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GUIDELINES FOR ECONOMIC EVALUATIONS IN ITALY: RECOMMENDATIONS FROM THE ITALIAN GROUP OF PHARMACOECONOMIC STUDIES

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Since 1997, in order for a new drug to obtain its price and reimbursement in Italy, the negotiation between authorities and the pharmaceutical industry must include an economic evaluation. The economic evaluation study leads to price and reimbursement negotiations together with such other requirements as the price of the new drug in other countries, the impact on the domestic market in terms of public pharmaceutical expenditure, and the effects on the national economy (employment and investments).

In response to the need to set methodological standards for the economic evaluation of drugs a group of about 40 experts (the Italian Group for Pharmacoeconomic Studies) made up of representatives of the regulatory authorities and ministries, academia, and the industry prepared recommendations concerning the methodology and the presentation of pharmacoeconomic studies. The principles were intensively reviewed and discussed during a number of workshops and meetings throughout one year, and then finally and officially presented to the regulatory authorities. The elements which must be contained in each study submitted to the authorities are briefly described in this paper, considering the main theoretical and regulatory contributions found in the literature.

In particular, the economic analyses suggested are cost-effectiveness and cost-utility, and they must be applied from the points of view of both society and the Italian National Health Service. Even though pragmatic economic-clinical trials are preferred, given the difficulties in releasing these kinds of studies for drugs which have just been authorized,

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the use of models is suggested when satisfying a series of requirements (the reproducibility of the results by the regulatory commission, detailed description of the methodology and the intermediate results, etc.). Preference is given to microcosting, that is, cost measurement performed at the health care provider level (eg, hospitals), from which representative data at the national level can be obtained. In terms of the presentation of an economic evaluation, a synthesis of the study must be prepared on the basis of a detailed list of issues in order to facilitate evaluation of the study by the regulatory authorities. The approach followed by the Italian Group for Pharmacoeconomic Studies is based on the belief that only the recommendations prepared with the active contributions of all subjects interested in the economic evaluation of drugs are likely to be efficiently applied and disseminated.

Key Words: Pharmacoeconomics; Italy; Italian Group for Pharmacoeconomic Studies

IN ITALY, PHARMACEUTICAL companies have been required to provide economic evaluations when applying for pricing and reimbursement negotiations since 1997 (1). As occurs in most European Union countries, almost all recently commercialized drugs in Italy come from the Centralised Approval Procedure, where the European Medicines Evaluation Agency must decide if a product constitutes a significant innovation in order to be evaluated. In a health care system such as Italy's, which is based on a National Health Service that provides most drugs free of charge to its citizens, pricing negotiations with the regulatory authorities take place at the same time when reimbursement, if any, is granted. Therefore, the legal requirement to present the economic evaluation of a new drug is an important innovation for both industry and those in charge at the Italian National Health Service. The pharmaceutical company is called upon to present indepth documentation for the new drug on the following points:

1. Economic evaluation (eg, a cost-effectiveness analysis),
2. Prices of the new drug when it is already on the market in other European countries,
3. Forecast of the expenditure for the new drug on the domestic market, and
4. Effects/commitments in terms of the national economy which stem from the introduction of the new drug (employment, productive investments, investments in research, export).

A nationwide group of experts was formed (Italian Group for Pharmacoeconomic Studies) in response to the need to have methodological standards available for the production and presentation of economic assessments to share among the Ministry of Health, the Ministry of Economic Planning, pharmaceutical companies, and experts in economic evaluations. During the course of plenary meetings which saw the participation of approximately 40 representatives from ministries, the European Medicines Evaluation Agency (EMEA), economists, epidemiologists, statisticians, and industry experts, the Italian Group for Pharmacoeconomic Studies gradually prepared the guidelines presented in this article. In March 1998, the Italian Group for Pharmacoeconomic Studies guidelines were officially presented to representatives of the Ministry of Health, the National Drug Evaluation Committee, the Inter-Ministerial Committee for Economic Planning, academia, and the pharmaceutical industry. These guidelines are not yet mandatory; they have been circulated extensively among experts and authorities, while waiting for the imminent establishment of a Commission of the Ministry of Economic Planning that is responsible for providing official guidelines.

This article reports the Italian Group for Pharmacoeconomic Studies's main recommendations, highlighting the most relevant theoretical and practical issues which could be useful for the regulatory authorities of the ministries involved, the Italian National

Health Service people responsible at various levels for financing, administrators of medical structures, and pharmaceutical companies. By distributing these recommendations, the group's intent is to contribute to the debate at the European level among the various groups which during these last few years have prepared guidelines for European countries (2–7), and also to make a methodological contribution to the issues concerning pharmacoeconomic evaluation.

COMPONENTS OF THE ECONOMIC EVALUATION AND RECOMMENDATIONS

Since economic evaluation studies are based on shared principles and methods, decision makers should be in a position to formulate opinions on the economic importance of the various courses of action. However, these studies must not be considered as decision making systems simply because they involve value judgments and methodological choices which are not neutral. For example, the Pareto principle (according to which the well-being of a community increases only when the utility of some of its members increases without decreasing for other members) does not take account of the relative importance of gains and losses (8). Following the Kaldor-Hicks criterion (9,10), if the gainers are willing to compensate the losers, a program would still result in an actual Pareto improvement; however, in practice, it seems quite unlikely that the reallocation from gainers to losers may occur, at least as far as health care programs are concerned (11,12). With the *maximin* principle of Rawls (13), however, social utility as a measurement of well-being is rejected. This principle identifies individuals who are in the most unfavorable conditions; then, the increase in well-being for the whole community is obtained by first increasing their utility. Furthermore, the use of discounting, especially in long-term prevention, may tend to favor current generations compared to future ones. Lastly, the application of any evaluation technique implicitly contains theories relative to the trend of innovative medical progress over a period of time (normally, in long-term studies this variable is not considered, assuming, therefore, that there is no progress).

In this situation, it must be openly recognized that no approach or discipline can provide the criteria for absolute rationality, which would make this a self-sufficient system for unified decision making. Inevitably, public decision making processes are also improved by evaluations which follow political theories or models of the government of public administration.

Therefore, the group recommendations represent an attempt to provide the authorities and the industry with methodological references to facilitate the assessment of economic evaluations, on the one hand, and their production on the other. These elements which, according to theoretical and regulatory contributions (2–7, 11,14,15,16), should be included in each study presented to the authorities are briefly described below, ending with several recommendations. In order to address the problem of practitioners' lack of ability to comply with any type of guidelines (17), we elaborated upon those recommendations involving all representatives facing economic evaluations, and made a commitment to periodically review their wording and application.

Techniques and Viewpoints for Analysis

The techniques applied in the economic assessment of medicines are: cost-consequence analysis, cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. Each of these tend to highlight different aspects and can, therefore, be complementary to others. However, the instruments which are believed to be the most appropriate for highlighting the economic consequences of the prices chosen for the new products are cost-effectiveness analysis and cost-utility analysis (which is sometimes included as a particular type of the former [11]). Cost-benefit analysis, which

represents the paradigm from which the other techniques subsequently derived (8), is not mentioned as the preferred technique because it has still rarely been used in actual evaluations; moreover, it is not likely to be helpful to the regulatory authorities in their deliberations, where the *willingness to pay* principle would not easily be accepted, also because of the difficulties related to dissemination of the decisions to the general public. The decisions made on the basis of economic evaluations affect the entire national territory in terms of cost of medicines and of their availability on the positive list (reimbursement); these studies should then capture the specific characteristics of the Italian context, from the viewpoint of compliance with the treatment, epidemiological situation, services delivered, and cost structure.

Different subjects (local health authorities, patients, the overall national community) have different interests and, therefore, assess the principles of economics in different ways. However, economic principles should be used in a general methodological system and in the technical solutions used to conduct these studies, even if the resource allocation decisions are made by the regulatory authorities who might maximize other values of society (political priorities, justice, fairness, etc.).

The selection of a therapy to use for comparison is a crucial subject. In theory, the perfect approach should require one to take into consideration all strategies which could be an alternative to the therapy being studied. In practice, this approach might prove to be unfeasible or extremely expensive. For these reasons, this document does not propose a rule to be used for identifying alternatives for comparison, but rather the solution to be adopted is left for debate between the government and the companies. However, two general criteria are proposed for an appropriate choice:

1. The comparator must be the most widespread treatment (pharmacological or non-pharmacological), and
2. Solid clinical documentation for a scientifically-based comparison must be available.

Different approaches may be used to collect the information required for an economic evaluation study. Generally, there can be four types of studies:

1. Economic trials (the study is designed to construct the economic evaluation),
2. "Piggyback" studies (the clinical trial is accompanied by a selection of elements which are useful for the economic evaluation),
3. Studies which combine data and information obtained from other studies, even of different types, and
4. Studies based on mathematical and statistical models.

Selecting an approach to the study design must generally strike a balance between what is needed and various types of constraints; it must also consider the costs and benefits of research designs with different precision and strength. It is, therefore, suggested that the approach to be used should have a solid base in reality and should combine the exactness of controlled clinical studies with elements obtained from observational studies, especially with regard to the utilization of resources. The studies which, more than any others, can provide reliable elements for economic evaluation are unblinded real-world trials (otherwise known as pragmatic trials), which, however, can only be carried out when the drug has already been marketed (Phase IV) or when previous trials, explanatory trials, have ascertained the potential benefits (18). Furthermore, it is believed that the use of models may play an important role in economic evaluation studies (19), especially when they are carried out before marketing authorization; this is the case of the price negotiation phase. It is also believed that the models must generally have a complementary function, compared to elements which originate from observations, and that the results of the simulations must be subject to continuous verifications and revisions.

Main Recommendations.

1. The preferred techniques are cost-effectiveness analysis and cost-utility analysis,
2. Studies must refer to the national context (treatments for comparison, medical practice, costs, institutional-organizational structures, epidemiological structure, and reference population). Only effectiveness data, which serve to register the treatment with the EMEA or for mutual recognition, obviously come from studies performed in various countries (almost all Phase III studies are multicenter and multinational). In those cases where the economic evaluations can utilize Phase IV studies, these studies must have been carried out in Italy,
3. The therapeutic alternatives used for comparison must be selected on the basis of their dissemination in medical practice and the availability of clinical data,
4. The analysis must be carried out at least from society's and the Italian National Health Service points of view. Other points of view (such as medical structure, patient, etc.) should be considered a useful subanalysis,
5. The use of a model requires details of the hypothesis (interrelation between the main variables, distribution parameters, probability values), the types (for example, simplified model for decision analysis, decision analysis with the "Markov" chain, the Monte Carlo simulation, the mathematical model, etc.), the procedures and software used, any description of the group of experts and the methods used to obtain their opinion. Furthermore, a table containing the main intermediate results (for example, the distribution of some of the events which influence the final result and the subordinate possibilities during the various stages) must be provided.

Effectiveness Evaluation

The registration of drugs, both centrally (EMEA) and by mutual recognition, takes into account the efficacy encountered during Phase III studies, where the new treatment is compared to the standard treatment. A thorough methodological-statistical examination is required to interpret these results and separate them into two readings, internal validity and external validity. Internal validity means that while planning, performing, or analyzing the study there are no conditions or elements which could produce a biased assessment of the efficacy, that is, an assessment that would remain biased even when the size of the sample increases.

For economic evaluations, external validity is the reference point used to estimate the denominator for the cost-effectiveness ratio (20). External validity means applying results to clinical practice: for this evaluation, it is necessary to consider the selection criteria used for both patients and the centers which conducted the trial and, the clinical importance of the endpoints used, compliance with the treatments used, as well as, naturally, the internal validity of the study.

In particular, with reference to analysis of the results, the "intention-to-treat" (ITT) principle today represents the standard for carrying out a primary analysis of the results of a randomized clinical trial (21). According to this principle, all randomized patients should be included in the analysis of the results on the basis of the treatment assigned during randomization, whether or not they comply with the therapy and follow-up protocols, and whether or not they are eligible, even though this last point allows for more flexibility. An analysis of all randomized patients guarantees the internal validity of the study because it precludes any distortions which may result from comparing any differences between the groups undergoing treatment or follow-up. Furthermore, an estimate of the effectiveness obtained this way should provide a better picture of the expected benefits of this treatment when it is administered to patients selected with less accuracy or patients who modify the therapeutic protocol.

When, during a cost-effectiveness analysis (CEA), the only estimates available on effectiveness come from studies which have not been analyzed using the ITT principle, it is the responsibility of the analysts to try

to reconstruct the estimates of effectiveness, even if indirectly, for the entire population of patients who are eligible for treatment, bearing in mind the number of patients excluded from the analysis of the various studies and the reasons for their exclusion. If this is not possible, the results of the CEA must be critically evaluated, with the possibility that the values used for effectiveness have been overestimated.

To evaluate effectiveness, a type of clinical trial with pragmatic objectives was recently developed; it is very close to broad-scale epidemiological studies, with the only peculiarity being the random assignment of treatments. In its most extreme form, this is defined as the large and simple clinical trial.

One last problem involves the use of endpoints which do not directly represent a benefit for the patient (eg, tumor response, decrease in glycaemia, etc.) but suggest its presence. These endpoints, when used in place of natural endpoints, are called surrogate endpoints. Their use in economic evaluations suggests that they can be validated for use as surrogate endpoints and may consequently be used to predict the actual effectiveness of the treatment. The validation of a surrogate endpoint is a notably complex methodological and statistical procedure; however, it is specific for drugs (or class of drugs). To summarize, this validation means showing that the "natural" primary endpoint (survival or death, quality of life, unfavorable events, etc.) allows for an estimate of the predictable effects of the treatment on the primary endpoint.

Main Recommendations.

1. The indicators for effectiveness in economic evaluations must express effectiveness for the population (the results obtained should the treatment be used in ordinary medical practice). Should it not be possible to present information regarding this type of effectiveness, efficacy under optimal conditions, gathered from controlled clinical trials, will be used by adapting it as much as possible to the target of the economic evaluation,
2. The effectiveness indicators, expressed in natural units or Quality Adjusted Life Years (QALYs), convey an improvement in health due to the treatment on the basis of primary or secondary endpoints, and
3. If only surrogate effectiveness indicators are available, an estimate must be made of the impact these results will have on nonsurrogate effectiveness indicators by using appropriate modeling.

Costing

In the evaluation carried out from society's point of view, the cost estimates must consider both direct costs (medical and nonmedical) and indirect costs. In this last case, even though the approach based on the friction theory proves to be promising (22), it is still subject to debate in literature (23,24), and would, in any event, require estimates (currently not available in Italy) for the period needed to substitute the worker; it is, therefore, suggested that the human capital method be used. According to this method, a person is regarded as producing a stream of output that is valued at market earnings: the healthy time for a working person produced by a treatment is an investment in a person's human capital and it is assessed in terms of the present value of future earnings (ie, the gross salary per working day gained). Since data about the time span which organizations need to restore the initial production level decreased because of the absence from work are not available (friction method), it seems simpler to allow the entire production loss due to the absence from work to be applied to the entire monetary value with the human capital approach.

The use of resources in a medical program should be evaluated by using their opportunity costs. The opportunity cost of a productive factor is the value of the best alternative way to use the same factor if it was not used in the project being examined. Since it is difficult, if not impossible, to evaluate the opportunity cost of a resource (only in a hypothetically perfect competitive market would the opportunity cost coincide with the

price), three types of cost measurements are normally used: market price, costs obtained from studies carried out in medical structures, and charges.

The use of one of these measures depends on the available information. However, it is believed that the quality of pharmacoeconomic studies would improve if the cost estimates carried out at various health care structures (hospitals, outpatient clinics, etc.), the so-called microcosting, were used. It is, therefore, appropriate to specify for each resource the measurement chosen for economic evaluation. In particular, the costs which derive from an in-depth examination of one or more health care structures, or from a study performed there, must include an appendix which specifies the analysis criteria used and the population referred to, both in terms of users and productive capacity (for example, the size of the hospital), in order to evaluate what the information represents. The alternative represented by the "standard costs," which is used in Australia (25), could be taken into consideration only after lengthy processing to obtain an acceptable degree of representation, with periodic publication of national statistics on the use of resources and costs.

As concerns whether or not to include some cost categories in the denominator of the cost-effectiveness ratio rather than in the numerator, there has recently been a debate which stems from recommendations made by the United States Panel on Cost-Effectiveness in Health and Medicine (11,26). For the Italian Group for Pharmacoeconomic Studies, even though the intangible costs would be duly quantified, they should not be included if the same costs would be counted twice. If, in fact, the intangible costs are represented by psychological and physical discomfort associated with the state of disease, they should already be adequately measured in effectiveness, for example, by faster healing or decreased side-effects, as well as by greater utility associated with the condition, that is, with the QALYs where they are reduced by one treatment rather than another since the former is more effective.

Lastly, the evaluation indicators must be obtained from the ratio between the incremental costs and incremental effectiveness of the alternatives examined, since the average cost-effectiveness ratio is not important for the analysis. However, it is important, since this is established by standards on price negotiation, that a scenario be provided for the first and second year of marketing of the new medicine, which deals with the economic impact on the entire health system: the increase or savings in the health budget based on the expected population to be treated.

Main Recommendations.

1. A list must be made of all cost categories (direct medical, direct nonmedical, indirect) with the types of resources (for example, doctor's visit, type of hospitalization, time dedicated by the caregiver, time lost at work, etc.) and their amount,
2. The gross salary paid to individuals who perform a similar job on the outside market is used to evaluate unpaid services provided by family members and volunteers,
3. Preference is given to cost measurements carried out through studies performed at health care structures. The choice of structures must be justified on the basis of how they comply with the objectives of the economic evaluation, and
4. Intangible costs are actually one of the results of the treatment (positive when decreased or avoided, negative when they increase). Therefore, they must not be included in costs but in effectiveness, both when they can be assessed concretely and when they are measured in quality of life or in QALYs.

Discounting

The type of discount and the appropriateness of using it for economic evaluations in the health field has been widely debated in the last few years (27–31). Furthermore, there have been discussions on whether in health treatments costs and benefits must be discounted using the same rate (32,33).

A further source of discussion is the application of discounts to the years of life gained, since different results are obtained depending on whether the effects are considered as number of expected years or as utility of the expected years of life (34). Furthermore, when the effects of a medical intervention are measured in utility (the QALYs combine life expectancy with quality of life), applying a discount rate may be "a duplication" since the time preference is already incorporated in these measurements, no matter how they are calculated, whether with the standard gamble technique or with the time trade-off technique (3,30,31,35). However, most experts still agree that it is correct to use discounting for these types of measurements (11,12).

Another subject of debate is the amount of the discount rate: the one most commonly used in practice (3%) seems more like the result of an "imitation effect" than the consequence of a rational and demonstrable choice. In fact, cost-effectiveness applications do not generally explain the reasons behind the chosen rate, and the existing rates present a fairly wide variety. On the basis of theoretical foundations, the Italian Group for Pharmacoeconomic Studies believes that the same discount rate should be applied both to the costs and to the benefits of medical interventions (even though in a nonmonetary form); thereafter it should be 3%, both because it is in line with cost-opportunity and because it is more appropriate for comparing the different existing studies. This discount rate may be subject to revision, as the result of the inevitable changes in the economy of the country.

With regard to the range of time, it is suggested that calculations should be limited to a duration of 30 years, since approximations for each subsequent year become negligible.

Main Recommendations.

1. The discount rate to use is 3%. Furthermore, the final results should also be presented using a rate of 0% (assumption of no discounting). The choice of the discount rate should always be made clear, especially when it differs from that most widely used in literature. The discount rate may be changed in time, in line with the changes in the country's economy, and
2. In the sensitivity analysis, it is suggested that rates from 0% to 8% be applied.

Quality of Life and Utility Assessment

Cost-utility analysis is a particular case of cost-effectiveness analysis in which the effects of the health care treatment are expressed in terms of how desirable (preferable, useful) a healthy condition would be for the individual. The denominator for cost-utility analysis may essentially be expressed in two units of measurement: the Quality Adjusted Life Year and the Healthy Year Equivalent (HYE). It is suggested that the QALY should be used since it is simpler and more widespread.

The method chosen to assign utility values to the different health conditions has a determining influence on the characteristics of the index, by establishing the arithmetic properties of the corresponding scale. Naturally, the same is true for the process of recruiting those who are called upon to judge the health conditions, that is, to assign a value to the health conditions described. Generally, the two most commonly used methods for deriving utility are recommended, namely time trade-off and standard gamble, both of which are based on the concept of sacrifice. The opinions of experts or the concise global index included in many quality of life profiles are not recommended to obtain utility values.

Lastly, it is suggested to simultaneously apply, if possible, general instruments, such as, for example, the Short Form 36 (a widely used quality of life questionnaire which in 36 questions gives the health profile according to six attributes: physical, role-emotional, social, mental health, health perceptions, and pain), specific instruments for the group of patients being analyzed or for the pathology, and instruments for surveying preferences/utility such as the Health Utility Index, similar in principle to the EuroQol but more complex with seven attributes and up to five lev-

els for each of them, the EuroQol (five attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression; since each attribute has three levels, thus defining 243 possible health statuses plus "unconscious" and "dead"; a score representing the utility has been attached to each status by a measurement with the time trade-off technique on a random sample of population), quality of well being, and so forth.

Main Recommendations.

1. The outcomes on the quality of life are measured using instruments (questionnaires and quality of life scales) which are nationally validated. If possible, the use of both a specific instrument, for the pathology examined in the economic evaluation, and a general instrument are suggested,
2. It is appropriate for the economic evaluation to contain a detailed explanation of the instruments, the method of application, and the results of the quality of life evaluation which provide elements for the utility analysis,
3. For the economic evaluation which uses the cost-utility analysis, a utility value is attributed to health conditions using specific techniques, preferably "standard gamble" and "time trade-off." The reasons for choosing either one or the other must be stated in the study, and
4. The utility indicator to be placed as the denominator in the cost-utility ratio is the "QALY."

Statistical Analysis

The "statistical evaluation of effectiveness" implies the overall evaluation of the study findings, with particular reference to its design and implementation. The ultimate purpose is to formulate an opinion on the possible effect of the study treatment T ($\hat{E}t$) in comparison to that of a reference treatment S ($\hat{E}s$).

It is crucial to keep in mind the clinical importance of the effect observed, rather than using the level of statistical significance as the driving criterion for judging the differences observed. Overemphasizing the statistical significance of the results may paradoxically lead to the wrong conclusion that the observed effect is significant when it has no important clinical meaning.

The first point to be considered, before carrying out the appropriate pharmacoeconomic analysis, is the effectiveness evaluation of the treatments under comparison. The possibilities which may occur during the CEA can be summarized as follows (36):

1. A purely deterministic CEA, where the cost parameters (C) and the effectiveness parameters (E) are available as precise estimates (ie, the variability *VAR* E = *VAR* C = 0). This may occur with new medical technologies for which there are few observations (for example, series of patients). In this case, it is indispensable to perform a sensitivity analysis in order to quantify reasonable doubts about the precise estimates that are available,
2. A partially probabilistic CEA, where the sample variability is available only for the clinical effectiveness parameters $\hat{E}$ (the *VAR* E is estimated directly by the clinical trial), while sample variations for costs associated with the treatments being compared are lacking (ie, *VAR* C is not estimated by the trial). In this case, the uncertainty of precise cost estimates is calculated indirectly, using a simulation method, and/or evaluated by sensitivity analysis, and
3. A purely probabilistic CEA when the clinical trial estimates both the effectiveness parameters ($\hat{E}$, VAR E) and the cost parameters ($\hat{C}$, VAR C) associated with the treatments under study. In this case, the situation is wholly probabilistic, and it is possible to proceed with a formal statistical analysis which includes a statistical evaluation of the differences observed, in terms of cost-effectiveness ratio (CER). Unfortunately, the availability of a CER which includes sample estimates for both the numerator and the denominator, with known variability, has a statistical disad-

vantage. There is no exact method for determining the variance of the CER and describing its frequency distribution in terms of confidence intervals. This difficulty can be overcome by diverting the variance of the CER using a Taylor's approximation (36) or by empirically distributing the CER and estimating its confidence limits (37). Recently, several contributions have been made to devise statistical techniques for the CER analysis (38–41).

In the absence of a precise estimate of the CER and its confidence intervals, the intrinsic uncertainty of the data subject to economic evaluation is generally held in due consideration by the sensitivity analysis (42). Its purpose is to evaluate the strength of the CER, that is, how much does it change within a range of plausible values attributed to one or more parameters of the economic evaluation? Sensitivity analysis should always be performed to identify which parameters affect the findings of a CEA study. Reasons should always be given for any changes in the parameters considered in the analysis.

Main Recommendations.

1. The results of the economic evaluation must include, for the indicator chosen: the precise estimate, and the indicators for estimated uncertainty,
2. A sensitivity analysis must be carried out at least on those parameters which have the most influence on the final results, whether they are for effectiveness and/or costs or for the discount rate,
3. It is better for the sensitivity analysis to be conducted showing the simultaneous effect of the variations for the more important parameters, and
4. The values to be used for each parameter in the sensitivity analysis will be established in relation to the problem to be handled: for effectiveness, use of the limits of the confidence intervals is suggested, while for the cost, any changes in the precise value of the unit cost are left to the choice of the author of the economic evaluation, who will provide a statement of the reasons.

Reporting Economic Evaluations

The way in which the economic evaluation is presented has a great influence on how it is read, in terms of ease of comprehension, and how it is assessed, since this allows, with different degrees of in-depth study, one to verify that it is accurate and complete. Furthermore, it is important to adequately structure the presentation to facilitate comparisons between different economic evaluations, whether for the same treatment condition or between different conditions. Lastly, a well-defined presentation facilitates carrying out the economic evaluation, thanks to a precise reference to the phases and contents to be observed.

The report, though bearing in mind the specificity regarding types of treatment and pathology examined, must be able to provide an adequate response to three fundamental questions, which are a basic aspect for both the authors and the readers:

1. Are the results to be considered valid and acceptable?
2. What information emerges from the results? and
3. What portion of the results can be applied to actual situations?

When reading the report, the essential results of the economic evaluation must be readily identifiable: incremental indicators of cost and medical outcome for each treatment examined; any differences in the result between subgroups of the patient population; and how much the uncertainty of some information can influence the results and therefore their applicability. Whether or not these results can be applied in a country context depends on the representativeness of the patients considered, on the cost categories considered, and on the methods used to estimate them, as well as on the degree of medical practice used for the economic evaluation.

The following recommendations have been compiled by extracting helpful hints from the most important documents, which also contain information on how to structure an expertise report (4,11,14,15,16,43,44).

Main Recommendations.

1. The Economic Evaluation (EE) report must be subdivided into three parts:
   - "Summary" of the EE which contains objectives, methods, and main conclusions,
   - "Synthesis" of the EE which specifies the basic elements of the economic evaluation, and
   - "Detailed version" of the EE, with as many appendices and attachments as possible so that the reader can verify the results and if necessary reproduce them, and
2. The "Synthesis" of the EE must contain the following points:
   1. The objective of the EE and the problem/subject with which it deals,
   2. The points of view of the analysis (society, Italian National Health Service, patient, medical structure, etc.),
   3. The treatments compared (pharmacological and possibly nonpharmacological) and the reasons behind the choice,
   4. Type of economic analysis used and the reasons behind the choice,
   5. Type of design for the EE (naturalistic, model, etc.),
   6. Source of the effectiveness information,
   7. Type of clinical studies used,
   8. Main indicator for the economic evaluation,
   9. Method used for estimating costs,
   10. List of cost items considered,
   11. Span of time covered by the EE,
   12. Results expressed as incremental cost-effectiveness indicator (cost-utility or cost-benefit) and, given the average cost per patient and the relative incremental cost, as a projection over the population of the entire national territory: in resource units, based on the total direct and indirect costs, and based only on the direct costs for the Italian National Health Service,
   13. Intervals used for the variables in the sensitivity analysis and their justification,
   14. Maximum and minimum values of the sensitivity analysis mentioned in point 12,
   15. Details on the statistical methods used,
   16. Conclusions,
   17. Authors of the EE, with a brief curriculum vitae, and
   18. Sponsor of the EE.

CONCLUSION

These recommendations summarize most of the information contained in previous guidelines, such as those of Canada and Australia, as well as the results of working groups such as the United States Federal Government Panel, with some original interpretations, particularly oriented toward a specific application for Italy. The methods and theoretical aspects of an economic evaluation undergo continuous adjustments and debates and, in some cases, differences persist among researchers. Therefore, the work carried out by the Italian Group for Pharmacoeconomic Studies to date is open to contributions from all those who would like to suggest improvements and changes, with the purpose of constantly updating the instruments for economic evaluation, in light of their use when making public decisions.

In particular, this document intends to contribute to consolidating a national scientific environment as homogeneous and advanced as possible, in order to provide both the government and firms with swift, operational instruments that are useful for defining and applying pharmacoeconomic methods; to support the implementation of procedures established by the Inter-Ministerial Committee for Economic Planning deliberation; and to operate with the complete involvement of all scientific operators and researchers who are interested in this subject. Lastly, the upcoming work of the Italian Group for Phar-

macoeconomic Studies will be focused at a European level, with a view to confronting the various countries in order to develop a shared method for establishing prices for medicines.

In this perspective, during a workshop held at the University of Pavia in November 1999 and organized by the group, participants from 13 European countries (national government bodies, European bodies, university centers, industry) discussed the main issues related to pharmacoeconomic guidelines. Among the existing national guidelines there is a quite significant homogeneity, in line with the more advanced theoretical research in this field. It has been recognized that national economic evaluation must take into account local medical practices and costs, and that the number of observational studies must be increased, particularly in order to assess the treatments after a sensible period of commercialization. About the utilization of models, great attention has to be paid to the methods applied, but they are an unavoidable necessity for the new drugs. On the one hand, the harmonization of the methodologies is already in progress, but on the other hand, there is still a lack of a shared reimbursement mechanism, particularly for the way in which each country considers economic studies. A consensus document has been proposed to the European bodies proposing the constitution of a working group with the objectives of producing high scientific level procedures of drugs for the single European market, according to the points of view of the different actors: national authorities, academia, industry, and citizens.

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