SPECIAL ARTICLE

Efficiency-Based Medicine (Cost-Effectiveness and Cost-Utility) Supporting Evidence-Based Medicine

Medicina basada en la eficiencia (costo-efectividad y costo-utilidad) como refuerzo de la Medicina basada en la evidencia

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Abbreviations

CBA	Cost–benefit analysis	**NPV**	Net present value
CEA	Cost-effectiveness analysis	**QALY**	Quality-adjusted life year
ACER	Average cost-effectiveness ratio	**VAS**	Visual analogue scale
ICER	Incremental cost-effectiveness ratio	**TTO**	Time trade-offs
CUA	Cost-utility analysis	**SG**	Standard gambles
PV	Present value	**Q**	Quality of life
FV	Future value	**Y**	Years of life
WTP	Willingness to pay	**HRQoL**	Health-related quality of life

Evidence-based medicine (1-4) attempts to establish the bioethical principles of Tom L. Beauchamp and James F. Childress, (5) who reformulated in 1979 the basic principles of human research in the Belmont Report, (6) to apply them to medical ethics. These are the principles of beneficence, closely linked to the principles of autonomy (based on the belief that the human being must be free from all external control and must be respected in his or her basic life decisions) and of non-maleficence (the obligation not to inflict harm on patients' health); however, it disregards other basic principles such as justice and equity. (7-11)

Cost analysis and economic evaluation have been defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences on the health status of the individuals. While economic assessment is systematically used in some countries for pricing and funding drugs and health technologies and for making recommendations on their use, other countries only use it occasionally. (12)

Nowadays, attempts are made to provide health care directly focused on the specific health care problem with economic analyses of medical practice to efficiently provide efficacious and effective health care. **Efficacy** can be defined as the performance of an intervention on a specific health problem under ideal circumstances when compared to other alternatives. Efficacy is an indicator of the potential ability of a health care intervention to achieve a positive outcome on health status. **Effectiveness** is the measure of the outcome obtained by an intervention on a specific health problem, not under experimental and ideal conditions, but under normal conditions when compared to other alternatives generally used in clinical practice. Effectiveness measures the real ability of a health care intervention to achieve a positive outcome in the health status of a population. **Efficiency** is the result obtained by an intervention on a specific health problem in relation to costs; it considers the ratio between effectiveness and costs.

Here, the key concept of "opportunity cost" arises, representing the results that could have been achieved had the money been spent on the next best alternative intervention. This opportunity cost (alternative cost) is what economic evaluation and efficiency-based

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medicine try to evaluate. Another aim of the economic evaluation is the estimation of the differential cost, the marginal cost, the incremental cost, the variable costs, the additional process cost and the break-even point or profitability threshold.

Direct and indirect costs are measured in monetary units; however, benefits can be measured in monetary units (cost-benefit analysis), in natural units (life years gained), in usual clinical units (cost-effectiveness analysis) or in quality-adjusted life years (cost-utility analysis).

Cost-benefit analysis is a way of determining the efficiency of an option; therefore, health outcomes measured in the cost-effectiveness analysis or cost-utility analysis are expressed in monetary terms as individual willingness to pay and productive capacity of individuals.

Costs and benefits that occur at different times are not comparable, as future costs are preferred to equal present costs, and for equal benefits, present costs are preferred over future costs. This problem is solved by updating or discounting, which consists of applying a correction factor to future costs and benefits in order to achieve equivalence at the present time. (9) An incremental analysis should be performed, comparing the added effectiveness of one alternative to another with the increase in costs that has been produced. Finally, every economic evaluation should undergo a sensitivity analysis to assess the robustness of the results according to the different values of uncertain data used in the analysis. The results of the analysis should be reported in disaggregated detail to allow a critical analysis and a reproducible study. (10) In this dual perspective of individual interest (the best for the individual patient) and social interest (the best for the entire society), takes place one of the debates about economic evaluation. The basic analyses in terms of economic evaluation methods in health care technologies (health economics) are:

1. Cost-benefit analysis (CBA).
2. Cost-effectiveness analysis (CEA).
3. Cost-utility analysis (CUA).

The results of a CBA are expressed in monetary units, while those measured in units that are inherent to the program under study (lives saved, life-years gained, diseases avoided, cases detected, natural units) are the expression of CEA. The results presented as life-years adjusted for quality of life express CUA; finally, when outcomes are equal in comparative groups, only the costs are compared and a simple cost-minimization analysis is performed.

Costs and benefits occurring in different time periods are not strictly measurable and the present value of a future benefit (or cost) will be to a certain extent lower than the same present benefit (or cost): **present value (PV) = future value (FV) × 1 /(1 + r)t,** where **t** is the number of years and **r** is the discount rate or interest.

The correction factor is the **marginal time preference rate or discount rate**, and the process whereby values for different time intervals are made homogeneous is called "**updating or discounting**".

$$A = \sum^{n} \frac{X}{(1+r)^{t}}$$

A is the updated or benefit cost, *X* is the benefit or cost within a period *t, t* is the time period in which the benefit is obtained, r is the discount rate and *n* is the different time periods in which the benefits are obtained.

The discounting of future benefits is a controversial issue; in other words, the updating of benefits that are not measured in monetary units. The most important reasons for discounting future benefits are as follows: 1) they are related to costs that have already been updated, and 2) they are consistent with other types of analysis measuring benefits in monetary units. In fact, the same discount rate should be applied to costs and benefits using a consistency criterion. (15-17)

COST-BENEFIT ANALYSIS (CBA)

In this type of analysis, costs and results are measured in monetary units. This analysis can be used to calculate the option with the greatest global benefit (net present value). The practical difficulty of monetary valuation of benefits in health gains limits the use of CBA. Both costs and results (benefits) of the options compared are measured in monetary units, and benefits are defined as the maximum amount of money a person would be willing to pay. called willingness to pay (WTP), to be in a given health state versus another.

It is the most comprehensive way of performing economic evaluation in which the costs of the different options and their outcomes or benefits are compared and measured in monetary units. The results of a CBA can be expressed as a benefit-cost ratio or as the criterion of net benefit (difference between benefits and costs). This greatly facilitates decision-making rules in this type of studies, since when the benefits of a program exceed the costs (when the net value is positive), the choice would be justified; on the contrary, when the net value is negative, an alternative use of funds would be more appropriate. The main advantage of this type of studies is the possibility of making comparisons with other projects which have used the same methods, regardless of the scope of action, since the measurement of costs and benefits is carried out in economic terms. However, this type of analysis is rarely used because of the difficulties involved in transforming health care benefits into monetary amounts. Two approaches are used to facilitate this type of transformations: the human capital method and the WTP. The result can be expressed as the difference between benefits and costs,

net present value (NPV), and also as the gross or net benefit cost ratio: BCR = B / C = (B – C) / C.

$$\text{NPV (net present value)} = \sum (B - C)$$

$$\text{Gross benefit / cost ratio} = \sum B \Big/ \sum C$$

$$\text{Net benefit / cost ratio} = \sum (B - C) \Big/ \sum C$$

A program is efficient when the NPV is > 0, the gross BCR is > 1 or the net BCR is > 0, and it is more efficient when the values are greater than 0 or 1, as applicable.

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis measures the effectiveness of health care policies in tangible and measurable "natural units", such as life years gained from using one treatment instead of another. Effectiveness can also be measured in results expressed as units commonly used in clinical practice, expressing such measured results as intermediate variables (reduction of blood pressure, complications avoided) or final variables (lives saved, life years gained). A requirement for this type of analysis is that the effects of the options compared should be measured in the same units. The relationship between the costs of an intervention and its consequences is calculated numerically. This relative value is commonly expressed as the net cost to net benefit or effectiveness ratio of the intervention and is called "average cost-effectiveness ratio" (ACER).

The incremental cost-effectiveness ratio (ICER) is the ratio of the costs and effects of one intervention to the costs and effects of another intervention for any health problem with results expressed in the same units. Although the use of ACER is correct, ICER provides more information, as it shows the extra cost per unit of additional benefit for each alternative. The ICER can be formulated as:

$$ICER = \frac{C_A - C_B}{E_A - E_B}$$

The cost-effectiveness analysis can be visualized in a graph referred to as the "cost-effectiveness plane". In such graph, the horizontal axis represents the difference of the effectiveness between the intervention of interest and the relevant or reference alternative, and the vertical axis represents the difference in costs (Figure 1).

The CEA is the economic evaluation most commonly used in health care economic studies. The effects of the options compared are measured in usual clinical units or in physical or natural units in terms of benefit; **changes in mortality** (lives saved or life years gained); **changes in morbidity** (incidence, prevalence, number of patients clinically cured, days free of disability or pain); and **changes in clinical parameters** (analytical or measurement units, such as cholesterol or blood pressure levels).

The summary measure in CEA is the cost-effectiveness ratio (or cost-efficacy ratio). This ratio expresses the cost per unit of outcomes associated with each program or intervention and can be used to compare the different options. In general, the interventions with low cost-effectiveness ratios are cost-effective (efficient), since they have a lower cost for each unit of benefit produced, and those with high ratios are less efficient. The use of ICER (the ratio of the difference in cost to the difference in results) is convenient when comparing two or more alternatives (Figure 2). (18-20)

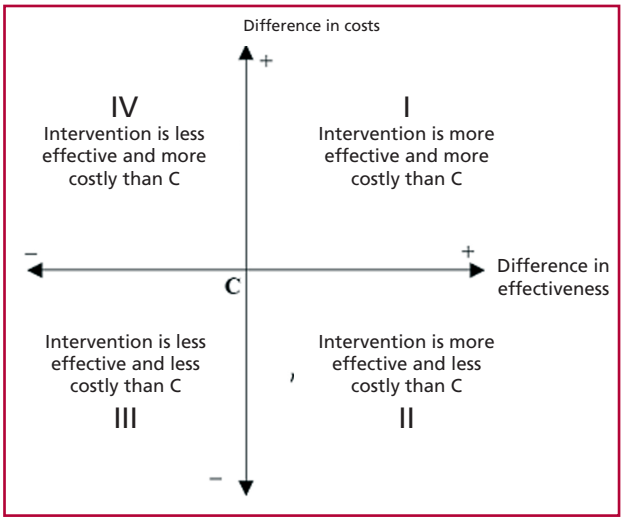

Fig. 1. Cost-effectiveness analysis. Position II. The intervention is more effective and less costly

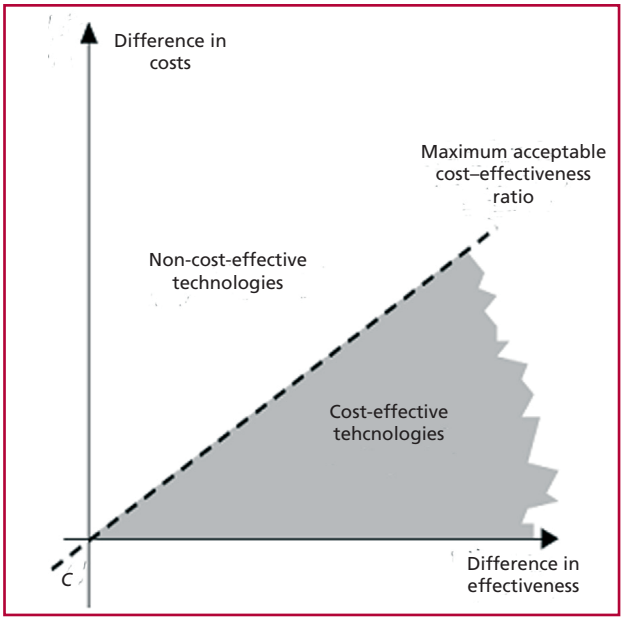

Fig. 2. Cost-effectiveness threshold

This type of analysis can only compare programs with a common result that can vary in magnitude within the different alternatives. The result of a CEA is expressed as an index, and calculated as the ratio of the extra costs of one alternative to another and the change in the results (incremental analysis), as follows:

$$\text{C / E ratio} = \frac{\text{Costs A - Costs B}}{\text{AE - BE}}$$

DECISION ANALYSIS. DECISION TREES

Decision analysis is represented by graphic models named "decision trees". A Markov decision tree is a visual representation of the logic and temporal consequences that have been considered before adopting a decision:

Each tree is composed of nodes describing choices or actions (decision, choice or action nodes), represented by a square; event, probability or chance nodes (represented by a circle or a dot); and terminal nodes, which are the final relevant expected outcomes expressed in terms of costs, effects, utilities or benefits (represented by a triangle) (Figure 3).

Putting into practice any decision analysis requires six basic steps:

1. Build a decision tree with all the lines of action, the resulting events and the expected results.
2. Determine the probabilities corresponding to all the branches emerging from chance or event nodes.
3. Assign the utilities (if that is the chosen outcome) corresponding to each potential outcome and try to quantify them on a common scale.
4. Combine the probabilities and outcomes at each tree node, folding it back (from right to left), to determine the expected consequences or costs that correspond to each action, option or alternative.
5. Choose from all the alternative actions available the most rational decision and choose the one that provides the highest expected result.
6. Test the vulnerability or sensitivity of the decision to clinically sensible changes that may develop in the probability or terminal nodes.

MARKOV MODELS

Markov models are very useful when a decision problem is subjected to a continuous risk over time, at the time events occur and when they can occur more than once, as Markov models assume that a patient is always in one of a finite number of discrete health states, called Markov states.

The time horizon of the analysis is divided into time intervals, referred to as "Markov cycles". Each state is assigned a utility, and the contribution of this utility to the overall prognosis depends on the duration of each cycle and the length of time the sick person remains in each state. The processes are classified according to whether or not the transition probabilities between states are constant over time and can be solved by a cohort simulation, a Monte Carlo simulation and by matrix algebra (which can only be used when the process has constant transition probabilities). Markov processes are supportive techniques for economic evaluations, where random factors or variables are involved and where the probability that an event occurs depends only on the probability of occurrence of the immediately preceding event. A special type of Markov process in which the transition probabilities are constant over time is called a "Markov chain" and its elements are a set of finite number of M states, mutually exclusive and exhaustive, as for example unhealthy states; a time period that serves as basis to examine the transitions between the states (Markov cycle); transition probabilities between states in a cycle (p-matrix); and the initial distribution of the system between the possible M states.

COST-UTILITY ANALYSIS

Cost-utility analysis uses quality-adjusted life years (QALYs), a measure of health states which assigns

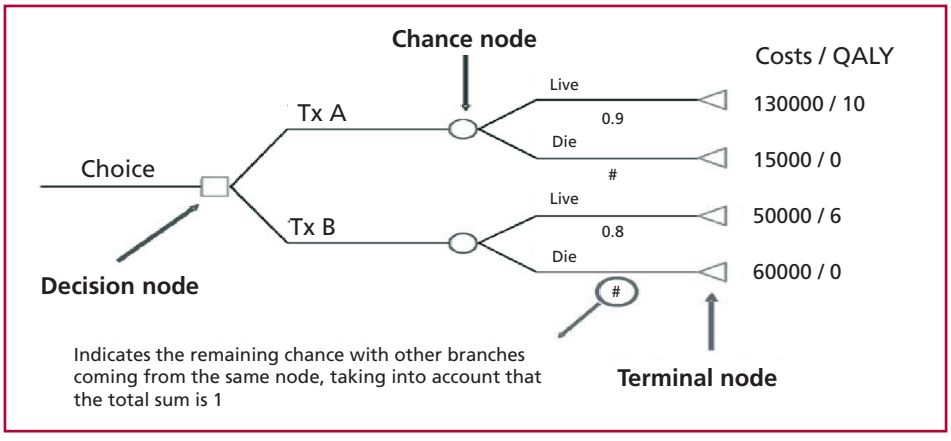

Fig. 3. Example of a Markov decision tree.

Table 1. Rosser-Kind matrix.

	Levels of distress			
	Absent A	Mild B	Moderate C	Severe D
1. No disability	1	0.995	0.990	0.967
2. Slight social disability	0.990	0.986	0.973	0.932
3. Severe social disability. Able to do all housework except very heavy tasks	0.980	0.972	0.956	0.912
4. Performance at work severely limited. Able to do light housework	0.964	0.956	0.942	0.870
5. Unable to undertake any paid empoyment	0.946	0.935	0.900	0.700
6. Confined to chair or only able to move with support from an assistant	0.875	0.845	0.680	0.000
7. Confined to bed	0.677	0.564	0.000	-1.486
8. Unconscious	-1.028		Non-applicable	

each time period a weight between 0 and 1 based on the quality of life during that period, with 1 representing perfect health and 0 representing death. The idea of QALYs is to integrate mortality (survival) and morbidity (quality of life) into a single index that measures health in terms of years of life in good health. This method is useful to adjust health care resources toward those protocols providing more QALYs per unit of expenditure. QALY is a measure of health that captures gains with the reduction of mortality (gains in quantity of life) and with the reduction of morbidity (improvement in quality of life).

Standard gamble (SG), time trade-offs (TTO), or the visual analog scale (VAS) are the techniques used to assess preferences for health states. The VAS consists of a line in which one end, defined as 0, is the worst state of health, and the other, defined as 1, the best state of health. In TTO and SG, the value of health states is estimated from the hypothetical decisions that subjects indicate they would make in certain situations.

QALY takes into account two components of health: the quality of life (Q) and the quantity of life years (Y). Therefore, any individual health state can be expressed by a pair (Q, Y). Usually, the state of "good health" or "perfect health" is associated with the value 1. Thus, one QUALY can be considered as one year of life in good health. As quality of life declines, V(Q) decreases and the number of QUALYs associated with that situation are reduced. QALYs can be considered as life-years weighted by their quality. The measure of health in an interval scale establishes that the usefulness of death is 0. "States worse than death" can exist and they would have a negative value. QALYs are a measure of health care program outcomes which combine the length of time spent in a health state (Y) with the quality of life experienced in that health state (Q). The weights used in QUALYs can be indirectly measured using multiattribute health status classification systems.

The main three classification systems currently available are the Quality of Well Being (QWB), the Health Utilities Index (HUI) and the EQ-5D —previously known as the EuroQol—. The QWB classifies health states or patients according to four items: mobility, physical activity, social activity and a combination of symptoms/problems. Several levels are defined for each of the four items and a score (utility) is assigned to each level. The system is completed with an algorithm that summarizes in a single value the health-related quality of life (HRQoL) associated with a health state. A second assumption underlying QUALYs is that the utility of any pair (Q, Y) can be measured as follows:

$$U(Q,Y) = V(Q) \times Y = nº \text{ of QUALYs}$$

Table 1 shows the Rosser-Kind matrix used to evaluate quality of life for estimating QUALYs

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