



Mini-review: Health Economics

HANDLING THE RESULTS OF PHARMACOECONOMIC EVALUATIONS

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ABSTRACT

As a consequence of limited financial resources, health economics, and particularly pharmacoeconomic analyses, are becoming a frequently used criterion for decision making in modern health care policy. The pharmacoeconomic studies cannot be universal and their results are impossible to be directly transferred beyond the study setting. This article draws the readers' attention to the main components of pharmacoeconomic studies, which have an influence on the generalisability of the results. The aim is for the readers to get an idea as to what extent pharmacoeconomic results are correct and how these correspond to their own setting.

Key words: Health economics, cost, benefit, generalisability

INTRODUCTION

A growing number of therapeutic options is in the process of introduction in clinical practice. Their efficacy and safety are proved in clinical trials. At the same time, when only limited financial resources are available, the factor "price" of a certain health strategy gains a larger importance in the decision-making of its implication. As a consequence in modern health policy, besides evidence-based medicine, a greater weight is placed on pharmacoeconomics (PhE). In the 1990s, only a few years after the introduction of the term pharmacoeconomics, Australia, Canada and other countries began to apply cost-effectiveness analyses in the implementation of their health policy (1). In the last years, the pharmacoeconomic data have gradually become obligatory or advisable in all the EU countries, both in price formation and reimbursement, and even in drug licensing. In Bulgaria, after establishing the National Health Service (NHS) in 2001, economic and pharmacoeconomic assessments are required for drugs that are about to be included in the reimbursement list.

It should be borne in mind, however, that both

pharmacoeconomic and clinical studies are expensive and time-consuming. Therefore, it is necessary at times to use the results of economic studies performed elsewhere, since this saves time and resources and can serve as an ideal option for decision-makers. Nonetheless, there exists the problem of the so-called generalisability of the results. As one of definitions goes "generalisability is the extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context" (2).

The informative value of pharmacoeconomic studies must be assessed according to the health care system and geographic location. The clinical practice, single-unit prices, health care system and a number of other factors vary from place to place and as a consequence these can decrease the validity of the results beyond the place where the economic study is carried out. This makes impossible the mechanical transition of results from one country to another and their internationalisation (3). The question arises whether the results of one economic study are applicable beyond its setting and how they can be used for making local financial decisions.

The aim of this article is to draw the readers' attention to the main components of pharmacoeconomic studies, which have an influence on the generalisability of the results.

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Thus each reader can decide for themselves to what extent pharmacoeconomic results are valid and how they answer the questions rising in his/her own setting.

Study question

Is the posed question economically important?

Health economics, and particularly its branch PhE, helps us choose between two alternatives, which we compare with regard to their clinical benefit on one hand and their cost on the other. Before persuading anyone of the economic arguments for the choice of a certain health strategy the authors have to make sure that their study poses economically important question to which it is possible to give unbiased and unambiguous answers. The users of pharmacoeconomic evaluations are not interested in the results themselves but in where and how these results can help them for a better care of their patients.

Selection of alternatives

Are the investigated alternatives and comparator clearly stated and is their choice justified?

PhE uses a comparative approach and assesses the costs and benefits of at least two therapeutic interventions. In order to interpret the results of an economic study, the reader should be acquainted both with the investigated alternative and the alternative used as a comparator. Even if the results of an economic study convincingly prove that the assessed alternative is more effective and less expensive than the comparator, this alternative must be described in detail so that the reader can consider if it is workable in his own setting.

The choice of a comparator is one of the critical moments for an accurate pharmacoeconomic analysis. If there is no comparability between the studied alternative and comparator or if the comparator is inaccurately selected this may lead to misleading results. In principle the comparator should be the most cost-effective alternative but in practice it represents the current standard practice, i.e. the most commonly used and the most available alternative in the authors' setting (1,4). The description of the comparator and the reason for its selection are useful and allow the readers to understand whether the comparator is a standard practice in the authors' setting. Some authors recommend that the reason for selection of a

comparator should be explained in the context of all relevant comparators (5) but this is often impossible. Unless the current practice is "doing nothing" it is not appropriate to use a placebo as a comparator (4).

One of the factors for distrusting pharmacoeconomics results is that a great part of the economic studies is sponsored by drug producers and a lack of independence of researchers is possible (5). A review of the literature implies that most pharmacoeconomic studies report positive findings for a sponsor's drug. However a more detailed analysis suggests that the main reason for positive results is that companies only sponsor economic studies where positive results are likely. It can be concluded that the best way to deal with the problem is to boost the public funding of economic research (6). The sponsor of the economic study should be clearly stated.

Perspective of the study

Whose viewpoint are costs and benefits considered from?

Health benefits and costs can be assessed from a different viewpoint called "perspective" of the study. There are three common types of perspectives in economic studies: a producer's perspective, a payer's perspective and a social perspective. The perspective of an economic assessment is important since one can derive different answers to the same question considered from different aspects. The selection of costs that have to be included (or omitted) in the analysis depends on the perspective chosen in the study. Therefore, the perspective has to be selected in the planning phase of a study and should be reported and justified by the authors. In general, the social perspective is the broadest and most appropriate for making financial decision because it leads to optimal decisions but other perspectives are also valid (4, 5).

Measure of health benefit

Are the main health outcome measures clearly stated?

An assessment of the clinical effectiveness of the two compared alternatives is a compulsory element of each comprehensive pharmacoeconomic study. In the *clinical practice* the medical doctors use different criteria for the effectiveness of a certain therapeutic intervention. Most commonly these criteria are intermediate, that is, directly related to the pathogenesis of a disease or a

drug action. More important but difficult to assess are the so-called end-point criteria, which are related to changes in mortality and/or morbidity, in the quality of life, etc. The *pharmacoeconomic studies* take interest in health benefits, which are assessed via different measures depending on the type of the economic analysis performed. Commonly health benefits are measured in terms of "natural units" (e.g. years of life saved, cases of heart attacks prevented, strokes prevented, etc.) or "utility units" (measured by quality adjusted life year (QALY), disability adjusted life years (DALY) and healthy years equivalent (HYE). All effectiveness and benefit measures and the methods for their assessment have to be mentioned in the economic study.

The validity of clinical and economic results can be generally regarded in two main aspects - internal and external validity. The internal validity refers to whether the results of a study describe a true causal relation between the intervention and the results (outcomes). The external validity refers to the generalisability and applicability of the results to other settings.

The primary initialisation of pharmacoeconomic studies is rare. Usually the pharmacoeconomic studies are based on the effectiveness data derived from a single clinical study or a review-synthesis of a few clinical studies. Every one of these options has certain advantages and weaknesses.

A single study is the source of clinical results assessed in comparatively ideal circumstances and these are indicators of efficacy. An issue of significance would be as to what extent the data of a clinical trial could be used in economic studies where the concern is aimed at effectiveness, i. e. what benefits and costs the investigated alternative is associated with in realistic conditions where the patients and the comparator are not selected and monitored (2). This issue remains open. Nevertheless, in order to improve the quality of economic evaluations, the randomised double blind controlled clinical trials are recommended as a gold standard of effectiveness data (1, 4, 5).

If the economic study is based on a single methodologically rigorous study the results are specified by high internal validity (4, 5, 7). A special attention should be focused on the study design, the relation between the study sample and the target population, the selection of patients and the comparability between the groups. The study design depends on the set goal and has to be appropriate in

order to clarify the hypotheses poised. One important factor influencing the generalisability of the results is the patients' population in the concrete practice as distinguished from the study population. To assess whether the patients in their practice can expect the same health outcomes, the readers need information about the basic patients characteristic such as age, gender, gravity of the disease, etc. as well as the criteria for including and/or excluding patients from the study (7).

The study sample is usually more limited than the target population for a certain health strategy. In principle the sample size is planned in advance to increase the probability of detection of statistically significant findings. The clinical study should report the determination of the sample size that would enable the detection of any important effect as statistically significant. The patients' selection has an influence on the validity of the results. The selection of the patients and their distribution in the groups has to guarantee random relations between the investigated intervention and the results (high internal validity). The patient groups should be comparable by number and basic characteristics, and if statistically significant differences are found they have to be discussed.

The compliance of patients is a negligible factor at a first glance but seems to be essential for the potential of the study in that it establishes significant differences between the investigated groups. When there is non-compliance the groups are similar. In reality the compliance is usually far lower than in the study and this has a certain effect on the generalisability of the results (4).

An evaluation based on the economic data collected during a single trial has a high internal validity. However, the results may have a low external validity (they may be non-generalisable) (7). This is due to the fact that the effectiveness rather than efficacy is assessed, the setting can be atypical, and the compliance higher than in a real clinical practice. An evaluation based on an overview of a number of trials is likely to be more widely generalisable because of an extensive range of patients and practice settings (4, 5, 7). A different number of studies can be included in the review. In order to improve the quality of the results the selection of the studies is usually performed by two or more independent researchers. The sources and methods of the study selection, study design, the criteria for including or excluding studies

from the review have to be described so that the readers would transfer the results to their own practice. The authors should discuss differences between the studies and how they influence the results. The review can express the results of the studies in a disaggregated form, or commonly the results can be combined using a meta-analysis.

Usually the clinical trials are not long enough to assess the end-point clinical outcomes such as mortality and morbidity. In this case or if the data are obtained from a variety of sources, previously studied data are not available or event rates of interest are extremely small; therefore modelling can be applied (4,5). Different types of modelling are used in economic evaluations to estimate both costs and/or benefits. Most commonly these types are specified as decision tree models and state transition models. When modelling is used the authors have to state the type and purpose of the model. The purpose of the model can be the transformation of the intermediate clinical outcomes into end-point clinical outcomes, to extrapolate costs and benefits for a different time horizon and to interpret the results in a different setting. When modelling is applied a sensitivity analysis is required to assess the validity of the model. A discussion of the potential limitations and implications of the modelling method should also be included.

Valuation of costs

Are the categories of costs considered appropriate for the perspective adopted?

Costs are composed of the unit price and the quantity of the resources consumed. Since the resource consumption and local unit prices differ from these used in the study, the costs data obtained may not transfer directly to another place and another time. Unit prices (unit costs) are the most frequently cited as a factor that generates variability in the economic results between locations (2). That is why the method of valuation of costs has to be clarified in order to allow the readers to make analogous calculations using their local prices. This is possible only if the quantity of the resources consumed and the unit prices are reported separately. There are three common types of relevant costs: direct, indirect, and intangible costs. Since there are different definitions of the types and categories of costs in health economics, it is useful that all costs included in the analysis be reported in detail. In this way the authors help the reader to find

out where all relevant costs are included and thus to facilitate comparisons with other studies. Readers should be able to distinguish costs by categories (for example indirect from direct costs) because each category has strengths and weaknesses (5).

When certain direct costs are deliberately omitted from the analysis the authors should discuss this issue so that the reader can understand the reason for this omission (i.e., whether these costs are negligible or difficult to collect). A number of contradictions exist as to whether and how the indirect and intangible costs have to be included in the economic analyses. On one hand, productivity may not actually be lost if a worker is absent for a short period. On the other hand, even for long period of absence, a previously unemployed worker may be recruited. Therefore, if the productivity changes are included in the economic analysis the authors have to describe this aspect as well as the reasons for the inclusion or exclusion of indirect costs (7).

Depending on the type of pharmacoeconomic analysis the authors can report average, marginal or incremental costs. The average costs are calculated by dividing the total costs for the intervention and comparator by the number of patients receiving them. The incremental costs represent the differences in costs between two alternative technologies. Marginal costs are the differences in costs due to the expansion or contraction of a program with one unit (e.g. increase or decrease of one day in the length of stay in hospital).

The pharmacoeconomic data can be obtained in a genuine economic evaluation but usually they are an additional part of a randomised clinical trial. Since the prospective pharmacoeconomic studies require time and funds, more frequently the retrospective pharmacoeconomic studies are performed by using data from previously conducted clinical trials. Different sources of data related to resource consumption and prices can be used in the economic studies such as medical papers, public prices and tariffs, etc., and these should be reported by the authors. The date to which resource consumption and prices relate, as well as the duration of the study, is important because it suggests the actuality of the results and the necessity for a discounting. The currency and any adjustment to inflation and currency conversion should be stated.

Synthesis of costs and benefits

In the cases when the assessed alternative is dominant (most effective and less expensive) both the benefits and costs can be presented in a disaggregated form (for example in a cost-consequence analysis). However, in most other cases a synthesis of costs and benefits is required and the results can be presented as cost-benefit ratios.

In cost-effectiveness analysis health outcomes are measured in natural units, which refer to mortality, morbidity or functional status, (e.g. 'life years gained', 'cases successfully treated', bed days, work loss days, usual activity days, etc.). The results are presented as cost-effectiveness ratio, e.g. costs per life years gained, costs per heart attack avoided etc. When a cost-utility analysis is performed, the health outcomes are converted in a commonly used composite measure, namely quality-adjusted life year (QALY). The results are presented as costs per QALY. In the cost-benefit analysis the outcomes are converted into monetary units and refer to the reduction in the indirect costs, such as productivity gains resulting from the therapy.

The most relevant information for the decision maker relates to incremental analysis, which presents the extra benefit that would be gained when compared with any extra cost (1).

Discounting

Are costs and benefits appropriately discounted?

In order to compare costs and benefits in a certain health intervention, they have to be related to the same moment. Discounting is a method that allows future costs and benefits to be reduced in order to obtain their net present value (NPV) (1). The rate of discounting is not conventional. There are debates over this rate and whether both costs and benefits have to be discounted at the same rate. The UK Treasury recommends a rate of 6% per annum (1, 8). The Washington Panel tends to use 3% rate of discounting. In practice, an annual discount rate of 5% (varying from 2 to 6%) is common in the published literature (4, 7). It is a reasonable practice to present both discounted and non-discounted results. In this way the readers can easily use the discount rate in their setting (1). Nonetheless, discounting is an important factor of transferability of the pharmacoeconomics results and is required when costs and benefits have occurred for more than 1 year (1, 4).

Allowance for uncertainty

Is an appropriate statistical analysis applied to sample data?

Is a sensitivity analysis conducted on uncertain parameters?

Without the appropriate consideration of uncertainty the reader may be unable to judge whether the conclusions are meaningful and robust. A review of published studies suggests that almost 20% of studies did not attempt any analysis to examine uncertainty (8). Three common types of uncertainties can be recognised (4):

- Extrapolation from primary data sources (for example when data have been modelled).
- Observed data inputs (when the patients and settings are different).
- Methodological controversy in methods and instruments used in the economic evaluations (when the alternative analytical methods exist).

If the economic studies are conducted concurrently with a clinical trial and observed data have been sampled from an appropriate population, this provides the opportunity to apply conventional tests of statistical significance to the treatment effect and the resource quantities or costs (1, 4). Except for sample data, the conventional statistical test is not sufficient and uncertainty usually handled using a sensitivity analysis (1, 4). A sensitivity analysis is a way of allowing for uncertainty in economic analyses, where the estimates for key parameters are altered in order to assess what impact they have on the study results. By a sensitivity analysis the authors explore whether their conclusions are valid for different patient populations and different settings. Via a sensitivity analysis it is possible to examine the variation in the effectiveness measures, but also costs, discount rate, etc. can be variegated. Simple sensitivity analysis (one-way or multi-way), threshold analysis, analysis of extremes, probabilistic analysis can be appropriate according to circumstances.

One sample test of generalisability is whether the results in a given study are also obtained in another setting. The authors' comparison with other studies helps the reader to understand if the results of a particular pharmacoeconomic study are applicable to other settings. But such comparison is reasonable only if the methods used are similar and settings in the different studies are comparable (1).

CONCLUSION

Pharmacoeconomic analyses are becoming a frequently used criterion for decision making in health care budgeting. As a fairly new field, there is still much to demand regarding the quality of pharmacoeconomic studies. The pharmacoeconomic studies cannot be universal since they include various settings, various patient populations and various costs of health services. Therefore, their results are impossible to be directly transferred beyond the study setting. At the same time, economic studies are expensive, time consuming and require professional expertise. Hence, the use of pharmacoeconomic results performed elsewhere in many cases is the only possible solution for the users needing economic assessments. This is the reason why bi-directional efforts are required. The first direction aims at a better quality of the performed pharmacoeconomic evaluations. For this purpose special rules and guidelines are set up which have to secure a transparency of pharmacoeconomic studies and generalisability of their results. Many institutions are established to assess health care interventions including their pharmacoeconomic characteristics. For example in the UK, the National Institute of Clinical Excellence (NICE) is responsible for making more efficient health decisions by applying health economic techniques (1).

The second direction of efforts addresses the users of pharmacoeconomic analyses. The aim is for the readers to get an idea as to what extent pharmacoeconomic results are correct and how these correspond to their own setting. For this purpose, different practical rules and checklists of questions that may be raised in the process of reading an economic study are developed. On the other hand, in order to facilitate the users, international databases (i.e. NHS EED,

EURONHEED) are created. They offer summarised and critically presented results of economic studies performed in different locations.

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