Pharmacoeconomics: The Economic Evaluation of New Medical Technology

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INTRODUCTION

The economic evaluation of medical treatments – especially involving treatments with new pharmacological products or medical devices – is a relatively young field. It is at most two decades old, but now engages several thousand health services researchers around the world. The endeavor goes under various generic labels, such as 'technology assessment' or 'benefit-cost analysis' or, when applied to pharmacological or biological products, 'pharmacoeconomics' (a term still so novel among the laity that Microsoft's spell check sees red when encountering it). As a young field, its practitioners still debate among themselves a whole host of challenging methodological issues. Some of these are purely conceptual, others are rooted in the techniques of procuring relevant data – e.g., how individuals subjectively evaluate different health states – and some of them concern issues of social equity, e.g., whether the value of medical outcomes varies with age. Although used only gingerly by public policy makers so far, it is a safe bet that technology assessment will become the core of health policy in the coming decade, as no country can afford much longer the vast sums of money traditionally spent on dubious medical practices and products. This chapter surveys that vast terrain, taking the wider perspective of technology assessment in general in healthcare, of which pharmacoeconomics is one specialized branch.

In societies that look to both government and investor-owned for-profit enterprises for the development of new medical technology, be it pharmacological or biological products or medical devices, the economic evaluation of such products can be made from several quite distinct perspectives:

- that of the product's developers and manufacturers;
- that of the product's end users;
- and, in countries with comprehensive health insurance, that of the private or public third-party payer who effectively purchases the product on behalf of the end user and pays for it out of some collective financial pool, be it a public treasury of a private insurance pool.

Although these perspectives are not totally independent of one another, they nevertheless may come to different conclusions about the economic merits of a new medical technology. These differences are poorly understood in the debate over health policy – even among people who should know better – and utterly confuse the general public.

This chapter will touch only briefly on the first two perspectives, but emphasize the third perspective, which may be loosely labeled by the vague term 'society's perspective'. It is the vantage point commonly adopted in the literature on technology assessment in healthcare – for example, in the classic text *Methods for the Evaluation of Health Care Programs* by Michael Drummond et al. (2005). Although the title of the chapter is pharmacoeconomics, the discussion often will take the broader focus of economic evaluation of healthcare in general.

It will become clear from the discussion that the economic evaluation of new medical technology is only partially based on scientific methodology. Either explicitly or implicitly, it involves strong doses of preferred social ethics, which in turn derive from widely shared theories of justice. That aspect of benefit-cost analysis is not always fully appreciated, in part because those who conduct economic evaluations in the context of healthcare prefer to style their work as pure science, which it rarely is.

THE EVALUATION OF NEW MEDICAL TECHNOLOGY: THE PRODUCER'S PERSPECTIVE

Usually the development of new medical technology requires considerable upfront investment of human and material resources during a research and development
(R&D) phase that can stretch over many years—sometimes in excess of a decade. The recovery of these investments through the future benefits yielded by the R&D effort can stretch over even more years. That circumstance makes spending on medical R&D a classic investment proposition.

**Private, investor-owned producers of new medical technology**

When the R&D process for new medical technology is managed and financed by a private, investor-owned, for-profit entity, such as a research-oriented pharmaceutical manufacturer, the firm subjects the process to what is known in business circles as ‘capital budgeting’. Specifically, the firm considers solely the opportunity costs borne by the firm’s owners—for a public corporation, the shareholders—and the future revenues reaped by these owners. The firm will not take into account in any way the legally tolerated spillover costs that the project may visit on other members of society or the spillover benefits yielded by the process to individuals other than the firm’s owners.

Usually the development of many new medical technologies requires up-front investments of hundreds of millions of dollars. In investor-owned entities, the owners must advance for this purpose their own funds, or funds borrowed in their name from creditors, before a chemical compound or a biological or a new medical device becomes a product that is approved by government for sale to end users. In the United States, the agency charged with making that approval—or rejecting a new product—is the Food and Drug Administration (FDA). Most other modern nations have similar government agencies. Many critics of the medical technology industry do not understand how many tests of clinical safety and effectiveness a new medical technology must pass during the R&D phase before the government will approve it for sale to the public.

To illustrate this process with a highly stylized set of assumptions, made solely for simplicity, suppose the development of a new prescription drug requires an R&D-oriented drug manufacturer to spend $40 million in cash per year for 10 years. As noted, these huge cash advances made by the corporation can come from but two sources: creditors and owners. Raising those funds is primarily the task of the firm’s Chief Financial officer (CFO), who can be viewed as the firm’s in-house banker. The CFO ‘lends’ the required funds—in this case, $40 million a year for 10 years—to project teams composed of production and marketing people who have formally applied for these funds with detailed and lengthy investment proposals. The CFO, the firm’s banker, first of all examines the proposals for realism and methodological soundness and, upon approval, lends the project team the requested funds, at an interest rate that is called the firm’s ‘weighted average cost of capital (WACC)’. (The weights in the WACC are the fraction of funds raised from creditors and the fraction raised from owners/shareholders.) A handy way for the CFO to track this loan would be to set up an amortization table, calculated at the WACC, of the sort bankers sometimes establish for regular mortgage loans.

The interest charged by the CFO to the project team is a weighted average of what it costs the firm for which the CFO acts, after taxes, to procure a dollar of funds from creditors (usually buyers of the corporation’s bonds) and from owners (in the form of retained profits or in return for newly issued stock certificates). The after-tax cost of debt financing is laid down by lawyers in detailed, legally enforceable contracts called ‘indenterces’. It is market-determined. The CFO’s cost of raising funds from owners, on the other hand, is the owners’ opportunity cost of those funds, that is, what the firm’s owners (shareholders in a corporation) could have earned on their money, had they invested it in other corporations with a similar risk profile. This is called the cost of equity capital. Estimating what that opportunity cost is is an art in its own right. As a general rule, the more risky that investments in the company’s stock are in the eyes of shareholders, the higher will be the firm’s cost of equity capital, that is, the rate of return to expect from owning the firm’s stock. In practice, the WACC for business firms currently ranges from 9% to 15% per year, depending upon the risk that the firm’s creditors or owners shoulder when they entrust money to the firm.

Assuming now a WACC of 12% per year for the R&D project assumed above, what would be a corporation’s total cumulative investment in bringing a drug to market by the time the drug is ready for launch into the market, if the firm had spent $40 million a year for 10 years on developing the drug? The figure turns out to be $702 million. In the jargon of finance, it is called the future value of the cash flow. Of that total, $400 would be the sum of the actual cash outlays of $40 per year for 10 years—the number the firm’s accounting would book as R&D expenses. The remaining $302 would be accumulated interest costs calculated at the WACC, that is, the firm’s opportunity cost of those cash outlays over the entire R&D phase.

For the firm to break even on the R&D project in question, the future net after-tax cash profit stream yielded by it, converted to present value equivalents at the WACC of 12%, would have to sum to $702 million. If that present value equivalent summed to more than $702 million, adopting the proposed R&D program would enhance the shareholders’ wealth. Finally, if, before launching the associated R&D effort, the present value of future net cash after-tax profits from the drugs at the point in time the product is launched were less than $702 million, the corporation’s Board of Directors should never have approved going ahead with the project, because it would diminish the shareholders’ wealth. Of course, one could also calculate the present values of the entire cost and cash profits stream as of the
time the R&D project itself began and would come to the same conclusions.

Some thoughtless critics of the pharmaceutical industry have used not the accumulated cost at time of launch in this context, but the present value of the 10-year stream of $40 million a year at the time when the R&D project was started, which turns out to be $226 million. It is an amount large enough such that, if it were in the bank at the time the R&D project is begun and if money in that bank account earned after-tax interest of 12% per year in any year on the amount still in that account at the beginning of the year, then that fund would be enough to support a stream of annual withdrawals of $40 million for 10 years. In other words, it is an entirely different concept than the $702 million calculated earlier off the same cash flow.

The future and present values we had calculated above for a 10-year cash flow of $40 million a year are highly sensitive to two variables: the WACC and the length in years of the R&D process. For example, if the WACC were 12% but the R&D phase only 6 years, then the future value of the project would be only $325 million and the present value only $164 million. On the other hand, if the R&D phase were 12 rather than 6 or 10 years, the future value would be $965 million and the present value $264 million. If with that R&D phase the WACC were only 8%, the future value would be $759 million and the present value $301 million, and so on.

In short, the total cost to the R&D-based manufacturer of bringing a new pharmaceutical product to market is a fluid construct not easily understood by the uninitiated. There is the added problem, beyond the compass of this paper, of what to do with the cash outlays on the R&D of projects that faltered along the way — the analogue of dry holes in the oil business. These costs must be allocated somehow to and recovered by projects that lead to marketable products.

Public producers of new technology

When a government undertakes the R&D for new medical technology — for example, the National Institutes of Health (NIH) in the United States — then it, too, should add up the cumulative opportunity costs to society of completing the R&D phase until a usable product emerges. To go ahead with the project, ideally these cumulative opportunity costs, calculated as the future value of these costs as of the point in time the product yielded by the R&D projects is ready for use, should be covered by the present-value sum of the future social benefits that use of the product will yield. In principle, if that condition is not met, the project should not have been undertaken.

In the public sector, this juxtaposition of costs and benefits is called ‘benefit–cost analysis’. It resembles in many ways what is called ‘capital budgeting’ in the private sector, although for public-sector investment projects both the social opportunity costs invested in the project and the social benefits expected to be yielded by the projects are calculated from a broad, societal perspective, which typically abstracts from which particular individuals in society bear the costs of the project and which individuals reap its benefits. It is a purely collectivist perspective.

The public-sector analogue of the WACC used by private corporations in their capital-budgeting exercises in the so-called ‘social discount rate’ whose proper magnitude has remained a controversy among economists for all public-sector investment projects, and in particular for projects yielding future health benefits. As will be explained further on, especially controversial is the idea to convert physical future health benefits — e.g., added life years — into present-value equivalents by means of discounting with a social discount rate. A full discussion of this issue, however, goes much beyond the compass of this chapter.

THE EVALUATION OF NEW MEDICAL TECHNOLOGY: THE END USER’S PERSPECTIVE

A nouvelle vague in health policy in many countries — certainly in the United States — is the idea that commercial market forces, rather than government regulation, should govern the allocation of healthcare in society. Embedded in that idea is the notion that ‘consumers’ (formerly ‘patients’), the end users of new medical technology, are best situated to perform the requisite economic evaluation of new medical technologies, including pharmaceutical and biological products.

At first blush, that may appear as an appealing idea, especially to economists indoctrinated with a belief in the beneficence of markets. As has been pointed out by the current author, however, the approach has powerful ethical and practical implications either not well understood by the laity or deliberately swept under the rug, so to speak (Reinhardt, 2001).

The ethical precepts driving markets

Commercial markets march to the ancient Roman dictum res tantum valet quantum vendi potest — in English ‘a thing is worth what you can sell it for’. Practically, in a genuine market system, it means that a new pharmaceutical product would be worth what one can sell it for to end users, who would have to pay for it out of pocket. That is, in fact, the general idea behind the new movement of Consumer Directed Health Care (CDHC), which is a code word for insurance policies with very high deductibles — up to $10,500 a year per family, coupled with personally owned and tax-favored health savings accounts (HSAs) from which deductible payments can be made.
It should be immediately clear to anyone that on the market approach the ‘value’ of a new medical product would vary not only with the end user’s perceived medical need for the product, but also with her or his ability to pay for it out of pocket. Concretely, a novel product that controls hypertension or asthma, or a drug-eluting stent, or a new implantable defibrillator, would be deemed to have a higher value if used by, say, a lawyer, a professor or corporate executive rich enough to bid high prices for these products than it would if used by a lower-income taxi driver or waitress who can afford to bid only lower prices for the same products. That proposition is not usually made clear by advocates of the market approach. If one does not accept the ethical underpinnings of this valuation, then one implicitly questions the ability of markets to allocate healthcare resources in accordance with society’s wishes, and someone other than the end user must perform the economic evaluation of medical products and treatment regimens. An additional implication of the market approach to healthcare and to the economic evaluation is that the products in question should be rationed among potential users on the basis of their income. The advocates of Consumer Directed Health Care clearly have that in mind, although they tend to be hesitant to articulate their goal quite this bluntly.

It is not clear that the distributive social ethic implied in a genuine market approach to healthcare is as yet acceptable among the general public, even in the United States, let alone in countries that like their health systems to march to the Principle of Social Solidarity. Yet, remarkably, one sees the market approach to economic evaluations of new medical technology advocated with increasing frequency, possibly without the advocates’ realization of the distinct social ethic they package into their prescription. In any event, the ethical implication of the approach should always be debated quite openly in discussion on health policy, such as discussions on Consumer Directed Health Care, for example.

It is not argued here that market forces cannot play a constructive role in a health system whose distributive ethic and other rules of conduct are strongly regulated by government. Judiciously regulated, market forces certainly can play a productive role in healthcare. The point here merely is that trusting the economic evaluation of new medical technology to the market is problematic if it implies that the individual end user’s ability to pay for the technology should drive this evaluation.

The implications of the market approach for the producers of new medical technology

The producers of new medical technology typically and understandably are enthusiastic about the contribution their innovations can make to humankind. They tend to speak glowingly about the great ‘value’ their products represent especially when their products contribute to saving lives. At the same time, few of them have any clear idea about who should determine that ‘value’ and how it should be determined.

One often hears spokespersons of the producers of new medical technology decry government’s role in healthcare and wax eloquent on the virtue of the market place. The question is whether they really mean it. Would they, for example, openly state that the value of their products rises with the income of the products’ end users, or would they openly advocate that their products be rationed among human beings by market price and the recipients’ ability to pay? If not, do they actually believe that the end users of their products are best suited to perform the economic evaluations of their products?

These blunt questions are provoked by the pharmaceutical industry’s steadfast opposition to “reference pricing” for its products. Under reference pricing, private and public insurers group pharmaceutical products aiming at the same therapeutic target into so-called ‘therapeutic groupings’ and then pay fully out of the insurer’s collective funds only for one of the lower-cost products in the therapeutic grouping. The price of that product is the so-called ‘reference price’. If a patient and his or her physician would prefer a higher-priced product that also is in the grouping — perhaps a more recent brand-name drug with fewer untoward adverse effects — that patient must pay out of pocket the full difference between the reference price for the grouping and the price charged for the higher cost brand-name drug. In effect, reference pricing can be said to be a marriage of social solidarity, practiced up to the level of the reference-priced drug, with a raw market approach that relies on individual end users to evaluate the qualities of the higher-priced drugs in the therapeutic grouping. It is like a business firm that reimburses its employees for coach class airfare, but allows employees to upgrade with their own funds to business or first class, leaving it up to the employee to determine whether the added benefits from upgrading are worth the added costs borne by the employee.4

Reference pricing is used in a number of European nations, notably in Germany, which was the first to adopt it formally for its Statutory health insurance system covering 90% of Germany’s population. Reference pricing for prescription drugs is also used in Canada, Australia and New Zealand. So far it has not been adopted in the United States, either by the private or public insurance sector, because it is vehemently opposed by America’s pharmaceutical industry, as it is by the pharmaceutical industries in other countries that use reference pricing. Private insurers in the United States, however, now do lean heavily in the direction of full-fledged reference pricing through sundry three-tiered reimbursement systems for drugs.

Those who oppose reference pricing, including some economists who are supportive of the pharmaceutical industry, typically argue that the end users of drugs are not
technically equipped to perform the required cost–benefit analysis for rival drugs in a therapeutic grouping and that physicians are too busy to undertake it for them.\textsuperscript{3} They further argue that such a system is inequitable, because low-income patients often cannot afford to pay the additional out-of-pocket costs for higher-priced brand-name drugs that may be more effective than drugs priced at the reference price (Danzon, 2000: 25). While that argument may well be right, those making it in effect question the entire proposition that a market approach to healthcare relying on individual patients as evaluators of their own healthcare cannot work and, even if it could, would be inequitable. To the extent that the producers of new medical technology are among the opponents of reference pricing for their products, they implicitly reject the entire market approach as well.

This circumstance, then, leaves one with approaches in which the leaders of some collectivity – be it a government or a private insurance company – perform the required economic evaluation of new medical technology on behalf of patients. In the United Kingdom, the government-run National Center for Clinical Excellence (NICE) is such a body, performing economic evaluations for the country’s government-run National Health Service (NHS). In Germany, it is the recently established government-funded Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG), also widely known in English as the Institute for Quality and Efficiency in Health Care.\textsuperscript{6} It performs economic evaluations of drugs for Germany’s statutory health insurance system. In Australia, it is the Pharmaceutical Benefits Advisory Committee (PBAC).

THE EVALUATION OF NEW MEDICAL TECHNOLOGY: SOCIETY’S PERSPECTIVE

The thrust of the previous section is that, although much lip service is being paid these days to the virtue of the private market in healthcare, when the rubber hits the road, so to speak, neither patients nor the producers of medical technology seem willing to accept the often harsh verdicts of the market place. In the end, either explicitly or implicitly, they call for some larger collective – a government agency or private insurers – to regulate the healthcare sector on behalf of patients and to perform the requisite economic evaluation of healthcare for them. Most textbooks on technology assessment in healthcare adopt this collectivist approach as well, as does the remainder of this chapter.

The general framework for technology assessment in healthcare

The economic evaluation of new medical products, new treatment options or new health policies in general always involves a comparison of the negative and positive consequences associated with two different courses of action, one of which may be called the ‘baseline’ (B) and the other the proposed ‘alternative’ course of action (A) that is to be evaluated. In other words, one evaluates one course of action (A) relative to the baseline (B), which requires one to evaluate the change in future costs and benefits when option A is adopted rather than the baseline B, assuming one of the two will be adopted for certain. Technically, we speak of the incremental costs and benefits of adopting option A rather than option B. Figure 34.1 illustrates this process.

The first step in the economic evaluation of medical technology is to specify precisely what the baseline and alternative courses of actions are. Often the baseline is simply the status quo, that is, the currently practiced course of action that would continue if the new product, treatment option or health policy were not adopted. The alternative course of action is the adoption of a new product, treatment option or health policy. But sometimes the ‘baseline’ may not be the status quo, but one of two new courses of actions of which one will in fact be pursued, because it has already been decided, for whatever reason, to depart from the status quo.

The next and most challenging step in the evaluation is identifying and measuring quantitatively – usually in terms of monetary values – all of the positive and negative, quantifiable consequences of each of the two courses of action. Quantifying these consequences is part of the art of benefit–cost analysis. Usually these positive and negative consequences are time-phased streams of costs and benefits that flow over long periods of time, which raises the issue of discounting, to be explored further on.

To the extent that some consequences simply cannot be quantified, they nevertheless should be considered by policy makers or other decision makers as well, after the formal, quantified benefit–cost analysis has been completed. These adjustments are called ‘qualitative’ considerations. They may modify the recommendation for action emerging from the quantifiable benefit–cost analysis.

Defining net incremental benefits (NIB)

Given the analytic framework sketched out in Fig. 34.1, one may define the net incremental benefits (NIB) yielded by the decision to follow course of action A rather than course of action B as:

\[
\text{NIB} = (\text{Benefits}_A - \text{Benefits}_B) - (\text{Costs}_A - \text{Costs}_B) \\
= (\text{Benefits}_A - \text{Costs}_A) - (\text{Benefits}_B - \text{Costs}_B)
\] (1)

Either of these definitions of NIB are the best way to describe the economic merit of that decision, because the NIB is impervious to how one arrays the separate benefits and costs associated with each course of action independently.
Some decision makers, however, prefer to think in terms of benefit-cost ratios (BCRs), and those ratios are sensitive to the way one arranges the costs and benefits of each course of action. Economists commonly use the concept of 'opportunity costs' to define the cost of a course of action. In terms of Fig. 34.1 above, the total cost of the decision to adopt course of action A rather than B therefore would include costs directly incurred on course of action A plus the benefits given up by not following course of action B, because these foregone benefits of course of action B are an opportunity cost to be charged to course of action A. Similarly, one could define the benefits yielded by course of action A as the benefits yielded directly by that course of action plus the costs avoided by not following course of action B. One would then write the benefit-cost ratio (BCR) of course of action A as:

\[
BCR = \frac{\text{Benefits } A + \text{Costs } B}{\text{Costs } A + \text{Benefits } B}
\]  

(2)

Others, however, might prefer to write the ratio in terms of incremental benefits and costs as:

\[
BCR = \frac{\text{Benefits } A - \text{Benefits } B}{\text{Costs } A - \text{Costs } B}
\]  

(3)

In sum, one has to be careful to describe in the analysis about how the separate benefit and cost figures are arrayed.

Whose costs and benefits?

Many times the economic evaluation of new medical products is made from the narrower perspective of a sub-unit of society — e.g., a business firm providing health insurance for its employees, an insurance company seeking to control its own outlays on healthcare for insured customers, or a family. Naturally, the decision makers in this sub-unit will exclude from their benefit-cost calculus any costs they do not bear and any benefits that do not accrue to them.

From society's perspective, such narrowly based benefit-cost analysis in healthcare can be highly misleading. An insurance company, for example, may prefer to cover only a product that must be infused at a clinic or outpatient department, rather than a much more expensive new, rival product that can be infused continuously on the job, thus reducing substantially the cost of absenteeism from the job. Similarly, a family may consider only its own cost of treating migraine without taking into account that a more expensive product will reduce the employer's cost through reduced absenteeism or better productivity on the job.

Research entities, such as NICE in the UK or the IQWiG in Germany, that perform technology assessment in healthcare usually adopt an all-inclusive societal perspective, which means that they include in their benefit-cost analyses, for every relevant future year, all costs, on Whichever they may fall, and all benefits, to Whichever they accrue. Many healthcare products or treatments, for example, are valued by their recipients more highly than the money price the recipient has to pay the providers of these products or treatments. This is certainly so for life-saving products and treatments. A proper societal benefit-cost analysis would use as a benefit measure the representative recipient's valuation. Economists have been able to estimate the average value people attach to added life years as revealed by their behavior in labor markets or vis à vis product safety (Viscusi, 1993). The providers of healthcare, on the other hand, would count in their benefit-cost calculus only the revenues they receive for that care.
The issue of discounting costs and benefits

As already noted above, when the benefits and costs from a course of action occur over many years, as usually they do, the question arises whether, say, a benefit occurring many years hence in the future should be valued the same as the same benefit accruing in the very near future (and ditto for costs). It matters not here whether the benefits and costs are stated in monetary terms or physical units (e.g., added life years, fewer disabilities).

Suppose a quantitative monetary or physical measure of benefits in some future year \( t \) is \( B(t) \). It could be an extra life year, for example. Then the idea of 'discounting the future' is to treat that future benefit as the present-value equivalent (i.e., now, at time \( t = 0 \)) as:

\[
B_0(t) = B(t)/(1 + r)^t
\]

where \( r \) is an annual compound discount rate, and similarly for all time-phased costs and benefits triggered by the course of action in question. Two questions arise in connection with this construct. First, should future costs and benefits be discounted at all and, second, if they should be discounted, at what discount rate \( r \) should they be discounted?

There are three distinct views on the first question.

One school would set \( r = 0 \), arguing that one should not count future benefits less than equally sized benefits accruing now or near term.

A second school argues that one should discount the future and use for it a discount rate \( r \) used for ordinary investments elsewhere in the economy. Those rates tend to be high – certainly above 5% per personal investments and, for business firms, usually in excess of 10%.

A third school argues that the future should be discounted, but not at observable rates used in business or in the financial markets, but instead at time preference rates people exhibit strictly in the context of healthcare. Those time preference rates might be gotten through contingent valuation techniques – loosely speaking, experiments in which respondents are asked to evaluate hypothetical scenarios.

These differences among these schools of thought remained controversial and have spawned a huge literature. In the meantime, textbooks on technology assessments generally do suggest that future cost and benefit streams should be discounted.\(^7\)

Should benefits be age adjusted?

Another area of lingering controversy is the question whether society, or policy analysts working on behalf of society, should assign the same social value to a health benefit – e.g., to an added year of life – regardless of the age of the person to whom that benefit accrues or, for that matter, regardless of that person's socio-economic characteristics. Is adding another life year to a person of working age worth more than adding that year to a non-working 80-year-old?

The World Bank in conjunction with the World Health Organization (WHO) and the Harvard School of Public Health developed during the 1990s the concept of the 'disability-adjusted life year' (DALY) to calculate the global disease burden (Murray and Zachary, 1997). In its application to measure the global disease burden, DALYs are multiplied by the age-weighting equation:

\[
W = (C)(x)e^{-\beta x}
\]

where \( x \) = the age of the person benefiting from a change in DALYs and \( e = 2.718 \), the natural logarithm (whose natural logarithm is 1). Figure 34.2 illustrates this weighing scheme. It is seen that the equation accords greater weight to life years of persons in their productive years, and less weight to very young and older people. This adjustment may appeal in low-income societies in which human productivity is crucial for sheer survival. This approach has triggered numerous critical reviews over its inherent subjectivity and especially over its age-weighting.\(^8\)

The late British health economist Alan Williams (1997) proposed in this connection the ethical doctrine of 'fair innings'. According to that doctrine a person is entitled to only so many 'fair innings' over the course of life, beyond which person can be thought to 'live on borrowed time'. From that premise it follows that if scarce resources must be rationed for life-saving medical interventions among people of different ages, greater weight should be given to adding another life year to a younger person of, say, age 40 than to a person aged 70 or 80. The argument is that the latter have already been blessed with a high number of 'fair innings' and should take second place behind the younger person when added life years wrested from nature through medical treatments must be rationed.

At this time, the idea of age-weighting the benefits from healthcare probably could not even be discussed openly in the United States, let alone be implemented. Indeed, the entire topic of rationing healthcare is taboo in the United States.

Like the issue of discounting, the issue of age-weighting the benefits from alternative courses of actions – e.g., treatments – in healthcare remains controversial and has spawned a large literature.

COST–BENEFIT, COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS

Given the researcher's decisions regarding discounting and age-weighting of benefits, economic evaluations of alternative courses of action in healthcare generally take one of three distinct forms:

- Cost-benefit analysis (CBA)
- Cost-effectiveness analysis (CEA)
- Cost-utility analysis (CUA)
The second approach, CEA, usually is based on a one-dimensional measure of health outcome (e.g., reductions in blood pressure or added life years) from medical treatments while the third uses subjective, individual preference valuations of multidimensional health outcomes from clinical treatments (e.g., added life years with various attributes of the quality of life).

In the end, however, all of these approaches require policy makers to come to terms with one of the most challenging problems in the economic evaluation of healthcare, namely, putting monetary values on the positive and negative consequences of medical interventions, including the use of new medical technology.

Cost–benefit analysis (CBA)

In a full-fledged cost–benefit analysis (CBA), monetary values must be explicitly put on all of the negative and positive consequences associated with the two courses of action being evaluated, where the emphasis is on ‘explicitly’. These consequences may be multidimensional, which complicates the analysis. The monetary value of these consequences sometimes can be objectively observed directly in the market place – e.g., as the prices or production costs of products. At other times, they must be specified.

One approach widely used for that purpose is rooted solidly in formal economic welfare analysis, that is, it seeks to obtain from samples of individuals their ‘willingness to pay’ (WTP) to avoid particular negative consequences (e.g., adverse effects of a drug) or to pay for positive consequences (e.g., the cessation of pain). Sometimes this can be done through inferences from observable market behavior, for example, how much people are willing to pay to avoid bodily harm can be inferred from the extra pay they require to do dangerous work. At other times WTP is inferred by what is called ‘contingent valuation’. Under that approach, researchers seek to infer WTP from experiments in which respondents are presented with hypothetical situations with negative and positive consequences and are then asked how much they would be willing to pay to avoid negative consequences or how much they would be willing to pay to enjoy positive consequences. Naturally, there always arises the question how accurate such information can be, because people will not always do in fact what they claim they would do under hypothetical scenarios.

The problem with the willingness-to-pay method of valuing benefits, however, is that WTP is bound to vary with the income of the potential bidder, which means that the measured benefits would be smaller when poor people do the bidding than when rich people bid. In research, one would therefore have to find potential bidders who can be deemed to be validly representative of the society for which the societal benefit–cost analysis is being conducted. Smith and Richardson (2005) discuss these issues in greater detail.

As already noted earlier, two distinct criteria can be used with CBA. They are (1) the net incremental benefit from following the alternative course of action A rather than the baseline course of action B, and (2) the associated benefit–cost ratio.

The net incremental benefit of course of action A over course of action B is defined as:

\[ NIB = (\text{Benefits } A - \text{Benefits } B) - (\text{Costs } A - \text{Costs } B) \]

\[ = (\text{Benefits } A - \text{Costs } A) - (\text{Benefits } B - \text{Costs } B) \quad (6) \]
where ‘Benefits A’ and ‘Benefits B’ in the equation may be the present (discounted) value of a time-phased stream of benefits, possibly age-weighted, and ‘Costs A’ and ‘Costs B’ would be the associated present (discounted) value of time-phased cost streams. If NIB is used as an evaluation criterion for action, one would prefer course of action A if NIB > 0 and baseline the baseline course of action B if NIB < 0.

The associated benefit–cost ratio is defined as:

$$BCR = \frac{\text{Benefits A} - \text{Benefits B}}{\text{Costs A} - \text{Costs B}}$$

(7)

or, as was explained earlier, as:

$$BCR = \frac{\text{Benefits A + Costs B}}{\text{Costs A + Benefits B}}$$

(8)

depending on how one defines the benefits and costs of course of action A. If the BCR > 0, one would go ahead with course of action A and if BCR < 1 one would prefer the baseline course of action B.

As a general rule, as already noted earlier, the NIB criterion is preferable to the BCR criterion, because the NIB is not sensitive to whether a negative consequence is treated as an increase in costs or a decrease in benefits, while the BCR ratio is very sensitive to such classifications.

Cost-effectiveness analysis (CEA)³

Because it is so challenging to put explicit monetary values on all of the negative and positive consequences associated with alternative courses of action in healthcare, researchers often prefer to leave at least the benefit side in physical terms, monetarizing only the cost side. For example, one may try to estimate the average cost per added life year saved with different preventive-care strategies, or with different acute-care treatment strategies — e.g., surgical treatment of lower-back pain versus medical treatment. The idea then would be to favor the treatment method with the lowest total cost (per year, or in present-value terms) of achieving given goals in a change in physical health status.

The CEA works well when the physical health status measure or other treatment goal in question is one-dimensional — e.g., a reduction in systolic blood pressure by 10 points. It is problematic when the change in health status is multidimensional or, in the case of ‘added life years’ or ‘change in life expectancy’ as a physical outcome measure, when life years can be associated with different degrees of the quality of life (i.e., degrees of disability).

For such cases, researchers have developed ‘cost-utility analysis’ (CUA), which seeks to collapse multidimensional health outcome changes into a one-dimensional metric, for example, health-adjusted life-year indices that collapse changes in mortality and morbidity triggered by a new medical technology into one unidimensional metric.

Cost-utility analysis (CUA): QALYs and DALYs

Under CUA, subjective valuations of the various dimensions of a multidimensional health outcome from a medical treatment are collapsed into a unidimensional metric. Two such metrics are now in wide use among health services researchers worldwide: the Quality-Adjusted Life Year (QALY) and the Disability-Adjusted Life Years Lost (DALYs) (Gold et al., 2002).

To explore these concepts, it will be useful to posit a very simple, stylized life-cycle model for the representative individual, which may be the average experience for a cohort of individuals. Thus, we shall imagine a 20-year-old person who is expected to live to age 65 in perfect health (without any degree of disability), and then spend the remaining years until death at age 60 with:

- a particular health status, which may have a number of dimensions, such as pain and mobility, such that one calendar year in that health status is scored subjectively by respondents in a survey as, on average, the equivalent of 0.6 calendar years in perfect health, so that each such year is set equivalent to 0.6 of a Quality-Adjusted Life Year or 0.6 QALYs; or, equivalently,
- a degree of disability such that losing or gaining that year with that disability status is scored subjectively by a set of respondents as the equivalent of 0.4 of a healthy year. For example, if a treatment yields an additional life year in that disability status, then that benefit is scored as 0.4 healthy years, or 0.4 Disability-Adjusted Life Years, or 0.4 DALYs.

It is assumed in this stylized example that the maximum life expectancy of persons in this society is expected to be 80 years. Finally, for the sake of simplicity it is assumed initially that future life years enjoyed, or lost, are neither age-weighted nor discounted.

With these preliminaries, let us define what is meant by QALYs and DALYs.

Quality-Adjusted Life Years (QALYs)

Under this approach, life years lived in less than perfect health are converted into what the representative individual would consider the equivalent number of years in perfect health. For example, if a person said he or she would be indifferent between living 20 more years in a particular lower health status described to him or her and only 16 more years in perfect health, then each of the 20 years in less than perfect health would be considered by that person the equivalent of \(16/20 = 4/5 = .8\) of a health year, or
0.8 QALYs. The fraction 0.8 would be the quality-of-life weight assigned to each year with the specified disability.

The beneficial outcome from a medical intervention or health policy is then the change in QALYs attributable to that course of action, which is then used as the denominator in the 'incremental cost per incremental QALY' or simply 'cost per QALY' attributed to that course of action.

Figure 34.3 illustrates this concept. The vertical axis is defined as health status such that death is indexed as 0, perfect health as 1, and a health status considered 'worse than death' (e.g., severe chronic pain) as less than zero.

At age 20 the person is expected to have another 40 calendar life years, of which, however, 15 years are expected to be in less than perfect health. To adjust for that lower quality of life, we calculate the person's expected QALYs as:

\[
\text{QALYs} = (45 - 20) + 0.6(60 - 45) \\
= 25 + 0.6(15) = 34
\]  

(9)

Note that at age 20 the person is expected to live another 40 calendar years, but we would count that as only 34 QALYs.

It can be asked how the quality-of-life-year weights used to calculate QALYs are determined. Three methods have been widely used for that purpose, namely:

- Visual analogue scales (VAS)
- Standard gambles (SG)
- Time trade-off adjustors (TTT)

Under the visual analogue scales (VAS) approach, a group of relevant interviewees are given a scale from 0 to 1 or from 0% to 100%, where '0' means 'worst imaginable health status' and '1' means 'perfect health.' A health status is then described and the interviewee picks a number from the scale that reflects his or her assessment of it. That number then becomes the weight assigned to the added life year in the described health status to obtain the implied number of QALYs. For example, if on average the interviewees score the year in that health status as 0.7, then that added life year is scored as 0.7 of a QALY or 0.7 QALYs.

Under the standard gambles (SG) approach the interviewee is given a choice between (1) a described health outcome, e.g., an added life year, with a described health status that will occur with certainty, or (2) a risky choice between one better health outcome (usually full health) and one worse outcome (usually 'death'). The person then picks a probability of having the better outcome such that (s)he would be indifferent between the certain outcome with the described less-than-perfect health status and taking the gamble of having either the better or the worse outcome. The chosen probability then becomes the weight assigned to the health outcome with the described health status. If, for example, the interviewees on average stated that to take the gamble rather than the certain outcome, the probability of the better outcome in the gamble would have to be 80%, then the certain outcome (added life year) with the described health status must be fairly tolerable and that extra year in the described less-than-perfect health status would be scored as 0.8 QALYs.

Under the time trade-off (TTT) approach, the interviewees are asked to imagine themselves living in the described health status for T years and then to tell how many years in that health status they would be willing to trade off in exchange for life years in full health. For example, if
T = 10 and the respondent says that that is equivalent to 8 years in full health, then 8/10 = .80 becomes the quality weight attached to the 10 life years to yield 0.8 QALYs.

One can imagine still other ways to tease quality weights out of people.

**Disability-Adjusted Life Years Lost (DALYs)**

Under this method, one posits as the ideal a maximum number of calendar years lived in perfect health, e.g., 80 years, and then counts as DALYs the appropriate fraction of calendar years lived in less than perfect health, as well as the number of calendar years short of 80 not lived at all.

The beneficial outcome from medical interventions or particular health policies is then measured by the reduction in DALYs— that is, the reduction in disability-adjusted life years lost— attributable to that course of action. Those DALYs are then used as the denominator in the 'incremental cost per incremental DALY' or simply 'cost per DALY' attributed to that course of action.

Figure 34.4 illustrates this concept for the simple, stylized example we had posited at the outset.

At the person's age 20, he or she is expected to lose:

\[
\text{DALYs} = (80 - 60) + 0.4(60 - 45) \\
= 20 + 4.2 = 26
\]  

(10)

from a maximum life of 80 years in perfect health (without any disabilities). The person is expected to die 20 years before the maximum expected life of 80, but we count those 20 premature calendar years lost as 26 DALYs because 15 calendar years are lived with disability degree 0.4.

In this simple illustration, we have counted a DALY as the same for any person at any age, and we did not discount future DALYs. In fact, as already noted the World Bank and the World Health Organization give more weight to a DALY lost by a person of working age than to a DALY lost by a person too young to work or too old to work.

**Change in QALYs and DALYs achieved through healthcare**

Suppose the projection depicted in the graphs above were the baseline course of action B and then a new medical technology (course of action A) were applied to someone before age 45 with the following two consequences:

- The new treatment will extend the number of calendar years of life for this person by 10 years.
- At the same time, the new technology will enhance the person's health status in a way so that, from age 45 to age 70, one calendar year of the person's life will be scored as the equivalent of 0.70 of a calendar year in perfect health, rather than only 0.60 under the baseline treatment, or, equivalently, that the degree of disability suffered by this person is such that 1 calendar year of life with these disabilities is scored as a loss of only 0.30 calendar years without disabilities (in perfect health), rather than the 0.40 under the baseline.

The associated change in health status can then be calculated in three ways:

- **Unadjusted life years**: the intervention is expected to yield 10 added calendar life years.
**Quality-adjusted life years (QALYs) gained:** The intervention is expected to yield 8.5 QALYs, calculated as \((60 - 45)(0.70 - 0.60) + (10)(0.70) = (15)(0.10) + 7 = 8.5\).

**Reduction in disability-adjusted life years lost (DALYs added to life):** After this intervention, the DALYs lost will be \(80 - 70 + (70 - 45)(0.3) = 10 + 25(0.3) = 10 + 7.5 = 17.5\). We had previously calculated that, before the intervention, 26 DALYs would be lost. Thus there is a reduction in DALYs lost of 8.5.

Figure 34.5 depicts the situation we have described above. In this illustration, the shaded area depicts QALYs gained by the intervention, and also the reduction in DALYs achieved thereby. Is that always the case? It is not. In this stylized example, the number of DALYs and the number of QALYs yielded by the hypothesized medical intervention are equal only because age weighting and discounting were not applied. Had the DALYs been age-weighted and had future QALYs and DALYs been converted to present values through discounting, the change in QALYs and DALYs would not have been identical.

**CAN ONE EVER AVOID PUTTING MONETARY VALUES ON HEALTH BENEFITS?**

Because cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) merely rely on costs per some physical metric of outcome from alternative medical treatments, it may be thought that use of these methods avoids having to assign monetary values explicitly to the benefits produced by alternative treatments. In many applications, it may appear that it is so; but in fact it is not.

**Comparing alternative treatments**

A cost-effectiveness analysis (CEA) could be based strictly on a comparison of the cost per unit of health outcome achieved with one treatment (A) with that of another (B). Dong et al. (2004), for example, compared thus two different approaches to treating type 1 diabetes mellitus with ACE inhibitors early or later, after the condition has been diagnosed. They calculated the incremental cost per added QALY yielded by earlier treatment.

Similarly, one might calculate the cost per unit reduction in the systolic blood pressure (bp) achieved with two alternative prescription drugs, A and B, on the assumption that the decision to lower pb by X units actually has been judged worth what it now costs, that is, that the average pb for a cohort of insured individuals is to be lowered by X one way or the other. If the cost per unit bp with product A is found to be lower than that with product B, the most cost-effective treatment would be the new pharmaceutical product. The rational, best clinical practice then would be to switch from product B to product A. In practice, of course, ignorance of the benefit–cost analysis and sheer inertia, coupled with the marketing tactics of different drug manufacturers (in some countries, including under-the-table payments to
practitioners) might stand in the way of a quick move to the evidently best practice.

If, in the previous example, product A was associated with lower costs per unit reduction in bp, but had one or two somewhat riskier adverse effects not present in drug B, then one would resort to cost-utility analysis (CUA) to modify the physical outcome measure, as described above. Here an implicit evaluation of benefits does creep into the analysis, but it is not a monetized one.

But even if one discovered through CEA or CUA the lowest-cost strategy among alternative treatment methods aimed at lowering the representative patient’s blood pressure by a given number of points – the most ‘cost-effective’ treatment – the decision maker acting on behalf of society in societal benefit–cost analyses still had to confront at some prior time the fundamental question: ‘Is lowering average systolic blood pressure of patients by X points worth it at all, even with the most cost-effective drug treatment?’ After all, many things are not worth doing even under the most cost-effective method of doing them. In our example, the decision maker using the analysis still must implicitly put a monetary value on the benefits from lowering blood pressure by X points and compare that value with the least cost method of achieving that reduction. The only difference between CBA and CEA (or CUA) analysis, then, is that under CBA exact monetary values must be put on benefits, while under CEA (or CUA) one merely needs to think about the minimum monetary values a set of health benefits must have to justify the cost of achieving those benefits.

**CEA and CUA and National Health Policy**

Cost-effectiveness analysis or cost-utility analysis can also be used to sharpen the public debate over national health policy – especially over cost-control strategies and the issue of rationing healthcare.

One can illustrate this proposition by thinking of a nation’s health system as a giant business firm – e.g., Health USA, Inc. Its managers (doctors, hospital executives, and so on) may tell ‘society’:

Taking as a state of nature how prudently (e.g., residents of Utah in the US) or sloppily (residents elsewhere in the US) you wish to live in regards to health maintenance, we in the health sector can wrest from nature additional, quality-adjusted life years (QALYs) for you, at prices that range from very low (e.g., with immunizations, or with good prenatal care) to very, very high (e.g., with expensive biologicals that purchase at best a few added life-months for terminally ill patients). Shown below is the current shape of our QALY-supply curve. Please tell us the maximum price at which you, the rest of society, are willing to purchase added QALYs from us, the health system, and we shall deliver them to you, up to that point.

The supply curve that might accompany this proclamation might look like Fig. 34.6. In the graph, point A may represent buying added QALYs purchased through low-cost preventive care (including furthering health literacy and education). Point B may represent a routine, life-saving surgery. Point C may represent more expensive chronic care, such as renal dialysis. Finally, point D may represent treatment of patients with biologicals such as Avastin and Erbitux. These products carry such a high price tag that they imply a price per added QALY of about $250,000.

The supply curve in the graph should be thought of as the locus of the most cost-effective clinical practices needed to achieve the level of QALYs on the horizontal axis. As noted in Fig. 34.6, health services researchers – really operations research – can help managers of the
health system get from an inefficient treatment strategy — one that costs more than is necessary — onto the efficient QALY-supply curve. That task done, however, it is up to politicians or health-insurance executives, as representatives of individual patients, to pick the maximum price at which they will purchase added QALYs for individuals, but with collective funds (taxes or insurance funds). Finally, it is up to the people to decide what they would like these representatives to do in this regard.

Figure 34.6 is a pictorial rendering of one of the most vexing and intractable issues in modern health policy. The graph clearly poses the questions:

- Is there a maximum price per QALY above which those purchasing healthcare on behalf of insured patients (private or public third-party payers) should not go, to purchase additional QALYs out of the collective funds (taxes or premiums) entrusted to them?
- If there is such a price, should it be the same for all members of society — e.g., for a poor American insured by the government-run Medicaid program as for a corporate executive, or a young American and an old American?

Some nations have boldly tried to explore these issues as part of the debate on health policy. Former Governor Kitzhaber of the State of Oregon had tried to force his citizenry to come to terms with this issue as well, openly and honestly, like mature adults. But many other nations — and certainly most Americans — still steadfastly refuse even to engage on the issue. These nations do ration healthcare of course; but it is done implicitly, either by leaving some members of society uninsured, or by strict healthcare utilization controls. In that context, economic evaluations of alternative healthcare strategies, including new medical technology, can turn out to be just like howling into the wind.

UNRESOLVED CONTROVERSY ON ECONOMIC VALUATIONS IN HEALTHCARE

In conclusion, it may be useful to examine briefly some of the lingering controversies on the economic evaluations in the context of healthcare.

Attempts by health services researchers during the past two decades to subject medical treatments — especially those based on new medical technology such as new drugs or medical devices — have remained controversial for a variety of disparate arguments, each driven by a different motivation. Some of the criticism of the technique rests on purely scientific methodology — e.g., how best to elicit valuations of health status from random samples of individuals. Others have rested on the ethical implications embedded in the application of technique which is, in effect, laden with subjective ethical values and not purely scientific. Finally, some objections are motivated strictly by narrow commercial interests — for example, the apprehension of drug- and device manufacturers to see their products and revenues potentially threatened by transparency on cost effectiveness.

Methodological issues

Like every endeavor to quantify the consequences of human activity, quantifying the positive and negative consequences of alternative medical treatments and using such metrics in benefit–cost analysis, which requires one to convert all benefits and costs into comparable units, is fraught with methodological difficulties. Pharmacoeconomics and all economic evaluations in healthcare are no exception. These methodologies difficulties are described and debated continuously, at conferences around the world, by sincere health services researchers without any ideological or pecuniary axe to grind.

As this author has pointed out (Reinhardt, 1997), while there is great scientific merit in the open and sincere dueling over methodology among health services researchers at these conferences — and in the literature — it does carry with it the danger that policy makers may distrust the entire approach and proceeds, as usual, to make decisions on the basis of folklore, hunches or their own ideological or pecuniary interests. Here it must be kept in mind that in their wresting matches over measurement methodology, health services researchers have very good company.

For example, financial accountants, who face similar methodological difficulties of definition and measurement, have solved this problem by a dual posture. Intra-professionally they engage in fierce arguments over issues such as the valuation of assets, depreciation, estimated bad debt expense or financial derivative contracts. Vis à vis the users of their product, however, accountants have written down and sown allegiance to a code of Generally Accepted Accounting Principles (the GAAP) that are accepted without question by the users of accounting information in government, in finance, and in business, even though every user educated in financial accounting knows that financial accounting data are systematically biased, highly imperfect and often misleading metrics. The entire so-called real world thrives on such imperfection.

Objections on ethical grounds

More serious than problems purely of measurement science are the ethical implications embedded in the economic evaluation of human activity of any kind, especially so in the context of healthcare. Many of these concerns have been ably summarized in papers by Erik Nord et al. (1999) and Jeff Richardson (2002).

One genre of criticism revolves around the question just who should be asked to collapse life years spent in particular
states of health into utility-equivalent QALYs or DALYs, as is done in cost-utility analysis (CUA). A common argument is that persons in reasonably good health asked to imagine themselves to be in a much worse state of health would convert life years spent in that worse state of health into much lower utility-equivalent QALYs than would someone already in that worse state of health, because people tend to adapt to it. Implied in this line of argument is the proposition that economic evaluations of new medical technology based on QALYs or DALYs may be biased against individuals already in the low health status.

A similar argument is that the use of QALYs and DALYs implicitly biases economic evaluations against older people, because a successful medical intervention generally produces fewer added life years for older people than for younger people. This argument applies even if QALYs and DALYs are not explicitly age-weighted. If they are, as was illustrated earlier in this chapter in connection with DALYs, then the criticism applies with even greater force, especially in a country such as the United States which finds age discrimination abhorrent.

Finally, as Jeff Richardson (2002) points out, survey data have consistently revealed that the general public typically does not wish to see scarce healthcare resources allocated to individual members of society so as to maximize the number of added QALYs or DALYs that can be wrestled from nature with a given national healthcare budget – the seemingly efficient thing to do – but instead wishes to see those budgets directed mainly to the sickest members of society, even at the cost of a much higher number of QALYs that could be more cheaply purchased for other members of society. On the basis of that research, Richardson advocates so-called 'empirical ethics', that is, a search for the socially most desired allocation of healthcare budgets through iterative allocations and surveys of the public on the merits of the latest allocation.

Objection on commercial grounds

Although commonly paying lip service to the merits of economic evaluations in healthcare – and using such evaluations in their marketing when they turn out supportive of a new medical technology – the producers of medical treatments and the products going into them tend to look askance at these valuations when they threaten to detract from the top and bottom lines of their income statements. It can explain, for example, why any prior attempt by the US Congress to establish technology assessment centers in the United States – such as NICE in the UK or IQWiG in Germany – have been met with stiff opposition from the producers of medical technology and, so far, have faltered. In this effort the industry has been successful even to enlist entire political parties. Thus, to any health services research it must come across as astounding that none other than the Republican Policy Committee of the US Senate (2003) condemned as a 'trade barrier' both the reference pricing and the cost-utility analyses performed on pharmaceutical products and devices in other countries.

One can understand why the suppliers of healthcare and healthcare products would be nervous about rigorous economic evaluations of their offerings. They are right in arguing that poorly performed evaluations can hurt not only these providers' economic position, but patients as well. And they are right to insist that any such evaluations be completely transparent and accessible to them for external audit, not only as to methodology, but also as to the raw data fed into the analysis. They are unlikely to be able to stop for much longer; however, the world-wide quest on the demand side for cost-effectiveness and benefit–cost analyses.

NOTES

1. For a formal presentation on the WACC, see Brigham and Earlhardt (2008), chapter 10
2. Calculated as $100 (1 - 0.12)^{10}/0.12.
3. For a fuller description of reference pricing, see Kavanos and Reinhardt (2003).
4. See, for example, essays in Lopez-Casasnovas and and Jonsson (eds) (2001).
6. In this connection, see Drummond et al. (2005), section 4.2, and Sherman Rolland et al. (2007), chapter 4.
7. See, for example, Anand and Hanson (1997).
8. For a rigorous review of this method, see Garber (2000).
9. For a thorough review of these methodological issues, see for a thorough review of these methodological issues, see Dolan (2000).

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