
The rationale of pharmacoeconomic analysis in rheumatologic indications

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ABSTRACT

Pharmacoeconomic analysis is aimed at supporting choices between alternatives available for the efficient management of specific conditions. Aim of the paper is to provide an overview of the main features of pharmacoeconomic evaluations, with the objective of providing the reader with the basic tools necessary to read and interpret or to design and conduct a pharmacoeconomic analysis in RA and in other rheumatic diseases. The paragraphs will cover in detail the definition of health economic evaluation and pharmacoeconomics, the alternatives to be compared, the perspective of the analysis, costs and effects (presenting in detail direct costs and effects, indirect costs and effects, intangible costs and effects and source of data), and pharmacoeconomic techniques.

Pharmacoeconomic analyses have to be conducted accurately to provide valuable information to guide the choice of options representing the best value for money without compromising the quality of care delivered. For this reason, as these analyses generally present some limitations, a very close and strong relationship between pharmacoeconomists and clinicians is crucial both in the design of pharmacoeconomic studies and in the interpretation of their results, and also in the development of more satisfactory methods and indicators.

Introduction

The high economic burden attributable to rheumatologic diseases and availability of new treatment options consuming a greater portion of health care budgets have stimulated increasing attention toward pharmacoeconomic evaluations to identify more efficient treatments (1-7). A similar trend has been observed in the field of medical devices and major technologies with development of health technology assessment (HTA) analy-

ses (8-10). As an example, significant progress in understanding the immunopathogenesis of rheumatoid arthritis (RA), combined with advances in biotechnology, has led to the development of new drugs, such as the inhibitors of the pro-inflammatory cytokine tumour necrosis factor α (TNF- α) (11). Introduction of TNF- α inhibitors has provided important new treatment options in the therapeutic approach for RA and, meanwhile, has sensitively impacted on the costs of treatment of these patients (12-17).

According to the results of a study conducted by Lundkvist and colleagues (14), there are around 6.7 million patients with RA in Europe (including the Russian Federation and Turkey), Australia, South Africa and North America. The total cost of this disease in 2006 was €45 billion in Europe and €42 billion in the US, and was close to €100 billion in all countries considered in the review. Of these, direct health care costs accounted for about €42 billion, representing around 1.4% of total health care expenditures in these Countries. In the same study, Lundkvist and colleagues (14) have also shown that the costs of RA varied with country, with an average of €17,000 per patient per year in Western Europe, and €5,000 in Central and Eastern Europe. The total cost of RA changes between countries for many regions, but one of the most relevant is the different use of biologic treatments, which has sensitively increased the cost of treatment (12-16, 18).

Pharmacoeconomic analysis is aimed at supporting choices between alternatives available for the rational management of specific conditions. The rational management of diseases is in first instance defined with respect to its quality and effectiveness. However, a further dimension to be considered is the efficiency of a treatment/programme compared with

the available alternatives. This dimension can be considered through pharmacoeconomic evaluations. Two different types of efficiency can be considered: technical efficiency and allocative efficiency. The technical efficiency may be crudely defined as the capacity of a programme to reach effects with the minimum cost possible. Allocative efficiency refers to a goal to keep opportunity costs at a minimum possible level. This has to do with the distribution and re-distribution of resources, considering various perspectives altogether (*e.g.* society). Accordingly, public decision makers are often concerned with allocative efficiency, while private parties (*e.g.*, industry) are generally interested in technical efficiency. The choice of the perspective may then influence the choice of the type of efficiency and, as a consequence, the technique of a pharmacoeconomic evaluation (19). The following sections of this article provide an overview of the main features of pharmacoeconomic evaluations, with the objective of providing the reader with basic background tools necessary to read and interpret and/or to design and conduct a pharmacoeconomic analysis in RA and in other rheumatic diseases.

Definition of health economic evaluation and pharmacoeconomics

Broadly speaking, economic evaluation can be defined as the approach aimed to compare costs and consequences (effects) of two or more alternative course of actions, which in healthcare generally include options to diagnose, prevent or treat a disease (19). In particular, pharmacoeconomics refers to health economic evaluations in which at least one of the compared options includes a drug therapy. To conduct an accurate pharmacoeconomic analysis it is necessary to clarify and decide on some key parameters, which are described below.

Alternatives to be compared

One crucial step for the conduction of a pharmacoeconomic analysis consists of deciding the alternative options to consider for the comparison. Pharmacoeconomics refers to health economic evaluations in which at least one of

the compared options includes a drug therapy. The alternative options may include any clinically relevant and available intervention such as a drug therapy, a different type of intervention (*e.g.*, surgery) or the option of no intervention.

Perspective of the analysis

Important to any pharmacoeconomic analysis is a comprehensive estimation of all costs and effects related to the disease and its management. The effects and the costs of using an intervention depend on which perspective, or point of view, of the analysis is adopted. Clarifying the perspective of the analysis is necessary because an item can be a cost from one point of view, but not from another point of view. For example, loss of productivity attributable to the disease or to its treatment is a cost for the patients and more broadly for the society; however, this is not a cost for the third party payer (*e.g.* National Health Service - NHS). The inclusion of loss of productivity or sick leave in pharmacoeconomic evaluations targeted to rheumatologic diseases increases significantly the costs from the perspective of the patient and of the society (20, 21). For instance, according to a pharmacoeconomic study conducted in Italy to assess the efficiency of biologic treatment of patients with psoriatic arthritis (21), the mean six-months health care cost (visits to physician, medications, hospitalisations, diagnostic procedures, etc.) was €883 per patient considering the perspective of the NHS. When adopting the perspective of the society, the total cost increased to €1,500 per patient-6 months, because it included also indirect costs (such as short-term absence/sick leave). The costs due to time lost from work or other usual activities (*e.g.*, housework, study) are typically not taken into account if the perspective of the third party payer is adopted, as it does not pay for these costs. Instead, a policy maker could be interested also in these costs borne from different perspectives, such as patients, caregivers, third party payer and healthcare provider (societal perspective).

The choice of the perspective may influence the choice of the either techni-

cal or allocative type of efficiency and, as a consequence, the technique used in a pharmacoeconomic study.

Costs and effects

Once the alternatives and the perspective of the analysis are clarified, costs and effects relevant for the analysis can be identified. After identifying them, costs and effects must be measured and, when appropriate, quantified in monetary terms. Both costs and effects can be categorised as direct, indirect and intangible.

The inclusion of each category of costs into the analysis depends on a number of factors, including the relevance of each item on the total cost (*e.g.* the loss of productivity and the cost of biologic therapy contribute importantly to the total cost in rheumatologic diseases) (12-16, 20, 21), the perspective of the analysis (*e.g.* the societal perspective requires the computation of loss of productivity, while the perspective of the third party payer does not require this item) and the availability of data (*e.g.* quantification of loss of productivity is particularly difficult to be performed). The adoption of standards for economic evaluation or matrix of cost domains applied to rheumatic diseases would greatly facilitate national and international comparisons (22).

A brief description of costs and effects category is reported below.

Direct costs and effects

Direct costs and effects refer to items that are more closely related with the disease and its treatment. For instance, costs of drug treatment, hospitalisations, surgery, physiotherapy, costs for the monitoring and treating toxicity. Direct costs can be further divided in two subgroups: medical costs (drugs, specialist consultations, hospitalisations, etc.) and non-medical costs (patient's travel costs, formal care at home, etc.). Effects can be expressed using different outcome measures. Final outcomes can include radiological damage, swollen joint count, functional capacity, Disease Activity Score, disability-days averted, lives saved, life of years saved (12, 23). However, sometimes biomarkers are used, *e.g.* C-reactive protein,

erythrocyte sedimentation rate (24). A biomarker is a biochemical or clinical parameter that is related to a final outcome (25). Biomarkers are frequently employed as surrogate endpoints in studies targeted to new health interventions. The use of biomarkers is generally more convenient than the use of final outcomes, because this may facilitate the reduction of the costs of the study or even to make the study feasible, due to the need of a reduced size of the study sample and a shorter study duration. However, to obtain reliable results on the efficiency of a treatment, it is fundamental that the biomarker used to estimate the efficacy of a treatment is valid and correlated with the final outcome of interest (*e.g.* disease activity and radiological damage).

Indirect costs and effects

Indirect costs and effects refer to productivity variation due to the disease and its management. Costs are associated with lost or impaired ability to work or engage in leisure activities, while effects are associated with gain or improvement. In conditions such as RA, indirect costs are extremely important; historically, indirect costs accounted for the majority of costs of RA, which remains the case in many patients at this time (26-29).

The quantification of indirect costs and effects is complex and often difficult. There are at least two possible ways that can be used to quantify indirect costs: the human capital approach and the friction cost method. Through the human capital approach, the loss of productivity attributable to the disease and its consequences in terms of absenteeism from work is converted in monetary terms multiplying the time (days, hours) lost from work due to the disease by the patients' remuneration. However, there are some caveats to be considered when using the human capital approach: first, the value of time lost is quantified only on individuals who have paid work, while there are subjects that do not have a paid work, *e.g.* students or housewives, but who can have productivity losses due to their condition. Furthermore, these valuations could overestimate the true cost to society if individu-

als are to be taken out of the workforce because of their disease. For example, for short-term absences, losses of productivity could be compensated for by the worker when returning at work, or by her/his colleagues. For long-term absence, the employer is likely to hire a replacement worker. Therefore, the amount of productivity lost depends on the time and cost of organising the replacement (19).

The friction cost method has been proposed as an alternative to the human capital approach (30). The basic idea is that the amount of production lost due to disease depends on the time organisations need to restore the initial production level. This friction period is likely to differ by location, industry, firm, and category of worker (19).

In addition, indirect costs may not include a full accounting of the impact of disease. For example, even if patients go to work, they could work with less productivity because of their disease, known as "presenteeism". Presenteeism is relevant especially in patients with RA, however, it is usually not included in the assessments of indirect costs. In many contexts, such as RA, the condition could also interfere with patients' career and related increases in income that would otherwise have been earned without the disease (31).

Moreover, the lack of productivity related to home care provided by a relative or friend, known as informal care, should be considered as well, but usually is not included.

Intangible costs and effects

Intangible costs and effects refer to consequences of a disease and of a medical programme in individuals' Quality of Life (QoL). Until around seven decades ago, the main objective of medical interventions focused on the improvement of physical aspects of life, *e.g.* amelioration of specific symptoms and signs of diseases, increase of quantity of life. Over the years, advancements in the medical and related sciences have allowed to dramatically improve the outcome and prognosis of many diseases. As a result, years have been added to the life of individuals. However, not necessarily the quality of

life could always be improved as well. During the Eighties the parameter of QoL was recognised to be important for measuring health and outcomes of interventions, together with the traditional and standard clinical parameters. Initially, the focus was on complementing or balancing the emphasis that had been placed on survival time, especially in areas such as oncology. In addition, there was a move to monitor long-term care for chronically ill people, particularly when cure was not seen to be an option, such as in rheumatic diseases. The focus was shifted to consideration of the patient's perspective on his QoL, in contrast with the opinions of physicians or other healthcare professionals. It was recognised that changes in the patient's QoL are among the main determinants of demand for care, compliance with treatment regimen and satisfaction. It was understood that this parameter, which allows the assessment of patients' health according to their perception, is to be taken into account in the evaluation of healthcare. As a consequence, considerable research has been conducted to produce appropriate instruments and to assess QoL in many clinical conditions. From 1990 to 1999, for example, the number of published reports about the development or evaluation of QoL instruments rose from 144 to 650 (32).

Although easy to conceive in an abstract manner, QoL is difficult to define. Numerous attempts have been made in this regard. Of the several available, the most widely used definition is the one by the World Health Organisation (33): "Quality of Life is individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, concerns. It is a broad ranging concept, incorporating in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationships to salient features of the environment. This definition highlights the view that quality of life is subjective, includes both positive and negative factors of life and is multi-dimensional". In healthcare, the term Health

Related Quality of Life (HRQoL) is frequently used. More specifically, HRQoL can be defined as the “impact of an accident/disease and of its management on the involved individuals’ QoL” (34). Hence, HRQoL is more focused on QoL related to phenomena that involve individuals’ health.

Among the instruments available to assess HRQoL we can distinguish between disease-specific and generic instruments, and between profiles and indexes (35, 36).

Disease-specific instruments have been developed for one particular condition or a range of related conditions, *e.g.* the arthritis impact measurement scale (37). Aim of these instruments is to obtain specific information on the target condition. However, comparability of HRQoL is compromised when studying different diseases. Furthermore, these instruments do not give a comprehensive measure of HRQoL and therefore cannot be used to compare the cost-effectiveness of programmes in different disease areas. On the other side, generic instruments are aimed to be applicable to a wide range of populations defined by age and gender, type and severity of disease, culture. The SF-36 (38) and the EQ-5D (39) are among the most frequently used generic QoL instruments worldwide. However, in some situations, these instruments may exhibit a lower precision or responsiveness to changes than disease-specific measures. Generally, the use of a battery of instruments, including a generic questionnaire and a condition-specific one can allow to combine the different and complementary advantages of each instrument.

Profiles describe HRQoL through a number of dimensions of health, while indexes allow to summarise in one number the information attributable to more dimensions. Because they are more informative than indexes, profiles may be more useful in clinical settings. On the other hand, profiles present some disadvantages for economic evaluations, because they generally provide different information that cannot be compared. Furthermore, to be inserted in a pharmacoeconomic analysis, the index should be indicative of the preferences of individuals for the outcomes.

These preferences can be included in a utility index. Utility can be defined as the preference that individuals have given to health states. A utility index is expressed on a scale anchored between 0 (death) and 1 (perfect health). Utilities can be measured directly using specific techniques, such as the standard gamble and time trade-off (19, 40), or derived from health state systems, such as those developed for the EQ-5D or the Health Utility Index (39, 41, 42).

The EQ-5D is a generic instrument that includes both a profile and an index, and allows to obtain an utility index (39). The standard version of the EQ-5D (EQ-5D-3L) consists of two parts. One part includes a profile (or descriptive system) with five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), which allow describing health according to three levels of severity (no problems, some problems, severe problems). The second part contains a Visual Analogue Scale to provide with an index ranging from 0 (worst level of HRQoL) to 100 (best level of HRQoL) a measure of individuals’ health perception. Furthermore, the EQ-5D was developed to obtain a utility index through the conversion of the answers provided with the profile into one index anchored between 0 (corresponding to death) and 1 (corresponding to perfect health). The utility index can be used to calculate the Quality Adjusted Life Years (QALY) parameter (43), which is generally used to conduct Cost-Utility Analyses.

In order to improve the potentialities of the EQ-5D, new versions of this instrument have been recently developed in a number of different languages: the EQ-5D-Y, to be self-completed by children and adolescents aged from 8 years (44-46), and the EQ-5D-5L, in which 2 levels of severity are added in each domain (47, 48).

Source of data

The availability of good quality data on the effectiveness of the options to be compared is crucial to conduct an accurate pharmacoeconomic evaluation. Different sources of data are potentially available. A major source of data is the existing medical literature. In particu-

lar, randomised controlled clinical trials (RCTs) are considered the most accurate source to assess the efficacy of a treatment option compared with the alternative (49). However, randomised trials have a number of limitations when applied to real world results, which often differ greatly from the carefully controlled settings of the clinical trial. For example, patients enrolled in RCTs generally are highly selected, the comparison is made with placebo rather than another active therapy that can be of interest for the pharmacoeconomic analysis, the patient is closely monitored to ensure compliance with therapy. Ideally, pharmacoeconomic evaluations should incorporate data on effectiveness, rather than on efficacy, but these could be not available from RCTs.

A more reliable source of data for a pharmacoeconomic evaluation may have to be drawn from more naturalistic studies, such as observational studies. Alternatively, it could be worth integrating the data available from using additional sources, such as conducting additional clinical trials with a more naturalistic design, using data from systematic reviews of literature on effectiveness (50). Nowadays, many more economic evaluations use data from different existing studies and incorporate these data into economic decision models (51). One main advantage of economic models is that they allow estimation of costs and consequences of alternative options beyond the time horizon considered in a RCT (52, 53). Furthermore, this approach could allow to analyse together different data from different studies and to obtain more comprehensive estimates applicable to wider settings and target populations (54). Decision trees, Markov models, and Monte Carlo models are examples of decision models that can be used in the pharmacoeconomic analysis (53). Every model has its own advantages and disadvantages. The choice of the model to be used for an evaluation is based on a number of aspects that depend on the economic analysis to be performed (55).

A further source of data that is increasingly used in recent years is the administrative database (56-58). Most major

health agencies collect in a database all administrative data records to monitor and track services provided. Administrative databases are used to record the details about each individual receiving the service and the information on characteristics of hospitalisations, medical consultations, drugs prescriptions, home care visits, diagnostic examinations. Among the advantages of using data from administrative databases, a very important one is that they provide data through extended periods of time (several years). However, when performing economic analysis using administrative datasets some important aspects must be taken into account: for instance, not always these databases capture all direct medical costs related to the target disease. Furthermore, they do not incorporate other items, such as indirect and intangible costs or effects. This could be an important limit for studies targeted to conditions such as those in the area of rheumatology, where disease and treatment consequences on productivity and on HRQoL of the patients are particularly important.

The use of more sources of data could help to combine the advantages of each of them and overcome their limits, hence, to obtain more complete data for obtaining more reliable pharmacoeconomic results.

Sensitivity analyses

There are situations where the data relevant for the analyses are not complete or do not exist and cannot be obtained with the available data sources. Further uncertainty could depend on the different methodologies used to analyse the data, on the availability of imprecise data, on the need to generalise results to other settings and countries, etc. (59). Sensitivity analyses are instruments aimed to handle uncertainties in pharmacoeconomic evaluations. They are aimed to assess the robustness of the assumptions and the impact of the uncertainty on the results obtained with the main analysis. For example, if the true values of time off work in a population of patients with RA are unknown or only a plausible range is known, a sensitivity analysis can help to understand how the uncertainty significantly impacts the results

and how acceptable are the assumptions made to fill the lack of data.

Pharmacoeconomics techniques

The primary requirement of pharmacoeconomic evaluations is the comparison of two or more alternatives with respect of both costs and effects. This comparison can be carried out through different techniques. The main pharmacoeconomic techniques are: Cost-Benefit Analysis (CBA), Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA). The feature that distinguishes the different techniques of analysis is the manner in which the effects of the alternative options are valued.

Many studies available in literature focus only on the description of costs of a disease, or on a treatment for a disease. Cost of Illness (COI) studies or Burden of Illness (BOI) studies fall into this category (19). These studies facilitate description and quantification of the socio-economic impact of a target condition, from the perspective either of the third party payer (as regards healthcare costs), or of the patients (loss of productivity, health related quality of life), or of the society as a whole. Estimating the cost of an illness can be a useful aid to policy decision making to underline the importance of a disease with respect to its socio-economic impact, together with the impact on morbidity and mortality (60), when compared with the burden of other diseases (61). Furthermore, these studies may allow identification of drivers of costs of a disease and may help in the design of more appropriate pharmacoeconomic evaluations. However, these studies cannot be considered as pharmacoeconomic evaluations, because they do not allow comparisons of costs and effects of alternative options, hence do not allow identification of programmes according to their relative efficiency.

A method that is sometimes adopted in pharmacoeconomics is the cost-minimisation analysis (CMA). This technique focuses on the comparison of costs only and can be applied when the alternative interventions are evaluated and demonstrated to be equivalent in terms of outcomes. Hence, the economic analysis can focus on the comparison of

costs associated with each intervention. CMA can be identified as a subset of the typical pharmacoeconomic techniques, which are described below.

Cost-Benefit Analysis

This technique was developed and initially applied in the sector of waterway infrastructure between the Thirties and Forties (62).

The technique of cost-benefit analysis (CBA) allows to compare in monetary units both costs and effects of alternative programmes. The result obtained from a CBA typically is reported as a net benefit, obtained from the difference between costs and effects of the compared alternatives. Since in CBA costs and effects are expressed in monetary units, there are some advantages attributable to this technique: first, it allows assessment of all costs and effects, including those that are not directly related with clinical outcomes (*e.g.* treatment satisfaction, patients' preferences) and that are difficult to be considered in the analysis if measured in different non-monetary units. Second, it allows comparison of options applicable to different sectors. Hence, this technique is straightforward to assess the allocative efficiency of investments targeted to different sectors (*e.g.* in the comparison of investments targeted to healthcare vs. public transport sectors).

While items such as drug treatment or hospitalisations are naturally expressed in monetary units, other items such as those related with health outcomes must be translated into these units, to be included in a CBA. There are several approaches to the monetary valuation of health outcomes: the human capital, revealed preferences and stated preferences of willingness to pay are among the most frequently used approaches (19, 63). However, quantifying in monetary units all the effects and costs can be very difficult and can raise some ethical considerations (*e.g.* on the assignment of a monetary value to a life).

Cost-Effectiveness Analysis

The paradigm of CEA for health and medical practice was published the first time in 1977 in the New England Journal of Medicine (64). Cost-effec-

tiveness arises from the difficulty in CBA analysis to convert all costs and benefits attributable to the programme or intervention into monetary units. In CEA, outcomes are measured in physical units such as lives saved or life-years gained, disability-days averted, swollen and stiff joints, joint damage, functional capacity, Disease Activity Score, American College of Rheumatology response criteria, etc. (12, 23).

The results of a CEA are expressed as incremental cost-effectiveness ratio (ICER), corresponding to the ratio between the difference of costs of the two programmes (numerator) and the difference of effects of the two programmes (denominator). The ICER shows the amount of incremental cost per unit of additional effect.

Since it does not require some items to be reported in monetary terms, CEA facilitates more easily conducted pharmacoeconomic evaluations and is generally preferred to CBA. However, the technique of CEA presents some limits (as do all methods). The main problem with CEA is that it does not allow comparisons of programmes for which effects are expressed with different parameters, such as programmes that are applicable to different conditions. Hence, CEA does not allow to comparing policy purposes across programmes targeted to different conditions.

Cost-Utility Analysis

Cost-Utility Analysis (CUA) was developed to overcome some of the limits of CEA, particularly the lack of capacity to compare interventions with effects reported in different units. In CUA, the incremental cost of a treatment is compared to the incremental health improvement attributable to the treatment, in which health improvement is generally measured in quality-adjusted life-years (QALYs) gained. The results are expressed as incremental cost per QALY gained. The QALY combines life expectancy and HRQoL by weighing life-years with a quality index named utility (43). For instance, living 2 years with a utility of 0.5 corresponds to one QALY, corresponding to the same value assigned to living 1 year in full health. The advantage of QALY as a measure

of health outcome is that it can simultaneously capture gains from quantity and quality of life, and combine these into a single measure.

For this reason, the distinguishing features of CUA are that multiple outcomes can be incorporated and the outcomes are not just measured but are valued according to their desirability. Because of the similarities between CEA and CUA, some authors do not distinguish between the two, a possible problem in the literature, in which CUA may appear under the label of CEA.

There are a number of situations where it could be worth using CUA. For instance, when HRQoL is among the most important outcomes, such as in RA, in which it is difficult to study mortality, the interest has been focused on how well the different programmes improve the patients' physical function, social function, and psychological wellbeing. In other contexts, the programme affects both morbidity and mortality, which should be combined in a common unit of outcomes, such as in cancer.

Also, if the objective is to decide where to allocate resources between different programmes applicable to different conditions (e.g. expansion of neonatal intensive care, treatment of hypertensive patients, expansion of rehabilitative services provided to post-myocardial infarction patients), it is important to have a common unit of output for comparison.

However, not always QALYs data are available or relevant enough for the target condition. In these cases, the technique of CEA constitutes an efficient approach to conduct the pharmacoeconomic analysis of interest.

Conclusions

Use of pharmacoeconomic evaluations to inform health care bodies for their decisions is increasing. In addition, there is increasing interest from physicians and other health care providers to consider both costs and benefits of interventions targeted to specific groups of patients. Given the current health-care environment, pharmacoeconomic issues can sensitively condition the use of new and more expensive therapies in rheumatology. Taking these issues into

account will help healthcare providers and budget holders to choose the most efficient strategies for patients. In other words, pharmacoeconomic analyses constitute a useful tool for identifying the options that allow to reach satisfactory results at an acceptable cost, optimising the net benefit deriving from the use of scarce resource available.

Pharmacoeconomic analyses must be conducted accurately to provide valuable information to guide the choice of options representing the best value for money without compromising the quality of care delivered (65, 66). For this reason, as these analyses generally present some limitations, a very close and strong relationship between pharmacoeconomists and clinicians is crucial both in the design of pharmacoeconomic studies and in the interpretation of their results, and also in the development of more satisfactory methods and indicators.

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