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# The transferability of international economic health-economic results to national study questions

Innovative drugs and other health care services are almost entirely tested today for both their effectiveness and safety and from the point of view of their economic efficiency. For this purpose multinational study data are usually available. However, this kind of data information has considerable disadvantages, as the economic relevant parameters can differ greatly according to place and country of origin. In addition to the problems associated with this, there are differing structures particularly in price and quantity consumption in the production of similar health products. We discuss current practice in order to solve these problems. Various approaches are presented and assessed as to how data from foreign studies can be transferred to one's own health service. In addition to the effects of capacity and scale, which can lead to considerably varied cost structures, the epidemiological and demographic framework conditions, the associated incentive structures, and their significance for the particular use of resources are discussed. There are different approaches to aligning data based on a foreign study to another health system. The initial solutions apply not only to the transfer between health systems in different nations but also at a national level if there are different treatment patterns in any particular country. In addition to a subanalysis within a nationally based context involving the entire data, smaller exploratory studies are possible which can be adjusted to these data. Different uses of resources will mean that there is a difference between the transfer of absolute and relative values as well as in procedures concerning decision analysis. Validity, transparency, and comprehensibility are considered particular requirements for such models, as well as adequate information about the supply situation in a particular health system.

**Keywords**

Modeling · Clinical study · Evaluation · Transferability · Health systems

## The significance of multinational data in health economic studies

In recent years health economic studies have become internationally more and more decisive in supporting the process of health policy. Considerable importance is attached to research of this kind in countries such as France, the United Kingdom, and Australia, especially on decisions relating to the replacement of drugs. Even in other medical services, however, the corresponding economic study results are consulted in order to decide, for instance, on the scientific feasibility of including them in the service catalogues of a particular national health system [5]. The question then arises as to how far the results of economic studies can be transferred from one country to another. Surprisingly, this issue has attracted little attention so far, and only individual empirical or conceptual work has been done on it [8].

In the case of drugs, this problem arises largely because it purely involves larger medical innovations, by which medical effectiveness and safety as well as economic viability is almost entirely judged today, and for which, as a rule, only multinational study data are available. Such a global study design has advantages for evidence of medical effectiveness and safety as the extensive regional cover and the large number of centers guarantee greater statistical safety than if participating patients are derived from one only a single region or clinic.

From an economic point of view this data survey is inclined to be problematic: thus the economic relevant parameters (i.e., the number of hospital days, the number and type of necessary laboratory tests or intensive medical treatment) within this study and based on each survey location, can differ considerably. By exact comparison – based on varied supply settings – the United States and Western European clinics frequently show greatly differing results in the cost of an intervention, and in possible savings or additional costs, to comparable alternatives [10].

This is one of the most serious disadvantages of the piggyback design in multicentric clinical studies. Here the economic evaluation is virtually imposed on clinical tests to include favorable study conditions of two comparable groups for economic analysis as well

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Table 1
**Issues related to transferability of health economic study data**

| Area of concern | Possible problems |
|---|---|
| Study design | • Multinational design (with different economic parameters in each centre)<br>• Number of patients in national sub-group not sufficient for statistical analysis<br>• Protocol driven cost<br>• Underestimation of resource consumption due to high documentation duties |
| Availability of prices | • Definition of prices may differ<br>• Factors important for pricing such as scale, the level of detail etc. may differ<br>• Study perspective may differ<br>• Definition of the quantity to be evaluated may differ |
| Comparability of resource consumption | • Capacity and scale effects (technological context) may differ<br>• Epidemiological context may differ (e.g., different case mix)<br>• Demographic context may differ (e.g., age structure)<br>• Differences in the institutional organization for determining health services (e.g., existence of a general practitioner system)<br>• Differences in the *incentive structures* in national health services (e.g., existence of a diagnosis-related group system) |

as the contemporary nature of the data survey, very comprehensive monitoring, and organizational integration of different centers. In many instances only the consumption of resources and the medical results of the study sample are published [18]. With this procedure several problems arise: the contrasting uses of resources, the varying structure in individual countries (or within one country in several institutions) [19], and also the degree of reality surrounding the study conditions. This means that certain tests in clinical investigations are only carried out for study protocol purposes (i.e., higher use of resources than in reality).

On the one hand, these investigations (protocol driven costs) inflate the resource consumption in all treatment countries in the study. On the other, protocol-driven investigations can also deflate the resource consumption: certain resources for every day practice are underestimated because, for example, suboptimal use of resources are less likely considering the high documentation duties in clinical trials [6].

In clinical studies the transfer of study results to foreign health systems has always been common practice. This is primarily because such clinical studies are based on very prescribed study protocols with ideal model study conditions, which may only have a marginal claim to representing the real everyday world of medicine. Substantially more must be determined by clinical studies as to whether, in the case of a particular health service under given study conditions, any positive treatment at all (as far as health improvement is concerned) can be statistically verified, and whether undesirable effects (side effects, complications) occur. It is assumed that the medical effect on all patients is the same, and that a pooling of centers and countries presents no problems [8]. Clinical studies take for granted that the results are universally acceptable. However, this is unlikely to be the case.

Multinational clinical trials not only improve the representativeness of patients, but also allow a quicker recruitment of patients. The difficulty in recruitment generally means that often there is an imbalance in patient numbers at different centers. Inevitably, some centers have more patients than others, and the statistical power at centers with few patients may not be achieved. It is also likely that the trial is powered for clinical endpoints rather than economic endpoints.

The *internal* reliability of data is thus highly conditioned by clinical studies in the study design [1]. However, the *external* economic validity of study results, as far as daily treatment practice is concerned is much less certain. In spite of these problems the increasing number of economically viable investigations into the health service lead to an increase in multinational data sources consulted for economic analysis. Particularly in the case of smaller countries and markets, and most often for cost reasons, data sources from foreign countries are the only way of carrying out a justifiable cost analysis for efficiency in the health service. Similar problems arise with reviews of international study literature to sum up evidence about cost-effectiveness from preexisting work ("secondary analysis") [9].

The objective of this article is to discuss current practice in solving these problems. Various approaches are presented and assessed as to how data from foreign studies can be transferred to one's own health service. These attempts at solutions apply not only to the transfer *between* health systems in different countries but also at a national level, because there is both a difference in the pattern of treatment within one country (e.g., from one clinic to another) and associated differences in the uses of resources [13]. Finally, these procedures can also be applied to the above appraisal of a Health Technology Assessment or to other reviews of economic studies of health systems, if the aim is to determine a certain (national or regional) health system on the basis of individual data derived from different settings.

## Comparison of the use of resources and costs in multinational studies

In this section we discuss some issues concerning aspects of comparability in multinational studies. These aspects are summarized in Table 1. We first review some possible problems in pricing which might lower the comparability of study data collected in different countries. We then discuss problems in the transfer of resource consumption data from one country to the other.

### Comparison of prices

The cost of a measure is the product of price and quantity vector. In theory the

strict separation of price and quantity vector is paramount. It is nevertheless questionable whether such a separation is at all possible. The applied amount affects the individual price, and the individual price influences the decision as to whether and how often a measure should be applied. A separation and substitution of national price vectors may therefore be inappropriate [8].

The availability of price data differs among countries and definitions of prices or how these values were derived also vary. Even in major markets, price data can be difficult to acquire, such as in Japan. Often analysts use a single set of prices to evaluate the costs of all the quantities (from all countries) in the trial. This can inevitably lead to over or underestimation of costs for particular countries in the trial.

In addition to the problems in acquiring the specific prices in each country for certain goods (e.g., medicaments), services (e.g., fees for an hour's physiotherapy) or medical procedures (e.g., the entire cost for intensive diagnostic cardiological treatment), the quantity framework for drawing up a health service that is specific to each country cannot be precisely obtained from the data of other health systems. However, it is possible to obtain approximations which can be interpreted and should be taken into consideration as regards the problem of transferability of study results, which we deal with below.

For the sake of simplicity let us presume that the quantity structure in the country of origin is the same as that in the target country of the study. Subsequently, national prices must be determined which correspond in value to the resources used. Even in this ideal case a simple substitution of prices may not be adequate, as pricing is dependent upon factors such as scale, the level of detail, bottom-up/top-down derivation, opportunity costs/charges etc. In addition, it is necessary to include the same study perspective as the country of origin, otherwise the pricing is incorrectly allocated. If resource consumption was levied from the point of view of hospital management, calculations made from a catalogue rate would not be a sufficiently exact basis for calculating prices, as rates in principle would be more inclined towards the viewpoint of health insurers or the national health service.

A further problem of assessment is the definition of the quantity to be evaluated. This differs considerably from country to country because of institutional factors. While it is usual in the United States, for example, for outpatient visits to physicians, or particularly the number of physician contacts to be recorded, this is less important in Germany as far as calculations of medical services are concerned. Each subsequent visit means that the outpatient physician simply receives (in addition to individual services) a relatively low basic fee per patient contact. If the United States pattern of data origin showed only the number of the contacts made, it would be insufficient for the calculation of German costs. In such cases, for example, the "usual" individual services per physician could be obtained in advance from the particular target country in order to apply the United States data. Such a cost measurement model (for example, the calculation of fees for individual services, with data on flat rate physician contacts) would lead to prices and costs no longer exactly reflecting those in the country of origin.

If the amounts to be quantified have been ascertained in an international study protocol, the problem exists of allocating national prices to each of these quantities. For reasons explained above this is not always possible directly, and therefore one must fall back on indirect methods instead. One of these indirect methods is the *basket of goods,* which was described by Schulman et al. in 1998 [18]. Seven countries took part in such a study. In each of these countries prices for certain procedures were to be levied, but the price lists showed varying degrees of discrepancy. To prevent this disparity the first stage was to define a basket of six different services, for which prices were available in every country. Every service, according to the average frequency of its use in the study as a whole, went into the basket. The result was seven national prices for the standard basket which was converted into one currency (in this case United States dollars). In stage two an index list was drawn up in which the basket prices were always compared in pairs taken from two countries (e.g., country 1 vs. country 2; country 1 vs. country 3). The result showed 49 comparable figures which expressed the differential basket price level (e.g., country 1 vs. country 2=0.74). If a price in a certain country is not available, the prices for this procedure are taken from other countries and multiplied by the relevant ratio. The average value is obtained by adding the resulting values and then dividing them by the number of countries for which this figure is available. This is used as a substitute for the missing national price. This method only works, however, if a price is available for the procedure in at least one country. If this is not the case, the prices for all countries must be generated in another way [18].

### Comparability of resource consumption

There are also a number of problems in the transfer of resource consumption from the original country to the target country. For example, the question of perspective must be examined. Even if all countries operated from the same perspective (i.e., that of the cost bearer), consumption of resources under consideration could vary because of a service catalogue differential.

In the matter of resource consumption Welte and Leidl [20] differentiate between technological, epidemiological and demographic contexts, as well as the division of technology and incentive structures. Capacity and scale effects belong to the *technological* context, which can lead to very different results depending on the exploitation of available capacity in the different countries. If, for example, a comparative technology is selected in the country of origin on account of its particularly large market share, and if this technology is hardly distributed in the target country, considerably different cost-effectiveness quotients may be produced due to their different capacity utilization or learning effect, which could not be attributable to the evaluated technology.

In the technological context there could be very different specialist factors that come into play with regard to executive personnel, which may have a considerable effect on costs. Thus, compared to a country in which the relevant technology has only recently become effective, the average time required for carrying out a health service function can be shortened, for example, by the acquirement of skills once these have been

fed through the system over a longer period. Added to this, various personnel can be engaged in widely identical work, greatly affecting the cost structure. Thus activities which are performed on principle only by physicians in many countries can be carried out by ancillary staff in others.

At any rate, identical health services can be practiced alternatively from country to country. The complication rate, for example, could be comparatively higher in a country where the regulations on sterility are less strict than in another country. Also, the supporting drugs deployment can vary in its standards: in some countries extremely potent drugs are deployed very early on in the course of an illness, partly even preventative, whereas in other countries which have a markedly different treatment pattern, particular drugs are only used when a particular complication arises (e.g., prevention against cytomegalovirus in transplants) [17].

The *epidemiological* context particularly comprises different incidences and prevalence of important illnesses that are specific to a country because in this way the particular case mixture is affected. This refers as much to the age structure, gender apportionment, and the distribution into grades of seriousness, as to the incidence and prevalence of comorbidities. If, for example, in a country where local nutritional habits or effective prevention of certain diseases means that certain illnesses only appear at a later average age or with less probability, as a rule the cost structure of the treatment is altered in so far as these illnesses are dependent on age or cost per patient.

In a *demographic* context, in addition to the above variables of age and sex, life expectancy and aspects of reproduction are of importance. Especially in a cost-effective analysis, mortality is frequently cited as an important factor in result parameters. If the data on life expectancy in the country of origin is less in relative terms to that in the target country, it is very probable that a comparably high addition in longevity can be attained through the evaluated intervention. However, in a country in which there is a relatively high average life expectancy it is less probable that a similarly large mortality effect is reached due to the higher starting level. An uncritical acceptance of study data from a foreign context would lead to an overestimate of the cost-effectiveness ratio in the target country. Analogous to this is the cost-need analysis in which changes in mortality also represent an important parameter. In reproduction the average age of conception is particularly important as this can have a statistically verified effect on the incidence of certain genetic diseases as well as complications in pregnancy [4].

Even at a European level there are considerable differences in the institutional organization for determining health services, i.e., the division of patients' treatment into various care levels such as general practitioner, specialist, and hospital. In different countries with a general practitioner system a series of services are provided exclusively by general practicioners which in other countries would be mainly carried out by specialists. Equally as differentiated is the access (and thus also the length of stay) in hospitals. In United Kingdom, for example, specialist work is mainly conducted by hospital consultants, whereas even the common strict division in other countries between outpatients and hospital care is less important.

Finally, different *incentive structures* in national health services are not unimportant in their bearing on the respective measurable use of resources for determining comparable services. In a hospital system that is financed on the self-sufficiency principle and exclusively with equal daily care rates, generally greater uses of resources are to be expected (and empirically more ascertainable) than in countries that have a more flat rate payment system (such as remuneration for a case flat rate system). In the latter remuneration system there is an incentive for the service provider to keep his own costs down, so that the revenue received (whatever the operational targets may be) cover costs, or provide a profit. This can also be applied to payment for outpatient care [15]. This discussion is linked to the possibilities and effects of offer-induced demand, when a physician, by virtue of his advantage in medical knowledge over his patient is in a position to decide for himself about a considerable part of the demand requirement. If the number of physician contacts in a health system is thus considerably higher than those in a comparable country, the transferability of study data is again restricted.

According to each individual case in the appropriate study, the above technological, epidemiological, demographic, and system-inherent factors of influence are of varying importance for the transferability of foreign study results to other health systems. It is therefore not possible to apply generalizations about which modifications to the original data are necessary in order to reach valid statements in the target country about the economic advantages of a health service. Consequently the advice in the following section about the practical procedural method in the transferability of data must be discussed separately and carefully for each situation.

## Attempts in the transferability of study results on other health systems

It is clear from the preceding sections that there is a large demand for the transferability of study data between health systems for the purpose of health economic evaluation studies. At the same time, reference was made above to the associated methodological problems. We now present and evaluate different methods which have until now been used to solve these problems.

In this section we discuss different attempts to transfer study results to other health systems. These attempts are based on different assumptions about the relation of cost differences in the data from the country of origin and the target country. The first assumption of identical or similar resources in the countries concerned is primarily discussed, followed by a review of methods which do not assume a similar use of resources.

### Identical or similar uses of resources

If identical or similar uses of resources are assumed, we must first differentiate between studies which were carried out multinationally (in the target country, among others) and those that have been completely carried out outside the target country. In the first case, the costs and results of the treatment of at least part of the study population are known and a national subanalysis could be con-

sidered. If no data or an insufficient amount of data from national sources are available from the multinational trial, exploratory studies for the adjustment of data are conducted; these are discussed in the second part of this section.

### Subanalysis of the study data

Willke et al. [21] have shown that under specific circumstances by means of linear regression and multivariate analysis, it is possible to draw conclusions from these data about cost-effectiveness in the target countries. In the example of treatment for an aneurysm conditioned by a meningeal hemorrhage the authors showed that for five participatory countries in a clinical study there were considerable differences in the average hospital costs and mortality rates, data which could be used for analyses in specific countries.

Due to the limited statistical significance of subanalyses of individual patient populations this form of assessment, however, is restricted to relatively large cost/result differences between countries. A solution could be by the collection of countries with similar resource consumption. It is a matter of compromise between the largest possible basic totality (because of the statistical significance of the results) and the most proximal locality (to reach relevant statements about the national health system). The question arises, however, as to how one should define "similar" uses of resources. As there are many different resources, group formation is often difficult or even impossible.

A good possibility of pooling always exists when the major determinants of cost differences between countries can be identified. In a myocardial infarct study the frequency, for example, of diagnostic catheterization as the major determinant was ascertained [14]. By means of cluster analysis three groups of countries having a similar rate of catheterization could be identified. The countries of one group were then pooled and analyzed regarding the entire use of resources.

However, this procedure is not often available as a classification of treatment patterns is difficult in practice, and the balance between a necessarily high quantity of data detail and a sufficiently large scope for differences is needed to collect groups for a significant purpose.

### Exploratory study for the adjustment of data

It is more difficult in the case in which the patient group of the target country in a multinational study is too small, or for other reasons, may be unsuitable for a statistical subanalysis (e.g., because of the basis of selection). In such cases exploratory studies are carried out in target countries to obtain an impression of the cost situation (and if necessary also of the current state of the probability of results of the relevant intervention). The data from these usually rather smaller studies which are in part still supplemented by expert assessment, are subsequently linked in model accounts to data from the available clinical study.

Even when a result is obtained among a small patient group in a subgroup analysis (in multinational studies), or in a smaller exploratory study in the country concerned, whose use of resources approximately corresponds to those which have been gained from the entire clinical study (which is rarely the case), it is still unclear how a new form of treatment could have altered the use of resources. If different patterns of treatment lead to a different structure in the use of resources, the hypothesis that the same starting values mean the same alteration values cannot be maintained (following intervention).

For this reason the Canadian guidelines for cost coverage in pharmaceutical studies, for example, expressly do not accept the transferability of foreign resource uses in terms of a simple equivalent in Canadian prices (source: Canadian Co-ordinating Office for Health Technology Assessment). Other guidelines make fewer explicit rules than the Canadian ones but simply require an adequate and transparent cost model (such as the guidelines of the Australian Commonweath Department of Health, Housing and Community Services) and the German recommendations for economic evaluation of health care; source: Hanover Consensus Group). In general, the existing national guidelines for economic evaluation in health care currently offer little advice on how economic data should be generalized to other settings. Inevitably, the guidelines agree that some degree of modeling is needed.

### Different uses of resources

Even more problematic is the situation in which the starting values in individual countries do not coincide, as happens in most cases. In these circumstances assumptions concerning use of resources through intervention are necessary. Three ways of dealing with these problems can be identified: the transfer of absolute values, the transfer of relative values, and a decision-analytic approach. These methods are discussed below.

### Transfer of absolute values

In the transfer of absolute values the ascertained effect of data from the country of origin of an intervention in the use of resources and benefits is transferred in absolute values to the situation in the target country. The procedure can be explained by a small hypothetical example. It can be assumed that in a clinical experiment to test the efficacy of a new drug in the United States patients of a certain indication are randomly divided into two groups. One group receives the new drug (verum group), and the other is treated with the only available therapy (control group). As regards the use of resources there is a reduction in average hospitalization of 25 days (control group) to 20 days (verum group). In a small exploratory study of the method of treatment used until then the average hospitalization was 30 days in Germany. For the sake of simplicity we may assume further that the complication and healing rates in the two countries were the same for traditional procedures. How can these data be transferred to a German context?

After the process of transferring absolute values for Germany, the starting point would also be a reduction in medium term hospitalization stay by 5 days i.e., from 30 to 25 days. The potential saving in medicine would then be calculated through an equivalent of an average price per hospital day. An example of a study which shows a simple principle of transferability of study data is that of Schulenburg et al. [16], which illustrates the cost-minimization analysis of a drug for treatment of cystic fibrosis.

In order to consider the effect of other cost influence magnitudes as the only directly measurable variables, such

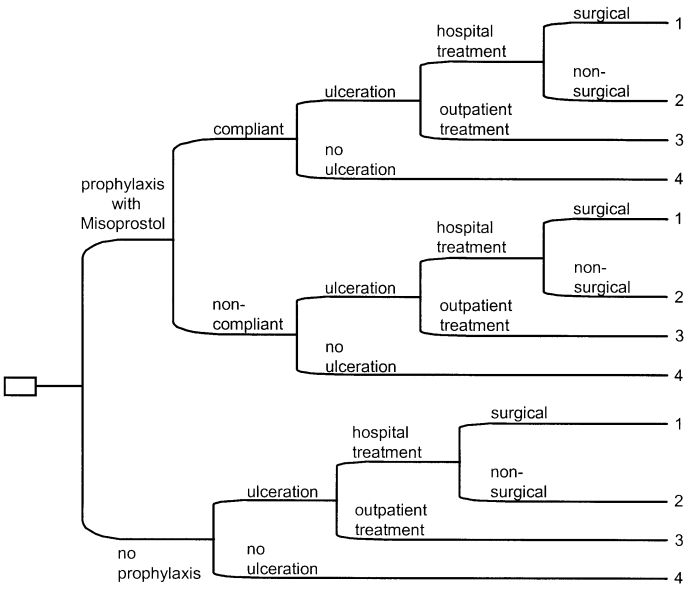


Fig. 1 ▲ **Example of a decision tree for preventive health care provision**

as hospital days or consumption of medicaments, it is also possible to generate *shadow prices* for further important determinants from the United States variables (such as age, gender, social or ethnic affiliation, for example) by means of statistical regression, which is then also analogously transferred to the German context. The same regression model is used (with the measured total cost per patient as a dependent variable) as in the country of origin (in the example, the United States) on a patient group from the target country (in the example, Germany). The ascertained regression coefficients represent shadow prices for the consumption of resources caused by the regression variables. These are applied in the example of the data collected from the United States study of the control and verum groups, and the potential savings are derived from the difference between the modeled average total costs of both groups. This technique was used by Rutten-van Mölken et al. [14], for example, in a study about the cost-effectiveness of formoterol versus salmeterol in patients with asthma. This method of procedure also represents a transfer of absolute values to the country of origin.

The problem with this simple procedure of transferring data to other health systems is the absence of any consideration of different cost structures. When, for example, in the target country the longer periods of hospital stay are exactly attributable to causes which can be helped with new technology (e.g., particularly expensive treatment of complications), the savings potential is, if necessary, considerably larger than suggested by the absolute values from the country of origin. The reverse applies when an overestimate of the savings potential is conceivable, when, for example, because of institutional facts such as the remuneration system, the hospital has no interest in shorter periods of stay and is therefore very reluctant to allow patients to leave earlier.

### Transfer of relative values

For the transfer of relative values the effect on the consumption of resources of an intervention in the country from which the data originated and the benefit to the situation in the target country is transferred as a proportional value, for example, as a percentage. In the example above, one would transfer the average number of days of hospitalization from the country in which the data originated to the situation in the target country, reduced by 20% (from 25 to 20 days). If in an exploratory study in German hospitals an average value of 30 days is determined for conventional therapy, on the basis of the American data one would assume a savings potential of 6 days in Germany. The basic assumption of this method is that consumption of resources brought about by the introduction of new technologies always changes by exactly the same proportion internationally. (A similar approach was suggested by Migliaccio-Walle [12] for adjusting the results from clinical trials to predict therapeutic effects in general practice.) This is not very realistic, as the cost structures, as described in the previous section, generally differ from country to country, and consequently any proportional changes in costs with regard to individual variables (such as length of stay in hospital) or with regard to the overall costs are at most coincidental. Therefore this method is unconvincing and cannot be recommended.

### Decision analysis methods

Decision analysis methods have continued to gain in significance over the past few years, even in the area of transferability of data between various health care systems. For this purpose reality-simplifying decision trees are generally developed which offer probabilities and cost data for certain possible treatment situations and results. These decision trees are intended to mirror relevant disease events and progress both medically and economically. For the transfer of study data, the probabilities of the occurrence of a certain event during the course of treatment (e.g., of a cure, a side effect, a complication, and also of the death of the patient) are taken from the foreign study data. Although the cost data with which these data are to be evaluated, are taken from domestic sources in the target country (e.g., published cost data or the results of exploratory studies). The model-like simplification of this method is due to the limited numbers of scenarios which can be taken into account, and the generalization of the cost and probability data of all cases included in the study.

An example for this approach is the study of Drummond et al. [7] on the cost-efficiency of a drug (Misoprostol) for the prevention of stomach ulcers in patients with osteoarthrosis, a painful disease of the joints. The long-term treatment of this disease frequently involves the use of nonsteroidal anti-inflammatory drugs, an adverse effect of which is stomach ulcers. Estimate the cost-efficiency of the drug, the following decision tree was used in Belgium, France, United Kingdom, and the United States (see Fig. 1) [4].

The probabilities for each individual branch of the decision tree with re-

Table 2
**Recommendation for the transfer of data in health economic studies**

| Methods to transfer study data | Recommendation |
|---|---|
| Subanalysis of the study data | Recommended, if national subgroup is sufficient for statistical analysis or if pooling of data of several countries is possible |
| Exploration study in target country | Recommended, if it is assumed that the intervention effect in target country is equal to country of data origin |
| Transfer of absolute or relative values | Not recommended, as different cost structures are not considered |
| Decision analysis methods | Recommended, if the intervention effect has a distinct association with a changed probability of certain disease events |

spect to the clinical effectiveness of the drug were obtained from the results of a randomized, double-blind, clinical study conducted in the United States. Compliance data were taken from the literature. Expert interviews were conducted to determine the costs of outpatient treatment, whereas the hospital costs were determined either using available data sources or by carrying out supplemental cost data surveys. In this way the clinical data from the United States were linked with nationally available data (particularly on resource consumption and the costs of the individual treatment scenarios) to produce a decision tree.

This approach has become increasingly popular in recent years, although it is not only the decision tree technique that has been employed, but also Markov models. Epidemiological data are taken from the literature (e.g., from large, population-related investigations) as, owing to the absence of national data, it is generally assumed that these values are also valid for other countries. Clinical data are taken from a current clinical study (national or international) and usually also applied for all countries. Information on resource consumption and on prices is obtained from national surveys. The results are then centrally evaluated separately for each country, or decentralized in each individual country. This procedure represents a compromise between the effort invested in survey work, the national significance, and the international comparability of the results.

Not to be neglected, however, is the problem of national surveying of resource consumption and costs. For reasons of time and cost one frequently limits oneself to exemplary data, for example, from one hospital. A one-sided selection can, however, lead to distortion of the results. (The problems that can arise in the selection of the hospitals to be considered are discussed by Goeree et al. [8].) However, this problem is not specific to studies based on international transference of data.

Decision analysis methods are particularly suitable for use when the effect has a distinct association with a changed probability of certain disease events, for example, if a certain disease event can be avoided with a certain probability by the use of preventive drugs. This procedure is less appropriate if (as is usually the case) the consumption of resources is changed by the technology being evaluated when a certain treatment event occurs. If, in the above example, the new drug had no preventive effect but accelerated the healing process in cases in which ulceration occurs, the costs associated with the decision tree branch "ulceration occurs" would no longer be equal but would differ depending on whether Misoprostol had been administered. A decision analysis approach is then no longer possible in the simplified manner shown in the decision tree above.

In spite of this, decision analysis methods can still be useful in such cases, at least for partial analyses. If, for example, part of the benefit of a new health care provision were to consist of lowering the mortality rate, the effect on costs of this one aspect can be made transparent with a simple decision tree consisting of just two branches (patients dies or not) for all treatment alternatives. The mortality data for this could also be taken from a foreign study, if required, while the average costs for the surviving patients and the average costs for those patients who died during treatment would need to be obtained from a national survey.

If permitted by the study design and the subject of the investigation, the decision analysis approach should be the method of choice for transferring study data to foreign health care systems. This is the best way to account for the various cost structures and institutional circumstances of the individual health care systems. The more detailed the analysis, i.e., the more branches the decision tree has, the easier it is to adequately make this differentiation. However, this also places increasing demands on the data and may increase the costs for generation of these data. The cost advantage of being able to use data obtained from existing foreign clinical studies can thus be lost fairly quickly. What does remain in this case, however, is the additional advantage of the international comparability of results of such evaluations of health care economics, provided that the study protocols of the individual investigations in the countries concerned were harmonized with each another. Those comparisons could give some insight about the different cost drivers in the countries concerned and might be of some additional advantage for the decision makers in these countries.

## Conclusions

It can be expected that in smaller countries in which it is inexpedient to produce a separate cost-benefits analysis, and in countries which have been involved in collective clinical studies, the use of data from foreign health care systems to provide information on the economic advantages of a health care treatment will also continue in the future. In contrast with the medical effectiveness, which has hardly any differences in an international comparison, additional national data sources are generally always needed for economic studies, whether for the evaluation of resource consumption, or even for adjusting the

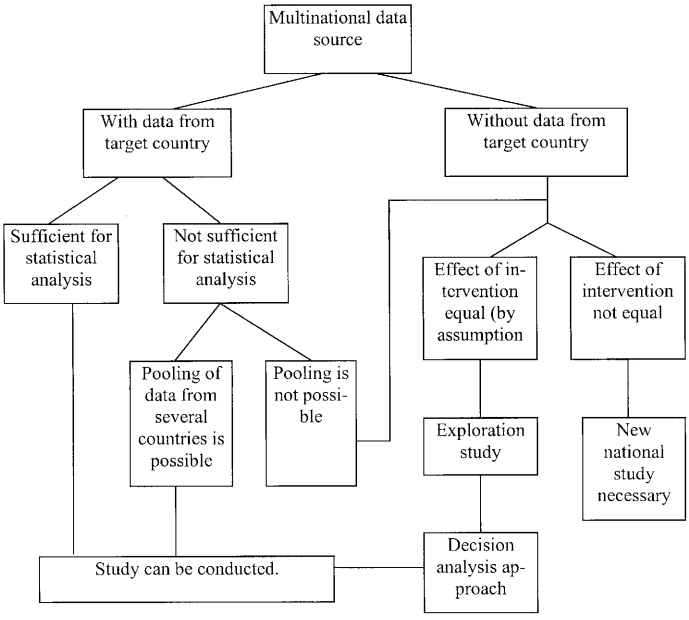


Fig. 2 ▲ **Model for a decision process about the possibility of transferring multinational data to national study questions**

foreign study data concerning the quantities consumed in order to put these in a national context. In this respect, it is advantageous to include appropriate surveys on a national level when planning the study. Some recommendations which must be considered when dealing with these problems are summarized in Table 2.

Based on these recommendations the model presented in Fig. 2 for a decision process concerning the possibility of transfering multinational data to national study questions can be derived.

In recent years (at least in Western industrialized nations), the rate of diffusion of medical innovations has considerably accelerated on an international level owing to the marketing strategies of the pharmaceutical industry, the more prolific exchange of information, and the degree of networking between the providers of health care services. Relatively complex technology has become available on a wide basis after only a relatively short period of time. On the one hand, this creates an ever-increasing international comparability of the diagnostic and therapeutic methods used. On the other hand, it can also be seen that the various forms of provision in the health care systems are in no way coming into line, but differ between more privately organized systems in competition with one another (e.g., Managed Care) and state-controlled systems with a large bandwidth [15]. The manner in which supply and demand are organized within the health care system cannot help but have an effect on the range of services in the individual health care system and the scope of the medical procedures that are actually available. For this reason the problem of international transferability of study results will continue to be of significance.

In the face of this challenge, the modeling of studies with a greater or lesser degree of complexity in order to adapt them to both medical practice and the national context will be unavoidable. Therefore, modeling will be inevitable for generalizing economic data to other health care systems. However, organizations (such as NICE in the United Kingdom) will always prefer economic data that has been collected in clinical trials for the target country of interest rather than the presentation of a modeling approach. Collecting economic data for every country in every trial is not realistic and would be prohibitive in terms of cost for pharmaceutical company development programs.

This requires the use of models which are sufficiently valid, transparent, and understandable, and which mirror the economic situation in the system concerned. This makes great demands in terms of knowledge of methods on the authors and also on the referees of their study reports, and not least on the readers of this article. The basic prerequisite for all considerations with regard to the use of international data is, however, a detailed study protocol in which the data acquisition and evaluation criteria are made known [10].

## References


1. Baltussen R, Leidl R, Ament A (1999) **Real world designs in economic evaluation – bridging the gap between clinical research and policy making.** Pharmacoeconomics 16:.449–458
2. Birch S (1999) **Appraising the methods for economic evaluation.** Pharmacoeconomics 16 [Suppl 1]:91–93
3. Bitzer E, Busse R, Dörning H, Duda L, Köbberling J, Kohlmann T, Lühmann D, Pasche S, Perleth M, Raspe H, Reese E, Richter K, Röseler S, Schwartz FW (1998) **Bestandsaufnahme, Bewertung und Vorbereitung der Implementation einer Datensammlung "Evaluation medizinischer Verfahren und Technologie" in der Bundesrepublik.** Schriftenreihe des Deutschen Instituts für Medizinische Dokumentation und Information im Auftrag des Bundesministeriums für Gesundheit zum Health Technology Assess, vol 1. Nomos, Baden-Baden
4. Buselmaier W, Tariverdian G (1991) **Humangenetik.** Springer, Berlin Heidelberg New York
5. Conseil d'Évaluation des Technologies de la Santé de Québec (1992) **Bone marrow transplantation – present status.** Conseil d'Évaluation des Technologies de la Santé de Québec, Montreal
6. Drummond MF, Davies L (1991) **Economics analysis alongside clinical trials – revisiting the methodological issues.** Int J Technol Assess Health Care 7:561–573
7. Drummond MF, Bloom BS, Carrin G, Hilman AL, Hutchings HC, Knill-Jones RP, Porvourville GD, Torfs K (1992) **Issues in the cross-national assessment of health technology.** Int J Technol Assess Heath Care 8:671-682
8. Goeree R, Gafni A, Hannah M, Myhr T, Blackhouse G (1999) **Hospital selection for unit cost estimates in multicentre economic evaluations. Does the choice of hospitals make a difference?** Pharmacoeconomics 15:561–572
9. Jefferson T, Mugford M, Gray A, Demichelli V (1996) **An exercise on the feasibility of carrying out secondary economic analyses.** Health Econ 5:155–165
10. Jönsson B, Weinstein MC (1997) **Economic evaluation alongside multinational clinical trials. Study considerations for GUSTO IIb.** Int J Technol Assess Health Care 13:49-58

11. Knill-Jones R, Drummond M, Kohli H, Davies L (1990) **Economic evaluation of gastric ulcer prophylaxis in patients with arthritis receiving non-steroidal anti-inflammatory drugs.** Postgrad Med J 66:639-646
12. Migliaccio-Walle K, Huybrechts K, Caro J (1999) **Estimating clinical effectiveness in economic analyses – why clinical trials don't tell the full story.** In: Abstracts book, 2nd World Conference of the International Health Economics Association (IHEA) – private and public choices in health and health care, p 139
13. O'Brian BJ, Heyland D, Richardson WS, Levine M, Drummond MF, for the Evidence-Based Medicine Working Group (1997) **Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients?** JAMA 277:1802–1806
14. Rutten-van Mölken MPMH, van Doorslaer EKA, Till MD (1998) **Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma.** Pharmacoeconomics 14:671–684
15. Schulenburg J-M Graf vd, Greiner W (2000) **Gesundheitsökonomik.** Mohr Siebeck, Tübingen
16. Schulenburg J-M Graf vd, Greiner W, Hardt HVD (1995) **Sozioökonomische Evaluation des Einflusses von rhDNase auf die Kosten der Behandlung von Infektionen der Atemwege bei Patienten mit zystischer Fibrose.** Med Klin 90:220-224
17. Schulenburg J-M Graf vd, Wähling S, Stoll M (1996) **German health economic cost evaluation on oral ganciclovir in treating CMV retinitis.** Pharmacoeconomics 10:522-530
18. Schulman K, Burke J, Drummond M, Davis L, Carlsson P, Gruger J, Harris A, Lucioni C, Gisbert R, Llana T, Tom E, Bloom B, Willke R, Glick H (1998) **Resource costing for multinational neurologic clinical trials: methods and results.** Health Econ 7:629–638
19. Späth H-M, Carrère M-O, Fervers B, Philip T (1999) **Analysis of the eligibility of published economic evaluations for transfer to a given health care system – methodological and application to the French health care system.** Health Policy 49:161–177
20. Welte R, Leidl R (2000) **Übertragung der Ergebnisse ökonomischer Evaluationsstudien aus dem Ausland auf Deutschland – Probleme und Lösungsansätze.** In: Leidl, R, Schulenburg J-M Graf vd, Wasem J (eds.) Ökonomische Evaluation im internationalen Vergleich. Nomos, Baden-Baden
21. Willke RJ, Glick HA, Polsky D, Schulman K (1998) **Estimating country-specific cost-effectiveness from multinational clinical trials.** Health Econ 7:481–493