the same time the principles of patient-centered
306 medicine and equity [26].

307 In spite of the innumerable economic evaluations conducted in recent years, the cornerstones
308 of these evaluations are rarely performed in clinical practice [14]. The conduction of randomized
309 controlled trials aimed at assessing the impact of various economic evaluations, could constitute
310 another step forward in order to draft specific guidelines providing economic indications for
311 medical choices.

312 Economic evaluation in health-care is important to critically assess medical interventions
313 and guarantee the most cost-effective management protocols [4]. The goal of such an approach is
314 not to do less or "rationalize" the expenditure, but to allow qualitative improvements in clinical
315 practice and to offer an equal assistance to as many citizens as possible.

316

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323 **Conflict of interests**

324 The authors state that they have no conflicts of interest to declare.

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Types of economic evaluation	**Measure**	**Advantages**	**Disadvantages**	**Examples of clinical studies**
Cost-minimization analysis	Difference in monetary terms between interventions	Easiness of execution	Focused on costs only	**An Economic Evaluation of Home Versus Laboratory-Based Diagnosis of Obstructive Sleep Apnea [30]** In a RCT, given that 3-month clinical outcomes were equivalent, the cost of home-based diagnosis of obstructive sleep apnea was $264 less for the payer (95% CI $39, $496) compared with laboratory-based diagnosis, whereas a difference of $40 (95% CI, $213 - $142,) in favor of the laboratory arm diagnosis was observed from the provider perspective.
Cost-benefit analysis	Net gain or loss in monetary terms	Same measure for benefit and costs	Limited applicability, not always possible to measure benefit in monetary terms (e.g., lives saved)	**A cost-benefit analysis of peer coaching for overhead lift use in the long-term care sector in Canada [31]** A peer-coaching program for patient ceiling lift use was associated with a reduction in the patient-handling injury rate of 34% during the program and 56% after the program concluded, with an estimated 62 lost-time injury claims averted, with a modest monetary cost. The monetary benefits and costs to the system were, respectively, $748431 and 894000, with a benefit-to-cost ratio of 0.84.
Cost-	Various outcomes	Reflects the complexity	Decision-making is	**Cost analysis of the Hemodialysis Reliable**

consequences analysis	(not a single measure)	of the real world	difficult because there is not a single measure to compare interventions	**Outflow (HeRO) Graft compared to the tunneled dialysis catheter [32]** A 100-patient cohort managed with the HeRO Graft experienced 6 fewer failed devices, 53 fewer access-related infections, and 67 fewer device thrombosis compared to patients managed with tunneled dialysis catheter (TDCs). Although the initial device and placement costs for the HeRO Graft are greater than those for TDCs, savings from the lower incidence of device complications and longer effective device patency reduces these costs. Overall net annual costs are £2600 for each HeRO Graft-managed patient compared to TCD-managed patients. If the U.K. National Health Service were to reimburse hemodialysis at a uniform rate regardless of the type of vascular access, net 1-year savings of £1200 per patient are estimated for individuals managed with the HeRO Graft.
Cost-effectiveness analysis	Cost-effectiveness ratio (CER) or incremental cost effectiveness ratio (ICER)	Measures the additional cost per unit of benefit and allows drawing a "health economical ranking" of different procedures	Applicable only if the compared interventions use a common health outcome (unit of effectiveness)	**The cost-effectiveness of tumor-treating fields therapy in patient with newly diagnosed glioblastoma [34]** Tumor-treating fields (TTF) therapy consists of a medical device that creates low-intensity and intermediate-frequency electric fields with an antimitotic effect on glioblastoma cells. According to the preliminary results of a RCT, the addition of TTF therapy to the standard protocol

			Analyses the interventions in terms of quantity and not of quality of life.	(radiotherapy combined with temozolomide) for newly diagnosed patients with glioblastoma resulted in a life expectancy of 22.08 months compared with 18 months after the conventional therapy strategy. The incremental effectiveness, expressed as life-years gained, was 4.08 months in favor of TTF strategy. The total costs, from a provider's perspective, were € 243 141 for TTF and € 57 665 for the standard therapy strategy. The incremental cost-effectiveness (ICER) was thus € 549 909 per life-year gained (see text for the formula).
Cost-utility analysis	Cost-utility ratio (cost per QALY[a], quality adjusted life years),	Focuses on patient's preference for being in a particular state of health Allows comparison between different treatments used in various stages of a disease with different unit of benefit Analyses the interventions in terms of both quality and quantity of life	QALYs reflect the mean value of the general population, which might differ from the specific priorities of the individual patient	**Day care versus inpatient management of nausea and vomiting of pregnancy: cost utility analysis of a randomized controlled trial [34]** Data were obtained from a recently published RTC to asses the cost-effectiveness of day care versus inpatient management of nausea and vomiting of pregnancy (NVP). Costs and outcomes were considered with the perspective of the health care provider and patients. The primary study outcome was the total number of inpatient nights related to nausea and vomiting. The median number of inpatient admissions were fewer for day care compared to inpatient management. The mean cost was **€** 985 per patient in day care management, and **€** 3837 per patient in inpatient management, considering both the health system and the patients' perspectives. Thus, day care management is less costly. The QALYs estimated for day care and inpatient

		Represents the best method to allocate resources from a fixed budget		management were, respectively, 9.49 and 9.42. Thus, day care management is more cost effective. The cost-utility ratio (the cost of a treatment divided for QALYs generated from that treatment) for day care management is € 985 /9.49= €103.79 per QALY, whereas for inpatient management is € 3837/9.42= €407.32 per QALY.

Table 1. Characteristics of different methods for economic evaluation in health care.

[a] QALY= utility value (from 0 to 1) multiplied with the length of time in that state