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"OVERVIEW OF PHARMACOECONOMICS"

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1.0 INTRODUCTION

The purpose of this research paper is to revise the terminology related to pharmacoeconomics, with the primary goals of an evaluation and with the different types of economic evaluations. This research will also show the importance of pharmacoeconomic evaluations and the general guidelines that are essential in conducting a pharmacoeconomic study. Finally, the challenges and concerns related to pharmacoeconomics will be examined.

Attention regarding the relationship between costs and efficacy of medicines has not always existed. Considering the escalating rise in healthcare costs, the demand for a more rational allocation of medications has never been more crucial. For instance, two decades ago, physicians only had to choose among available interventions by employing clinical endpoints (safety and efficacy); sales representatives could inform a physician on a medication intervention and expect him to prescribe and adopt it. Today, physicians must also examine costs, whether they like it or not, as governments and hospital administrators are striving to decrease total costs progressively. A product can no longer be safe and efficacious, it must also be efficient.

Reading this research paper will improve the understanding of pharmacoeconomics and of the debates revolving around it. Consequently, healthcare professionals will be able to update themselves on all the different pharmacoeconomic evaluations that are published because they are responsible for providing efficient healthcare services.

Since healthcare professionals are often faced with the difficult task of assessing the value of a new therapeutic agent or justifying the addition of a new clinical service, cost or effectiveness is often the only factor considered. After reading this research paper, they should be more inclined to develop efficient strategies rather than strategies that are

primarily cost-containment ones. Healthcare professionals must understand the importance of finding the most efficient interventions (therapies) and/or interventions which will most significantly improve the patient's quality of life, since they are dealing with public funds and human lives.

2.0 TERMINOLOGY

This research paper emphasises on terminology because it is ESSENTIAL to use it correctly in this developing science. Below are the important expressions used in the pharmacoeconomic (and economic) vocabulary.

2.1 What is Economics?

Economics is the science which analyzes choices in order to maximize the welfare of a society, of a healthcare system, of an organization or, of an individual. The starting point of economics is that choices must be made concerning the deployment of resources (e.g., time, money, facilities, knowledge, etc), since, by definition, resources are limited. Due to the resource scarcity phenomenon, it is impossible to yield all desired outputs because there are not and there will never be enough resources to fulfil everybody's wants. Choices must then be made in all realms of human activities. These choices are adopted on the basis of numerous criteria, which are sometimes explicit but most frequently implicit. Awareness of economics can provide a more rational allocation of resources.

2.2 What is an Evaluation?

"An **evaluation** consists of expressing a value judgement on an intervention¹ or on any of its aspects² in order to help the decision-making process. This judgement is either a result of the application of criteria or norms (called normative evaluation) or of the elaboration of a scientific approach (called evaluative research)"³.

¹ See definition in section 2.5.

² See appendix 1.

³ Geneviève Tessier, from the GRIS (Groupe de Recherche Interdisciplinaire en Santé), Université de Montréal, personal communications.

It should be mentioned that according to André-Pierre Contandriopoulos, from the GRIS (Groupe de recherche interdisciplinaire en santé), an evaluation differs from a study, an appreciation and, an analysis, eventhough in the dictionary these expressions may sound as synonymous. A study⁴ relates to the process of defining a research question and determining assumptions in order to obtain a result, a value. An appreciation observes and compares a state relatively to a normative value; it is simply a review (it can be a literature review or any other type of review⁵). An analysis is a more complex process than an appreciation since it studies and examines two or more aspects of an intervention; usually an appreciation only examines one aspect of an intervention.

Therefore, an analysis must be undertaken in order to do an evaluation since the decision-maker must depend on something valid in order to express a value judgement. Consequently, in order to undertake an evaluation, first a study must be conducted, second an analysis of the study must be done and, finally the evaluation can be undertaken. In order for an evaluation to be rigorous and scientific, the study and the analysis must obviously be conducted with a lot of care.

2.3 What is an Economic Evaluation?

An **economic evaluation** is a form of evaluation which identifies, measures, evaluates and compares the various alternatives, in an incremental fashion, in terms of both their costs and their outcomes. The purpose of an economic evaluation is to select the most efficient solution. Consequently, the application of economic evaluations to healthcare does not imply that less should or can be spent, rather that resources should be distributed in the most efficient manner.

⁴ *A study can also be seen as a trial.*

⁵ *An appreciation is frequently what managers do on a day-to-day basis.*

To be considered COMPLETE, an economic evaluation has to be characterized by the two following features, regardless of the type of analysis and of economic application (e.g., healthcare, environment, engineering, etc) to which it pertains:

- (1) An economic evaluation weighs both the COSTS and OUTCOMES (pecuniary and non pecuniary) of interventions. It is the relation between costs and outcomes that helps one to make a choice, a decision⁶.
- (2) An economic evaluation must be INCREMENTAL and COMPARATIVE among one or more relevant alternatives (including status quo).

If one of these two criteria is not met, the economic evaluation is then considered PARTIAL. Partial economic evaluations, as the term indicates, are mainly concerned with certain components of an economic evaluation: the evaluation can only be a cost (comparative or not) study, such as a cost-of-illness study⁷, an outcome (comparative or not) study, such as quality of life studies⁸, or a non comparative cost-outcome study. Partial evaluations are a valuable tool because they enable one to have a better comprehension of the intervention's costs and/or outcomes; however, they cannot empower one to answer EFFICIENCY questions. Only complete evaluations achieve to answer efficiency questions.

Economic evaluations can either be based on prospective or retrospective studies depending of the research question, the data, the time and the budget at one's disposal. PROSPECTIVE studies are usually more expensive and more time consuming than retrospective studies; however, they enable one to obtain accurate and randomized

⁶ *When the economic evaluation bears on pharmaceutical services, the concept of pharmaceutical care would imply that the consequences to look at should be linked with the prevention or resolution of medication problems or more generally with the improvement of the patient's health status.*

⁷ *Cost-of-illness studies are a form of economic evaluation that measures the economic impact of a disease or of an illness. A popular topic of cost-of-illness studies are migraines.*

⁸ *See definition in section 2.9*

results since economic parameters can be added into clinical trials, thus, providing high quality studies⁹. They also provide a means of measuring outcomes pertaining to quality of life (which can be difficult to do when a retrospective design is chosen, since this kind of data, specific to the patient's well-being and personal expenses, can generally be obtained through a patient questionnaire; however, depending on the type of quality of life approach chosen, for instance, choosing the standard gamble approach, retrospective studies can also be undertaken, obtaining also high quality studies, by consulting physicians and nurses). RETROSPECTIVE studies are used for numerous reasons. First, they can be executed much faster and are less expensive. Secondly, their growing importance within the pharmaceutical industry is a consequence of escalating costs of healthcare; this is partially due to the significant cost increase of new technologies. Pharmaceutical companies are aware of the impact these analyses have on product sales.

There are three different extent of an economic evaluation. First, the economic evaluation can be based on a sensitivity/competitive pricing analysis. This type of analysis is conducted mostly when the intervention does not have additional outcomes compared to the competition, hence, this type of analysis determines which price the pharmaceutical manufacturer could consider for the new intervention, in order to be competitive. Secondly, the economic evaluation can be based on a pilot-project analysis. This type of analysis is used when the concerned party wants to make sure that the intervention is efficient on a smaller scale, prior to initiating a larger and costly economic study. Finally, the economic evaluation can be based on a comprehensive analysis. This type of analysis is the most thorough. It is used to confirm and convince, to the concerned party, the efficiency of the product. This type of evaluation is presently rarely undertaken because it is highly expensive and time consuming; however, due to the healthcare cost containment issue, comprehensive analyses will become an essential component to assist decision-makers.

⁹ *However, depending of the research question, the type of efficacies and costs which are chosen to be studied (e.g., practical evidence versus clinical evidence) and other factors, a retrospective study can provide just as high quality study than a prospective study.*

An economic evaluation should not be confused with a cost containment strategy since, unlike a cost containment strategy, it aims at allocating resources in the most rational and efficient way, in order to maximize the outcomes pertaining to each strategy.

It should be stressed that many terms have been used INCORRECTLY in the literature to indicate generic expressions concerning economic evaluations; health economics has witnessed a confusing vocabulary. The expressions most often misused are: cost-savings analysis, cost-containment analysis, cost-justification analysis, cost-impact analysis, cost analysis, cost-benefit analysis, and cost-effectiveness analysis. The last three expressions refer to specific types of economic evaluations and hence satisfy the criteria for partial/complete economic evaluations. They are NOT a generic expression to denote economic evaluations. The most employed "PROPER" generic terms to indicate an economic evaluation are: economic analysis, economic assessment, economic appraisal, economic study, and technology assessment. However, following the definitions mentioned above, attention should be oriented to use appropriately the expressions "study", "appraisal", "analysis" and "evaluation". Once again, here are the steps of an evaluation: first a study is conducted, then the study is analyzed and, once the study is analyzed, the analysis can be evaluated, meaning that a value judgement can be expressed on the intervention's analysis or on any of the intervention's aspects in order to help the decision-making process. Consequently, depending of the stage of the evaluation, different terms are used. However, if you want to be assured that you are using the correct expression, use "evaluation", you cannot go wrong since it globalizes all these processes.

2.4 What is Pharmacoeconomics?

Pharmacoeconomics is a relatively "trendy" word used to denote the application of economic evaluations to pharmacotherapy. Several editors, reviewers, policymakers, pharmaceutical manufacturers, health and university professionals are still unfamiliar with this new, evolving and complex science.

A pharmacoeconomic analysis identifies, measures and compares, in an incremental fashion, the costs and outcomes of medications' interventions. In essence, a pharmacoeconomic analysis employs tools for examining the costs and outcomes (desirable and undesirable) of different medication therapies. Pharmacoeconomics, thus, is helpful in determining how limited healthcare resources can be allocated in the most efficient manner for a concerned party (e.g., patient, hospital administrator, government, etc)¹⁰. This concerned party becomes the perspective of the study, therefore, all costs and outcomes will be analyzed and evaluated in order to help the decision-making process of this concerned party.

Pharmacoeconomic analysis can be employed to evaluate existing programs and/or to help select future programs among various alternatives. Pharmacoeconomic analysis deals with the following examples of questions¹¹, which may be asked by hospital administrators, pharmaceutical manufacturers, governments (provincial and federal), insurance companies, labour unions, influential disease associations, healthcare professionals, etc:

- What medications should be included/delisted on a hospital, provincial formulary?
- What is the most efficient medication for a particular type of patient?
- Which medication distribution system is the most efficient for an institution?
- What is the cost per QALY (Quality-adjusted life-year) of a medication?
- What is the most efficient intervention for a specific disease?

Decisions about health expenditures without appropriate objective findings might become too subjective; however, objective findings can be acquired through pharmacoeconomic analyses. There are four different types of complete pharmacoeconomic evaluations employed: cost-minimization analysis, cost-effectiveness

¹⁰ See Appendix II regarding the major perspectives which can be chosen for pharmacoeconomic evaluations.

¹¹ Inspired of the document by Draugalis JR, Bootman JL, et al., 1989, p5.

analysis, cost-utility analysis and, cost-benefit analysis¹².

Notice that pharmacoeconomics is not health economics but a component of health economics. Health economics is concerned with everything which is related to healthcare whereas pharmacoeconomics is only concerned with what is related to medication interventions (pharmacotherapy). If you want to make sure that you are employing the correct term concerning economic evaluations related to a specific aspect of healthcare, always refer to "health economics", you cannot go wrong!

2.5 What is an Intervention?

"An **intervention** is the total mechanisms (physical, human, financial, symbolic, etc) established in a certain structure, at a certain time, to produce goods and services in order to resolve a problematical situation. An intervention can be a technique, an organization, an application, a program, a legislation, a treatment, a service, etc"¹³.

2.6 What is a Cost?

A **cost** is the value of the resources (inputs) consumed by an intervention. In pharmacoeconomic studies, the types of costs that are incurred are: direct medical and non medical costs and, indirect non medical costs. However, in a pharmacoeconomic evaluation, the type of costs that are evaluated are direct medical and non medical costs, indirect non medical costs and, opportunity costs. Costs are always measured in the country's currency (e.g., canadian dollars).

Direct medical costs are directly related with the intervention itself. These costs are the most simple to determine and measure. Examples of these costs are: medications, laboratory tests, hospital costs, etc.

¹² *Definitions of these type of analyses will be elaborated in section 4.0.*

¹³ *Geneviève Tessier, personal communications.*

Direct non medical costs are directly related with the medical intervention but are not part of the intervention itself. Examples of these costs are: travel expenses associated with the visit to the physician, home assistance, etc.

Indirect non medical costs are not directly related to the medical intervention itself, but are repercussions to illness. Examples of these costs are: lost work productivity, unpaid family assistance, etc.

Opportunity costs¹⁴ are the net economic outcomes foregone when selecting an intervention rather than an alternative. Once a resource has been used, the opportunity to use it for another purpose is lost because this resource cannot be recuperated and transferred for another intervention. Its value in the next best use, which is no longer possible, is called the opportunity cost. For example, when a dollar is spent towards an intervention, the opportunity cost of this dollar is that it cannot be transferred to a person for a medical intervention or, to a department for buying equipment or having additional personnel, etc.

Opportunity costs are the basis in an economic evaluation. They are frequently intangible, hence, they become difficult to quantify since they represent the human cost of illness/mortality. But, no matter how difficult opportunity costs are to measure, it is of paramount importance that these costs be valued as thoroughly as possible, just as clinical endpoints must be valued, for the decision to be optimal; however, if some opportunity costs are impossible to value, they should not be left out. These opportunity costs must be enumerated and expressed clearly why they cannot be valued in order that the decision-makers weigh these factors during the decision-making process. Cost-utility analysis, however, offers an alternative for measuring illness/mortality costs.

Given the limitation of resources, the real problem with the excessive use of medical interventions is not the pecuniary expenditures themselves, but the fundamental

¹⁴ *Opportunity costs are not part of a pharmacoeconomic study and analysis since they are a consequence of the project; they are not an input. However, they must be taken into account for the evaluation.*

cost of sacrificed outcomes when an intervention is chosen, including statu quo, rather than another one. This is why economists define the economic cost of an intervention as an opportunity cost. When economists argue that attention should be paid to efficiency in healthcare, they are implying that healthcare interventions should be compared not only in terms of their relative outcomes, but also in terms of their relative outcomes FOREGONE (i.e., relative costs).

In the consideration of costs and outcomes, it is important that readers verify when they are incurred because in the future, nominal costs (outcomes) are likely to be higher simply because of inflation. These future inflated costs need to be corrected to their real value at the time the decision is being made so that present and future costs can be compared without the bias of inflation generating future costs or outcomes to appear greater.

To be complete, a pharmacoeconomic study must contain the three types of costs mentioned above (i.e., excluding opportunity costs), whereas a pharmacoeconomic evaluation must contain the four costs mentioned above (i.e., including opportunity costs), since, as mentioned in the footnote #14, opportunity costs are not part of a pharmacoeconomic study and analysis because they are a consequence of the intervention; they are not an input. If some costs are insignificant or difficult to compute, they may be exempted from the analysis. Nevertheless, if these costs are exempted, it **MUST** be mentioned and explained clearly in the assumptions why these costs were excluded, in order to avoid bias in the study and the analysis.

One last aspect worth mentioning concerning costs and outcomes is the concept of MARGIN. This concept is central in economics. Efficiency primarily states that the total outcomes of an intervention should exceed or equal the total costs. Efficiency secondly states that the marginal cost¹⁵ MUST EQUAL the marginal outcome (corresponding to point a in figure 1). This can be logically deduced: if the marginal outcome is greater than the marginal cost, then more outcomes can be gained by further expansion of the intervention, until the marginal cost equals the marginal outcome (corresponding to point b in figure 1); if the marginal outcome is less than the marginal cost, there should be a contraction of the intervention since the total costs are not worth the total outcomes (corresponding to point c in figure 1). This concept of equality between the marginal cost and outcome is crucial because most physicians would agree that one of the basic question in medicine is not whether or not procedures are totally worth less but to which extent the intervention should be pursued or contracted. Consequently, for an intervention to be optimal, it should be pursued or contracted until its marginal cost equals its marginal outcome.

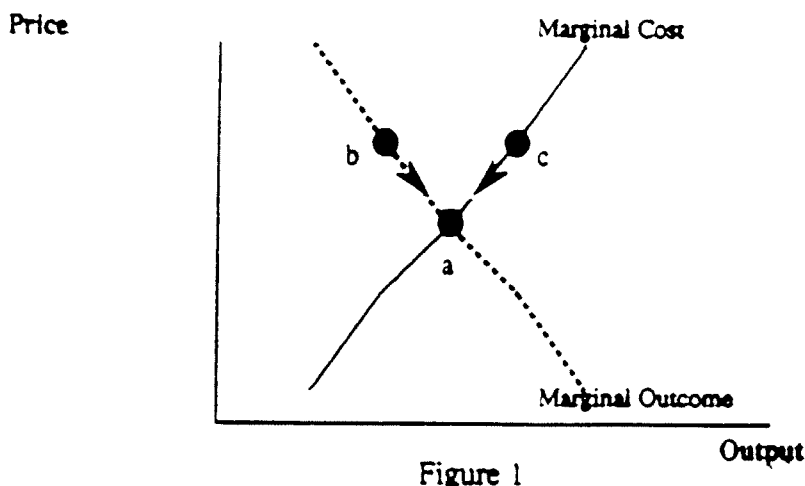


Figure 1

¹⁵ Marginal cost (outcome) represents the costs (outcomes) of producing one more unit or aspect of a given intervention

Average cost must also be distinguished from marginal cost. A popular example, of the difference between average and marginal cost, is in the determination of savings resulting from one less day of hospitalisation¹⁶. Usually, the intensity of care is at its peak in the first days of hospitalisation, hence, hospital costs are more significant at the beginning and then they decrease over time. Consequently, marginal cost, in economic evaluations, should be used, rather than average cost since it is a better representation of the real costs, rather than the average daily cost.

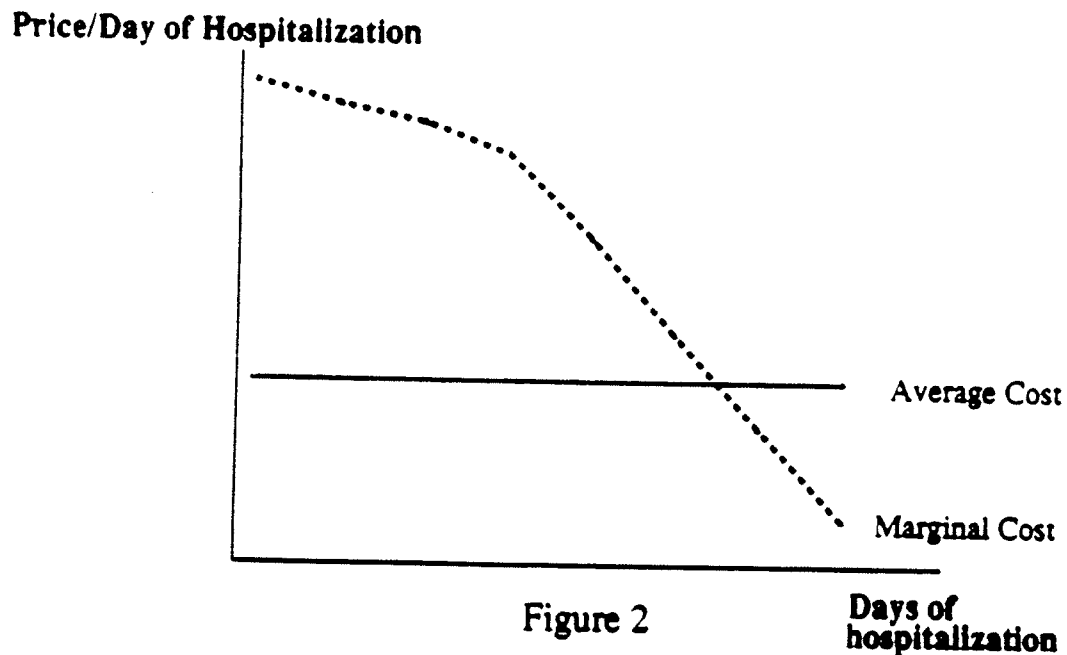


Figure 2

¹⁶ Inspired by Lewis N, 1992, p6.

2.7 What is an Outcome?

Outcomes are the effects, advantages, benefits, or consequences of an intervention, (e.g., effectiveness, security, tolerance, and superiority to a competing medication for the same price or equality to a competing medication at a lower price). Outcomes can be positive (i.e. advantages) or negative (i.e. disadvantages). As with costs, when we mention the term outcome, it includes: direct, indirect, and intangible outcomes.

Health outcomes can be expressed in three different manners, these may be:

- a) natural quantitative units, such as the number of lives saved;
- b) natural qualitative units, such as adverse reactions avoided, or intervention success/failure;
- c) pecuniary units, such as a country's currency.

2.8 What is a Utility?

According to the British philosopher J. Bentham, who first introduced the NOTION of utility:

"Nature has placed mankind under the governance of two sovereign masters, *pain* and *pleasure*. . . . The *principle of utility* recognizes the subjection. . . . By the principle of utility is meant that principle which approves or disapproves of every action whatsoever, according to the tendency which it appears to have to augment or diminish the happiness of the party whose interest is in question"¹⁷.

¹⁷ Hirschleifer, *Price Theory and Applications*, p59.

Utility can then be defined as an economic jargon that indicates the "quantity" of well-being of an individual, considering ceteris paribus (e.g., constant prices, constant individuals' tastes and preferences). A utility, therefore, indicates the preference direction of an individual (e.g., the desirability of (and/or preference for) a certain state), such as financial, job status, health, etc. Consequently, utility varies from one individual to another.

The utility THEORY, which has been developed by Von Neumann and Morgenstern in 1944, is a normative, quantitative, ordinal (not cardinal), and rational model for decision-making based upon uncertainty. It is a theory of "OUGHT" people do, rather than "IS". Consequently, it is not a behaviour model of decision-making under certainty because if it was, everybody could anticipate every individuals' behaviour in consequence to a certain stimuli.

The different utility measurement techniques that are currently being used, which are not necessarily based on the theory of Von Neumann and Morgenstern, are the standard gamble approach¹⁸, the time trade-off approach, and the rank and scale approach. Using the results of one of the various techniques permits the valuation and combination of various outcomes which generate a utility score. Usually, utility scores are on a scale of 1.0 (good health) to 0 (dead). The scale can also range in negative numbers if the individual considers his state worse than death. The utility measure is a valuable scaling method because it permits the use of estimates to compute quality-adjusted life-years¹⁹ gained (QALY) and health-related quality of life (HRQOL)²⁰ in order to measure cost-utility ratios.

¹⁸ *The standard-gamble approach is the only utility measurement, in my enumeration, which is explicitly based on the theory developed by Von Neumann and Morgenstern.*

¹⁹ *See definition in section 2.11*

²⁰ *See definition in section 2.12*

It is important to mention that, presently, no standard criteria have been established for measuring utilities. Many researches, nevertheless, are undertaken in this area in order to improve cost-utility studies. Even though cost-utility analyses are not yet perfect, according to G. Torrance of McMaster University (Ontario, Canada), "the utility approach is beyond the experimental stage and is now a viable alternative for investigators to use in measuring health-related quality of life (HRQOL)"²¹. Cost-utility studies, nevertheless, should be conducted AND trusted because of the important impact induced for the patient.

2.9 What is Quality of Life?

The expression **quality of life** is a vast notion that involves all facets of a human being's existence - including health. Quality of life analyses can relate the use of healthcare resources to various measures of the improved functioning and well-being of the patients, such as their social, psychological, mental, intellectual, physical and, general functioning and well-being. These measures are obtained through patient questionnaires. Quality of life analyses are conducted when a new intervention will not necessarily decrease the costs of treating the patient, but will enhance the patient's functioning and well-being.

Quality of life analyses are a partial economic evaluation, since they only examine the outcomes of the intervention, in a comparative manner or not. This method has been most frequently used in the evaluation of interventions for disabling diseases such as arthritis, and its use is expanding for many other diseases as well. As standardized tools continue to be developed, quality of life measures will become an increasingly important component of pharmacoeconomic analyses.

²¹ *Torrance, 1987, p593.*

According to Professor Williams, "quality of life measures should be more widely applied in clinical trials. Also, greater attention should be given to the collection of more broadly representative data on the relative values that people actually attach to different sorts of improvement in health"²².

2.10 What is Quality-Adjusted Life-Year (QALY)?

A **Quality-adjusted life year** is a common measure of utility employed in cost-utility analyses. It has the advantage of combining changes in mortality and morbidity factors in a single measure that reflects tradeoffs between them.

Quality-adjusted life-years calculates the extra year of life achieved by a successful intervention discounted by the patient's degree of disability and distress. "Since an intervention that adds one year of good/excellent health is more appealing than one that adds one year of poor health, expressing outcomes in quality-adjusted life-years is useful because it perceives the discrepancy between these two different interventions which both add one year of life, without the same repercussion"²³.

2.11 What is Health-Related Quality of Life (HRQOL)?

Health-related quality of life (HRQOL) is becoming an important measure of utility used in cost-utility analyses. It is a subset of quality of life which considers only the **HEALTH** aspects of human beings (e.g., it excludes the aspects which are unlikely to be influenced by health interventions, such as social status, education, job satisfaction, etc.). As mentioned above, the utility approach can be employed to measure a single cardinal value (which is usually between 1 and 0, but can also range into negative values) that indicates the health-related quality of life of the person at a particular point in time.

²² *Scrip*, Nov 1989, p9.

²³ *Reference unknown.*

Health-related quality of life analyses can support pharmaceutical companies in the regulatory approval procedure (for marketing objectives) and also assist healthcare professionals and managers in the decision-making process about the different medication therapies. Health-related quality of life analyses thoroughly inform physicians about the intervention's outcomes and risks on the patient's physical, psychological, social functioning and well-being. The health-related quality of life measure definitely represents a significant indicator of the intervention's outcomes.

2.12 What are Clinical Trials?

Clinical trials are currently used to evaluate clinical endpoints, i.e., determine the efficacy and safety of therapies. These trials, however, can provide data for an economic evaluation. Economic and clinical endpoints can, therefore, be measured simultaneously during the trial. An elaboration of the relationship between clinical trials and pharmacoeconomic studies will be discussed in section 6.0.

One caveat about clinical trials is that the results obtained from them are clinical evidence rather than practical evidence. The clinical evidence of the efficacy and safety obtained from a clinical trial is based on the results of the intervention's application to a specified patient sample under controlled conditions. They generate theoretical results which are referred to as "efficacy". These results may differ under normal (non controlled) conditions; meaning that the evidence is not obtained under a controlled environment. The results obtained under normal conditions are referred to as "effectiveness".

Factors such as the patient sample, the compliance of the patient and of the prescriber are some of the many fundamental aspects which distinguish clinical evidence from practical evidence. First, the patient sample of a clinical trial is chosen with great attention, whereas in reality, the patient population to whom the treatment is applied may differ in several respects. Second, in a clinical trial, there is a follow up in order to make sure that the patient is compliant to the therapeutic regimen, whereas in reality this

may not be the case. Finally, before beginning a clinical trial, the environment is analyzed; for instance, the choice of the research physicians is based on highly specific criteria. In reality, the physician should respect the conditions of the manufacturer which are based on the clinical evidence; however, it is not assured that the prescriber will be compliant.

As mentioned in section 2.15, effectiveness is the relevant outcome to be included in economic evaluations, however, effectiveness is more difficult to measure than efficacy. Consequently, this is why many evaluations are based upon clinical trials which give an insight of the effects of the intervention.

2.13 What is a Discount Rate?

Inflation essentially revalues the dollar. Consequently, most people believe that discounting is due to inflation because inflation decreases the buying power (e.g., in other words, they believe that the purpose of discounting is to convert future costs and outcomes into current ones).

What is often misunderstood is that inflation is not the genuine reason for discounting future costs and outcomes. Even when inflation has been taken into account, the value of a cost or an outcome today is not equal to the future costs or outcomes since, in general, most people would prefer to have something today instead of having it in the future. To be indifferent, they would want more if they had to wait to have it. The genuine reason, hence, is that individuals normally prefer to have money in the present rather than in the future since a dollar not spent can be invested productively to yield a larger quantity of real dollars in the future. The discount rate represents in this case, the opportunity cost of holding money.

Discounting is, therefore, not because of inflation, but because of the opportunity cost. The rate by which future outcomes and costs are discounted is described as the social rate of time preference.

Time plays an important factor in economic evaluations of healthcare since all costs and outcomes rarely occur at the same time, particularly for screening or preventive programs. The appropriate use of discounting procedures is then essential for the adjustment of these temporal discrepancies in order to combine present and future costs and outcomes in comparable units.

Although economists agree that costs should be discounted, controversies are first about the rate at which it should be discounted; however, a certain consensus lies that the social rate of discount should range between four and eight²⁴. The second controversy is about the discounting of outcomes. Every outcomes should be discounted, even future life years saved. The reason for discounting future life years saved is not that life years can be invested to yield more life years as dollars can be invested to yield more dollars, nor because life years in the future are less valuable than life years today. Rather, the reason for discounting future life years is because they are being valued relative to dollars and, since a dollar in the future is discounted relative to a present dollar, so must a life year in the future be discounted relative to a present dollar.

2.14 What is a Sensitivity analysis?

Since cost and outcome values can both fluctuate, and some of their aspects can be difficult to compute, a process determining how sensitive the results are to some specific "sensitive" parameters should be undertaken. This method is called **sensitivity analysis**.

This method (sensitivity analysis) allows the analyst to vary systematically the values assigned to the most uncertain features and assumptions in the economic evaluation's calculations (for example, probability of intervention success, costs of medications, discount rate), over a range of possible values. If the basic conclusion does not change when a particular feature or assumption is varied, there can be confidence in

²⁴ *Many economists agree to use 5% as the social rate of discount.*

the conclusion. If instead, the conclusion is sensitive to variations in particular features or assumptions, further research to learn more about the features/assumptions may be especially valuable. Sensitivity analysis can, therefore, suggest areas where further research may be needed. Sensitivity analysis thus provides a powerful tool by which analysts can see how robust their conclusions are, and identify which variables could affect their recommendations.

The conclusions of an economic evaluation that rests on uncertain data and subjective values, are bound to be interpreted as too definitive by some, even with all possible sensitivity analyses; critics of economic evaluations argue that this uncertainty renders useless any attempts to quantify the outcomes of medical interventions. Despite warnings that the conclusions must be updated as new evidence becomes available, users of an analysis tend to apply its conclusions to initiate programs that then build up their own momentum and become difficult to alter. Flexibility for change must be maintained. Nevertheless, decisions regarding the allocation of resources must be made and the choice is often between relying upon a responsible analysis, with all its imperfections, or upon no analysis at all. The former, in these times of increasingly complex decisions, difficult tradeoffs and limited resources, is by far the preferred choice.

While more healthcare professionals are becoming aware of pharmacoeconomics - and some are even involved in these studies - many more of them will rely on published studies as a guide in selecting interventions. Thus, the ability to recognise the validity of a study is imperative to wise decision-making.

2.15 What is the Difference Between Efficacy, Effectiveness and Efficiency?

- **Efficacy** is the evidence of outcomes from clinical trials conducted in ideal circumstances. Efficacy is one of the objectives of a classic clinical trial.

- **Effectiveness** is the true benefit which can be expected in clinical practice. Usually, effectiveness is influenced by factors such as the patient sample who receive the medication, the duration of therapy and the convenience and acceptability of the medication compared to alternative interventions. Effectiveness is the relevant outcome to be included into economic studies.

- **Efficiency** is when the desirable level of effectiveness is reached with the optimal allocation of resources. The underlying premise of efficiency is that for any given level of resource available, society (or the decision-making jurisdiction) wishes to maximize the total outcomes. Alternatively, for a given outcome goal, the objective is to minimize the cost of achieving it. These criteria, in economics, are called respectively "mini-max" and "maxi-min". In either formulation, the methodology is the same. Outcomes and costs must each be expressed in terms of some common unit of measurement: costs are always measured in the country's currency and outcomes may be expressed in a variety of ways.

3.0 WHAT ARE THE PRIMARY GOALS OF AN EVALUATION

The primary goals of an evaluation, no matter its field of application, are²⁵:

- 1) To help with the planning and launching of an intervention (strategic goal);
- 2) To provide information in order to improve an on-going intervention (formative goal);
- 3) Determine the effects of an intervention in order to determine if the intervention should be maintained, transformed in an important manner, or discontinued (summative goal);
- 4) Contribute to the advancement of the know-how, to the theoretic elaboration (fundamental goal);

Furthermore, other goals that are considered important are:

- 5) To determine if a specific intervention is an efficient allocation of resources by gathering data in a methodical framework;
- 6) To identify which criteria can be useful in selecting the best use for scarce resources;

Finally, it can be concluded that the bottom line of an evaluation is to help the decision-making process. These six goals are worthwhile for sponsoring pharmaceutical companies, governments, healthcare professionals, influential associations, etc.

²⁵ *Geneviève Tessier, personal communications.*

4.0 WHAT ARE THE DIFFERENT TYPES OF ECONOMIC EVALUATIONS?

The most important types of complete pharmacoeconomic analyses are: cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost-utility analysis (CUA). Many think that risk-benefit studies are categorized as pharmacoeconomic studies when in fact they are pharmacoepidemiologic studies. Below are the definitions of the terms mentioned above.

It should be noted that the method for identifying and measuring costs is parallel for all types of economic evaluations, however, the distinguishing characteristic of these evaluations is the procedure by which the outcomes are measured and assessed.

4.1 Cost-minimization analysis:

Cost-minimization²⁶ analysis has a central assumption: the outcomes of each interventions analyzed are considered identical. Cost-minimization analysis, therefore, only asks the question: What are the costs of the different potential interventions that could be incurred because of the disease/illness?.

In a cost-minimization analysis, the outcomes of two or more relevant alternatives are compared and perceived to be the same²⁷. When considerable clinical evidence suggests equality of the outcomes among the alternatives, cost-minimization analysis allows one to only evaluate the costs of each intervention. Due to the equivalent outcomes, the evaluation strives to find the least expensive intervention for accomplishing the desired outcome. Consequently, cost-minimization analysis is only appropriate when

²⁶ *Cost-minimization analysis is also frequently expressed as cost-identification.*

²⁷ *Different types of outcomes (efficacy, side effects, etc) which are measured in different units, can be involved as long as everyone of them is achieved to the same degree by the various alternatives. Some efforts should be made to verify the assumption of identical outcomes through a literature review or through a theoretical argumentation.*

alternative interventions have been found to have identical outcomes but differ in costs.

Cost-minimization analyses are frequently perceived as partial economic evaluations because only the costs are evaluated. Some may wonder how cost-minimization analysis differs from cost analysis. In practice, if the outcomes of the alternatives are identical, then there is no difference in the techniques: only the costs are assessed. In theory, however, a full economic evaluation requires that both costs and outcomes be assessed. It is only when the outcomes are compared and perceived to be the same, or the outcome differences of the alternatives are considered unimportant, that the analyst can decide not to include the outcomes into the study; the study becomes a cost-minimization analysis. If the analyst decides that he will only analyze the costs, hence, not consider the outcomes, then the study becomes partial: a cost study.

The major focus of cost-minimisation analysis, as mentioned above, is essentially to determine which intervention is the least costly. Due to the strict requirements of therapeutic equality, cost-minimisation analysis is not commonly used to assess medical interventions. Nevertheless, this method can be useful to assess the cost difference among dosage forms of the same medication or among generically equivalent medications for which patient outcomes have proven equal. Cost-minimisation analysis can be a useful tool when it is used appropriately; however, if there is any uncertainty regarding the equality of the outcomes, a more exhaustive evaluation, such as a cost-effectiveness/benefit/utility analysis, should be conducted.

An example of a cost-minimisation analysis, is the comparison of a generic medication versus a brand name. The use of a generic medication is frequently a cost-minimisation strategy since it can produce the same outcome as using a brand name one with a significant lower price.

4.2 Cost-effectiveness analysis:

Cost-effectiveness measures the net cost (expenditures minus savings) of providing a service as well as the outcomes obtained. Cost-effectiveness analysis is appropriate when alternative interventions differ in clinical effectiveness but can be examined from similar therapeutic health outcomes (which are not expressed in pecuniary terms), such as life-years, QALY's gained, unit of success, etc. The output of a cost-effectiveness analysis is a cost per (quantitative) outcome, such as cost per life year saved, cost per patient treated, etc. Cost-effectiveness considers only a single quantitative outcome. This outcome must be highly relevant to the intervention evaluated; it must be common to the alternative interventions and must represent their main outcome.

The advantage of cost-effectiveness is that it can consider the possibility of exchanging improved outcomes for the use of more resources. Since outcomes are measured in non pecuniary terms, COST-EFFECTIVENESS INTERVENTIONS ARE NOT NECESSARILY THE LEAST EXPENSIVE INTERVENTIONS, rather, they are the one which best achieve the desired outcome at a minimum, acceptable cost. An intervention can be considered cost-effective if it is:

- a) Less expensive and at least as effective as other interventions;
- b) More expensive than alternative interventions but the additional outcomes are worth the additional costs;
- c) Less expensive and less effective when the extra outcomes provided by the competing interventions are not worth the additional expense.

Cost-effectiveness analysis can be used to evaluate therapies, programs or services. For instance, pharmacists/physicians can use this method to evaluate different antibiotics used to treat the same infection. The cost of purchasing, preparing, administering and monitoring each antibiotic can be identified, as well as the treatment costs of adverse events, intervention failures, and additional hospital days.

A key distinction between cost-benefit and cost-effectiveness analysis is that a cost-benefit analysis must value all outcomes in pecuniary terms (e.g., canadian dollars), including lives or years of life and morbidity. Cost-effectiveness analysis places priorities on alternative expenditures without having to assess the dollar value of life and health.

A typical example of cost-effectiveness analysis is the comparison between a renal transplantation and dialysis. In this example, the renal transplantation is more efficient than using dialysis²⁸.

4.3 Cost-utility analysis:

Cost-utility analysis is an extension of cost-effectiveness analysis in which the common measure of effectiveness is intended to capture the effects of mortality as well as the effects on quality of life (the multidimensional aspects of morbidity); whereas cost-effectiveness analysis combines mortality and a unique dimension of morbidity. The outcomes considered incorporate the patient's perception of the intervention's impact on quality of life, in addition to its impact on clinical parameters or years of life. The common outcome measure, therefore, takes into account changes in survival and health-related quality of life (e.g. days of well-being or quality-adjusted life-years). The advantage of cost-utility analysis is that it incorporates a common measure of effectiveness across all alternative approaches to a single healthcare problem and across all healthcare problems. Cost-utility analysis is particularly important when:

- a) a spectrum of health outcomes are important;
- b) the quality of life is the single most important outcome;
- c) the quality of life is one of the most important outcomes;
- d) morbidity and mortality are important outcomes and a single measure of effect is desired and;

²⁸ *Croxson BE, Ashton T, 1990*

e) a program is to be compared to another whose cost-utility is already established.

Cost-utility analysis, hence, will be appropriate when quality of life concerns are the most important outcome and when morbidity and mortality concerns need to be assessed simultaneously.

As mentioned above, cost-utility is a method that accounts for effectiveness while integrating patient preference and satisfaction. This method, unlike cost-effectiveness analysis, evaluates outcomes not only for the associated monetary costs but for the added costs of patient discomfort or, change in function or, level of satisfaction. For instance, postoperative nausea and vomiting are of concern in cost-effectiveness analysis because of the added cost involved in their intervention. Comparatively speaking, cost-utility analysis evaluates nausea and vomiting not only for the additional cost of intervention but for the impact they have on the patient's life.

Almost all physicians would agree that, at some point, the extra money spent for poor improvements in clinical outcomes are not worthwhile and represents inappropriate practice. The money misspent could have been devoted to medical care that would achieve greater outcome or to some other more meaningful social purpose. This is one of the reasons why cost-utility studies should be conducted.

An example of cost-utility analysis, is the comparison of a renal transplantation versus dialysis²⁹. In this case, the renal transplantation increases significantly the quality of life of the patient. A renal transplantation is, therefore, not just cost-effective, but also cost-utility. Some studies have even shown that transplantation is a cost-benefit intervention³⁰. Renal transplantation is consequently a highly efficient solution compared to dialysis.

²⁹ *Morris PL, Jones B, 1988*

³⁰ *Guzzanti E, Picca S, 1989.*

4.4 Cost-benefit analysis:

A cost-benefit analysis differs from the other types of economic evaluations because it quantifies both costs AND outcomes in pecuniary terms. It requires that outcomes, such as lives saved, or years of life gained, also be valued in pecuniary terms. Contrary to a cost-effectiveness analysis or a cost-utility analysis, the output of a cost-benefit analysis does not necessarily have to be a ratio, it can also be a net actual value (NAV).

Although cost-effectiveness/utility analyses are useful to decision-makers, they do not explicitly assess whether the outcomes are worth the costs. Cost-benefit analysis takes the analysis beyond measuring effectiveness in clinical terms or abstract concepts, such as utilities. Cost-benefit analysis has the advantage over the other types of economic evaluations in that it allows the computation of the net outcomes of an intervention; thus, the intervention with the greatest net benefit/least net cost is the most preferred. Consequently, cost-benefit analysis is a valuable tool for providing guidance on the most appropriate allocation of resources.

Cost-benefit analysis has been applied in many health contexts. To value life years, time lost from work, and quality of life in dollars, the traditional approach is to use the value of a productive year of life. The rationale is that society, including the individual in question, will lose potential consumption of goods and services in proportion to lost productivity. This method, however, is often criticized. Some favour, as alternatives, the assessment of an individual's willingness to pay (WTP) (or willingness to accept (WTA)) to reduce (increase) the probabilities of death and disease, and/or of the imputation of the added wages that workers in hazardous jobs require as compensation for their risks. The human capital method is another popular method for evaluating the indirect valuation of production gains or losses of an individual.

Cost-benefit analysis is practical for comparing the value of two or more interventions which have different costs and outcomes. Since outcomes (benefits) and costs are expressed in common currency, different comparisons can easily be done. Cost-benefit analysis can also be used to evaluate the value of a single intervention: if the cost-benefit ratio is inferior to one, then the intervention is worth undertaking. Interventions for which the cost-benefit ratio is greater than one may also be worth undertaking, provided that the intervention yields an improved quality of life for the patient.

Another advantage of the cost-benefit framework is that it leads to a positive or negative (or null) value for each intervention and, therefore, it does not require knowledge of a cost-effectiveness cutoff level to decide whether a particular intervention should be undertaken or not.

The result of a cost-benefit analysis may be expressed as a ratio (cost/benefit) or in terms of net costs or benefits. When all the outcomes are converted to pecuniary values, the cost-benefit ratios or the net costs can be directly compared so that the alternative with the least costs or greatest outcomes can be chosen. For instance, by converting outcomes to pecuniary values, cost-benefit analysis will allow a pharmacy department to compare the costs and outcomes of initiating an antimicrobial-monitoring service (outcome = number of intervention successes) with those of hepatitis B cases avoided. Cost-benefit analysis is particularly useful when resources are limited and only ONE program can be implemented.

ATTENTION: be careful when you read a cost-benefit ratio, do not only look at the end result (i.e., 0.673 or 1.759). The numerator and denominator should be verified because there are no standards regarding whether the ratio should be cost-benefit or benefit-cost!

Although all these features of cost-benefit analyses seem very enchanting, cost-benefit analysis is rarely the technique of choice because it requires that mortality and

morbidity features be valued in pecuniary units, which is highly difficult; mostly, it engenders many philosophical and ethical debates regarding the price (cost) associated to mortality and morbidity.

An example of cost-benefit is Isotretinoin versus the conventional combination of antibiotics and topical therapies for the treatment of severe nodulocystic acne. The results show that Isotretinoin is cost-benefit³¹.

There is a difference between cost-benefit/cost-utility analysis and cost-effectiveness/cost-minimisation analysis. In the cost-benefit/cost-utility study, we question whether or not the intervention should be undertaken. These studies are performed to see if the intervention is worthwhile. In the cost-effectiveness analysis/cost-minimisation analyses, we do not question if the intervention should be undertaken or not. We know that the intervention should be done. In these type of analyses, the question we ask is which intervention should be chosen to warrant the most efficient solution.

It should be noticed, however, that price is only a small part of determining a cost-benefit/effectiveness/utility analysis. A more expensive product may prove to be less expensive to use if it has a longer wearing time or better patient outcomes, etc.

4.5 Risk-benefit analysis:

Risk-benefit analyses are a technique for combining the risks and outcomes to human health and reporting these impacts in a way that facilitates judgement about the balance of risks and outcomes to the population. These analyses, as mentioned above, are not economic analyses, rather, they are epidemiologic analyses because they answer the question of safety and efficacy while economic analyses do not answer such questions.

³¹ Lee ML, Cooper A, 1991

5.0 WHY ARE PHARMACOECONOMIC EVALUATIONS IMPORTANT?

The interest in the use of pharmacoeconomic analyses stems from the growing realization that we live in a world of scarce resources and that the fundamental economic problem of society is to allocate these resources in a way that will best satisfy human wants. Health is perhaps the most basic human want but it is still only one of many competing wants. Neither this society nor any other can allocate to healthcare all the resources that physicians and other healthcare professional believe might benefit their patients. What can then be done? Given a wide range of potential choices in the use of healthcare facilities, personnel, and technologies, decision-makers clearly need a better understanding of the consequences of the various alternatives.

It is now almost universally understood that the resources available to meet the demands for healthcare are limited. This fact was not perceived to be so a few decades ago because medical technologies had not proliferated to the extent it has today and, health insurance was not as broad. Throughout the years to come, the development of new medications will be stimulated by an increased understanding of disease processes and the application of biotechnologic discoveries. The use of these new clinical agents in practice will be increasingly determined not only by their effectiveness but also by the cost of the technology.

The rising cost of healthcare will force decisions to be made regarding both the effectiveness of the technology and the overall cost implications, since historically, Canada's healthcare system has emphasized improvements in the quality and scope in healthcare. Canada's healthcare system, incidently, is one of the best systems in the world, however, health expenditures are growing faster than government budgets and faster than the growth of the economy as a whole. As a result, there is increasing concern about the percentage of the national wealth consumed in healthcare.

Increasing attention is being devoted towards the consideration of the economic value in medication usage. This is due to several factors which include the spiralling costs of healthcare and the resulting emphasis on cost containment. In 1987, Canada spent \$45 billion on healthcare, representing about 8.6% of the nation's GNP (Gross National Product)³². In addition, the total expenditure by Canadians on medications was \$5.5 billion, \$2.8 billion was for prescription medications.

There are over 17 000 pharmaceutical products registered with the federal government³³, of which approximately 57% are non prescription products, 30% are prescription and prescription-like medications for human use, and 13% are products for veterinary use. According to the PMAC (Pharmaceutical Manufacturers Association of Canada), the Canadian pharmaceutical industries' expenditures on R & D were approximately \$200 million in 1990.

The cost of medications and pharmacy services have become an important issue to patients, third-party payers, and governments. The basic value of medication therapies to prescribers and patients in Canada is illustrated through the increased therapeutic use of prescriptions. Medications available without prescription (Over The Counter (OTC)) also serve an important role in Canada's healthcare system. Their use in this country, over the past number of years has greatly increased. These figures may be indicative of the value and perceived benefit that society attributes to medications. Pharmaceutical and other therapeutic interventions have contributed to the important progress being made in the health status of Canada corresponding to the introduction of new medication entities during the past two decades. In 1989, over 700 patented medication products were being sold in Canada.

Medications have played a major role in declining death rates for many diseases. In addition, improvement in quality of life and life expectancy has occurred with the

³² See Appendix III.

³³ P.M.P.R.B., 1987

introduction of medications to treat diseases or illness such as, infections, cancer, and cardiovascular diseases. Current cost-containment pressures in the healthcare system have forced hospitals and other healthcare institutions to look for ways to reduce operating budgets. Due to the nature of the expenditures associated with pharmacy operations, it appears that significant savings could easily be generated simply by using the cheapest therapeutic alternatives. Medications have produced important improvements in the health of the Canadian's population and because the cost of prescription medications represents only, in 1992, 16% of the total healthcare costs in Canada, focusing only on medication expenditures in the healthcare system may be an inappropriate way to save costs. In addition, economic analyses are beginning to show that the least expensive intervention is not inevitably the most economical in the long run. "A number of challenges lie ahead, but perhaps the most important is to ensure that questions of efficiency are not lost in the search for cost containment."³⁴

A common strategy of manufacturers in the past concentrated on the acquisition cost of a product. Cost-effectiveness does not mean low acquisition cost. There are other factors that can influence efficiency far more dramatically than acquisition cost. Critical areas in evaluating pharmacoeconomic evaluations include: length of therapy, therapeutic failure, patient's compliance, patient satisfaction, therapeutic success, and many other factors.

An important question which is frequently addressed is: how can the economic effect of an intervention be considered in addition to its therapeutic effects? The emerging field of pharmacoeconomics addresses this and other questions. Pharmacoeconomic analyses provide a mechanism by which the total costs of an intervention can be compared to its therapeutic outcomes. They allow the relative economic and therapeutic outcomes of one medication to be compared with those of others. Pharmacoeconomics is a useful tool to select a medication or another medical intervention, whether decisions are being made on an individual patient basis or for an

³⁴ *Evans DB, 1992, p6.*

entire population.

According to Dr. Joel Hay³⁵, pharmacoeconomic evaluations are here to stay because:

- a) healthcare cost containment is a major priority;
- b) pharmacoeconomic evaluation is a non controversial approach to cost containment;
- c) providers and consumers both benefit when efficient technologies are used.

This is why pharmacoeconomic evaluations become important.

³⁵ *Presentation at the 1991 DIA meeting in Washington.*

6.0 DOES EVERY MEDICATION NEED AN ECONOMIC EVALUATION?

According to Catherine Tak Piech³⁶, Director of Health Economics at Sandoz U.S.A., many factors should be considered in order to decide first of the relevance and second of the extent of an economic evaluation. The principle factors are:

- The primary current therapy the medication is displacing;
- The degree of payer shifting caused by the medication;
- The degree of scientific advance the medication represents;
- The type of market the medication faces;
- The primary function of the medication;
- The length of time before the medication's benefits are realized;
- The source of concentration of payment for the medication;
- The level of public interest in the medication;
- The medication's level OR serious side effects;
- The intervention setting in which the medication is primarily used;
- The medication's dosage form compared to what's already available;
- The degree of difficulty in measuring the end outcome;
- The age of the targeted patient population.

Consequently, by the enumeration of these factors, it is rational to conclude that not every medication needs a comprehensive ("full blown") economic evaluation nor any extent of an economic evaluation.

³⁶ Piech 1990, Sandoz U.S.A. Inc. internal document.

7.0 WHAT HEALTH ECONOMICS CAN AND CANNOT DO?

According to C. Tak Piech³⁷, health economics and its results can be a useful tool, however, the power of this analytical tool should not be overstated. Below are the "can and can't's" of health economics.

7.1 What Health Economics Can Do?

According to C. Tak Piech, what health economics can do for you is:

- Clarify to all relevant parties the true financial impact of medication therapies;
- Lobby for additional corporate resources;
- Build contacts and relationships with multidisciplinary leading researchers in the field;
- Design, place, coordinate, and assure quality of economic evaluations in the field;
- Work with you on effective promotion and dissemination of completed studies;
- Support pharmacies with information needed to further their own resource needs.

Furthermore, what health economics can do for you is:

- Recognize the scarcity of resources and the principle that decisions should depend on outcomes obtained as well as outcomes foregone;
- Offer a framework in which value judgements can be made explicit;

³⁷ Piech 1990, Sandoz U.S.A. Inc. internal document.

- Force one to be explicit about the beliefs and values that underlie allocation decisions³⁸;
- Embody a systematic approach to decision-making, as opposed to "muddling-through";
- Enables decision-makers to test the implications of each decision against all the objectives that they set themselves;
- Be a key to better decision-making;
- Offer a method of critical thinking, of approaching choices and often placing difficult choices in the open for discussions;
- Improve the quality and consistency of decision-making;
- Generate quantitative statements about the value of program costs and outcomes;
- Generate frameworks for comprehensive identification and display of economic factors involved in decision-making;
- Be an analytical tool to arrive at pricing decisions.

7.2 What Health Economics Cannot Do For You?

According to C. Tak Piech, what health economics cannot do for you is:

- Say yes or no to everything and everybody;
- Allow standards to be low;
- Let priorities be driven by anything but a realistic assessment of need and potential;
- Suppress unfavourable findings;
- Use statistics to deny the obvious;
- Defy the law of good and cheap;
- Be a panacea for all marketing challenges.

³⁸ *Opposing points of view can be clarified in terms of specific disagreements over assumptions, probability estimates or value tradeoffs.*

Furthermore, what health economics cannot do for you is:

- Be an umbrella to cover high prices;
- Be the total basis for decision-making³⁹;
- Be a magic formula for removal of judgement, responsibility, or risk from decision-making activities.

³⁹ *There are other criteria than efficiency that can be the basis of the decision-making, such as equity, ethics, politics, environment concerns, etc.*

8.0 THE RELATIONSHIP BETWEEN CLINICAL TRIALS AND PHARMACOECONOMIC EVALUATIONS

Increased pressures on healthcare budgets in most industrialized countries have emphasised the need to demonstrate the money value from health technologies. As part of this general change in the environment for the provision of healthcare, most major pharmaceutical companies are beginning to commission pharmacoeconomic analyses of their products. Pharmaceutical manufacturers are becoming highly aware that pharmacoeconomic analyses are influent for the acceptance of their products on the hospital and provincial formularies, and towards the P.M.P.R.B. (Patent Medicine Price Review Board). There is, therefore, a certain analogy between clinical trials, which are required for product licensing, and economic evaluations, which are perceived as being useful for securing adequate prices, reimbursement status, and for marketing of products.

The application of health economics has attracted an unprecedented amount of attention during the 1980's. Greater recognition has been given to the importance of examining the economic and social implications of such interventions in concert with clinical outcomes of medical care.

Presently, randomized clinical trials are used to evaluate efficacy and safety of therapies. However, these trials can also be employed to collect data to undertake an economic evaluation, since they provide facts which would probably not be available otherwise (e.g., number of visits to the physician, duration of absence from work, and information on patient functioning that may be used in the measurement of health status)⁴⁰. An economic study should not impose much of a burden on clinical trials since various variables required for the economic study are available in the trial protocol; those variables that have to be added are usually simple and, most of the time, are not time consuming for the physician or the nurse.

⁴⁰ Hertzman, 1987, p6.

Economic and clinical endpoints can, therefore, be measured simultaneously during a clinical trial. The three possible relationships between clinical trials and pharmacoeconomic evaluations are:

- 1) the economic evaluation may be a secondary objective of a clinical trial designed fundamentally for safety and efficacy;
- 2) the economic evaluation may be the principal goal of the clinical trial;
- 3) the economic evaluation may be done retrospectively with the clinical data obtained from previous trials.

Usually, trials for economic evaluations have different interests than traditional clinical trials in two respects:

1) the economic evaluation is concerned with additional and different outcomes of clinical trials. Although a traditional clinical trial primarily focuses on medical indicators (e.g. blood pressure and temperature), the clinical study with an economic evaluation can also determine the effects on some factors such as the resource consumption, productivity or quality of life.

2) a trial with an economic evaluation is more concerned about inferring what happens under real-life rather than controlled conditions. In other words, the economic study is more interested in answering questions relative to its effectiveness as opposed to efficacy.

Consequently, due to these differences, the intensive clinical monitoring that is part of a clinical trial is not essential in an economic trial. Other design aspects of a clinical trial, however, are important in an economic evaluation, (such as the specific patient selection criteria, random assignment, blind clinicians and patients), in order to guarantee appropriate validity and reliability of the trial.

Notice that, because economic evaluations are inputs to the decision-making process, rather than clinical ones, they should NOT be conducted with less attention to scientific rigor than clinical studies.

According to Pennifer Erickson⁴¹, the order in which the questions are asked is very important; the results can vary depending on whether the question is asked at the beginning, in the middle, or at the end of the questionnaire. Also, it is important to well address the questions, hence, performance questions should be asked rather than capacity questions. For instance, you should ask the question: "did you drive your car ...?", which is a performance question, rather than: " could you drive your car ...?", which is a capacity question.

A question which is repeatedly brought up is: when should pharmacoeconomic studies be planned and conducted. The answer is: pharmacoeconomic studies may be planned and conducted at any phase of the clinical development stages and/or at the Phase IV stage of postmarketing; however, the IDEAL time to evaluate economically an intervention is before its widespread introduction into clinical practice, preferably at the same time the randomized controlled trial is conducted, in order to measure its clinical efficacy or, shortly after. This is rarely done PRESENTLY and there are many reasons why. First, economic data are not required presently for the approval or licensing of most medications and nonpharmaceutical technologies, and therefore, there is presently no incentive for manufacturers to perform or encourage such studies, since they might indicate that the new technology is relatively cost-ineffective. Many physician researchers are interested solely in the clinical endpoints of the technology but not in the costs. Adding an economic evaluation to a clinical assessment can be expensive in terms of expertise and personnel, therefore, there is a reluctance to perform an economic study before the clinical efficacy of the technology has been established. Only once the technology is found to be effective that the manufacturer will begin to think of including economic parameters into the next protocol. Consequently, like resources for the

⁴¹ *Presentation at the 1991 DIA meeting in Washington.*

healthcare system itself, funds to undertake an economic study can add considerable costs to a clinical study and it would be unfeasible to perform a comprehensive ("full blown") economic evaluation on all new technologies. Nevertheless, pharmaceutical manufacturers being aware of the fierce competition, should always perform an economic evaluation for most new technology, no matter its extent, IF they wish to position their products.

Studies designed to evaluate the costs of illness/disease and costs associated with current interventions can begin in phases I and II. Economic evaluations and costs associated with toxicities and intervention failures can begin in phase III, however, because phase II trials are rigidly controlled, much of the pharmacoeconomic profile of a medication will be generated after the medication is marketed. Once a medication is marketed (phase IV), either retrospective or prospective pharmacoeconomic studies may be designed and conducted using pharmacoepidemiologic and pharmacoeconomic methodologies.

Pharmacoepidemiologic studies are frequently used to further the study on the efficacy and safety of the medication. Epidemiologic data about the disease/illness and interventions under investigation can yield highly important information in the economic evaluation of a specific medication therapy. Understanding the natural progression of the disease and intervention enables one to estimate variables that may have pharmacoeconomic implications for cost of illness and quality of life analyses.

In short, beyond the elements of a well-defined clinical trial, the additional elements in a pharmacoeconomic study are to monitor or estimate:

- 1) consumption of health service and other resources (direct costs and outcomes);
- 2) productivity through morbidity and/or premature death (indirect costs and outcomes);
- 3) the impact of the disease/illness and of the intervention on quality of life features of the patient.

Pharmacoeconomic data are becoming increasingly important to practitioners making medication formulary decisions. It is important to have this data as soon as possible after approval by the HPB (Health Protection Branch). Consequently, to do this, discussion and planning for pharmacoeconomic evaluation should begin during the early stages of the medication development.

Economic evaluations differ from clinical trials conducted at academic centres subject to governmental regulations. First, in contrast to clinical trials, economic evaluations generally use data and analytical methods of varying degrees of precision and power that are usually unstandardized, rather than standardized designs and analytic techniques used under the strict scrutiny of an external regulatory agency. Also, economic evaluations involve subjective opinion and interpretation about what the results demonstrate, rather than limiting themselves to narrow conclusions about safety and efficacy.

Second, in contrast to clinical trials, economic evaluations are not assigned to a determined department in a pharmaceutical company. It is well known that clinical studies are the responsibility of the medical department, however, it is yet not established which department should be responsible of health economics. There are three possibilities for where health economics should be: medical department, marketing department, or scientific development department. There are pros and cons for each alternative⁴², however, since within five years many pharmacoeconomic studies should be done in a prospective manner, and other reasons discussed in Appendix IV, medical and mostly scientific development should be responsible of these studies.

Scientific development department should be responsible of the prospective economic studies before the clinical trial, in order to include the economic parameters within the clinical trial. While the clinical and economic study is being conducted, medical department should be responsible of the monitoring since they already monitor

⁴² In Appendix IV, the advantages and disadvantages of locating the coordination functions of pharmacoeconomics in either medical, marketing or scientific development are listed.

the clinical study. Once the clinical trial is completed, the responsibility of the economic evaluation should then be transferred to the scientific development department, alongside a pharmacoeconomic steering committee, since the products that will be evaluated economically will mostly be the ones "in the pipeline", i.e., the ones who are being processed to receive their NOC (notice of compliance).

The principal mission of formal health economics is that it forces one to be explicit about the criteria that underlie allocation decisions. Point of views are frequently conflicting concerning the assumptions, probability estimates, value tradeoffs, etc. To simplify such studies, accurate data on the efficacy and costs of health interventions are imperative. The design of clinical trials and observational studies should take this perspective into account. Clinical trials are clearly an important vehicle for assessing the efficiency of medicines since they have to be performed for other purposes and offer the possibility of controlled evaluations.

9.0 HOW DO ECONOMIC EVALUATIONS RELATE TO ETHICS AND POLITICS?

According to Laupacis, Feeny et al.⁴³, the introduction of a new technology is influenced by a combination of effectiveness, economics, ethics and politics. The relative impact of each parameter depends from a situation to another one. Pharmacoeconomic analysis is not the solution to all. Economic evaluation methodologies were originally created to aid decision-making in the public service sector where the market force of supply and demand do not necessarily apply. These situations include decisions for such items as bridge building and free vaccination programs. More and more, economic evaluations' concepts are being applied to various segments of society such as individual hospitals and specific patients. When economic evaluation pertaining to healthcare was originally considered seriously, the only perspective considered was that of society as a whole. When the methods are applied to smaller, more focused areas, other issues and perspectives must be considered such as who incurs the costs and who receives the outcomes. For instance, under the medicare program of a country, it may be efficient for a hospital to use a medication that allows the patient to be discharged earlier to the nursing home; however, this early discharge may become costly to the family that now must pay the nursing home cost.

Economic evaluation FIRST satisfies the EFFICIENCY criteria, however, it can also strive to include other criteria (objectives) such as equity, environment protection, welfare of future generations, etc. Economic evaluation helps the decision-maker who has to judge the relative merit of various interventions in order to optimize the allocation of scarce resources. It might well be that an intervention which produces better outcomes, but generates more costs, will not necessarily be rejected following an economic evaluation.

⁴³ Laupacis A, Feeny D, et al., 1992, p479.

Economic evaluations take into account effectiveness and costs in order to select the most efficient intervention. Society must also consider the ethical consequences of healthcare policies when analyzing and interpreting the results of an economic evaluation are analyzed and interpreted. For instance, for a society, saving the life of a retired person may produce less direct economic outcomes than saving the life of an employed person⁴⁴ or of a child. However, there are highly ethical concerns when it comes to establishing priorities among these human beings.

As an example, Canada chose not to prioritize any group of citizens (i.e., neonatal intensive care, children, employed and unemployed adults, senior citizens), while the Oregon state chose to prioritize groups of citizens. The Oregon state even chose not to treat or to administer minimum treatments to some groups of citizens. Consequently, both societies (Canada and the state of Oregon) made ethical choices. It may seem at first glance that Canada did not make any ethical choices; however, Canada did make ethical choices just by not prioritizing any special group of citizens.

Economists, therefore, do not have the responsibility to requestion the ethical and political environments of a society, unless it is asked for. Their responsibility is to undertake thorough and vigorous economic evaluations subject to the ethical and political constraints the society chose.

The political process is the final one. During this process, most decisions are made regarding the allocation of healthcare resources in Canada. This stage is highly important because factors other than effectiveness, economics and ethics come into play at this stage. For instance, the perspective of an economic evaluation is extremely important. Usually, it is argued that a societal perspective is the most appropriate, where every costs and outcomes related with the introduction of the new intervention are taken into account. The ranking of economic evaluations ratios calculated from society's point of view should be neutral to value or distributional decisions, however, it is difficult for

⁴⁴ *Laupacis A, Feeny D, et al., 1992, p479.*

many decision-makers to decide whether a program should be introduced to adopt an entirely societal point of view or not. For example, the use of a bone marrow transplant program will result in losses for patients with nonlymphocytic leukemia and gains for those who receive the alternatively funded interventions.

10.0 THE IMPORTANCE OF A GOOD METHODOLOGY

A major distinction between clinical trials and economic evaluations is that the former provide mandatory data which are monitored by the government, whereas economic evaluations data are required only in a few countries. In many companies the medical director has to verify the authenticity of data and criminal proceedings that could follow if false declarations are made. In contrast, the same standards may not be applied to economic data.

A recent article⁴⁵ by Hillman et al. has noted this trend and has raised some concern about potential bias in the conduct and reporting of economic evaluations sponsored by pharmaceutical companies. Furthermore, economic data appears to be used increasingly in pharmaceutical company promotional material and it is not clear whether government staff who oversee promotional material, are competent to assess claims of economic evaluation. In this section, the following issues are addressed:

- a) is there a greater potential for bias in economic evaluation than in clinical trials?
- b) does the use of economic evaluations for price setting and marketing of pharmaceutical raise any ethical concerns?
- c) is there a need to set methodological standards for economic evaluation and to develop methods for scrutinizing the results of studies?

⁴⁵ Hillman et al., 1991, p1363.
See appendix V.

11.0 SOURCES OF BIAS IN CLINICAL TRIALS AND ECONOMIC EVALUATIONS

There are three potential sources of bias in economic evaluations pertaining to healthcare, the following are: the choice of question for the study, the analytical methods used, and the reporting of results.

11.1) Choice of Study Question

The most fundamental issue in health economics is to establish whether intervening is preferable to statu quo. Most clinical trials of medications address this question through placebo-controlled trials which are usually required by the HPB (Health Protection Branch). This method works well to a point since other relevant clinical alternatives are not always compared in the same trial.

By contrast, the methodological standards for economic evaluation state that all RELEVANT alternatives must be considered. Unlike a clinician conducting a trial where comparisons are limited to the immediate interventions under study, an economic analyst could be accused of bias if any relevant alternatives were omitted. These could include the statu quo alternative and other alternatives for the condition concerned. The analyst may also be accused of bias if appropriate margins, or increments, in the extent of therapy, are inadequately assessed.

At this point, it is relevant to consider the role of the sponsor of economic evaluations. Sponsors normally expect to provide funding in order to have their own questions answered. Should pharmaceutical companies be expected to provide funding to answer the questions of their competitors or the government? The answer is not straightforward, especially when addressing a wide range of issues does not serve the sponsor's direct interest.

11.2 Study Methodology

Most discussion of the bias in clinical research relates to choices in study methodology. It has long been accepted that the randomised controlled clinical trial is the best form of medical evidence to answer a certain type of clinical evidence. In addition, it is usually argued that an "intention-to-treat" analysis should form the basis of primary reporting of results. The statistical methods used to analyze controlled clinical trials have greatly improved over the years.

In contrast, economic evaluation is relatively young in its development, having been extensively practised in healthcare for approximately 20 years only. The methodological standards laid down for economic evaluation require that these standards be based on good medical evidence. A practical problem often arises when reliable data are not available.

Due to its relative youth, economic evaluation has some catching up to do. In particular, the challenge in the future will be to make fewer assumptions about variables that are, in principle, observable. In this respect, considerable effort has to be devoted to resolve the methodological problems of undertaking economic evaluations alongside clinical trials.

11.3 Reporting of Results

There is a major problem concerning the under-reporting of negative study reports. Hillman et al.⁴⁶ have pointed out that economists should consider carefully any contract that forbids publication unless the work is being carried out on a consultancy basis for the sponsor's information only. They also argue that when projects are commissioned on a stepwise basis, the results of one stage should not be released until publication is guaranteed and funded. A relevant source of bias is inevitable if the

⁴⁶ Hillman et al., 1991, p1363.

pharmaceutical industry has an inhouse pharmacoeconomic department.

Although there is practically universal agreement among pharmaceutical manufacturers concerning the increasing need to generate economic data for their products, companies differ considerably in the way they are organising themselves to produce this information. At one end of the spectrum, some pharmaceutical manufacturers have established inhouse teams dedicated to this new specialty, at the other end, they contract their studies to exterior consultants.

It is, of course, of paramount importance to ensure that the results of economic analyses be the product of sound data and correct methodological approaches. Unfortunately, the ideal data required for a particular pharmacoeconomic analysis may not always be available and, as a result, economic analysis becomes an art requiring assumptions and proxies. Yet it is essential that these analytical inputs to the decision-making process be capable of standing up to rigorous expert inspection or else, it will serve to perpetuate the opinion held by some sceptics that economic data are soft and that economic studies can be designed to support whichever story the originator wishes to tell. It is, therefore, in the industry's own interests to undertake good quality work, not only to reassure these critics, but also to avoid the possibility of having strict regulations practice imposed, by external authorities on economic evaluations.

Hillman et al.⁴⁷ proposed eight guidelines designed to help ensure that this developing new field grows to fulfil its mandate as a tool to help decision-makers allocate resources effectively. Some of the guidelines, however, would undoubtedly pose problems for pharmaceutical companies commissioning research. The sixth recommendation, that "investigators should publish valid results regardless of their promotional value to the sponsoring company, and journal editors should try to avoid a bias against publishing negative results"⁴⁸ clearly sits uncomfortably with the same authors' observation that

⁴⁷ Hillman et al., 1991, p1365.

⁴⁸ Hillman et al., 1991, pp1365-1366.

pharmaceutical companies' main interest in economic research is to promote sales. Yet such conflicts should serve as an encouragement, not as a barrier, to more open and direct dialogue between academic researchers and the pharmaceutical industry since continued development of pharmacoeconomic evaluation requires collaboration between these two parties.

Recent years have seen economic health economics become a growth industry because it is essential for healthcare providers to understand that simple cost containment strategies are not the route to efficient resource allocation. Without this understanding, the reason of economic evaluation will be unworthy. The increased interest in economic analyses presents certain dangers. These include:

- the possibility of bias, especially when industry funds the research;
- absence of a standardised methodology, making comparisons between studies difficult;
- poverty of skills in government to assess such studies.

Perhaps the greatest danger is that efficiency studies will be used by governments simply to control costs. For example, the technical notes accompanying the Australian guidelines on economic evaluations indicate clearly that a product which will add to a government's medication bill may yet be efficient in that it could lead to cost reductions elsewhere in the system.

12.0 ACTIONS REQUIRED TO UNDERTAKE A PHARMACOECONOMIC EVALUATION

12.1 Steps Involved Before Conducting an Economic Evaluation

Before undertaking a pharmacoeconomic study, several steps should be undertaken⁴⁹. These actions are worthwhile for all types of economic studies. The preliminary actions to follow are:

- Review the literature;
- Define the problem and state the different potential research questions;
- Set goals for the study;
- Identify the potential caveats that can be encountered which could bias the study;
- Interview experts;
- Recruit a multidisciplinary advisory board and, educate and inform them as appropriately;
- Identify all potential adverse and beneficial effects;
- Plan/develop a draft study protocol;
- Survey appropriate clinical environments (for the clinical/economic trials);
- Research and verify all potential significant direct and indirect costs and outcomes;
- Revise the draft study protocol objectively;
- Present the draft study protocol to the advisory board for revision;
- Perform projections;
- Present recommendations.

⁴⁹ See appendix VI.

12.2 Steps Involved for Conducting an Economic Evaluation

The steps involved for conducting a pharmacoeconomic evaluations are:

- State precisely THE research question in an answerable form;
- Determine the perspective(s)⁵⁰ and the reason for choosing this perspective;
- Determine the extent of the study⁵¹;
- Select the appropriate type of economic evaluation;
- Determine the way to carry out the study(ies);
- Determine the competing alternatives (including the statu quo) to be studied;
- Develop the final study protocol;
- Identify the costs, outcomes and their probabilities⁵²;
- Present the final draft of the study protocol to the advisory board for revision;
- Assign dollar signs to the costs;
- Lay out the assumptions of the analysis;
- Quantify the value of each outcomes either as a dollar value, an effectiveness measure or a utility measure (depending on the type of analysis);
- Identify the time horizon of the study and express the reason;
- Allow for uncertainty in costs and outcomes;
- Transform the costs and outcomes from nominal dollars to current (real) dollar⁵³;
- Perform data collection;
- Adjust costs and outcomes for differential timing;

⁵⁰ *The determination of the perspective of the analysis is important because it will determine the costs and outcomes of a treatment that will be included in the analysis.*

⁵¹ *There are three possible extents of a study, as mentioned in section 2.3. First, the study can be a sensitive/competitive pricing study; second, the study can be pilot-project study and; third, the study can be a comprehensive ("full blown") study.*

⁵² *For example, for a given intervention, what is the probability that the patient's health will be improved, be the same, or be worse?*

⁵³ *Or vice-versa, depending if the study is prospective or retrospective.*

- If maximising expected value is selected as the decision rule, the "expected value" of each intervention is computed by multiplying the probability of each cost and outcome by its value and summing the results;
- Do the calculation;
- Analyze the results;
- Revise the analysis;
- Perform sensitivity of results;
- Recommend/Present results for different decision-makers.

You may have noticed that the steps are not numerated. This has been done on purpose because the steps do not have to be done in this respective order; however, there still exists a certain chronology that must be respected. These steps are the principle steps to conduct a pharmacoeconomic evaluation; however, they are still very superficial and to each questions are many subquestions.

13.0 CONCLUSION

No matter how wealthy the economy is and how strong the economic system is, there are never unlimited resources to satisfy the society's wishes. Policymakers, consumers and all other individuals and groups comprising the economy must make hard choices about how to allocate resources. When an individual chooses to purchase a medication, he cannot purchase something else with the same funds. Similarly, when federal policymakers authorise expenditures on medications, there are competing demands that cannot be fulfilled. This idea can be generalized into one of the most important concepts guiding economics: the opportunity cost. Economics, whether applied to pharmaceutical or more generally, is not about reducing costs (cost containment strategies), it is about maximizing the net outcomes obtained from the goods and services produced by society, subject to its available resources.

There is a consensus that evaluation of medications can no longer only consider safety and efficacy criteria but it must also include the economic impact of medications on the rapidly rising cost of medical care which is a major public policy issue in every developed country.

For many years limited government budgets have been facing the pressures of rising demand for healthcare, increasing costs, and also the "impossibility" to rise the level of taxation. All these pressures entwined generate that the government's ability to fund health services is restricted. In order to control, up to a certain point, certain aspects of the healthcare system's expenditures, a popular control form is the use of medication lists or formularies, for which governments may or may not pay; canadian provincial governments subsidise only listed medications.

Most of the developments seek to control costs rather than to improve the efficiency of resource allocation. Indeed some, such as the ceiling on medication company profits, could discourage efficiency by removing competitive pressures and the

incentive to reduce costs. Recognizing this, some governments have moved to incorporate economic efficiency considerations into the decision-making process. The Australian government has notified companies that they will be required to include an economic analysis in applications for inclusion on the list of subsidised medications and it has provided guidelines for them to use. The Canadian and American⁵⁴ governments are presently developing similar guidelines; a first Canadian draft⁵⁵ is already in circulation and a second one should be "published" in the near future. Maintenance of good methodological standards is, in the long run, the best policy both for pharmaceutical industry sponsors and economic analysts.

Pharmacoeconomic analyses can help healthcare professionals in allocating scarce resources. Economists, however, can help by working to improve the methodological issues and principles of economic evaluations of pharmaceutical, in order to simplify this new and complex science of health care. Economists are the first to agree that economic considerations are not the only ones to take into account. Political or ethical factors may be equally or more important. It is necessary to recognise that clinical considerations alone can no longer be the criteria for deciding on the most desirable pattern of medical care.

"The jury is still out the question whether the economic evaluation of medicines gives good value for money but in the current environment, what is the alternative? asked Professor Michael Drummond of the Centre of Health Economics, York University. The costs of the investigations are modest compared with those of clinical trials, and some marketing activities, and demonstrations of cost-effectiveness can be used by physicians to defend their prescribing costs and to justify the use of newer, more expensive medications, he suggested".⁵⁶

⁵⁴ *The Americans are now preparing a first draft.*

⁵⁵ *See Detsky A. Guidelines for preparation of economic analysis to be included in submission to drug programs branch for listing in the Ontario drug benefit formulary/comparative drug index. 1991*

⁵⁶ *Scrip, Nov 89, p9.*

It is not important for healthcare professionals to be able to perform pharmacoeconomic studies, but it is essential for them to understand how and why these analyses are performed. Healthcare professionals should remember that the National Health Care system is seeking to deliver the most efficient healthcare, not the cheaper one. "Cost is not the enemy - waste is the enemy".⁵⁷

⁵⁷ *University Centre for health Economics Research, 1992*

14.0 PERSONAL COMMENTS

In order to complete my research paper, my director, Dr. Georges Dionne, asked me to write a few personal comments regarding my research paper's contribution to economics. After a few days of reflection, below are my comments.

First, I would like to begin by explaining the purpose of my research paper as an economist to fellow economists. Pharmaceutical manufacturers, health professionals, the governments, etc, are aware of the problems related to healthcare. In a few words, they are conscious that the demand for healthcare is largely superior to its supply. On one side, the high demand is largely due to the aging population and the increased attention/importance that this generation is according to their health and their quality of life, and on the other side, the supply side is constrained by limited budgets the governments have due to the lack of new money; citizens do not want to increase the amount of taxes they are paying, hence there is no new money to pay for these services. One of the response of the governments, facing this problem is rationalization. The problem is that most solutions are cost-containment strategies rather than efficient strategies. It is crucial to evaluate the total costs of an intervention, including indirect costs, opportunity costs and the externalities that can be engendered when an intervention is chosen, rather than another one.

So far, what I have mentioned above is yesterday's news for economists.

Secondly, from my work in institutions which are directly related to healthcare, such as Sandoz Canada Inc. (Pharmaceutical Company) and the Association des hôpitaux du Québec, I have discovered that most healthcare professionals, including economists, were not aware of this new science called pharmacoeconomics, or if they were, they were not aware of the extent and the complexity of pharmacoeconomics. Therefore, I realize that this research paper should not only be addressed to healthcare professionals but also to economists, in order to inform them about this new science.

I believe that this research paper can be a highly useful tool to economists for two purposes. First, I think that my research is relatively thorough concerning the environment of health economists. I mean that economists can read my research paper and rapidly understand the global environment surrounding pharmacoeconomic studies. Second, I believe that my research paper covers many research questions. Pharmacoeconomics is a relatively new science, hence, it could be an economist's concern to research these caveats which are presently limiting pharmacoeconomic studies. Below are the important highlights of my research paper concerning pharmacoeconomics and the topics that should be researched more thoroughly.

First, this paper is a highly handy tool for an economist who wishes to start working in health economics or more precisely, pharmacoeconomics. Maybe after reading this research paper, some economists will smell the hot coffee that is presently being brewed in pharmacoeconomics. This field is relatively new, complex and full of great challenges. At my great surprise, a lot has been written on the subject and for a long period of time. You will find in my bibliography that some articles were written in the 60's. But since cost containment issues were not considered yet, these articles were not highlighted; nobody felt the need to really understand the bottom line of these articles. Today, however, cost containment issues are high priorities with the healthcare costs escalating at a frightening pace. One of the reasons of the escalating costs is due to the new technologies. These technologies are the fruit of many researches, investments and high risks. Consequently, when these new technologies are marketed, they are highly costly. According to an article published recently in the Gazette (October 22, 1992), medications are now monopolizing 16% of the healthcare budgets; this is quite an impressive percentage.

In response to high healthcare costs, decisionmakers are now reading and scrutinizing economic papers. Economists have a crucial role to play in order to control costs since economists are the experts concerning the study of costs; many are realizing that economists can help. Therefore I think my paper can assist many economists who wish to reorient themselves towards pharmacoeconomics.

The section 2.0 is concerned towards the terminology used in pharmacoeconomics. I think that even though economists are aware of most of the expressions mentioned, it is always useful to read them again. Also, some expressions are probably new to some. For instance, quality of life (QOL), quality-adjusted life-years (QALY), health-related quality of life (HRQOL), clinical trials, etc. It is important to well discern the difference between the different types of pharmacoeconomic studies such as cost minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit-analysis, and then to understand the difference between efficacy, effectiveness and efficiency; these are crucial concepts in pharmacoeconomics. Hence section 2.0 is of paramount importance, even for economists, if they wish to undertake research in this new field.

More attention should be devoted to cost-benefit and cost-utility analysis. These two types of pharmacoeconomic studies are the most criticized one. Cost-benefit should be more researched in order to decrease ethical problems surrounding the valuation of morbidity and mortality in dollar signs. The application of the utility theory should be more researched for conducting cost-utility analyses since the utility measure combines mortality and multidimensional aspects of morbidity.

A second important factor in my research paper is the importance of pharmacoeconomics. As mentioned above, pharmacoeconomics has been existing for a few decades, however, it was not given much attention since there were no monetary problems surrounding the health sector. A few researchers were publishing on the subject but it was not a popular topic; decisionmakers did not see the need to pay real interest to these articles. Today, pharmacoeconomics is a very hot topic in healthcare, just as environment features are crucial today. If you read my research paper, you will understand that the bottom line of pharmacoeconomics is a search of efficiency for the allocation of resources and most importantly, the ones that comes from the citizen's: their tax money. Pharmacoeconomics is about choices and these choices must not only be done to satisfy politicians, legislators, but to satisfy the TAXPAYERS: they are the one who will receive now or in the future some kind of intervention; some how, this

concept had vanished more specifically during the last two decades.

It is of paramount importance to decide how to spend wisely their money, in order to satisfy, as best as possible, the society's needs. As I said in my research paper, the purpose of pharmacoeconomics is not necessarily to decrease the healthcare spending, but to decrease the pace of the escalating costs in healthcare and to spend the taxpayers money intelligently, EFFICIENTLY. Cost is not the ennemy, WASTE is. Therefore, this what economics is about, more specficly, this is what pharmacoeconomics is about.

In section 5.0 of my research paper, I discuss about the relationship between clinical trials and pharmacoeconomic studies. Further research should be conducted in this field because clinical trials are highly similar to pharmacoeconomic evaluations. While one has a medical concern, the other is an input to the decision-making process, however, both studies are conducted with the same basic data (from case report forms), by professionals but the professionals do not manipulate the data the same way because they do not have the same objectives. Since clinical trials have existed for a long time, they once faced the difficult task of standardizing the procedure, and now they are supervised under legal authority with precise rules. Pharmacoeconomics should follow some standards of clinical trials, in order to create a certain standardized methodology, which will not have to be under legal supervision if the methodology is strict enough.

In section 7.0 of my research paper, it was shown that not every medication needs a pharmacoeconomic evaluation, it depends of multiple factors. Also, even if a pharmacoeconomic evaluation needs to be done for a product, it does not have to be a comprehensive study. Consequently, depending of the factors mentioned in section 7.0, it can be deduced if a pharmacoeconomic study should be conducted and to which extent. There should be further research in this section also because there might be other important factors that should be considered in an economic evaluation.

In section 8.0 are described the "can and can't's", therefore the opportunities and limitations of pharmacoeconomics. It is well known, among economists, that economics is not a magic formula to solve everybody's problems. It is a tool in order to help the decision-making process. Consequently, I think that for economists that are thinking of heading towards pharmacoeconomics, they should be aware of the opportunities and limitations of pharmacoeconomic studies.

Finally, the most important and interesting research aspect that must be undertaken in pharmacoeconomics is the study methodology. One of the most criticized aspects of pharmacoeconomic studies, eventhough if they are done with the most scientific approach, is the methodology. The principle purpose of the methodology is to minimize the source of bias when conducting a pharmacoeconomic evaluation. There are three important different source of study bias:

- a) The study question;
- b) The methodology of the study;
- c) The publication of studies.

It is rather difficult for economists to find a solution to a) and c) because it is not their field of specialization (expertise), however, the methodology of the study is their concern. I think that it is crucial that a multidimensional team should be gathered in order to create a rational methodology that will include the multidimensional aspects of pharmacoeconomics⁵⁸.

The pharmacoeconomic methodology is a crucial factor in order for the study to become credible. Also, a good methodology will permit pharmaceutical manufacturers to conduct themselves the economic studies⁵⁹. One of the problems of the

⁵⁸ *An example of a multidimensional team is the GRIS at the University of Montreal.*

⁵⁹ *In the short term, pharmaceutical companies might have an interest to be dishonest while undertaking pharmacoeconomic evaluations, however just as in everything, they do not have interest to be dishonest in the long term since they will lose their credibility, hence, nobody will believe in their evaluations.*

pharmaceutical manufacturers is to decide whether they should conduct themselves the pharmacoeconomic studies, at a reasonable cost, or if they should have external agencies conduct their economic studies. More research should be given to this aspect.

If I can just make understand that using the correct terminology is essential to people surrounding pharmacoeconomic studies, including famous pharmacoeconomists, I think that I will have accomplished something important. Too many so-called pharmacoeconomists are, I'm convinced, very "connaissanceur" about pharmacoeconomics, but unfortunately they have forgotten to return to the source in order not to confuse the amateurs who are beginning to learn this new science.

As an economist, I prone efficiency and I would like to spread the word to remind people that they can do what ever they want with their money, but they cannot do what ever they want with the taxpayers money.

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Interviews

Geneviève Tessier, responsible of economic evaluations at the GRIS, University of Montreal.

François Schubert, director of strategic planning, pharmacy and pharmacoeconomic affairs, Sandoz Canada Inc.

David Feeny, professor of economics, Mc Master University.

Georges Torrance, professor of economics, Mc Master University.

Jeremiah Hurley, professor of economics, Mc Master University.

Greg Stoddart, professor of economics, Mc Master University.

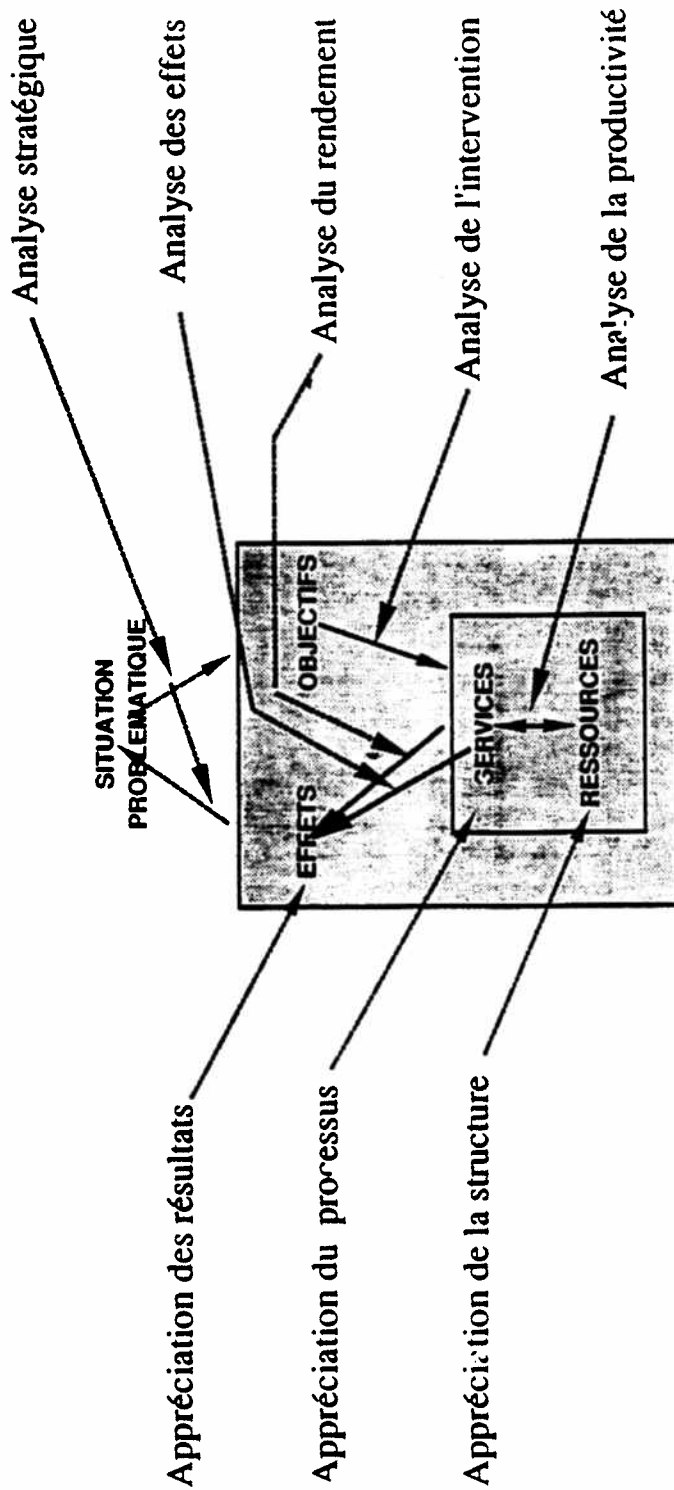
Andrew Orfanos, director of clinical research, Sandoz Canada Inc.

Pierre Boyle, director of the project OPTIMAH, Association des hôpitaux du Québec.

L'évaluation d'une intervention

Evaluation administrative

Recherche évaluative



⁶⁰ Hand-out for the course ASA 6054, University of Montreal, 1992.

APPENDIX II⁶¹

PHARMACOECONOMICS: PROJECT/PRODUCT ANALYSIS

PRODUCT: _____ **PRODUCT/PROJECT MANAGER:** _____

The following key groups/players/organisations should be considered, especially with regard to their importance to this project/product. They should be scored on the following basis:

0 = Not important 1 = Somewhat important 2 = Important 3 = Very important 4 = Extremely important

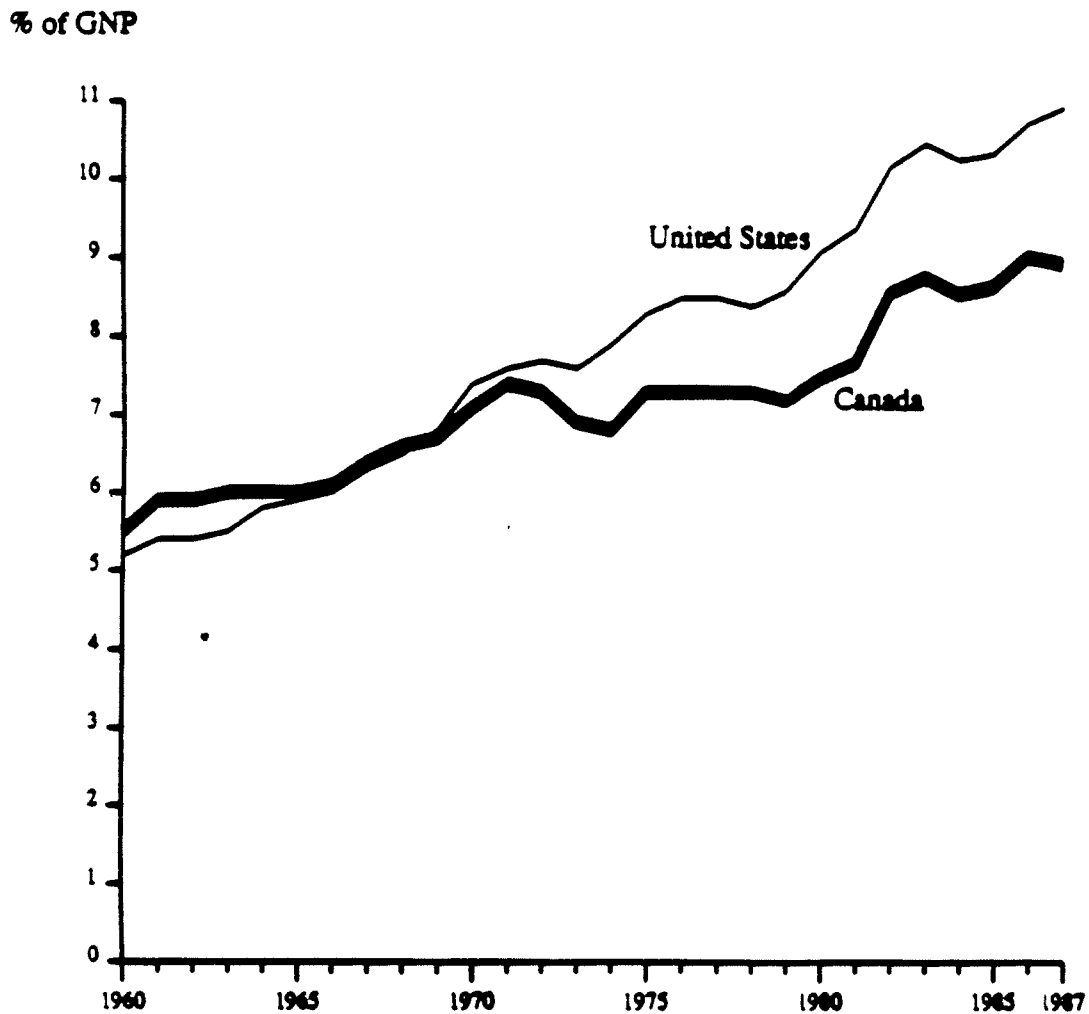
The rationale for the score should be given

GROUP/ORGANIZATION	SCORE	RATIONALE
HPB		
Federal Government		
Provincial Government		
Provincial Formularies		
Hospital Formularies		
Hospital Administrators (includes nursing homes, etc.)		
Medicare		
Private Insurers/Drug Plans		
Pharmacists		
Opinion Leaders		
Prescribers - Hospital Based - Private practice		
Patients		
Patient Lobby Groups		
Public Opinion		
PMPRB		
Competitors		
Basle/U.S. Activities		
Basle Pricing Policy		
Trade Unions		
Other Groups:		

⁶¹ Sandoz Canada Inc. internal document prepared by Judy Macer and Dr. Andrew Orfanos.

APPENDIX III⁶²

Health expenditures as a percentage of gross national product,
Canada and the United States, 1960 to 1987

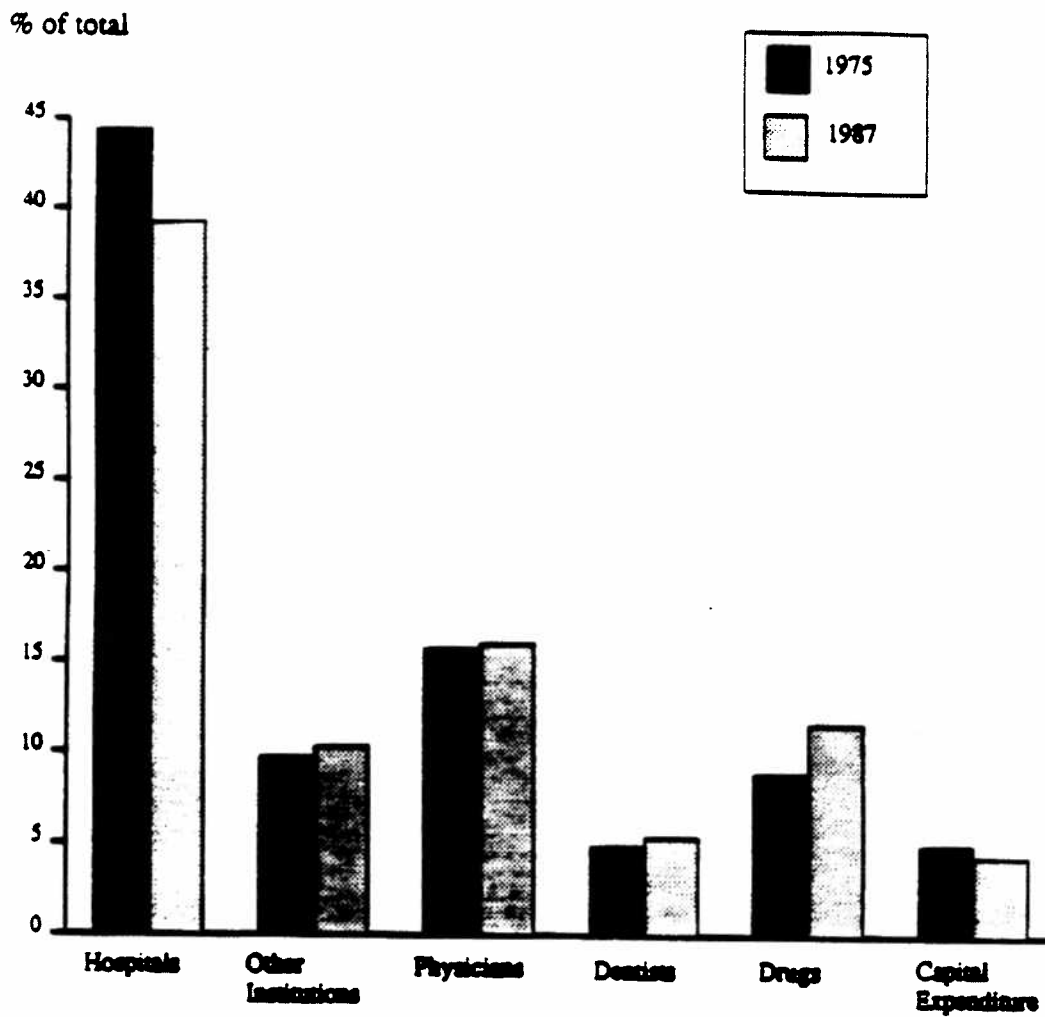


Canadian statistics for 1987 and United States' statistics for 1985, 1986 and 1987 are provisional.

⁶² *National Health Expenditures in Canada (1990)*, p19.

APPENDIX III⁶³

Expenditures for selected categories,
percentages of total health expenditures,
Canada, 1975 and 1987

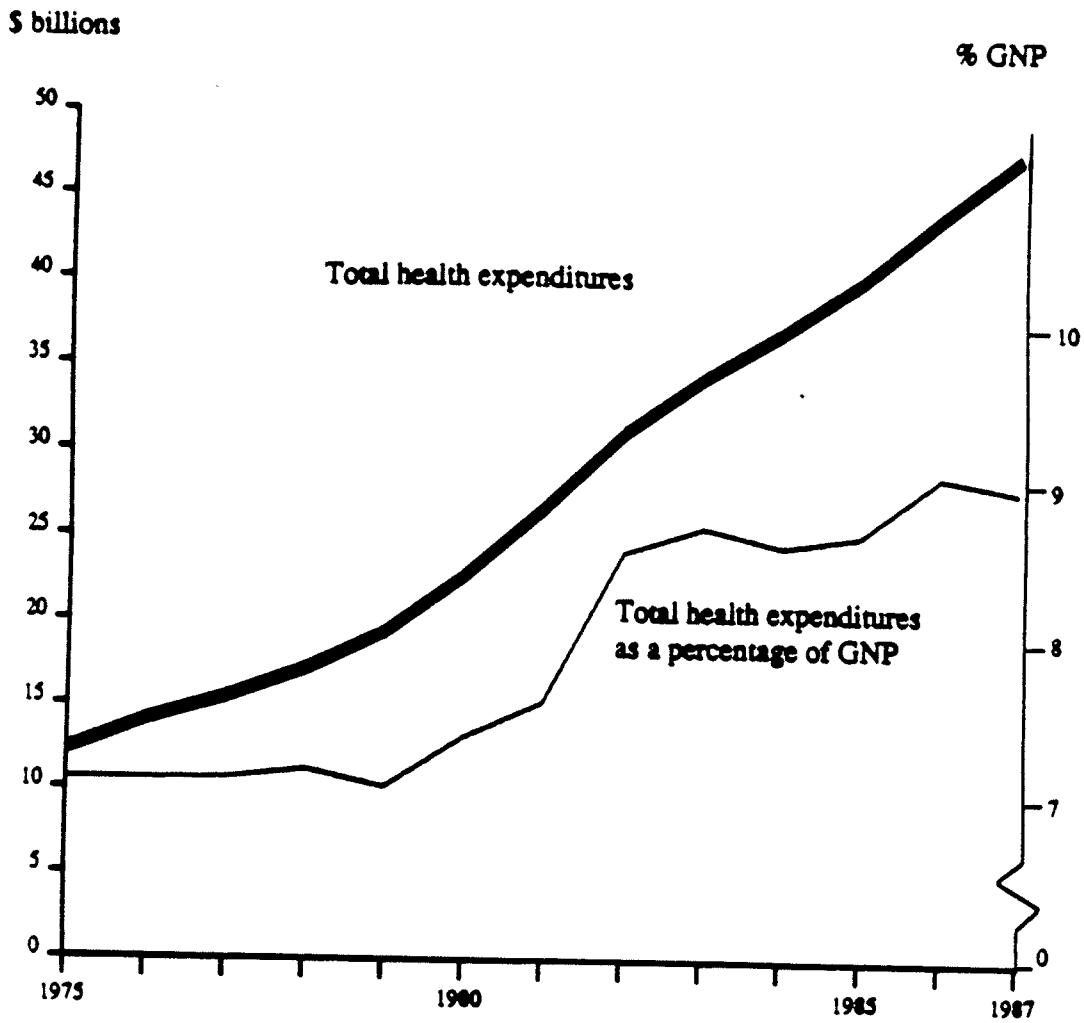


Statistics for 1987 are provisional.

⁶³ *National Health Expenditures in Canada (1990), p5.*

APPENDIX III⁴⁴

Health expenditures in billions of dollars and
as a percentage of gross national product,
Canada, 1975 to 1987

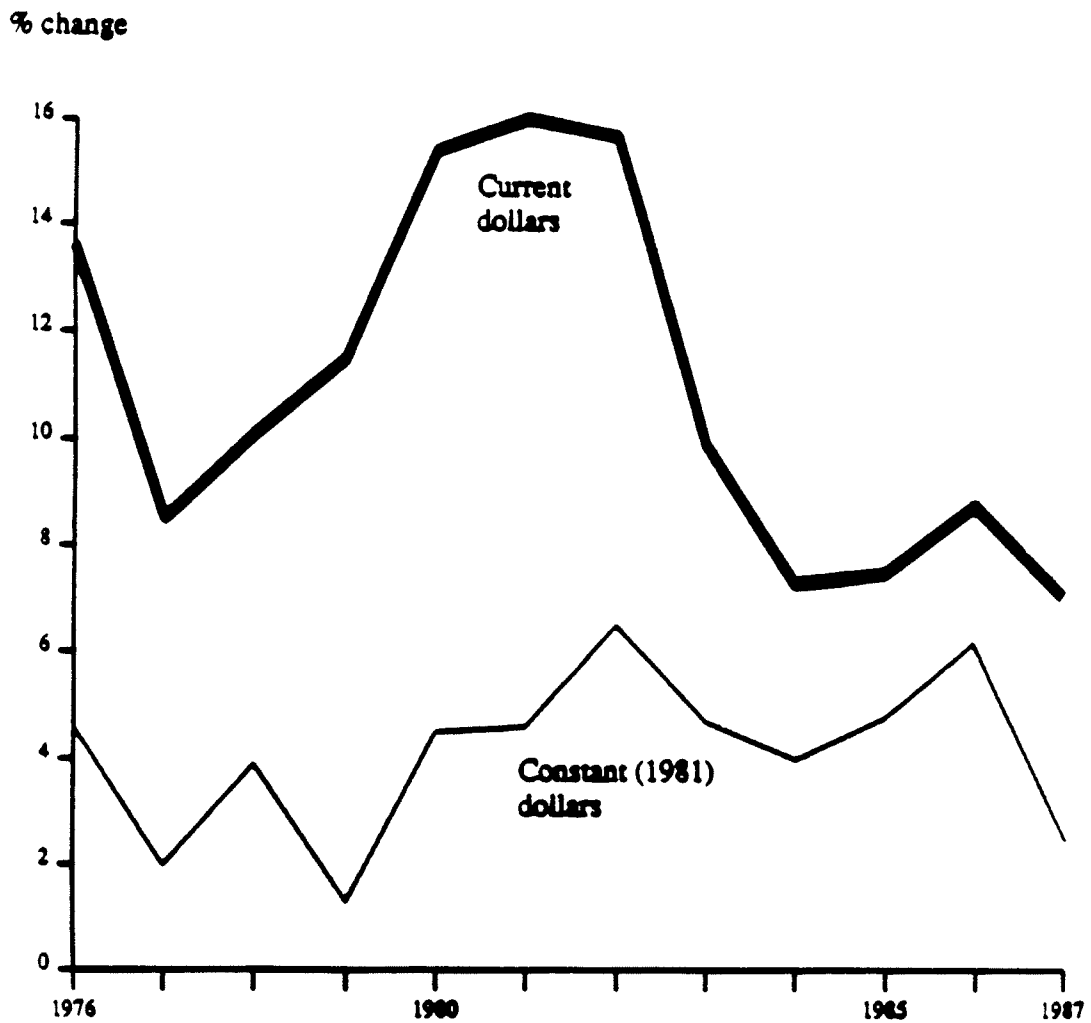


Statistics for 1987 are provisional.

⁴⁴ National Health Expenditures in Canada (1990), p9.

APPENDIX III⁶⁵

Annual percentage changes in per capita health expenditures
in current and constant (1981) dollars,
Canada, 1976 to 1987



Statistics for 1987 are provisional.

⁶⁵ *National Health Expenditures in Canada (1990)*, p7.

APPENDIX IV⁶⁶

LOCATION OF COORDINATION FUNCTIONS OF PHARMACOECONOMICS WITHIN SANDOZ CANADA:

1. Pharmacoeconomics in Clinical Research Department

Advantages	Disadvantages
<ul style="list-style-type: none">● Clinical research staff has the skills and expertise to design and conduct rigorous studies.● Clinical research is best equipped to establish and maintain the intellectual integrity of pharmacoeconomic studies.● Economic evidence in the early life cycle of the product will facilitate reimbursement. This economic evidence could be collected alongside potentially influential trials, at the premarketing stage.● The location of pharmacoeconomics in clinical department will convey to outside observers the message that Sandoz regards it as being as scientifically rigorous as efficacy studies.	<ul style="list-style-type: none">● Clinical research department is remote from the ultimate users of the pharmacoeconomic information and may not be responsive to their needs.● The objectives of clinical and pharmacoeconomic studies are different. The main focus of clinical research is to demonstrate safety and efficacy, not efficiency. As a result, clinical researchers may tend to "sacrifice" economic end-points, if they are judged unethical or less important, which may hinder the quality of the economic study.● Pharmacoeconomic studies conducted in Phase II and III may be of limited usefulness as they are conducted in an artificial setting: not real population, blinding, small sample size, forced compliance, regulation of concomitant medications instead of monitoring and variable follow-up. Furthermore, the intensive clinical monitoring that is part of clinical trial is not necessarily desirable in an economic trial.● Regardless of the current expertise in conducting efficacy studies, there will have to be considerable learning about pharmacoeconomics.

⁶⁶ Sandoz Canada Inc. internal document prepared by Francine Gagné.

APPENDIX IV⁶⁷

2. Pharmacoeconomics in Marketing Department

Advantages	Disadvantages
<ul style="list-style-type: none">● Cost-effectiveness is fundamentally, a marketing issue that reflects the value of a product in the eyes of key decision makers.● Staff from marketing department already deal with major consumers of pharmacoeconomic information on a routine basis.● The familiarity with the needs and perceptions of the various formularies and physicians provide useful insights into what kinds of information to produce and how to package it to influence behaviour.● The location of pharmacoeconomics in marketing would ensure the timely production of information needed to determine the product price.● Marketing is best qualified to quickly detect the market need for post-approval pharmacoeconomic studies (Phase IV). Pressure to obtain economic information may build up after launch only, as the product grows and starts to consume larger budgets.● Marketing staff is best qualified to detect changes in healthcare environment. The primary focus of companies' attention should be healthcare policy, not pharmacoeconomics. A too early focus on specific economic studies may lead the company to concentrate on the technical aspect of the studies themselves and lose sight of how to maximise the eventual utility of the studies when they are completed. A technically perfect economic study may be disregarded by policy makers and healthcare managers because of wider policy considerations.	<ul style="list-style-type: none">● The comparative advantage of marketing staff is in the dissemination of information, not its production.● Marketing is traditionally interested in short-term results. Conversely, the production of pharmacoeconomic information requires time. There could be a reluctance to commit money "now" in order to obtain results in a longer time-frame (2-3 years).● The location of pharmacoeconomics in marketing may be perceived by outside observers as less than fully ethical (information more likely to be biased and used to engage in self-interested advocacy).● Prospective studies initiated at a later stage in the product development could seriously delay publication of results.

⁶⁷ Sandoz Canada Inc. internal document prepared by Francine Gagné.

APPENDIX IV⁶⁸

3. Pharmacoeconomics in Scientific Development

Advantages	Disadvantages
<ul style="list-style-type: none">● The scientific development is responsible for the coordination of activities in bringing a compound to market during the time when it is most appropriate to conduct pharmacoeconomic studies. Economic evidence in the early life cycle of the product will greatly facilitate reimbursement.● The location of pharmacoeconomics in scientific development will be perceived as equally ethical as its location in clinical research.● Scientific development's mandate includes a market oriented component with a scientific point of view.● The location of pharmacoeconomics in scientific development would reinforce the department's role as a bridge between the marketing and clinical departments.	<ul style="list-style-type: none">● Pharmacoeconomic studies (Phase II or III) conducted at the time scientific development will be responsible for the product, may be of limited usefulness (conducted in an artificial setting: not real population and atypical of normal medical practice).● As scientific development is neither the department responsible for delivering the information, nor the one producing it, it may lack the major sets of skills to select, implement and disseminate the appropriate pharmacoeconomic studies.

⁶⁸ Sandoz Canada Inc. internal document prepared by Francine Gagné.

APPENDIX V
PROPOSED GUIDELINES BY HILLMAN ET AL.⁶⁹

«Pressure toward bias is to be expected in a competitive marketplace. The selective production and presentation of results by one firm will provoke a competitive response from other firms. This impedes scientific progress by casting doubt on the objectivity and validity of results, whether favourable or unfavourable. Identifying studies that have followed protocols designed to reduce bias would allow readers to recognize the likelihood of bias in studies not so designated. As a result, competitive pressures would be channelled toward less biased, more useful research. Adherence to these standards would generate a seal of approval that could in itself be valuable in selling pharmaceuticals in an increasingly skeptical and competitive marketplace. We offer the following eight recommendations.

First, written agreements between pharmaceutical companies and investigators should be in the form of research grants to universities, rather than contracts with individual investigators or universities. The agreements should stipulate that the researcher may publish findings regardless of their nature and retains sufficient access to proprietary data to allow publication even if funding is withdrawn. Such arrangement will also ensure that questions raised by readers and other investigators can be addressed effectively. Private research and consulting firms should establish similar rules.

Second, economic analyses are by their nature comparative. The selection of alternatives to be compared should be based on their clinical relevance, not on the potential favorability of the results. At a minimum, comparisons required by the FDA for controlled clinical trials should be included. Research reports should be explicit about the comparisons chosen and those omitted. Data from all relevant studies, rather than a selected subset, should be made available to the investigator.

Third, investigators should be allowed to expand the company's study design to include additional types of costs, economic perspectives, and comparison drugs as data permit. If the funding group has placed constraints on an investigator, this information must be clearly disclosed to editors, reviewers, and readers.

⁶⁹ Hillman et al., 1991, p1364.

Fourth, if projects are funded in a series of steps rather than by one large grant, results should not be provided to the sponsor until publication is guaranteed and funded. (Initial steps can include, for example, a review of the literature, general advice, and the planning of the economic model.

Fifth, investigators should be vigilant to the temptation to reduce favourable findings. The assumptions required in a study should be conservative (i.e., biased against the results sought by the funding company), clearly identified, and supported with formal sensitivity analyses. Editors should encourage the publication of these details despite current limits on the length of articles in many journals.

Sixth, investigators should publish valid results regardless of their promotional value to the sponsoring company, and journals editors should try to avoid a bias against publishing negative results.

Furthermore, researchers who receive a grant should not act as consultants on projects related to the study medication during the active period of the grant. Journals should require that all financial relations between authors and their sponsoring companies (as well as their direct competitors) be disclosed, including equity interests other than the ownership of shares in mutual funds.

Finally, researchers should take all reasonable steps to ensure that the level of funding permits methodologically sound, clinically relevant results with enough statistical power to detect important differences among the alternatives compared. Projects should avoid a «good enough for marketing» mentality.

All published studies should include a statement that their authors have adhered to this protocol. Universities and nonacademic researchers should develop and enforce standard agreements that meet these conflict-of-interest guidelines. Also, academic research societies, journal editors, pharmaceutical companies, and federal funding agencies should adopt these guidelines, perhaps after modification by a joint task force. Such actions will help ensure that this burgeoning new field of academic endeavour grows to fulfil its promise as a stool to help decision makers allocate resources effectively.

APPENDIX VI
A SUGGESTED CHECKLIST FOR ASSESSING ECONOMIC
EVALUATIONS⁷⁰

- 1. Was a well-defined question posed in answerable form?**
 - 1.1 Did the study examine both costs and effects of the service(s) or programme(s)?
 - 1.2 Did the study involve a comparison of alternatives?
 - 1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

- 2.0 Was a comprehensive description of the competing alternatives given? (i.e., can you tell who? did what? to whom? where? and how often?)**
 - 2.1 Were any important alternatives omitted?
 - 2.2 Was (Should) a do-nothing alternative (be) considered?

- 3.0 Was there evidence that the programmes' effectiveness had been established?**
 - 3.1 Has this been done through a randomized controlled clinical trial? If not, how strong was the evidence of effectiveness?

- 4. Were all the important and relevant costs and consequences for each alternative identified?**
 - 4.1 Was the range wide enough for the research question at hand?
 - 4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
 - 4.3 Were capital costs, as well as operating costs, included?

⁷⁰ Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes.* pp35-38.

5. **Were costs and consequences measured accurately in appropriate physical units? (e.g., hours of nursing time, number of physician visits, lost workdays, gained life-years)**
 - 5.1 Were any of the identified items omitted from measurement?
 - 5.2 Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. **Were costs and consequences valued credibly?**
 - 6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements).
 - 6.2 Were market values employed for changes involving resources gained or depleted?
 - 6.3 Where market values were absent (e.g., volunteer labour), or market values did not reflect actual values, (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
 - 6.4 Was the valuation of consequences appropriate for the question posed' (i.e., Has the appropriate type or types of analysis - cost-effectiveness, cost-benefit, cost-utility⁷¹ - been selected?)

7. **Were costs and consequences adjusted for differential timing?**
 - 7.1 Were costs and consequences which occur in the future "discounted" to their present values?
 - 7.2 Was any justification given for the discount rate?

8. **Was an incremental analysis of costs and consequences of alternatives performed?**
 - 8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?

⁷¹ *Cost-minimization analysis should also be added to this enumeration since it is also a complete form of economic evaluation.*

- 9. Was a sensitivity analysis performed?**
- 9.1 Was justification provided for the ranges of values (for key study parameters) employed in the sensitivity analysis?
- 9.2 Were study results sensitive to changes in the values (within their assumed range)?
- 10. Did the presentation and discussion of study results include all issues of concern to users?**
- 10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g., cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
- 10.2 Were the results compared with those of others who have investigated the same question?
- 10.3 Did the study discuss the generalizability of the results to other settings and patient/client groups?
- 10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g., distribution of costs and consequences, or relevant ethical issues)?
- 10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the "preferred" programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?