ESTUDIOS DE ECONOMÍA APLICADA VOL. 24-3, 2006. PÁGS. 731-754

Health Technologies Assessment: Analysing The Role Of Uncertainty

NAVARRO ESPIGARES, JOSÉ LUIS Y HERNÁNDEZ TORRES, ELISA
University of Granada, Spain, Faculty of Economics, Department of Applied Economy
Campus Universitario de La Cartuja s/n. E-18071 GRANADA.
E-mail: jnavarro@ugr.es - elisah@ugr.es

RESUMEN

La mayoría de países desarrollados se enfrentan en la actualidad a un reto fundamental en sus políticas sanitarias: el rápido aumento de los costes sanitarios. Se estima que un tercio de este incremento anual se debe a la incorporación de avances en tecnologías médicas en la práctica clínica. Por tanto, la evaluación económica (EE) se ha convertido en requisito práctico y ético para los sistemas sanitarios. Incluso algunos países han establecido requisitos de evidencia de coste-efectividad como parte de las decisiones sobre prestaciones incluidas en la financiación pública. No obstante, la EE debe superar ciertas limitaciones relativas a la fiabilidad de sus resultados para ser realmente útiles en los procesos de toma de decisiones, siendo una de las más importantes la consideración de la incertidumbre en los resultados de la EE. Considerando todo lo anterior, el objetivo de este trabajo es analizar la inclusión de la incertidumbre en las evaluaciones económicas realizadas por autores españoles hasta la fecha, y establecer el estado del arte en este tema.

Palabras clave: incertidumbre, evaluación económica de tecnologías sanitarias

Evaluación De Tecnologías Sanitarias: Análisis Del Papel De La Incertidumbre

ABSTRACT

Currently, most developed countries' decisions about health-care policy must address a major challenge: the rapidly rising costs of health care. It is estimated that one third of this annual increment is due to the incorporation of health technology advances in medical practice. So the economic evaluation (EE) of health technologies has become an ethical and practical requirement for health systems. Even several industrialised countries have introduced formal requirements for evidence of cost-effectiveness as part of pricing and reimbursement decisions. But EE must fulfil several requirements regarding the reliability of the results to actually be useful for decision makers. There are several aspects affecting this reliability, one of the most important being the inclusion of uncertainty in the results of EE. Therefore, the objective of this paper is to analyse the inclusion of uncertainty in Spanish economic evaluations published up to now and to establish the state of the art in this field.

Keywords: uncertainty, economic evaluation, health technologies.

JEL Classification: D81, H40, I19,

Este trabajo fue financiado por el programa de promoción de la investigación biomédica y en ciencias de la salud del Instituto de Salud Carlos III para la realización de estudios de investigaciones sobre evaluación de tecnologías sanitarias (Resolución de 29 de julio de 2004, BOE de 10/09/2004) Proyecto PI04/90112.

Artículo recibido en Diciembre de 2005 y aceptado para su publicación en Marzo de 2006.

Artículo disponible en versión electrónica en la página www.revista-eea.net, ref.: e-24306.

ISSN 1697-5731 (online) – ISSN 1133-3197 (print)

1. EFFICIENCY IN HEALTH SYSTEMS: MAIN CHALLENGE IN 21ST CENTURY

Currently, most developed countries' decisions about health-care policy must address a major challenge: the rapidly rising costs of health care in the last two decades. It is estimated that one third of this annual increment is due to the incorporation of health technology advances in medical practice.

This shows that it is necessary to assess the efficiency of each new procedure or piece of equipment before introducing it into the public health system. So decision-makers have progressively adopted criteria of economic rationality to assign resources in the "most appropriate" way (González, 2000). Concretely, in an effort to contain health care costs, health care decision-makers, throughout the last two decades have incorporated criteria derived from utilitarianism to allocate resources in order to obtain maximum usefulness. The general idea contained in the concept of efficiency is that waste shouldn't exist: this implies obtaining the maximum product with the given resources or, alternatively, to obtain a stipulated production level at minimum cost (Navarro, 1999).

One of the most controversial subjects in efficiency measurement in the public health sector (as well as in the public sector in general) is the choice of the output. Although this problem is still under discussion, notable advances have been made in recent years.

Health results are the main objective of a health system, which implies improving population health status. From this viewpoint, the use of methods for the measurement of health status (individual or populational) is justified. It is accepted that methods for human life valuation must be consistent with the basis of cost-benefit analysis and the Paretian criterion of social gain. As mentioned above, the objective of health care systems is to improve people's health. So it is not surprising that we observe an increasing interest in quantitative measurement of individual and population health status, in order to evaluate changes in health status over time and identify and quantify differences among population groups. An important application of this measurement is the decision-making related to resources allocation.

The economic evaluation of health care programs compares the resources consumed by the programs (costs) versus their results (health improvements). Since there are different ways of comparing these costs and results, different health technologies economic evaluation methods are needed. Regarding the costs, we can differentiate direct, indirect or intangible costs. And in terms of health output, three types of measures can be considered: natural units of the health programs, economic benefits associated with health improvements and the subjective value given by patients for health improvements.

As stated above, the economic evaluation of health technologies has become an ethical and practical requirement for health systems. In fact, several industrialised

countries have introduced formal requirements for evidence of cost-effectiveness as part of pricing and reimbursement decisions.

2. HEALTH TECHNOLOGY ASSESSMENT IN BRIEF

The term Economic Evaluation (EE) refers to a set of analytical tools, whose immediate objective in the health care sector is the valuation of costs and effects of health technologies (including drugs, medical equipment, public health programs, etc.). Actually, EE compares benefits and costs of several options, in a context of scarce resources where it is always necessary to set priorities among alternatives. A rational criterion derived from utilitarianism allocates resources looking for the maximum benefit or utility of resources employed. From the basis of economic analysis, EE is defined as the comparative analysis of alternative actions, which includes the valuing of costs and consequences of each alternative. So a complete EE must fulfil two requirements, that is, compare several alternatives and take into account costs and consequences as well.

Under the general heading of economic evaluation (EE) applied to health technologies, there are several related but distinct approaches to the assessment of health practices. These approaches allow comparisons among interventions so that decision-makers can choose the best option for health care investments.

Cost-minimization analysis (CMA): Compares interventions based solely on their net cost. This method is applicable when alternative options have (or are assumed to have) the same effectiveness.

Cost-effectiveness analysis (CEA): Compares interventions based on a common measure of their health effectiveness. The measure used for health effectiveness may be the number of prevented cases of a disease, cases cured, lives saved, or years of life gained. It could also be a preference-based measure such as quality-adjusted life years (QUALYs). Analyses using health measures that are expressed in quality adjusted units are referred to as cost-utility analyses (CUA). Many authors use the term CEA in reference to this subset of analyses (Gold et al, 1996; Hunnink et al, 2001).

Cost-benefit analysis (CBA): Requires that all effects of alternative interventions as well as costs should be valued in monetary terms. It can be used to compare very different interventions, including health and non health investments of resources. Alternatives are considered on the basis of their net benefit: options with a positive net benefit should be implemented while those with a negative net benefit should not. Cost-benefit analysis is used less frequently in health care than CEA, because many people are uncomfortable with valuing health effects, such as human lives and the quality of life, in monetary terms. Objections are both ethical and technical, the latter relating to the validity of methods used to assign a value to health effects.

The difficulties surrounding cost-benefit analysis have lead to a preference for CEA in the realm of health care. Nevertheless, cost-benefit analysis is used in a sizeable fraction of economic analyses concerning health, particularly those examining environmental programs and other interventions that have important effects in health as well as non health domains.

3. HEALTH TECHNOLOGY ASSESSMENT AND DECISION-MAKING IN HEALTH POLICY

Although the increase in the number of evaluations published year after year is well known (García-Altés, 2000; Oliva, 2002), the systematic collection of evidence regarding the effect of those analyses is rare. Thus, commentators in this area are forced to use their own judgement, on the effects of these studies.

3.1. Uses of Economic Evaluation in Health

The primary purpose of EE is to determine the best way to allocate scarce resources among various alternatives. Because markets for medical care and health insurance have a natural tendency to fail in optimising allocation of resources, no country in the world has left these decisions entirely up to private markets. Instead, health system policies present a continuum based on the degree to which governments intervene to establish health care as a social right (Sloan and Conover, 1995).

Potentially, EE is helpful in reaching any decision in health care, that is, any decision which involves use of resources. In practice, for most routine decisions, clinical judgement is an efficient alternative. There may, of course, be an indirect influence from evaluation if clinicians follow guidelines reflecting the results of evaluations. EE, being costly, are usually reserved for significant decisions such as provision of new facilities, introduction of new therapies, use of new medical devices, introduction of new diagnostic equipment and changes in organisation of services.

In the last decades, the acknowledgment of EE as a support tool in health policy decision-making processes has increased notably. Currently, it is broadly accepted that economic health technology assessment (EHTA) is an analytic tool to support decision-making in financing and regulation of health technologies. Although little is known about decision-makers' viewpoints on these reports, there is ample evidence that EHTA results are hardly utilised in adopted decisions (Sloan y Conover, 1995; Davies, Coyle y Drummond, 1994; Briggs, 1995; Russell et al, 1996; Oliva et al, 2000; 2001; Hoffman et al, 2002; Drummond et al, 2003; García-Altés, 2004). Since the beginning of the nineties, a number of authors have been pointing out that, due to methodological limitations of the reports, decision-makers lack confidence in their results (Briggs, 1995).

Consequently, the most important issue currently is how much more widespread and influential EE will become in coming years. The general opinion seems to be that in the future EE will gain in use. The following two facts make this evident. Firstly, in response to a simple questionnaire in which pharmaceutical industry health economists from several European countries were asked about their perception of the use of economic health evaluation in their own countries, six replied that it was gaining importance in reimbursement and pricing decisions, while two were noncommittal. Secondly, there is a growing list of countries which have already produced, or are in the process of producing, EE guidelines. After a long period of inactivity in Europe, presently there is escalating pressure to set priorities regarding health technologies.

3.2. Applications of CEA in health policymaking

Up to the middle of the nineties, evaluation of pharmaceuticals by public agencies was based almost exclusively on criteria of safety and efficacy. Some public agencies faced with pressures to cut expenditures, have been basing selection of pharmaceutical drugs to be included in their official lists solely on a comparison of drug costs. Four relevant examples of EE use in policy-making are the priority-setting process for Medicaid coverage in Oregon, the guidelines for Pharmaceuticals in Australia, the draft guidelines for pharmaceuticals in Ontario and the National Institute for Clinical Excellence (NICE) in the United Kingdom.

Oregon developed a unique approach to determine the benefits package available to those eligible for Medicare. Rather than deciding which specific types of services to cover or how to limit them, the Oregon approach eliminates specific treatments for specific conditions based on rankings from a public prioritization process. This ranking is the first large-scale public attempt to apply CEA to set priorities for medical services, but was ultimately abandoned in favour of a hybrid process in which cost was not a major factor in determining the final rankings.

On the other hand, Australia and Ontario (Canada) established that for a new drug to be included in their public plans, manufacturers must submit, among other materials, an economic evaluation of the drug in question. Consideration is given to effectiveness, safety and cost. Their health agencies offer guidance about the information that manufacturers should provide to decision-making bodies to facilitate their understanding of the economic implications of reimbursement for new products.

Finally NICE, although recent (as of April 1, 1999), is an example of transference of results from research to decision-making in the United Kingdom (Buxton, 2001). NICE is a special health authority whose main role is to make recommendations to National Health Service (NHS) clinicians and managers in England and Wales regarding the use of selected health technologies, produce clinical guidelines, and develop audit methodologies. It is hoped that NICE appraisals will lead to clarity and consistency within the NHS concerning key technologies and will help eliminate

postcode rationing whereby each health authority makes its own, and often differing, decision on availability of health technologies.

3.3. Looking for performance in HTA: NHS-EED, EURONHEED, IRYSS

Health care decision-makers need easy access to reliable information about the costs as well as the effects of drugs, treatments and procedures to better inform their decisions. Although there is a growing literature evaluating the cost-effectiveness of health care interventions, these studies can be difficult to identify and appraise. Several initiatives have emerged to solve this problem: NHS-EED, EURONHEED, IRYSS Net.

National Health Service Economic Evaluation Database (NHS-EED) was funded by the Departments of Health of England and Wales to assist decision-makers by systematically identifying and describing economic evaluations, appraising their quality and highlighting their relative strengths and weaknesses. Economic evaluations are systematically identified by searching a range of electronic databases and by means of hand searching journals and other paper-based resources.

EURONHEED's, (European Network of Health Economics Evaluation Databases Project), objective is to implement databases on the economic evaluation of health care interventions in several European countries (France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom and associated countries). The goal is to index the published literature in health economics evaluation for the countries covered by the network. The project, coordinated by the College des Economistes de la Santé (CES), started in January 2003. More information is available in the EURONHEED's web site http://infodoc.inserm.fr/euronheed.

IRYSS Net (a Spanish acronym of the network Research in Health Results and Health Services) was launched by means of a public proposal in Spain in 2002. It is a broad project that includes an economic evaluation research line, whose main objective is to identify and prioritise technologies. Since the beginning of IRYSS Net, the economic evaluation research line has been focused on the elaboration of structured abstracts of EHTA papers database, which facilitate the comprehension of methods employed and the evaluation of their quality. These structured abstracts are elaborated based on the guide of structured abstract of the NHS-EED, which contains the items shown in the Table 1. Structured abstracts provide users with rapid and complete information about original papers so that they can decide whether the papers are of enough interest and quality to be used in decision-making processes. The number of references, among the different sources of data consulted in the bibliographical revision, surpassed a thousand. Once the duplications were eliminated, and after a first classification, 378 papers were selected, and 364 were definitively included in the database. After the revision, the studies were classified as follows: 157 Spanish economic evaluations, 22 international economic evaluations (including Spain), 136

cost studies, 25 methodological studies and 24 revisions. The structured abstracts are presently being grouped in a virtual library of health program economic evaluation, which can be consulted in IRYSS Net's web site) http://www.rediryss.net. To date, the virtual library of IRYSS Net contains 60 structured abstracts of EHTA, published between 1995 and 2002.

Table 1:
Items of the IRYSS Net structured abstracts

1.	SUBJECT OF STUDY
1.1.	Health technology
1.2.	Disease
1.3.	Type of intervention
1.4.	Hypothesis/study question
2.	KEY ELEMENTS OF STUDY
2.1.	Economic study type
2.2.	Study population
2.3.	Setting
2.4.	Dates to which data relate
2.5.	Source of effectiveness data
2.6.	Modelling
2.7.	Link between effectiveness and cost data
3.	DETAILS ABOUT CLINICAL EVIDENCE
3.1.	*Single study*
3.1.1.	Study sample
3.1.2.	Study design
3.1.3.	Analysis of effectiveness
3.1.4.	Effectiveness results
3.1.5.	Clinical conclusions
3.2.	*Review/synthesis of previous published studies*
3.2.1.	Outcomes assessed in the review
3.2.2.	Study designs and other criteria for inclusion in the review
3.2.3.	Sources searched to identify primary studies
3.2.4.	Criteria used to ensure the validity of primary studies
3.2.5.	Methods used to judge relevance and validity, and for extracting data
3.2.6.	Number of primary studies included
3.2.7.	Method of combination of primary studies
3.2.8.	Investigation of differences between primary studies
3.2.9.	Results of the review
3.3.	*Estimates of effectiveness based on opinion*
3.3.1.	Methods used to derive estimates of effectiveness
3.3.2.	Estimates of effectiveness and key assumptions

4.	ECONOMIC ANALYSIS
4.1.	Measure of health benefits used in the economic analysis
4.2.	Direct costs
4.3.	Indirect costs
4.4.	Currency
4.5.	Statistical analysis of quantities/costs
4.6.	Sensitivity analysis
5.	RESULTS
5.1.	Estimated benefits used in the economic analysis
5.2.	Cost results
5.3.	Synthesis of costs and benefits
5.4.	Author's conclusions
6.	CRITICAL COMMENTARY
6.1.	Choice of comparator
6.2.	Validity of estimate of effectiveness
6.3.	Validity of estimate of health benefit
6.4.	Validity of estimate of costs
6.5.	Other Issues
7.	IMPLICATIONS OF THE STUDY

4. UNCERTAINTY IN HTA

Uncertainty occurs when the true value of a parameter is unknown, reflecting the fact that knowledge or measurement of it is not perfect. Expressing the uncertainty surrounding the true value of a parameter involves identifying the range of values that could reasonably be attributed to the parameter (Berger et al, 2003).

To carry out an EHTA, evidence about costs and outcomes is necessary. Such evidence will typically be drawn from a number of different sources. These sources might include cohort studies for parameters relating to the natural history of the condition, randomised trials for relative treatment effects and cross-sectional surveys for resource use and costs. There are always likely to be deficiencies in the evidence base available for health technology assessment. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. Therefore, analyses should quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis (NICE, 2004).

As with other estimates, the use of the estimated cost-effectiveness ratio requires that the analyst provide some indication of how much confidence can be placed in it, or how uncertain the result may be. So, in order for economic evaluations to be useful for decision-making purposes, the results should include some estimate of the impact of uncertainty on the payoffs (costs, effects, cost-effectiveness) attributable to a technology, and ultimately the uncertainty surrounding the decision in general (Berger et al, 2003). Uncertainty, implicit in every EHTA, affects the decision-making process (Berger et al, 2003; Briggs y O'Brien, 2001; Hutubessy et al, 2003).

4.1. Why quantify uncertainty?

By directly relating the costs and benefits of two (or more) alternative interventions, economic evaluation seeks to improve the efficiency of health care provision at two levels: firstly, by identifying the least-cost alternative for providing health care of a minimum standard within a particular area; and, secondly, by identifying the appropriate allocation of resources among medical specialities. To achieve the former, it may be appropriate to measure the effectiveness of alternative interventions in units relevant to the particular medical area (for example, the number of episode-free days in the treatment of asthmatics). If the results of an economic evaluation demonstrate both, cost-savings and increased benefits for a particular health care intervention, then that intervention is clearly cost-effective, and it is said to dominate the alternative. However, if one health care intervention is shown to be more costly but also more effective than an alternative it is impossible to say a priori whether that intervention is cost-effective. Instead, an incremental cost-effectiveness ratio can be calculated and compared to other cost-effectiveness ratios representing alternative uses of health care resources. How uncertainty affects the position of the base case analysis, regarding the relative cost-effectiveness ratio, is crucial.

Uncertainty associated with the results of economic evaluations has important implications for the decision making process. Wrong decisions are costly. The failure to implement a cost-effective strategy is, in principle, just as costly as the implementation of a non-cost-effective strategy, in the sense that such decisions will result in a failure to maximise health benefit from available resources. Decisions cannot be said to be 'fully informed' unless they are taken with knowledge of the implications of uncertainty. Where a situation of dominance exists for the base case parameters (i.e., one intervention is both less costly and more effective), uncertainty in the value of those parameters could potentially lead to a situation where that intervention no longer dominates the other option. The importance of uncertainty will depend on the extent to which it influences the appropriate decision (see example in Box 1). It is clear that given such a scenario, a decision-maker seeking to invest additional health care resources might prefer one intervention over another more cost-effective one, due to the relative precision of its incremental cost-effectiveness ratio (Briggs, 1995).

Box 1 Importance of uncertainty

A study by Darba et al (2002) compares the costs to Spanish healthcare of 35 days of treatment with triflusal (600 mg/day) and aspirin (300 mg/day) for patients with confirmed acute myocardial infarction within 24 hours of onset of symptoms.

A one-way sensitivity analysis was conducted in relation to clinical parameters, by varying the incidence rates, using 95% confidence interval, and the cost of resources (using max and min possible values).

The sensitivity analyses showed that extreme values of the outcome estimates might modify the results when the worst-case scenario is applied.

4.2. Types of uncertainty

One of the least addressed areas of CEA concerns how to incorporate the inherent uncertainties regarding parameters, relationships and model structure into the estimated C/E ratios, or other intermediate calculations, and further how to represent the impact of this uncertainty in the elements of the analysis critical to decision making, to the user of the CEA. Nevertheless, in the CEA literature, several authors have catalogued different sources of uncertainty, and have suggested methods for dealing with this uncertainty (Briggs, 1995, 2000; Manning, Fryback and Weinstein, 1996; Berger, 2003). In this paper, we assume the categorisation by the US Panel on Cost-Effectiveness Analysis, which distinguishes two major types of uncertainty that can arise in cost-effectiveness models: modelling uncertainty and parameter uncertainty. Parameter uncertainty is uncertainty about the true numerical values of the parameters used as inputs. Model uncertainty includes both uncertainty about the correct method for combining these parameters (model structure uncertainty) and uncertainty introduced by the combination of decisions made by an individual analyst (modelling process uncertainty). The overall uncertainty in the final cost-effectiveness ratio reflects all three sources, parameter uncertainty, model structure uncertainty and modelling process uncertainty.

Uncertainty must be considered separately from the source in EHTA valuations. Different methods for quantifying uncertainty are required by different sources of uncertainty (Rubio-Terrés et al, 2004). Methods to handle uncertainty in EHTA can be grouped into two main categories: qualitative sensitivity analyses and statistical analyses of uncertainty.

Parameter Uncertainty

These uncertainties can arise in a number of ways:

When some key parameter of a quantifiable feature of the CEA problem cannot be known because we have not observed it or could not observe it (e.g., future rate of medical inflation relative to other goods and services).

When there is a disagreement about what the appropriate value is, and it is not likely that the issue will be resolved in time for the completion of the current CEA (e.g., the appropriate rate of discount for social decisions of a continuing problem of this type).

Uncertainty concerns key elements of the process, such as the epidemiology of the disease or patterns of physician behaviour and patient compliance. These could, in principle, be estimated if data from a study with a suitable design could be collected.

When the analyst has (asymptotically) unbiased estimates of key parameters, but these estimates will have sampling variability.

When we have a relatively precise estimate of the costs and the treatment effects for some ranges of the data or subpopulations (uncertainty related to extrapolation or generalisability).

Methods to handle parameter uncertainty

Traditionally, uncertainties have been examined using sensitivity analysis. But in recent years, there has been an increased interest in developing statistical measures of uncertainty in the estimated cost-effectiveness ratio.

Sensitivity Analyses

Simple Sensitivity Analysis: This is the most common form of sensitivity analysis. One or more parameters are varied across their plausible range. A distinction can be made between one-way and multi-way analysis. In a one-way analysis, extreme values are taken for each parameter individually to examine the effect on the results of a study. Multi-way analysis allows the variation of more than one parameter at a time. However, the greater the number of parameters varied, the greater the difficulty becomes to present the results of a multi-way analysis.

Extreme scenario analysis is merely a special case of a multi-way simple sensitivity analysis where all the most favourable values for a given intervention are combined to give a 'best case' scenario and all the least favourable values are combined to give a 'worst case' scenario.

Threshold analysis does not explicitly involve the specification of ranges for parameters. Rather, the critical value of a parameter relating to the decision threshold

is identified. The problem in economic evaluation is identifying the relevant decision rule. In theory, this decision rule is the maximum acceptable cost-effectiveness ratio; in practice however, it may be impossible to agree to a universally acceptable value for such a ratio.

Statistical Approaches: Probabilistic Sensitivity Analyses

Deterministic sensitivity analysis indicates what the outcome value is for any specified combination of input values. It allows the investigator to assess results under any plausible set of circumstances. However, deterministic analyses have a major drawback: i.e., they do not indicate the likelihood of particular results, given the uncertainties in multiple inputs.

In clinical evaluation, statistical analysis is accepted as the appropriate method for representing uncertainty, with the random clinical trial (RCT) widely regarded as the appropriate vehicle for generating the sample data. In economic evaluation the role of statistical analysis for estimation and hypothesis testing may be limited. Despite the increased use of economic analysis alongside clinical trials, the number of technologies for which there are high quality sample data regarding costs and effects of all alternatives is relatively few. The potential for unit costs to be sampled clearly exists, although care must be taken to ensure that the sample is representative of the appropriate population. Where there is a possibility of obtaining suitable sample data, and as the methods for applying statistical methods in stochastic cost-effectiveness studies are continually refined, it may come about that statistical analysis will become the method of choice for dealing with uncertainty in the data sources of a study (Briggs, 1995). Clinical trials offer the potential to sample economic as well as clinical data, which allows the use of standard inferential statistical techniques. In principle, the advantage of such an approach would be that uncertainty in economic evaluation could be represented by confidence intervals which are a widely understood and accepted method for quantifying uncertainty. Difference in cost-effectiveness could then be tested by the accepted methods of inferential statistics.

In this sense, probabilistic sensitivity analysis attempts to overcome the problem regarding deterministic analyses described above, by applying distributions to the specified ranges and sampling at random from these distributions to simulate uncertainty, thereby generating an empirical distribution of the cost-effectiveness ratio. Other methods for stochastic cost-effectiveness studies are delta method, simulation approach, bootstrap analysis and Bayesian estimates.

Model Uncertainty

In some cases the analyst, in addition to being uncertain about the values of particular parameters, is also uncertain about the mathematical forms by which they

should be combined. The choice of using multiplicative or additive functions is often made for mathematical convenience in the absence of clear evidence that one or the other of the functions is the appropriate one to use.

It is difficult to formally incorporate this type of model structure uncertainty. Some alternatives can be combined into a single, more general model. Beyond the suggestion to compute the estimates under each alternative structural assumption deemed reasonable, little more is offered in the literature about this source of uncertainty in economic evaluation analysis.

From the viewpoint of the user of the analytic results, there is one remaining source of potential error: the entire process by which the CEA was completed in each particular instance has been carried out by one particular analyst or analytic team. It may be the case that if the analysis had been conceived, structured, parameterized and computed by another analyst, the results would have been different. In this view, the particular analysis presented is but one sampled from a universe of possible analyst-analysis pairs.

There is no known simple method to test the reproducibility of the modelling process. It is likely that some choices would be made differently by different analysts, leading to different results.

Uses of sensitivity analysis

Sensitivity analyses have applications from the beginning to the end of the CEA process. They are used in planning the analysis, debugging the model, documenting expected relationships and revealing unexpected relationships, identifying thresholds, influencing policy, and identifying research needs. Perhaps the most exciting use of sensitivity analyses is in influencing policy. It sometimes occurs that there is an agreed-upon threshold and that a CEA team is in a position to answer the question: What would have to happen to reach that threshold?

5. UNCERTAINTY IN HTA IN SPAIN

The importance of dealing with uncertainty in EHTA is evident, but very little is known about how analysts in fact do it. Guidelines published for EHTA accomplishment are in agreement regarding the requirement of carrying out a sensitivity analysis on the base case results, but operational aspects about how to perform this analysis remain a controversial aspect, due to the discretional decision of the researcher on this aspect.

In the absence of clear guideline on this aspect, knowledge about how uncertainty has been dealt with in previous analyses and the preferred ways used by various analysts would definitely be useful in future studies.

5.1. Methodology

Objective

To analyse the state of the art in dealing with uncertainty in economic health technology assessment (EHTA) reports.

Design of the study

This is a descriptive analysis of criteria and tools for dealing with uncertainty in EHTA reports carried out in Spain. The source of data is the "Virtual Library of Economic Evaluation Studies of Health Programs", elaborated by IRYSS Net (www.rediryss.net), which provides structured abstracts of EHTA reports carried out by Spanish analysts, independently of language and publication type.

Scope of the study

The scope of the study is conditioned for the source of data. Currently, the virtual library of IRYSS Net contains 60 structured abstracts, of papers published between 1995 and 2002. So the scope of this study includes EHTA reports published in the period 1995-2002, incorporating at least one Spanish author.

Population of study

Structured abstracts of IRYSS Net follow a pattern for classifying elements of EHTA which facilitates the analysis and comprehension of the whole report. One of the items includes details about uncertainty. Concretely if a sensitivity analysis was carried out, the methodology and the analysed variable.

So, inclusion criteria are the following: (1) Papers included in IRYSS Net Virtual Library of Economic Evaluation Studies of Health Programs and (2) Papers including uncertainty analysis

Papers fulfilling these criteria are revised and classified according to featured aspects that deal with uncertainty and other general attributes of the papers.

Variables of study

General features of EHTA reports and methods to handle uncertainty, as detailed in Table 2.

Analysis

We present a descriptive analysis, using frequencies and percentages, to outline the use of methods of analysis of uncertainty in economic evaluation by Spanish authors.

Limitations

The small number of structured abstract included in the Virtual Library of Economic Evaluation Studies of Health Programs to the date.

Table 2:
Variables of study

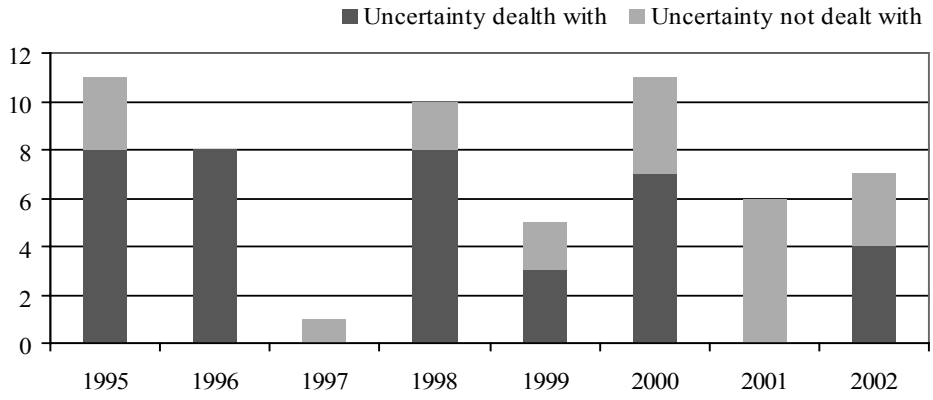
General features of EHTA reports	
Year of publication	
Country	
Language	
Type of economic analysis	- Cost-effectiveness (CEA) - Cost-utility (CUA) - Cost-benefit (CBA) - Cost minimization (CMA)
Source of effectiveness data	- Single study - Review/synthesis of previous published studies. - Estimates of effectiveness based on experts opinion - Composite of previous
Methods to handle uncertainty	
Type of uncertainty	- Parameter uncertainty - Modelling Uncertainty: model structure, model process
Uncertainty Analysis	Sensibility analysis - Univariate - Multivariate - Threshold - Extreme scenarios Statistical analysis - Delta - Simulation - Probabilistic sensitivity analysis - Bootstrap - Bayesian analysis Comparison of different structural assumptions

Possible limitations in this paper are related to the temporal scope and the source of data, due the reduced number of papers considered.

5.2. Results

Of the 60 papers currently available in IRYSS Net database, published between 1995 and 2002, 38 (64.41%) fulfilled inclusion criteria, of which 29 were Spanish publications.

FIGURE 1:
Yearly distribution of structured abstracts in IRYSS Net (March 2005)



The most frequent type of economic analysis is CEA (86% of analysed papers), followed by papers where CEA and CUA are combined (7.89%). Very few CUA and CMA were found, and no CBA.

The source of data most frequently used by analysts is literature (50%), being the majority. The rest of the papers obtain data from single studies (15.79%) and experts opinion (7.89%) in the minority. The frequent practice of combining two different sources of data was observed in a high percentage of mixed studies (26.31%) (Table 3.1).

Every reviewed paper coincides about dealing with uncertainty from parameters, but only two papers treat model uncertainty.

The majority of studies analyse several types of uncertainty, mainly the parameter related to the analytical model (related with extrapolation, generalization…), and the sampled parameter. Variability in population is scarcely analysed.

The most frequent method used by Spanish authors in dealing with uncertainty is the sensitivity analysis, and they seldom use multivariate sensitivity analysis, threshold or extreme scenario analysis. There are many papers in which uncertainty analysis has been carried out, but the method is not specified (Table 3.2).

TABLE 3.1:
General features of EHTA reports

N=38	Nº	%
Publication		
▪ National (Spanish)	29	76.32
▪ International	9	23.68
Language		
▪ ES	27	71.05
▪ EN	10	26.32
▪ Others	1	2.63
Type of economic analysis		
▪ Cost-effectiveness analysis (CEA)	33	86.84
▪ Cost-utility analysis (CUA)	1	2.63
▪ Cost-benefit (CBA)	0	0.00
▪ Cost Minimization analysis(AMC)	1	2.63
▪ CEA + CUA	3	7.89
Source of effectiveness data		
▪ Single study	6	15.79
▪ Review/synthesis of previous published studies	19	50.00
▪ Estimates of effectiveness based on opinion	3	7.89
▪ Mixed studies	10	26.31

Table 3.2:
Methods to handle uncertainty

N=38	Nº	%
Type of uncertainty		
▪ Parameter	38	100.00
▪ Model	2	5.26
Uncertainty analysis		
Sensitivity analysis	24	63.16
▪ Univariate	2	5.26
▪ Multivariate	2	5.26
▪ Threshold	4	10.53
▪ Extreme scenarios	0	0.00
Statistical methods		
▪ Delta	0	0.00
▪ Simulation	0	0.00
▪ Probabilistic sensitivity analysis	0	0.00
▪ Bootstrap	0	0.00
▪ Bayesian analysis	0	0.00
Comparison of different structural assumptions	0	0.00
Not specified	13	34.21

5.3. Discussion

The results obtained in the prior analysis follow the same line as some previous papers (García-Altés, 2000; Oliva et al, 2002), confirming the preference of analysts for CEA versus other methods of economic analysis.

Despite the fact that all published pharmacoeconomic guidelines suggest the use of sensitivity analysis, only 64.61% of studies between 1995 and 2002 in Spain did so. No time trends in the conduct of sensitivity analyses were detected. However, the sample may not have been sufficient to detect such trends. Our results are aligned with previous literature. A prior study by Agro et al (1997), where 90 English-language health economic articles on studies published between 1989 and 1993 were reviewed, found that 53 (59%) conducted sensitivity analyses.

Regarding the specific features of uncertainty analysis, the majority of papers analyse uncertainty related to the analytical model by univariate sensitivity analysis.

Statistical analysis of uncertainty is only applicable in uncertainty due to variability in sampled data, that is, in economic analysis included in clinical trials (the so called naturalistic or pragmatic trial) (Briggs, 1995).

Notwithstanding the trend to include economic analysis studies in clinical trials, these studies are still a reduced percentage with respect to the total number of EHTA carried out: in 1996, only 6% of economic analyses were included in clinical trials (Briggs, 2000). A revision by Briggs and Sculpher (1995) of economic evaluation papers published in 1992 noted that 38% of studies do not apply sensitivity analysis adequately. Regarding that issue, the most adequate method must be stated. Polsky et al (1997) evaluated the suitability of statistical methods for sensitivity analysis of randomized clinical trials. They found that non parametric bootstrap and Fieller methods were the most accurate. Nonetheless, Spanish EHTA does not apply these methods even when it is carried out as a *piggyback* economic evaluation. So the majority of EHTA encompassed deterministic estimations, the sensitivity analysis being the only method of handling uncertainty. But even when stochastic data collected from a clinical trial are available, a role remains for sensitivity analysis in parameters where uncertainty is not related to a sampled error (e.g., discount rate is a deterministic datum independent of the source of data that will always need sensitivity analysis). Consequently it is quite unlikely that sensitivity analysis will fall into disuse, since it represents a logical approach to understanding the structure of an EHTA, gives the natural groups for multivariate analysis and is useful for focusing attention on critical variables that are very influential in the final result of the analysis and therefore determinant in the final decision.

Uncertainty in the structure of the model or in the global decision process is assuming a relevant role in statistical literature, where it is argued that the consideration of uncertainty in parameters regarding a model structure tends to underestimate the global uncertainty affecting the model. Manning, Fryback and Weinstein (1996) proposed the application of different models as a solution, specifying the probability of each one within the range of possible models.

These conclusions support the fact that decision-makers do not incorporate economic evaluations in their decision-making processes because of the low degree of confidence they have in the robustness of their results.

In summary, all inputs in an EHTA will be estimated with a degree of imprecision. The use of univariate, extreme or scenario-base sensitivity analysis to quantify the effect of parameter uncertainty in an analysis cannot incorporate the uncertainty in more than two or three parameters simultaneously. The use of probabilistic sensitivity analysis or stochastic analysis of patient-level data allows complete characterization of the uncertainty associated with all input parameters.

Following the NICE recommendations regarding the use of probabilistic analysis, Mar et al. (2006) have recently published a probabilistic CEA on the nasal continuous positive airway passage (nCPAP) treatment of obstructive sleep apnea syndrome

(OSAS). The probabilistic analysis showed that nCPAP was the optimal treatment in 98.5% of the simulations, and the expected value of perfect information (EVPI) showed that the parameter causing greatest uncertainty in the final results was the quality of life gained through nCPAP treatment. This kind of study allows uncertainty to be quantified and, furthermore, reveals what parameter information should be improved in future research. Thus these studies represent a notable advance in quantifying uncertainty and narrowing the gap between research and decision-makers.

6. REFERENCES

AGRO KE, BRADLEY CA, MITTMANN N, ISKEDJIAN M, ILERSICH AL, AND EINARSON TR. Sensitivity analysis in health economic and pharmacoeconomic studies. An appraisal of the literature. Pharmacoeconomics 11 (1):75-88, 1997.

BERGER M. L. et al (2003) Health care, cost, quality and outcomes. ISPOR book of terms (ISPOR).

BRIGGS A. H. (1995) Handling Uncertainty in the Results of Economic Evaluation. OHE Briefing No.32.

BRIGGS A. H. (2000) Handling uncertainty in cost-effectiveness models, Pharmacoeconomics 17 (5), pp. 479-500.

BRIGGS AH AND SCHULPHER M. Sensitivity analysis in economic evaluation: a review of published studies. Health Economics 4 (5):355-377, 1995.

BUXTON M. (2001) Implications of the Appraisal Function of the National Institute for Clinical Excellence NICE, Value in Health, 4 (3), pp. 212-6.

DARBA J, IZQUIERDO I, PONTES C, NAVAS C, AND ROVIRA J. Economic evaluation of triflusal and aspirin in the treatment of acute myocardial infarction. PharmacoEconomics 20:195-201, 2002.

DAVIES L., COYLE D., DRUMMOND M. (1994) Current status of economic appraisal of health technology in the European Community: report of the network. The EC Network on the Methodology of Economic Appraisal of Health Technology, Social Science Medicine, 38 (12), pp. 1601-7.

DRUMMOND M., BROWN R., FENDRICK A. M., FULLERTON P., NEUMANN P., TAYLOR R., BARBIERI M. (2003) Use of Pharmacoeconomics Information. Report of the ISPOR Task Force on Use of Pharmacoeconomic/Health Economic Information in Health-Care Decision Making, Value in Health, 6 (4), pp. 407-416.

GARCÍA-ALTÉS A. (2000) Twenty years of health care economic analysis in Spain: Are we doing well?, Health Economics, 10 (8), pp. 715-729.

GARCÍA-ALTÉS, A. (2004) La introducción de tecnologías en los sistemas sanitarios: del dicho al hecho. Gaceta Sanitaria, 18 (5), pp. 398-405.

GONZÁLEZ LÓPEZ-BALCÁRCEL, B. (2000) Acerca de la medición y valoración de los costes de las intervenciones sanitarias, Revista de Administración Sanitaria, 4 (15), pp. 475 -481.

HOFFMANN C., STOYKOVA B. A., NIXON J., GLANVILLE J. M., MISSO K., DRUMMOND M. F. (2002) Do Health-Care Decision Makers Find Economic Evaluations Useful? The Findings of Focus Group Research in UK Health Authorities?, Value in Health, 5 (2), pp: 71-79.

HUTUBESSY R., CHISHOLM D., TAN-TORRES EDEJER T. (2003) Generalized cost-effectiveness analysis for national-level priority-setting in the health sector, Cost Effectiveness and Resource Allocation, 1 (8), pp. 1-13.

MANNING W. G., FRYBACK D. G., WEINSTEIN M. C. (1996) Reflecting uncertainty in cost-effectiveness analysis. En Gold M., Siegel, J., Russell L., Weinstein M., (eds) Cost-effectiveness in Health and Medicine (New York, Oxford University Press).

MAR J., GUTIERREZ-MORENO, S., CHILCOTA, J. (2006) Análisis coste-efectividad de tipo probabilístico del tratamiento de la apnea del sueño, Gaceta Sanitaria, 20 (1), pp. 47-53.

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE). Guide to the Methods of Technology Appraisal. 2004. http://www.nice.org.uk/.

NAVARRO ESPIGARES J. L. (1999) Análisis de la eficiencia en las organizaciones hospitalarias públicas. (Granada, Editorial Universidad de Granada).

OLIVA J., DEL LLANO J. E., SACRISTÁN J. A. (2002) Análisis de las evaluaciones económicas de tecnologías sanitarias realizadas en España en la década 1990-2000. Gaceta Sanitaria, 16 (supl 2), pp. 2-11.

OLIVA J., DEL LLANO J., ANTOÑANZAS F., JUÁREZ C., ROVIRA J., FIGUERAS M. (2000) Impacto de los estudios de evaluación económica en la toma de decisiones sanitarias en el ámbito hospitalario, Gestión Hospitalaria, 11 4, pp. 171-179

OLIVA J., DEL LLANO J., ANTOÑANZAS F., JUÁREZ C., ROVIRA J., FIGUERAS M., GÉRVAS J. (2001) Impacto de los estudios de evaluación económica en la toma de decisiones sanitarias en atención primaria, Cuadernos de gestión para el profesional de atención primaria, 7 (4), pp. 192-202.

POLSKY D, GLICK HA, WILLKE R, AND SCHULMAN K. Confidence intervals for cost-effectiveness ratios: a comparison of four methods. Health Economics 6 (3):243-52, 1997.

RUBIO-TERRÉS C, COBO E, SACRISTÁN JA, PRIETO L, DEL LLANO J, BADIA X, AND ECOMED GROUP. Análisis de la incertidumbre en las evaluaciones económicas de intervenciones sanitarias. Med Clin (Barc) 122 (17):668-674, 2004.

RUSSELL L. B., GOLD M. R., SIEGEL J.E., DANIELS N., WEINSTEIN M. C., 1996, The role of cost-effectiveness analysis in health and medicine. Journal of the American Medical Association, 276 (14), pp. 1172-1177.

SLOAN F., CONOVER C. (1995) The use of cost-effectiveness/cost-benefit analysis in actual decision making: current status and prospects. En Sloan F (ed) Valuing Health Care: Costs, Benefits and Effectiveness of Pharmaceuticals and Other Medical Technologies (Cambridge, Cambridge University Press).

VANOLI A., TREVOR S., DRUMMOND M. F. (2001) Improving Access to Cost Effectiveness Information for Health Care Decision Making: The NHS Economic Evaluation Database. NHS EED.