

**INFARMED**

# **GUIDELINES FOR ECONOMIC DRUG EVALUATION STUDIES**

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## **FOREWORD**

There is a growing need for new criteria that will be able to improve investment decisions in the assessment of the latest health technologies.

Indeed, expenditure on health has been growing much faster than the resources available to support it, which is why choices and decisions must be made on the basis of more and better information.

In health technology, drugs are especially important because of their extraordinary capacity for innovation. With drugs, we have to consider not only new molecules and those that replace or increase the effect of other existing ones, but also the rise in consumption per capita.

Globalisation, social development, the ageing population and a growing awareness of social rights and duties have generated an increase in the consumption of health products. Satisfying this demand not only poses immediate problems but also raises issues of future sustainability.

While we are aware that this market is developing and improving and that scientific knowledge in this area is capable of finding solutions of great therapeutic value, we are also aware of the treatment needs for which we have yet to find an answer. These are the reasons why we feel it is necessary to apply new scientific knowledge in the field of pharmaco-economics in order to improve the information provided to decision makers.

It was these considerations and our awareness of the social and economic situations in the health sector that led INFARMED to foster the development of research to devise economic assessment methodologies to be used in effectiveness and utility studies and any others whose conclusions will facilitate better decisions on co-payment.

This publication is the culmination of methodical work that began with the realisation of the need for better information. Information and the ways of

obtaining it were then systematised and group of outside experts was formed to provide technical and scientific support for the preparation of the methodologies. These methodologies were then adopted under the law for systematic application.

We believe that the Ministry of Health and the National Health Service now have yet another tool that will enable them to achieve better results within health in a framework of sustainability.

Member of the Board of Directors

## **MINISTRY OF HEALTH**

### **OFFICE OF THE SECRETARY OF STATE FOR HEALTH**

Order no. 19064/99 (2<sup>nd</sup> series) – Until the coming into force of Decree-Law no. 305/98 of 7 October, which altered some of the rules laid down in Decree-Law no. 118/92 of 25 June regarding the co-payment of the price of medications by the State, the elements supplied by applicants and used to assess the pertinence of applications for co-payment were sometimes insufficient or inappropriate.

In order to correct this insufficiency, nos. 3 and 4 of article 4 of Decree-Law no. 118/92 of 25 June with the changes made to them by Decree-Law no. 305/98 of 7 October established that, whenever necessary for the assessment of an application for co-payment of a drug, the applicant should submit an economic assessment study conducted according to the rules defined by order of the Ministry of Health. The purpose of this study was to facilitate an informed analysis of the application and, as a result, a fairer and more balanced decision.

For this purpose, a work group consisting of members of recognised technical and scientific merit was set up, assisted by a consultant specialising in the drawing up and implementing of rules and standards to be followed in economic drug assessment studies.

The work is now complete, without prejudice to possible subsequent alterations resulting from the need to adapt these rules to technical progress.

Thus:

Under the terms of no. 4 of article 4 of Decree-Law no. 118/92 of 25 June with the changes made to it by Decree-Law no. 305/98 of 7 October, I decree the following:

1. The methodological guidelines to be followed in economic drug assessment studies in the annex to this order, of which they are an integral part, are hereby approved.
2. The methodological guidelines in the annex to this order shall be developed and detailed in a document to be published by the Portuguese Drug and Pharmaceutical Institute.

## ANNEX

### **Methodological guidelines for economic drug assessment studies**

Introduction - The inclusion of economic criteria in the analysis of funding for new technologies in the health sector and of new drugs in particular, has been increasing in most OECD countries in general and in the European Union countries in particular. The accentuated rise in the prices of these technologies, allied with the realisation that this investment is not always rewarded by proportional improvements in the health of the population, has led many governments to complement their analysis with some economic indicators when making a decision as to the degree of public spending in the sector.

Economic criteria were introduced in two stages. From the mid-seventies to the late eighties, the main concern was to compare the growth rate of expenditure with the budgetary limits imposed by the slow-down in the growth of the product. This led governments to adopt policies of containing costs. These policies were reflected by a reduction in the real growth rates of this spending. As was seen later, not only did the results of these policies leave a lot to be desired, but they also had negative effects on access to health care.

The realisation that cost containment policies could jeopardise the improvement of the population's health over time meant that, in the early nineties,

governments began to try to implement comprehensive reforms in their health systems, where economic criteria played an important role in achieving health gains.

Generally speaking, a factor that all the reforms had in common was the separation of funding and health care in an attempt to stimulate competition, at least between health care providers. Everyone was aware right from the start, however, that this competition should be regulated, especially where the adoption of new technologies was concerned. This was not only because they constituted the main factor that raised the costs but also because partial and exhaustive revisions of the pertinent documentation found that, in most cases, their efficacy had been grossly overestimated.

In this context, the economic assessment of technologies and, particularly, of drugs is an excellent instrument for determining whether what consumers, insurers and governments spend is compensated by health gains, given the alternatives of using other available resources for the same purpose. This approach is particularly necessary where drugs are concerned, as they are the front-line treatment for preventing and treating the great majority of diseases and also because, in many countries, their weight in the health budget is considerable.

: Although there is a consensus in the specialised literature on a vast number of methodological options, for pharmaco-economic studies, there are still some aspects that are controversial. This is due, mainly, to the fact that this is a relatively new area, in which the problems are very different from those that arise in fields where it is possible to adopt standard approaches for the economic assessment of investment projects.

One way of trying to minimise these difficulties is to lay down methodological guidelines for this type of study. The basic aim of these guidelines in the countries that have them is to present a set of principles of reference to guide the authors of the studies in their analyses, rather than to introduce regulations for conducting the studies. In view of the fact that the problems are highly

varied, the orientations cannot, however, be exhaustive or compulsory. Indeed, the use of alternative approaches is permitted, provided they are properly justified.

But there is another objective that the guidelines have to achieve. They should be pedagogical, in that, when reading them, their authors will perfect their technical ability to conduct studies.

This document is intended to reflect these principles. It was drawn up by a work group whose main concern was to build a very general frame of reference for preparing economic drug assessment studies. It was necessary, as the law allows the authorities to demand economic studies when applications for co-payment of drugs are submitted.

But they are by no means “administrative” guidelines. Above all, the idea was for them to be a guide of good practice that was sufficiently general to be used in any institutional context and could, with a few changes, be applied to the assessment of all health technologies.

On the other hand, it cannot be regarded as the definitive text. As knowledge in this area progresses so rapidly, we can expect successive revisions to perfect it and adapt it more and more to the objectives with which it was written.

#### 1. Perspective of analysis

The perspective should be that of society. This means considering the costs and consequences for the patient, for his or her family and also for third parties, i.e. public and private payers in particular. Society’s perspective should be broken down into other relevant points of view, with special attention to the third payers if they are the users of the study.

#### 2. Data sources

Preference will be given to the results obtained in clinical trials with validated methodologies and relevance for Portugal. Other data sources will also be accepted, provided that they are clearly justified and validated. In all cases,



the population covered by clinical trials should be representative of the target population.

### 3. Comparators

The reference alternative should be that of current practice, i.e. the most common treatment used for the health problem in question.

If the most common treatment is not the one recognised as the most efficacious, or is not the cheapest of the efficacious treatments, these treatments should also be used as terms of comparison.

If there is a problem with identifying the appropriate terms of comparison, they should be agreed upon by the author and the party for which the economic assessment study is destined.

### 4. Population

The population considered in determining the costs and consequences should be described in great detail, especially with regard to morbidity and mortality. The population should correspond as closely as possible to the potential users of the treatment under analysis.

### 5. Assessment of therapeutic effect

Therapeutic effect should be assessed in terms of effectiveness whenever possible. If this information is not available, the use of efficacy data will be accepted. In this case, the hypotheses and models used to estimate effectiveness should be described in detail and an appropriate sensitivity analysis should be made of the results.

### 6. Time horizon

The length of the study should coincide with the duration of the treatment and its consequences. If this is not possible, the length of the study should enable us to identify unequivocally the main costs and consequences that may lead to different results. The use of models is permitted provided that it is duly

justified. In this case, we should present the hypotheses and the methodology on which their construction was based.

#### 7. Analysis techniques

Any scientifically recognised economic evaluation technique can be used.

If it can be shown that the consequences associated with all the alternatives are the same where the characteristics relevant to the study are concerned, a cost-minimisation analysis (CMA) can be made. If this is not the case, we should conduct a cost-effectiveness analysis (CEA). It is advisable, however, whenever possible, to make a cost-utility analysis (CUA) or cost-benefit analysis (CBA) to make it possible to compare the results of the studies of different pathologies. A cost-utility analysis is preferable in this case.

Studies of the cost of the disease and cost-consequence studies are accepted as a first approach in the economic justification of the choice of treatment alternatives. They should not, however, be used to replace formal economic evaluation studies.

#### 8. Identifying costs

All costs relevant to the analysis must be identified. Whenever possible, we should present a clinical decision tree showing all events relevant to the different treatments. When the analysis adopts the perspective of society, the costs included will be the direct costs of providing health care, the costs of social services and other sectors related to health care and the costs borne by patients and their families. The only indirect costs included should be those of an employee's lost productivity. After their inclusion has been properly justified, these costs should always be reported separately and the impact of their results analysed.

#### 9. Measuring and valuing costs

Separate, detailed information should be given on the resources used (measured in physical units) and the way in which the resources have been valued (unit prices or costs). The information on the use of resources should

be based on clinical practice in the country. If this is not possible, it is necessary to use foreign data, they should be validated by local health care providers.

The basic economic principle for valuing resources is that the units of measurement should reflect the opportunity cost of these resources, i.e. the value lost if the resources are not applied in their best alternative use. We should therefore begin a process of creating, validating and maintaining cost tables for use in economic assessment studies. Nevertheless, even after these tables have been drawn up, other data can still be used, provided they are justified.

#### 10. Measuring consequences

The unit used to measure consequences should be clearly identified. In cost-effectiveness studies, the consequences can be measured using several indicators, such as the years of life gained by using each alternative. If we use intermediate results in a study of this type, they should be properly justified. In any case, the efficacy indicator should be presented first, before the effectiveness indicator.

If we adopt the cost-utility approach, we should present the quality of life weightings for each level of limitation of activity and the years of life gained. The aggregation of these two elements should be transparent. In cost-benefit studies, the monetary valuation of the consequences should preferably use the contingent valuation method.

#### 11. Total and incremental analysis

The cost and consequences of each alternative should be presented in terms of variation from those of common clinical practice - incremental analysis. The total values should also be calculated so that the decision maker can analyse the costs and consequences of each alternative.

## 12. Discount rate

All costs and consequences should be discounted at a rate of 5 percent. A sensitivity analysis should be made of this rate. If the consequences are not valued in monetary terms, the sensitivity analysis should include the zero rate, which corresponds to not discounting the consequences.

## 13. Assessing the impact of uncertainty on the results

We should make a sensitivity analysis of the key parameters with values that are subject to uncertainty. If these values have been obtained by sampling, the analysis should be conducted considering the confidence intervals for each estimate. In other cases, the choice of variation intervals or alternative values for the parameters should be justified in detail on the basis of empirical evidence or of logic.

## 14. Model for presenting economic assessment studies

The presentation of economic evaluation studies should comply with a form identifying all relevant aspects needed to understand the analysis of the studies.

For this effect, authors should adopt the model in the document provided for in no. 2 of the official order, of which this annex is an integral part.

## 15. Ethical and procedural aspects

When presenting the results of a study, regardless of the form the presentation takes – final report, public presentation or publication – we should always refer to the source of funding and the real contribution made to it by the all the authors. The researchers should be completely free to choose their methodology in all stages of the study and should be entitled to publish the results in the scientific journal of their choice.

## **INTRODUCTION**

The inclusion of economic criteria in the analysis of funding for new technologies in the health sector and of new drugs in particular, has been increasing in most OECD countries in general and in the European Union countries in particular. The accentuated rise in the prices of these technologies, allied with the realisation that this investment is not always rewarded by proportional improvements in the health of the population, has led many governments to complement their analysis with some economic indicators when making a decision as to the degree of public spending in the sector.

Economic criteria were introduced in two stages. From the mid-seventies to the late eighties, the main concern was to compare the growth rate of expenditure with the budgetary limits imposed by the slow-down in the growth of the product. This led governments to adopt policies of containing costs. These policies were reflected by a reduction in the real growth rates of this spending. As was seen later, not only did the results of these policies leave a lot to be desired, but they also had negative effects on access to health care.

The realisation that cost containment policies could jeopardise the improvement of the population's health over time meant that, in the early nineties, governments began to try to implement comprehensive reforms in their health systems, where economic criteria played an important role in achieving health gains.

Generally speaking, a factor that all the reforms had in common was the separation of funding and health care in an attempt to stimulate competition, at least between health care providers. Everyone was aware right from the start, however, that this competition should be regulated, especially where the adoption of new technologies was concerned. This was not only because they constituted the main factor that raised the costs but also because partial and exhaustive revisions of the pertinent documentation found that, in most cases, their efficacy had been grossly overestimated.

In this context, the economic assessment of technologies and, particularly, of drugs is an excellent instrument for determining whether what consumers, insurers and governments spend is compensated by health gains, given the alternatives of using other available resources for the same purpose. This approach is particularly necessary where drugs are concerned, as they are the front-line treatment for preventing and treating the great majority of diseases and also because, in many countries, their weight in the health budget is considerable.

The methodologies generally used for assessment studies are, however, far from being consensual. This is due, mainly, to the fact that this is a relatively new area, in which the problems are very different from those that arise in fields where it is possible to adopt standard approaches for the economic assessment of investment projects.

One way of trying to minimise these difficulties is to lay down methodological guidelines for this type of study. The basic aim of these guidelines in the countries that have them is to present a set of principles of reference to guide the authors of the studies in their analyses, rather than to introduce regulations for conducting the studies. In view of the fact that the problems are highly varied, the orientations cannot, however, be exhaustive or compulsory. Indeed, the use of alternative approaches is permitted, provided they are properly justified.

But there is another objective that the guidelines have to achieve. They should be pedagogical, in that, when reading them, their authors will perfect their technical ability to conduct studies.

This document is intended to reflect these principles. It was drawn up by a work group whose main concern was to build a very general frame of reference for preparing economic drug assessment studies. It was necessary, as the law allows the authorities to demand economic studies when applications for co-payment of drugs are submitted.

But they are by no means “administrative” guidelines. Above all, the idea was for them to be a guide of good practice that was sufficiently general to be used in any institutional context and could, with a few changes, be applied to the assessment of all health technologies.

On the other hand, it cannot be regarded as the definitive text. As knowledge in this area progresses so rapidly, we can expect successive revisions to perfect it and adapt it more and more to the objectives with which it was written.

## 1. Perspective of analysis

The perspective should be that of society. This means considering the costs and consequences for the patient, for his or her family and also for third parties, i.e. public and private payers in particular. Society's perspective should be broken down into other relevant points of view, with special attention to the third payers if they are the users of the study.

An economic assessment study should have clearly defined objectives. This means asking a question and then using empirical work to answer it. The whole study is therefore conditioned by the way in which the question is asked.

The study's objectives and, therefore, the initial question generally reflect the interests of whoever ordered it, resulting in a selection of the data (costs and consequences) to be included in the analysis.

If, for example, a hospital management requests the assessment of a new surgical technique, it will be interested, above all, in the effect its use will have on the hospital's resources and, possibly, on the length of the patient's hospitalisation.

This has two main consequences. Firstly, the other players in the sector (especially patients) are denied any knowledge of the impact of the decision taken on their situation. Secondly, as the technique in question is used in more than one environment, the results may not be applicable to all of them, meaning that a different study will have to be conducted for each institution.

This is why we recommend that society's perspective should be used when conducting an economic assessment study. All the relevant costs and



consequences should be analysed before listing alternatives in order of importance, regardless of who ordered the study.

When we take society's perspective, we can normally break the information down into other perspectives at little extra cost. We therefore recommend that studies should show the balance of costs and consequences from different relevant points of view, and in particular from that of the third payers, if they are the users of the study.

At the same time, as almost all studies are conducted to help public financiers reach their decisions, we also recommend that, if appropriate, an estimate should be made on the effects on their budgets. It should be noted that an analysis of this type, which is called a financial impact assessment, is technically different from the consideration of the third payer's perspective in an economic assessment study.

## 2. Data sources

**Preference will be given to the results obtained in clinical trials with validated methodologies and relevance for Portugal. Other data sources will also be accepted, provided that they are clearly justified and validated. In all cases, the population covered by clinical trials should be representative of the target population.**

In an economic assessment study of medical technologies or strategies, it is necessary to have three types of data:

- a) Data referring to the epidemiological parameters of the disease, syndrome or condition to be dealt with. It is particularly important to base the analysis on information about the prevalence and incidence in the region covered by the economic assessment study.
- b) Data referring to the effectiveness of the medical technologies or strategies in question.
- c) Data referring to the characteristics of the medical practice.

Statistics of the epidemiology of the disease, syndrome or condition should, whenever possible, be obtained from population-based epidemiological studies. If there are none, hospital-based epidemiological studies or others may be used as long as they are properly weighted. If there are no statistics of this nature at all, the data available for other regions may be used as estimates.

In any case, the origin of the data used and the hypotheses adopted should be clearly specified.

A controlled, random clinical trial is the most reliable method of determining a relationship of causality and, therefore, of assessing the efficacy or effectiveness of a treatment. Preference should therefore be given to

information from clinical trials or meta-analyses of clinical trials with these characteristics.

It is the data on effectiveness that are of essential interest in economic assessment studies. As these data refer to current clinical practice, it is extremely important for them to reflect the situation in the country. If no data on effectiveness are available from clinical trials of this nature, efficacy data obtained in appropriate clinical trials can be used after being corrected by modelling. Effectiveness data obtained from observational epidemiological studies are also acceptable.

At the same time, prospective data are preferable to retrospective data. In any case, they should reflect the situation in the country. The justification of the choices should be exhaustive.

In terms of the scientific validity of the data generated, the weakest choice for estimating effectiveness is a panel of experts. This option should be considered as a last resort and should be based on efficacy data obtained in clinical trials. In other words, a panel of experts cannot estimate efficacy; it can only estimate effectiveness on the basis of real efficacy data. The only exceptions to this rule are diseases, syndromes or conditions with a low prevalence and incidence (“orphan strategies”), which make it logistically impossible to conduct clinical trials.

Economic assessment studies should reflect current medical practice in the region to which they refer, particularly when it comes to identifying medical technologies or strategies actually used there most. Using hypertension as an example, a study should find out which drug is most often chosen as a primary treatment, after how long alternative treatments are sought, how often drug associations are used and which drugs are most frequently associated.

Epidemiological studies in general and cross sections in particular are especially appropriate for obtaining this type of information. The consensus of a panel of experts is an acceptable method. Nevertheless, the composition of the

panel should be described in detail and the representativeness of its members justified. For example, if a disease, syndrome or condition is treated by specialists and general practitioners, both groups should be represented.

### 3. Comparators

**The alternative of reference should be current practice, i.e. the most common treatment. If there is more than one treatment and the most common one is not the most efficacious, the latter should also be considered. If the cheapest treatment is neither the most common nor the most efficacious, it should also be included.**

The comparator in an economic assessment study of a new treatment should, above all, be appropriate. The comparison should not be artificial because we have chosen a comparator that is not used in everyday practice but which is favourable to the new strategy. An appropriate comparator is that which is, in fact, used in current clinical practice. We therefore recommend using as a comparator the technology or strategy that is used for the most patients for the same indication. An exception would be the contradictory situation in which the technology or strategy used for most patients was not the most efficacious. In this case, the technology or strategy with the best proven efficacy for the same indication should also be included.

On the other hand, if the technology or strategy with proven efficacy and the highest number of users is not the cheapest, the lowest costing technology or strategy with proven efficacy should also be considered.

In practice, one, two or three comparators can thus be included in an economic assessment study. There will be one comparator when the medical technology or strategy used most is, at the same time, also the most efficacious and the cheapest. Two comparators should be considered when the most efficacious is not the one used most but is the cheapest or when the most efficacious technology or strategy is the cheapest but is not the one used most. Finally, three comparators will be included when most efficacious, most used and cheapest do not coincide in the different alternatives.

The main purpose of these guidelines is to identify the relevant alternatives enabling us to make as accurate an assessment as possible of the opportunity cost of the new treatment being analysed.

If we have any difficulty in identifying the appropriate comparators, they should be established by agreement between the author and recipient of the study. In all cases, economic assessment studies should include a discussion of the most important alternative treatments together with a justification of the choice of comparators in the analysis.

#### 4. Population

**The population considered in determining the costs and consequences should be described in great detail, especially with regard to morbidity and mortality. The population should correspond as closely as possible to the potential users of the treatment under analysis.**

The real population, i.e. the population that will be the target of the treatment, should serve as a reference for the economic assessment of a treatment. In other words, the population analysed or used as a model should be representative of the potential users of the treatment in current clinical practice. For this aspect to be completely explicit, the target population should be clearly described, indicating prevalence, diagnosis, the severity of the disease, the age group and distribution by gender. Other factors that may be relevant in this description are mortality rates, the existence or not of co-morbidity, the use of similar treatments and the distribution of the disease in geographical areas and relevant socio-economic groups.

This question is particularly important when planning prospective studies and in modelling. In the latter, the population covered in the studies making up the models must be taken into consideration. In the case of clinical trials, we must assess how restrictive the inclusion and exclusion criteria were and the resulting external validity.

A chapter that merits special attention is the analysis of subgroups. The target population can be divided into subgroups. We can expect them to be defined by demographic or clinical characteristics based on the results of prior scientific studies, in which effectiveness is different from that defined for the population as a whole. The analysis of subgroups is prone to bias, manipulation and loss of statistical power because of the reduction in the sample that it involves. To avoid these disadvantages, the analysis of subgroups should only be

considered if defined in advance and if the number of subgroups *post hoc* can be managed as a generator of hypotheses. This aspect should be explained if we do this.



## 5. Assessment of therapeutic effect

**Therapeutic effect should be assessed in terms of effectiveness whenever possible. If this information is not available, the use of efficacy data will be accepted. In this case, the hypotheses and models used to estimate effectiveness should be described in detail and an appropriate sensitivity analysis should be made of the results.**

Efficacy is a measurement of the beneficial effect of a technology or treatment under ideal conditions, i.e. in a controlled environment in which the technology or treatment is used by research-oriented physicians under a strict protocol on motivated patients. This is usually the case in a clinical trial.

Effectiveness is a measurement of the beneficial effect of a technology or strategy assessed in normal clinical practice. It is sometimes very difficult to reconcile the methodological precision of a clinical trial with the environment of real clinical practice. In the real world there are many health care providers with different prescribing profiles, writing prescriptions for heterogeneous groups of patients, who are normally not so well informed and more prone to co-morbidity and/or the use of drugs that were not studied in the original clinical trials.

It is, however, basically the data on effectiveness that are of interest in economic assessment studies. As they refer to conditions in current clinical practice, it is extremely important for the situation in the country to be reflected in the data obtained.

The measurements used to assess therapeutic effect depend on the type of study. The following are generally used. (1) Measurements related to the disease, which are usually physical measurements (e.g. lower blood pressure, reduction in cholesterolemia or increased nervous conduction speed) (2) measurements related to the patient (e.g. reduction in motor disability, reduction

in the number of cardiovascular events, reduction in the number of hysterectomies or years of life gained) (3) measurements of the quality of life and (4) monetary units.

When the consequences are assessed on the basis of measurements related to the disease or the patient, the studies will be cost-minimisation or cost-effectiveness analyses. When quality of life is measured, a cost-utility study can be made. If it is a question of monetary units, the study will be of cost-benefit.

An important problem that pharmaco-economic studies have to face is that only efficacy data are available when a new product is launched. Any studies carried out at this stage will inevitably have to extrapolate the effectiveness of the treatment on the basis of its estimated efficacy in the clinical trials. Modelling is normally used to do this. If this is the case, the models used and the assumptions underlying them will have to be explained in detail and a sensitivity analysis will be made of the results.

## 6. Time horizon

The length of the study should coincide with the duration of the treatment and its consequences. If this is not possible, the length of the study should enable us to identify unequivocally the main costs and consequences that may lead to different results. The use of models is permitted provided that it is duly justified. In this case, we should present the hypotheses and the methodology on which their construction was based.

The alternatives should be compared on the basis of all their costs and consequences, regardless of when they occur. The time horizon of the study should therefore coincide with the period of time in which the costs and consequences that can be attributed to the treatment occur.

There are, however, situations in which this means extending the period of reference too much without any significant benefit to the accuracy of the study. Indeed, a long time horizon may lead to less accurate results given that the randomness of estimates increases with the length of the study. In these cases, the time horizon may be restricted.

Nevertheless, limiting the time horizon should not jeopardise the identification of the costs and consequences of each alternative leading to different results. The identification should be unequivocal.

For example, an exhaustive assessment of different strategies for controlling dyslipidaemia has to consider all the costs and consequences of the alternatives. This, however, requires a very long time horizon, as it is necessary to quantify the costs and end points of the coronary disease during the “representative” patient’s life. If treatment began at an early age, it is practically impossible as, if there are no epidemiological studies identifying the occurrence

of the events leading to the use of resources and/or associated with the end points, the degree of uncertainty is very high. In this type of case, it is acceptable to identify the costs and consequences that can be expected to occur over a shorter time horizon (e.g. five years), provided that we can demonstrate that there is enough time to compare the alternatives or that the estimates referring to a longer period would be too random and would compromise the accuracy of the study.

The extension of the time usually requires the use of models. If this is the case, they should be presented in such a way that the user of the study can verify their consistency and analyse their reliability. This means explaining the methodology used and all the hypotheses on which they were based.

In some studies, it may be useful to use more than one time horizon to analyse the available information. For example, a short-term analysis could be based solely on data taken from controlled clinical trials and another, long-term analysis would include modelled data.

## 7. Analysis techniques

**Any scientifically recognised economic evaluation technique can be used.**

**If it can be shown that the consequences associated with all the alternatives are the same where the characteristics relevant to the study are concerned, a cost-minimisation analysis (CMA) can be made. If this is not the case, we should conduct a cost-effectiveness analysis (CEA). It is advisable, however, whenever possible, to make a cost-utility analysis (CUA) or cost-benefit analysis (CBA) to make it possible to compare the results of the studies of different pathologies. A cost-utility analysis is preferable in this case.**

**Studies of the cost of the disease and cost-consequence studies are accepted as a first approach in the economic justification of the choice of treatment alternatives. They should not, however, be used to replace formal economic evaluation studies.**

There is no point in limiting the types of analysis to be used in assessment studies in advance. The cost-minimisation, the cost-effectiveness, the cost-utility and even the cost-benefit approach can all be adopted.

The analysis technique chosen should be justifiably appropriate to the problem being studied.

If it is shown that the consequences associated with all the alternatives are the same where the characteristics relevant to the study are concerned, a cost-minimisation analysis (CMA) can be made. This type of analysis can be regarded as a special case of the CEA, CUA and CBA techniques, where only the costs are considered, due to the similarity of the impact of the treatment.

The consequences of two treatment alternatives are rarely exactly the same. It is therefore important for studies to present a detailed, sustained justification whenever they use the CMA technique.

In cases in which the consequences of the different alternatives are not the same, a cost-effectiveness analysis can be made. This technique, which is based more on decision analysis than on economic theory, answers two types of question. Which treatment can achieve a pre-established level of effectiveness at the lowest cost and which treatment maximises effectiveness at a pre-determined overall cost? Several different measurements of effectiveness can be used, ranging from clinical observations, like a reduction in blood pressure, to the number of deaths prevented. The basic question is that the measurement of effectiveness must be appropriate and common to the treatments being studied. It is therefore essential to justify the dimension(s) of the consequences chosen for analysis.

If the alternatives can only be distinguished by considering multiple consequences that may not be common to all of them, cost-utility or cost-benefit analyses should be used. It is also advisable to use these approaches as a complement to a cost-effectiveness analysis, as they enable us to compare the results of studies of different pathologies. In these cases, a cost-utility analysis is preferable to a cost-benefit analysis.

CUA can be regarded as a kind of CEA, in which the consequences are measured in terms of years of life gained weighted by the variation in the quality of life. The weighting factors should reflect the aggregate of individual preferences with regard to the results of the treatment. They can be estimated directly from patients or the general population, obtained from published data or from data estimated on the basis of panels of experts. CUA is sustained by economic theory and is the fastest growing economic evaluation technique in the health field.

CBA is different from other economic evaluation methods in that it values both costs and consequences in monetary terms. It is based on the economic theory

of welfare and, as such, has more solid theoretic foundations. It enables us to make comparisons with public investments in sectors other than health. CBA studies do, however, raise complex issues of measurement, such as contingent valuation. Generally speaking, it is not advisable to value benefits using the human capital method.

In addition to these four techniques, estimates of the cost of the disease and cost-consequence analyses can also be used, although they are not formal (complete) economic evaluation studies. In fact, they are partial and/or descriptive approaches of the problem and cannot be used as a basis for choosing between treatment alternatives. These types of approach should be regarded as preliminary analyses of the problem and as a complement to, but never a replacement of, the conclusions of the formal economic evaluation.

Finally, note that the techniques suggested here are not mutually exclusive and that a study presenting results based on the CEA and CUA methods will serve as a better basis for a decision than another using only one economic assessment technique.

## 8. Identifying costs

All costs relevant to the analysis must be identified. Whenever possible, we should present a clinical decision tree showing all events relevant to the different treatments. When the analysis adopts the perspective of society, the costs included will be the direct costs of providing health care, the costs of social services and other sectors related to health care and the costs borne by patients and their families. The only indirect costs included should be those of an employee's lost productivity. After their inclusion has been properly justified, these costs should always be reported separately and the impact of their results analysed.

Identifying costs consists of listing all the relevant resources used as a result of the adoption of each treatment alternative so that they can then be measured and valued.

To do this, whenever possible, we must first establish a decision tree showing the probability of the occurrence of all the events and of the clinical choices involving the use of resources. The relevant events should then be selected according to the re-established perspective of the analysis.

If the analysis is made from the perspective of society, the relevant costs are the overall ones, i.e. the costs borne by all players in society. In this case, transfers of income (e.g. sickness or unemployment benefit) should not be considered as they represent a gain for some individuals and a loss, in the same amount, for others. No resources are used; they are just redistributed.

If another perspective in addition to that of society is also adopted, the relevant costs associated with this perspective and which have not been duly demonstrated in the first analysis should be listed here. Indeed, the main point



to bear in mind when identifying and estimating costs (whichever they are) is that they should be appropriate to the aim of the analysis.

All direct and indirect costs should be identified. It is also advisable to include intangible costs (e.g. the pain suffered by the patient due to the use of invasive surgical techniques), even if we recognise that it is not strictly speaking an economic cost and can never be quantified or valued, as it is immeasurable.

The direct costs included are those of health care given as a result of the treatment and its consequences, such as hospitalisation costs, consultations, expenditure on tests, treatment, nursing and rehabilitation, or as a result of the patient's death. Non-medical expenses arising from the treatment should also be included, together with those incurred by informal nursing provided by the patient's family at home and other services used to prevent or eliminate the risk of relapse or the occurrence of other diseases.

Other direct costs that affect society are those associated with research, training, building health facilities and the administration of services by public or private agencies, all of which provide support in the prevention and treatment of disease.

We should also consider as direct costs the health care expenses incurred as a result of the fact that patients' life expectancy is increased thanks to the treatment and they will therefore use more health products in the future. We should, however, only include the expenses that are a direct result of the treatment in question. For example, the use of a drug to reduce dyslipidaemia may result in gains in the patients' survival. These gains are generally long term and it is not, therefore, possible to relate the subsequent use of care with the treatment. In this case, the cost should not be included, as we cannot prove that the care was a direct consequence of the initial treatment.

We should also consider as direct costs all those arising from the treatment and affecting the patients and their families, such the cost of transport to the place in which health care is provided, accommodation expenses (if the patient has to

leave his or her area of residence, for example) or the cost of the upkeep of the patient's residence if s/he has to hire someone to replace or help him or her with domestic tasks.

Where indirect costs are concerned, we should only consider those associated with loss of productivity on the part of an employee. At the same time, there may be gains in productivity as a result of the treatment. These costs should therefore be reported in net terms, i.e. as costs calculated and deducted from gains.

The inclusion of indirect costs should be properly justified by showing that an employee's productivity has increased or decreased as a result of the disease and/or treatment. These variations should be reported separately and a sensitivity analysis should be made of their impact on the results.

Finally, we must remember that the objective is to compare alternatives, and so the costs that can be shown to be the same for all the alternatives should not be included. Only those that are different in quality or, if they are of the same type, diverge in terms of quantity in the different treatments should be considered.

## 9. Measuring and valuing costs

Separate, detailed information should be given on the resources used (measured in physical units) and the way in which the resources have been valued (unit prices or costs). The information on the use of resources should be based on clinical practice in the country. If this is not possible, it is necessary to use foreign data, they should be validated by local health care providers.

The basic economic principle for valuing resources is that the units of measurement should reflect the opportunity cost of these resources, i.e. the value lost if the resources are not applied in their best alternative use. We should therefore begin a process of creating, validating and maintaining cost tables for use in economic assessment studies. Nevertheless, even after these tables have been drawn up, other data can still be used, provided they are justified.

Total costs should be obtained from the product of a vector consisting of the average quantities of resources used per case (Q) by the vector of their unit prices (P). Measuring costs means determining the elements associated with each treatment alternative in vector Q. They are valued by determining the unit cost or price of each of these resources in order to build vector P. These two vectors should be presented separately, thus making it possible to use standard costs when valuing resources.

In the first phase, we should therefore quantify the resources used for each patient in physical units, such as the number of hours of nursing required for the treatment, the average hospital stay and the number of consultations, based on clinical experience in the country. When this is not possible and the data on the amount of resources used have to be obtained on the basis of foreign studies, they should be reassessed in the light of the situation in the country.

Measurement of costs should be exhaustive so that they can all be quantified in physical terms and valued. Precautions should, however, be taken to prevent double counting. This can happen if we do not distinguish clearly the costs of a disease and the benefits of treatment.

In fact, as economic assessment refers to treatment alternatives, we should not consider years of life lost as a result of premature death as a cost. And the prolonging of life should only be quantified when it is the result of a certain treatment. There is no point in considering as a cost of a given alternative the difference between the probable age of death associated with it and the average life expectancy. What we should consider is the added survival time the alternative offers.

Resources should be valued (i.e. vector P specified) on the basis of the economic concept of cost. Market prices are the best tool to use if the perspective of the analysis is that of society. By definition, prices constitute the “signs” that enable consumers to choose between all types of goods according to the marginal benefit associated with each choice.

There are, however, several arguments against using prices for this purpose in the health sector. The main one is the fact that the sector does not meet the conditions stipulated for the prices generated in it to reflect the true marginal benefits brought by using each type of care.

A possible alternative is to use shadow prices associated with the use of the resources. Although this method is preferable to the one mentioned above, it is prone to a degree of subjectivity. An example of this is the use in Portugal of the values from DRGs or convention tables as the approximate price of health care. This is done on the assumption that the NHS is the market regulator and that it fixes these prices on the basis of its knowledge of the relationship between the value of the resources used and the social benefits obtained. Although this is not, in fact, the case, as these values reflect considerations (especially administrative and budgetary ones) that have nothing to do with market

mechanisms, they should be the preferred source for valuing costs if there is no table of standard costs.

One way of obtaining a better approximation to shadow prices is by fixing standard costs for economic assessment studies in health. Cost tables should be created, validated and maintained for use in these studies. The tables should value resources at their social opportunity cost. If the value needed is not in the tables, the valuation should be made using the most appropriate methods for each case. For example, if we want to update the price of drugs, we should use the drug price index and not the Consumer Price Index.

Certain cases deserve particular attention. Rules should be laid down for determining the prices of drugs used on inpatients (in order to define standardised costs), even if it is necessary to use a panel of doctors. On the other hand, in case of hospitalisation, the use of average costs will mean carrying out a sensitivity analysis.

The time a patient wastes because of the treatment (doctor's appointments, hospitalisation or time spent on transports) should reflect its opportunity cost. The value attributed in this case should therefore be that of the income the patient would have received if s/he had not had to take time off work.

Situations may arise in which the unit prices used are taken during the study, especially when it is being conducted at the same time as clinical trials or when it is necessary to gather specific data for the analysis. In these cases, we obviously do not use the standard costs and researchers should clearly identify the values used and the procedures used to obtain them justify adopting them rather than standard costs. These rules should also be followed when costs are estimated on the basis of samples obtained, for example, in small geographical areas, population subgroups, particular cases of diseases or others. Whenever values are estimated for costs, the methods and the sources used should be appropriate to the situation in the country and should also be properly identified.

The least consistent method of valuing resources used is book costs. This is because they reflect administrative procedures and simplified points of view (especially in the case of public departments) that bias the values obtained. A clear example of this is the way depreciation is considered in public accounting, which does not allow it to be reflected in the unit costs of using facilities. If the perspective adopted in the study is that of a public department, however (that of a hospital or health region, for example), these should be the costs included in the analysis because it is on the basis of these values that public administrators make their decisions.

We can therefore see, once again, the importance of specifying the perspective of the analysis and the way it affects the profile of the study.

## 10. Measuring consequences

The unit used to measure consequences should be clearly identified. In cost-effectiveness studies, the consequences can be measured using several indicators, such as the years of life gained by using each alternative. If we use intermediate results in a study of this type, they should be properly justified. In any case, the efficacy indicator should be presented first, before the effectiveness indicator.

If we adopt the cost-utility approach, we should present the quality of life weightings for each level of limitation of activity and the years of life gained. The aggregation of these two elements should be transparent. In cost-benefit studies, the monetary valuation of the consequences should preferably use the contingent valuation method.

In cost minimisation studies, the problem of choosing the scale for valuing the consequences does not arise. In this case, the consequences associated with each alternative are clearly identified, so it is enough to compare the different costs. When adopting any of the other analysis techniques, however, there are several different methods available.

In cost-effectiveness studies, the consequences should be measured taking into account that what we want to assess, in the end, is the contribution each alternative can make towards improving patients' health. The end points we consider should, as far as possible, be those related to the impact of treatments on the duration of life. Given the difficulty of quantifying this impact, however, we can adopt indicators like the reduction in disability time or the improvement of clinical parameters, even if they are not directly associated with prolonging life. If this is the case, the choice should be justified in detail.

At the same time, the effectiveness indicator chosen is usually related to that used to measure efficacy in epidemiological studies and clinical trials. It should be specified first, before the chosen effectiveness indicator. The relationship between the two (if they are different) should be discussed.

In a cost-utility study, years of life are weighted by the quality of life, which can be measured with several instruments. Some of them are based on value, i.e. they enable us to measure the different degrees of limitation of activity on a cardinal scale between 0 and 1 (like the “standard gamble”, the “time trade-off” and the EQ-5D, for example), in which 0 represents death and 1 perfect health. Others, on the other hand, are merely descriptive of these degrees of limitation (e.g. the SF-36).

The literature on the comparative advantages of any of the value-based methods does not enable us to say that any one of them is better than the others. We cannot, therefore, exclude the possibility of using any of them, provided that it has been validated for Portugal and we can justify that the choice is appropriate for the study.

In any case, it is advisable to consider at least one properly qualified group of reference. The role of this group of reference is to give its opinion in order to correct the values calculated in patients' answers and obtain weightings that reflect the opinion of society on the quality of life corresponding to each degree of limitation of activity. It should therefore consist of people that are familiar with the evolution of the disease. If this is not the case (a significant sample of the population, for example), this should be properly justified.

Descriptive tools should be presented, as they are an asset to any assessment study. Whenever possible, it is advisable to present results based on generic measurements (such as the SF-36, Sickness Impact Profile or Nottingham Health Profile) and specific instruments (i.e. those designed to measure concrete health problems) at the same time. Descriptive instruments cannot replace value-based ones, however, and do not constitute an adequate base for a cost-utility study.



If we have chosen a cost-benefit approach, the gains associated with treatments are valued in monetary units. The human capital method, which is traditionally used for this purpose, presents a number of problems (e.g. it is not applied directly to the inactive population) and should therefore only be used in exceptional, duly justified cases. We recommend that the “willingness to pay” should be assessed using the contingent valuation method. This method has not been developed much in the area of health, but shows a lot of promise in terms of its capacity to measure relevant gains from treatments. This method has two advantages over the human capital method: (a) it measures the basic result, and (b) it can pick up on important aspects such as external use and satisfaction (utility) with the treatment process.

## 11. Total and incremental analysis

**The cost and consequences of each alternative should be presented in terms of variation from those of common clinical practice - incremental analysis. The total values should also be calculated so that the decision maker can analyse the costs and consequences of each alternative.**

In the first evaluation studies conducted, it was common practice to present only the overall costs and consequences of each alternative. In the research done in the meantime, however, it soon became apparent that this way of presenting the results was inappropriate for two reasons.

Firstly, as common practice is always included among the treatments being compared, the decision to be made is which additional costs should be incurred and what can be gained by replacing usual procedure with one of the alternatives.

On the other hand, the fact that we compare overall results implies that the costs and consequences of each alternative have homogeneous behaviour to scale, i.e. we assume that, if they rise or fall over time, these changes occur at a constant rate. Well, this may not be the case.

As a result, the costs and consequences of each alternative should always be presented in terms of their increase (or decrease) compared to the treatment of reference, which should be current practice.

At the same time, the totals should also be calculated to enable us to assess the overall costs and consequences of each alternative. Otherwise, we run the risk of obscuring the total impact of the alternatives being analysed. Moreover, by presenting the totals, we enable future users to compare the results with

treatments that have not been included in the study (e.g. new drugs) or with results obtained in other geographical contexts (regions or countries).

## 12. Discount rate

**All costs and consequences should be discounted at a rate of 5 percent. A sensitivity analysis should be made of this rate. If the consequences are not valued in monetary terms, the sensitivity analysis should include the zero rate, which corresponds to not discounting the consequences.**

If the alternatives are to be comparable, the costs and consequences should refer to the same moment in time and they therefore have to be discounted if they occur at different moments in time, depending on the treatment. As the rate used only reflects pure preference for time and this is highly subjective, there is no way to calculate it empirically.

Nevertheless, we can give an approximate value based on the real long-term market interest rate. In Portugal, this has been about 4 – 5 percent in recent years.

Five percent has been adopted as the discount rate for costs and consequences. The choice of this figure was influenced by the fact that it is the one used in most of the countries that have guidelines for economic assessment studies. Recent studies, like the Washington Panel, point to a rate of 3 percent, however, so this figure can be used in a sensitivity analysis.

It is debatable whether consequences that have not been valued in monetary terms should be discounted. If, for example, we valued the impact of the alternatives using the number of years gained, discounting them would mean considering that the current value of a year of life gained decreases over time.

If we do not discount the consequences, there will be biases, as it will favour the alternatives with a long-term impact at the expense of those with shorter-term results.

In these cases, we can also consider not discounting the consequences, while their discount at the reference rate would continue to be the basic scenario.

The consequences can also be discounted at a different rate from that used to discount costs. If this is the case, it should be duly justified.

Finally, given the subjective nature of the value stipulated, a sensitivity analysis should be made of this rate.

### 13. Assessing the impact of uncertainty on the results

**We should make a sensitivity analysis of the key parameters with values that are subject to uncertainty. If these values have been obtained by sampling, the analysis should be conducted considering the confidence intervals for each estimate. In other cases, the choice of variation intervals or alternative values for the parameters should be justified in detail on the basis of empirical evidence or of logic.**

In most studies, to a greater or lesser extent, the results reflect fairly weak estimates of the variables. This may be due either to insufficient statistics or to questionable methodological procedures.

If the values have been obtained from population samples (for example, results obtained from clinical trials), the sensitivity analysis should be conducted on the basis of the confidence intervals for which the results were obtained.

Alternatively, when there are doubts about the accuracy of the data used (about the discount rate, the incidence of a pathology or the amount of certain types of costs, for example), the sensitivity analysis should either consider the variation intervals of the parameters in question (threshold analysis) or stipulate *ad hoc* estimates for these values.

If we choose the first of these techniques, the analysis is made by calculating lowest and highest values to which the order of the alternatives changes. The values obtained should then be discussed in the light of the available economic and clinical evidence.

If we opt for the second one, the analysis is made by specifying alternative values for the parameters (the specification should be justified) and comparing the results we have obtained with those of the initial scenario.

The choice regarding hospital costs illustrates the difference between the two techniques mentioned. If the alternatives being analysed require the patient to be hospitalised, the costs can be calculated in different ways. For example, we can use a weighted average of the different types of hospital or only the data on the central hospitals.

If there are controversial assessment standards, all the alternatives should be considered. An example of this is the decision as to whether or not to include the costs to society of the reduction in patients' productive contribution as a result of permanent or temporary disability associated with their clinical condition. When we have doubts as whether to include them and it is considered important to the order of the alternatives, all possible scenarios should be presented – not including these costs, including only those resulting from permanent disability or including all costs of this type.

#### **14. Model for presenting economic assessment studies**

**The presentation of economic assessment studies should comply with a form identifying all relevant aspects needed to understand the analysis of the studies.**

**Authors should therefore use the attached model.**

It is a good idea to have a standard model for presenting an economic evaluation study as it enables us to compare studies in terms of their transparency and possible reproduction and to make an objective assessment of their quality. The model does not limit the authors' use of any particular technique.



## 15. Ethical and procedural aspects

When presenting the results of a study, regardless of the form the presentation takes – final report, public presentation or publication – we should always refer to the source of funding and the real contribution made to it by the all the authors. The researchers should be completely free to choose their methodology in all stages of the study and should be entitled to publish the results in the scientific journal of their choice.

The basic requirement for an economic assessment study is that it should be credible. This means, on one hand, that the relationship between the authors and between them and their financial backers should be transparent and, on the other hand, that the technical accuracy of the study can be subject to external validation.

The transparency of the procedures means that we identify not only each author's contribution to the work but also the financial backer of the study and the main clauses of the contract signed by both parties, especially those regarding methodological aspects and any limitations on the publication of the results.

The external validation of the study should be as broad as possible, using “inter-peer discussion”. This is why the authors should be allowed to publish their findings in scientific journals, especially those that require articles to be edited by independent experts (or arbiters) before they are published. The authors should also be encouraged to present their results at local and international meetings of experts.

## ANNEX

### MODEL FOR PRESENTING ECONOMIC ASSESSMENT STUDIES

An economic evaluation study means addressing all the aspects listed below and answers should be given to all the questions.

#### **I. Introduction**

##### **I.1 Objective**

Generic identification of the study's goals and the perspective from which it will be conducted

##### **I.2 Perspective**

- Society
- Third payer
- Information for prescribers
- Hospital managers
- Marketing
- Patient information

##### **I.3 Social importance of the disease**

- Socio-demographic characterisation of the population
- Epidemiological data
- Description of the pathology
- Characterisation of current clinical practice

##### **I.4 Description of the new product**

- Classification of the treatment, brand name and generic name, dosages and form of administration
- Approved indications

- Indications for which the economic assessment is being conducted, including pharmaco-epidemiological data and the correlation with epidemiology in studies and current clinical practice for these indications

### **I.5 Conditions for access to the study**

- Relationship between the financial backers and those responsible for conducting the research and presenting the final report
- Autonomy of the researchers and publication rights

## **II. Development of the study**

### **II.1 Analysis techniques**

- Studies may be prospective, retrospective, modelled or they may combine different methods
- Analysis techniques that can be used:
  - Cost minimisation analysis
  - Cost effectiveness analysis
  - Cost-utility analysis
  - Cost-benefit analysis

The reasons for choosing a particular technique should be indicated.

### **II.2 Design of the study, procedures used, statistical analyses and validation methods**

- Decision trees
- Markov's Model
- Extended revision of literature relevant to the clinical and economic analysis of the problem

### **II.3 Comparators**

We should indicate the reasons that led to the choice of the comparators, according to the guidelines

#### II.4 Time horizon

- The period of reference for obtaining results

#### II.5 Identifying and measuring consequences

- Consequences.
- Results obtained from clinical trials
- Physical units of measurement and the the method and instruments used to value the consequences

#### II.6 Identifying and measuring costs

The types of resources used, the physical units in which they were measured and the data sources on which their measurements and valuation were based

#### II.7 Rate for discounting costs and consequences

Justification of the discount rate(s) used

#### II.8 Presentation and publication of results

The results should be presented and published in such a way as to be easily accessible and comprehensible to the recipients of the study. The presentation and form of publication should vary accordig to the targets. The table below gives some examples.

Aim of the Study	Results	Publication of results
To justify repayment or co-payment of the price of a drug by public bodies	<p><b>a.</b> Total incremental (social) costs and consequences of each alternative</p> <p><b>b.</b> Overall, incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, depending on the analysis technique chosen</p>	Informative documents on prices and co-payment

	<p><b>c.</b> Total incremental costs and consequences, from the perspective of the third, public payer</p> <p><b>d.</b> Incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, from the perspective of the third, public payer, depending on the analysis technique chosen</p> <p><b>e.</b> Estimated impact of adopting the proposed alternative on the drug budget of the NHS</p>	
<p>Doctors, pharmacists and medical opinion leaders</p>	<p><b>a.</b> Total incremental (social) costs and consequences of each alternative</p> <p><b>b.</b> Overall, incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, depending on the analysis technique chosen</p> <p><b>c.</b> Incremental costs and consequences, from the perspective of the health care provider</p> <p><b>d.</b> Incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, from the perspective of the health care provider, depending on the analysis technique chosen</p>	<p>Seminars, conferences, scientific journals</p>

<p>Families and patients' associations</p>	<p><b>a.</b> Total incremental (social) costs and consequences of each alternative</p> <p><b>b.</b> Overall, incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, depending on the analysis technique chosen</p> <p><b>c.</b> Incremental costs and consequences, from the perspective of patients and their families</p> <p><b>d.</b> Incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, from the perspective of patients and their families, depending on the chosen analysis technique</p>	<p>Direct presentation to associations, publication in the specialized press</p>
<p>General public</p>	<p><b>a.</b> Total incremental (social) costs and consequences of each alternative</p> <p><b>b.</b> Overall, incremental cost-effectiveness ratio, cost-benefit ratio or cost-utility ratio of the alternatives, depending on the analysis technique chosen</p>	<p>Press conferences, formal announcements, publication in consumer associations' magazines</p>

## II.9 Sensitivity analysis

- Presentation and analysis of the parameters and variables subject to a sensitivity analysis
- Discussion of methods of analysis
- Results

## **II.10 Discussion**

- Analysis of the models used in the study and of the hypotheses on which they are based
- Assessment of the main limitations and biases arising from them

## **III. Conclusions**

The conclusions should be exhaustive in that they must give an accurate reflection of the main issues addressed in the study. It is particularly important to list the alternatives in order of priority.

## **IV. Bibliography**

## **V. Annexes**

- Detailed data tables
- Steps of the analysis
- Intermediate results
- Questionnaires used
- Explanation of the theoretical bases of the instruments adopted